Active Ingredients for Addressing Youth Anxiety and Depression 2

The knowns and unknowns of SSRI treatment in young people with depression and anxiety: efficacy, predictors, and mechanisms of action

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This is the second in a **Series** of three papers about active ingredients for addressing youth anxiety and depression

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The use of SSRIs for the treatment of depression and anxiety in young people is increasing. However, the effects of SSRIs in adolescence, a time when there are substantial changes in neural, cognitive, and social functioning, are not well understood. Here, we review evidence from clinical trials about the benefits and risks of SSRIs in young people and consider their mechanisms of action, as shown through human experimental work and animal models. We emphasise key outstanding questions about the effects of SSRIs in youth, identified through gaps in the literature and in consultation with young people with lived experience. It is crucial to characterise the mechanisms underpinning risks and benefits of SSRIs in this age group to progress the field, and to narrow the chasm between the widespread use of SSRIs in youth and the science on which this use is based.

Introduction

The effective treatment of depression and anxiety in young people (ie, younger than 24 years) is a key priority for public health. Rates of these disorders have been rising[1] and are associated with increased risk of suicide, comorbid conditions, impairments in social functioning, poor educational attainment, and low levels of future employment.[2–7] Early effective treatment decreases the risk of negative outcomes in the long term, with a sustained positive effect on functioning and life satisfaction into adulthood.[8,9] However, many young people with depression and anxiety do not access support.[10,11]

Psychological treatment approaches for anxiety and depression are a preferred first-line treatment approach for many young people and their parents.[12–14] Most clinical guidelines, including those from the USA, Europe, and WHO, suggest that the use of antidepressant medication should be reserved for young people with moderate to severe illness whose condition does not respond to or who are unable to effectively engage with psychological therapies, although medication can be part of initial approaches in severe depression.[15–19] Despite these guidelines, prescribing rates have steadily risen over the past 20 years, which is likely to be driven by increases in diagnoses, the comparative effectiveness of pharmacological treatment approaches for depression,[20,21] and limitations in provision of specialist services and psychological therapy (appendix p 1).[22]

The increasing use of antidepressants in young people necessitates the development of a solid, evidence-based understanding of the effects of antidepressants within this age group. Given the substantial changes in cognitive, social, and neural development during adolescence, it is probable that the effects of antidepressants might be different from those in adults, in whom most of the scientific investigations have been done. Here, we review current evidence of the effects of SSRIs for depression and anxiety disorders in young people (ie, aged 14–24 years). Obsessive compulsive disorder, acute stress disorder, and post-traumatic stress disorder are outside of the scope of this Series paper. We consider evidence for the benefits and risks of SSRIs, for whom and in what contexts they work best, and their mechanism of action, as shown through studies in humans and preclinical animal models. We outline the gaps in our knowledge on the basis of the literature and our consultation with young people with lived experience (panels 1, 2; appendix p 2), which are crucial to address to narrow the gap between the widespread

See Online for appendix

Panel 1: **Advantages and disadvantages of SSRIs from the perspective of young people**

Themes that emerged from a workshop with our Young Person Advisory Group (appendix p 2):

- Antidepressants are not an instant fix but can help to give you the tools to work at improving your mental health yourself. They can help an individual to engage more fully with psychological therapy and interact better with others than the individual would do without antidepressants.
- Antidepressants have side-effects and the net outcome of symptoms needs to be considered (eg, low mood might improve but anxiety could also increase at the start).
- There is social stigma associated with taking antidepressants, which can come from friends, peers, teachers, and family.
- Taking an antidepressant can help to validate a diagnosis as a real illness.

use of SSRIs in youth and the science on which their use is based.

The benefits and risks of antidepressant treatment in young people

Are antidepressants an effective treatment for depression and anxiety in young people?

Many randomised controlled trials have investigated the efficacy of antidepressants in young people with anxiety and depression. The most comprehensive systematic reviews and meta-analyses of this evidence (as identified by a meta-review[23]) report that fluoxetine is more efficacious than placebo in the treatment of major depressive disorder,[24] and fluoxetine, sertraline, and fluvoxamine are more efficacious than placebo in the treatment of anxiety disorders.[25]

Despite this evidence, there has been ongoing concern about inconsistencies across trials and the clinical relevance of the effect size of the drug–placebo difference in depression studies.[24] However, the estimated efficacy of antidepressants in young people needs to be interpreted in the context of the high response rate to placebo that was seen in these trials. Young age and short time since depression onset are known to be associated with high rates of remission during treatment with placebo.[26–28] Interestingly, placebo response rates are higher in studies that are funded by industry, which have also been shown to have a smaller effect size than publicly funded trials.[29] One proposed explanation for these differences is that many studies that are funded by industry were done quickly in response to a scheme that was launched by the US Food and Drug Administration in the late 1990s, which was designed to encourage industry to do trials in children and adolescents. Unfortunately, this scheme had the unintended consequence of incentivising a large number of poor quality studies, which were done over multiple sites and had a high response rate to placebo (ie, approximately 50–60%). These studies introduce substantial variability in meta-analyses and might negatively distort the estimation of antidepressant efficacy for young people with depression.[30]

Within this context, publicly funded trials of antidepressant effects in young people that are high quality and done on a large scale give the most reliable estimate of antidepressant efficacy. The largest study of this kind, the US-based TADS (n=439, 12–17-year olds), directly compared the efficacy of the SSRI fluoxetine and cognitive behavioural therapy (CBT). Notably, this study showed that the rate of response to fluoxetine (61%) was significantly higher than to CBT (43%) or placebo (35%) at the 12-week primary endpoint.[21]

Some evidence exists that combining SSRI treatment with evidence-based psychological therapy (eg, CBT) gives an additional benefit to medication alone in young people. This evidence is perhaps strongest in young people with anxiety, where the combination of SSRIs and CBT has been shown to be more effective than either treatment alone.[31,32] In young people with depression, the evidence is scarce and mixed.[33] The TADS study showed that CBT plus fluoxetine had a higher rate of response than fluoxetine treatment alone;[21] however, there was no additional benefit of combined therapy over medication alone in patients with the most severe depression.[34] This result is consistent with the findings from a trial of combination therapy for young people with moderate to severe depression, which reported no benefit of CBT plus fluoxetine compared with fluoxetine alone.[35] A study in young people aged 15–25 years with moderate-to-severe depression reported no additional benefit of combined CBT and fluoxetine compared with CBT alone for depressive symptoms after 12 weeks of treatment, although anxiety was significantly lower in people who were given combined treatment compared with CBT alone.[36] Some evidence in this study showed that combined treatment was more effective for depression and anxiety symptoms in participants who were older than 18 years, which might have been driven by the poorer response to CBT alone that was seen in this age group compared with other age groups.[36]

Despite the evidence supporting the effectiveness of SSRI treatment in young people with depression and anxiety, there is a high level of individual variability in response[37] and improved treatment options are needed

Panel 2: **Key outstanding questions about SSRI treatment in young people identified by our Young Person Advisory Group**

Questions that emerged from a workshop with our Young Person Advisory Group about priorities for future research on the effects of SSRIs in young people:

- What are the effects of antidepressants on cognition and academic work? Antidepressants can help improve an individual's ability to cope with stressful situations in school, work, and university. However, they could also impair their ability to think clearly.
- What are the long-term effects of antidepressant use on brain function, fertility, and growth?
- Does long-term use of antidepressants lead to dependency and withdrawal symptoms? How long should a young person be on antidepressants to maximise effectiveness and safety?
- Are there biological factors that predispose some individuals to react positively or negatively to different antidepressants? This could help to explain how antidepressants work for young people and why some individuals can have more side-effects than others. A better understanding of who antidepressants work best for and a consideration of other factors, such as neurodiversity and gender diversity, is also needed.
- How do antidepressants interact with recreational drugs or alcohol? Young people should be given clear information rather than simply being told to avoid all drugs or alcohol when taking antidepressants.
- How do we reduce the stigma that is associated with taking antidepressants and the misrepresentation of some of the effects of antidepressants in the media (eg, that they cause suicide)?
- Is there racial bias in the diagnosis of depression and anxiety in young people and in the use of antidepressants?

for the substantial minority of young people who have conditions that are resistant to treatment.[37,38]

What are the risks of SSRIs in young people?

The benefits of antidepressants need to be carefully balanced against the potential risks when considering medication for the clinical management of depression and anxiety in young people. Antidepressant-related adverse effects are known to affect adherence and increase medication discontinuation,[39] and concerns about side-effects can be a barrier to antidepressant use (panel 1, appendix p 2).

Side-effects and physical adverse effects, such as headache, nausea, and abdominal pain, are commonly reported by young people initiating treatment,[40,41] although the low discontinuation rate for SSRIs suggests that these side-effects are typically manageable and decline over time.[42] Many side-effects are similar to the somatic symptoms that are seen in patients with untreated depression and anxiety, and patients who are given placebo also report treatment-emergent adverse events, making a true estimation of the rate of SSRI-related side-effects challenging.[40,43] In adults, sexual side-effects (eg, erectile dysfunction, anorgasmia, and decreased libido) are commonly associated with SSRI use; however, these side-effects are less well understood in young people.[44] SSRI use in young people has also been associated with other physical adverse effects, including weight gain,[45] reduced growth,[46] reduced bone-mass density,[47] and a small increase in risk of type 2 diabetes,[48] which need to be considered carefully in the context of long-term antidepressant use.

SSRIs commonly cause insomnia and increased anxiety early in treatment. These and other psychiatric adverse effects (eg, irritability, agitation, impulsivity, emotional lability, hostility, restlessness, and aggression) have been clustered together and defined as symptoms of an activation syndrome, which is estimated to occur in 11–14% of children and adolescents[49] and is associated with high amounts of treatment discontinuation.[39,50,51] Activation symptoms are particularly pronounced in the first weeks of treatment and are more common in children than in adolescents.[52] It has been suggested that SSRI-induced activation might be associated with an increased risk of suicidality, although evidence to support such a link is scarce.[50,51] Some individuals might be more susceptible than others to SSRI-induced activation; for example, some small-scale studies suggest that polymorphisms in serotonergic genes might confer risk of such adverse effects.[53,54] Mania symptoms have also been reported in young people who are at high risk of bipolar disorder and are treated with antidepressants, and particular care should be taken when treating this group, although identifying this group can be challenging given the scarcity of good markers for risk.[55]

In 2004, the US Food and Drug Administration did a review and meta-analysis of 24 placebo-controlled trials of antidepressant medication in children and adolescents. They noted that, relative to placebo, SSRIs significantly increased the risk of experiencing adverse events of suicidal ideation and behaviour (risk ratio 1·66 [95% CI 1·02–2·68]).[56] This finding led to a series of regulatory warnings of an increased risk of suicidality in young people taking antidepressant medications. Two subsequent meta-analyses, which studied randomised trials of antidepressant treatment over a wide age range, suggested that the effect of antidepressants on suicidality is strongly age dependent; that is, although antidepressants might increase the risk of suicidal ideation and behaviour in children and young people, they are apparently increasingly protective against suicidality in people aged 30 years and over.[57,58]

The clinical trials from which these data were derived were not optimally designed to establish drug-related suicide risk; they generally excluded patients who were at high risk of suicidality, they were underpowered to detect rare events, such as suicide, and had a short follow-up period. The data from early trials were mainly based on reporting of adverse events rather than systematic measurement of suicidality, which is vulnerable to ascertainment bias, since those participants reporting other antidepressant-related side-effects are often more likely to be asked about other adverse events, including suicidality.[56,59] Other network meta-analyses of randomised trials, which include trials with structured clinician-administered suicidality measures, have reported that only selected drugs that are frequently used in the treatment of depression, notably the serotonin, norepinephrine reuptake inhibitor venlafaxine in patients with depression[24] and the serotonin reuptake inhibitor paroxetine in patients with anxiety,[25] are associated with increased risk of suicidal ideation and behaviours in young people. Sertraline was associated with a lower incidence of treatment-emergent suicidality in patients with anxiety disorders compared with placebo.[25]

Generally, suicidal thinking and behaviour in young people diminish during the course of SSRI treatment.[43,60] Additionally, ecological studies raise the important concern that suicide risk might actually increase due to the undertreatment of severe illness when antidepressant treatments are not used,[61–63] a concern that is supported by evidence that the use of antidepressants in young people who have died from suicide is rare.[64,65] Taken together, however, the available studies suggest that some young people can experience an increase in suicidal thinking and behaviour during SSRI treatment. It is therefore important to consider the risk of increased suicidality with SSRIs when making collaborative decisions about treatment. Further studies are needed to identify predictors for SSRI-induced suicidality in young people and to elucidate mechanisms that might underpin these effects.

Summary

SSRIs are a reasonably effective treatment for depression and anxiety in young people and can be particularly

suitable for the treatment of severe disorders and in circumstances where psychological therapy is not effective or possible. The combination of SSRIs with CBT can be a more effective approach than either treatment modality alone, although it is not yet understood how these two therapies are best combined to maximise effectiveness.

There are many outstanding questions about the risks of antidepressant use in young people. In particular, psychiatric adverse events, such as anxiety, irritability, and other symptoms of activation, need further investigation to understand the circumstances in which they occur and what factors make some young people more susceptible to their development. The effects of antidepressants in the long term on brain development, physical growth, and sexual function and fertility are not well understood and were emphasised as key concerns by our Young Person Advisory Group (panel 2). Although these unknowns make it tempting to deprecate the use of antidepressants in young people, the risks of SSRIs need to be carefully weighed against those of inadequately treating depression and anxiety in this vulnerable group. Given that medication is a necessary tool for clinicians treating young people, there is an ethical imperative that careful scientific investigations are done to fully understand the effects of antidepressant medications in this age group.

How do SSRIs work in young people?

Applying a mechanistic approach to characterise the effects of SSRIs in young people could resolve some of the outstanding questions emerging from clinical trials. Such an approach can help to identify which patients have conditions that will respond best to treatment, derive frameworks for combining different treatments, understand unwanted effects of treatment, and define targets for future treatment development.[66] Even in adults, however, knowledge of how the acute pharmacological actions of SSRIs are translated into their clinical effects in anxiety and depression is incomplete, and in young people there are few relevant mechanistic studies.

Serotonin mechanisms

The pharmacological effect of SSRIs on the developing brain is not well understood, and dosing is primarily based on information that is derived from adult studies. PET-imaging studies show that, in adults, minimal therapeutic doses of SSRIs occupy about 80% of brain serotonin transporters (ie, the pharmacological target of SSRIs; appendix p 1).[67] Analogous imaging data for young people are not available but young people are typically treated with SSRI doses in the adult range, though lower starting doses are often recommended.

In animal models, SSRIs are generally less effective in adolescent animals compared with mature animals, however, there are strain and species differences in these studies.[68,69] It might be relevant that expression and function of the brain serotonin transporter is lower in juvenile and adolescent animals than in adults. Additionally, the effect of repeated SSRI treatment on the expression of the transporter differs according to developmental stage, with a decrease in expression in adult animals and an increase in adolescent animals.[68] Increased expression of the brain serotonin transporter in adolescent animals could be associated with diminishing transporter occupancy by SSRIs and a decrease in serotonin availability in the synapse. Whether such an effect occurs in humans is not known.[68]

Brain plasticity

Neurobiological theories of antidepressant action, derived from animal experimental studies, have focused on drug-induced increases in brain plasticity, a process that enables the brain to adapt successfully to the changing environment. Neuroplasticity can encompass synaptogenesis and neurogenesis, which are mediated by changes in intracellular signalling and the elaboration of neurotrophic factors, such as BDNF.[66] Generally, SSRI treatment appears also to stimulate synaptic plasticity in adolescent animals, with increases in hippocampal neurogenesis, protein markers of cellular plasticity, and BDNF,[70,71] although there are some studies that have not noted this effect.[72]

Investigating plasticity in the human brain is challenging, although increases in human brain plasticity might be detectable through anatomical changes shown by MRI. There are hints in adult studies that SSRI treatment increases hippocampal and cortical volumes[73] and that this increase is related to treatment response,[74] but there are no analogous studies in adolescents. Peripheral measures of BDNF are increased by antidepressant treatment in some studies of adults with depression and can correlate with clinical response.[75] Conversely, in adolescents with depression, one study suggested that therapeutic response to escitalopram was predicted by early decreases in serum BDNF.[76]

Corticolimbic circuitry and affective processing

Affective cognitive processes, such as emotion regulation and resistance to peer influence, show large developmental changes across adolescence.[77] Large shifts in brain circuits supporting these processes are also evident, including changes in structure (ie, reflecting changes from synaptic pruning and increased myelination), function (ie, changes in activation or engagement of different neural circuits), and neurochemistry (eg, changes in prefrontal neurochemistry). The protracted development of the prefrontal cortical areas, which are important for emotion regulation, can increase risk for mood and anxiety disorders during this crucial developmental period.[78] Consistent with this increased risk, functional MRI studies have reported decreased functional connectivity between the prefrontal cortex and amygdala and exaggerated (or unregulated)

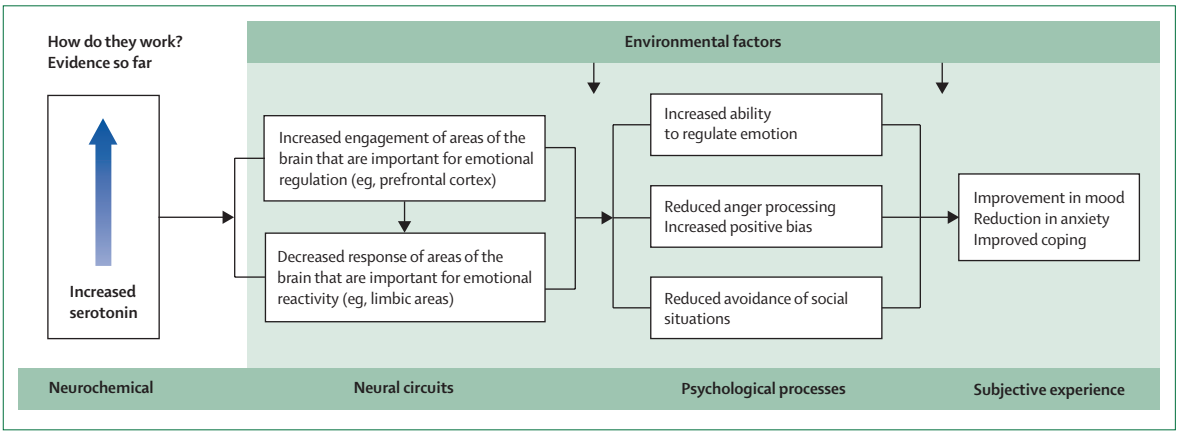

Figure: **Across levels of analysis: a mechanistic framework for SSRI action in young people**
Environmental factors can influence SSRI action at any point.

amygdala responses to negative stimuli in adolescent depression.[79]

SSRI effects on this corticolimbic circuitry are a core mechanism of antidepressant action in adults, with reductions in amygdala reactivity seen within hours of drug administration[80] and predictive of therapeutic effects.[81] Little mechanistic work has been done in adolescents, and developmental changes in this circuit undoubtedly complicate investigations by introducing high amounts of between-person heterogeneity. Treatment with fluoxetine over 8 weeks decreases amygdala and subgenual cingulate responses to negative faces in adolescents with depression.[82] Another study showed a similar effect after a single dose of fluoxetine versus placebo, suggesting fast effects of SSRIs on limbic function in adolescents with depression.[83] Decreases in limbic and increases in prefrontal response have been associated with clinical response (both to SSRIs and CBT) in adolescents with depression and anxiety.[84–86] These preliminary findings suggest that changes in emotional processing might be important in the mechanism of SSRI treatment action in young people, as has been suggested in adults.[66]

At a neuropsychological level, antidepressants have been shown to decrease negative affective bias; that is, the tendency to focus on, interpret, and remember negative information.[66] CBT works, in part, by challenging such automatic negative thoughts and mechanistic studies have shown that this reduction in negative bias is also a key mechanism of antidepressant action in adults.[66] In one study extending this perspective to young adults, acute fluoxetine reduced the perception of angry and sad facial expressions compared with placebo.[87] Increased sensitivity to angry facial expressions has been associated with irritability,[88] and the effect of fluoxetine on the recognition[87] and neural processing of anger[83] might be relevant to its action in adolescent depression, which is particularly characterised by symptoms of irritability.[89]

There is also the question of whether SSRIs have distinct or overlapping mechanisms with treatments such as CBT. Studies have reported a range of effects with SSRI treatment either alone or in combination with CBT that are associated with clinical response. These effects include improved emotional reappraisal,[90] enhanced problem solving ability,[91] decreased perfectionism,[92] decreased hopelessness,[93] improved coping efficacy,[94] decreased negative interpretative bias,[95] reduced somatic symptoms,[96] reduced social distress and behavioural avoidance,[97] and improved sleep.[98,99] However, most studies use self-report measures, making it difficult to understand the mechanisms of change.

Interactions with the environment

The idea that SSRIs work by reversing negative biases suggests that we also need to consider potential interactions with the environment. In particular, it has been hypothesised that changes in affective bias translate into improved symptoms of depression and anxiety via social and environmental interactions.[66] This hypothesis can help to explain the delay in clinical effects of antidepressants, since a period of responding to and learning from this new perspective is required (ie, changes in emotional bias would be expected to improve social interactions and help to deal with stress across time, leading to gradual improvements in mood; figure). Indeed, studies in adults have suggested that environmental factors can moderate the effects of SSRIs, with the best response seen in people in supportive social environments.[100,101]

However, this interaction deserves special attention in young people. Adolescence is a time of social transition, during which the influence of peers increases and the negative effects of social rejection can be stronger.[77] The role of social, environmental, and family influence can also be different across the adolescent period and require close analysis. Some studies have reported that low amounts of family conflict are associated with high treatment response.[102–105] However, there has been

little attention to the role of peers and social context in moderating the effects of SSRI treatment. Further research is needed to explore interactions between SSRI treatment and social, emotional, and socio-demographic factors since this research might help to show potential blocks to treatment success. This perspective also emphasises the potential benefit of integrating mechanistic understandings of psychological and pharmacological treatment to allow crosstalk between these approaches and the identification of optimal treatment combinations.

A mechanistic approach to understand the psychiatric adverse effects of antidepressants

The mechanisms by which SSRIs produce adverse effects, such as anxiety and other activation symptoms, are largely unknown. Most studies exploring this question have been done in animals and might not translate directly to humans. In adult rodents, acute SSRI administration can produce anxiogenic responses in behavioural tasks but, with repeated treatment, anxiolytic effects usually emerge.[106] A similar time course of effect is often seen in adult patients who are given SSRIs. In two strains of juvenile mice, repeated fluoxetine treatment produced a persistent increase in anxiogenic behaviours.[107] A similar effect in humans could result in an increased risk of troublesome SSRI-induced anxiety in young people. However, work that we have reviewed here suggests that acute fluoxetine does not have general anxiogenic-like effects in young adult volunteers (ie, aged 18–21 years), showing instead a profile that is more consistent with anxiolysis.[83,87]

Individual differences are likely to be important here, and more work needs to be done to understand the exact mechanisms that could contribute to SSRI-induced behavioural activation and arousal, which are most likely to occur in a subset of young people. Studies in adults with depression have shown a link specifically between irritability and suicidal ideation.[108] Hence, SSRI-induced increases in irritability in a subgroup of young people could be an important mechanism in the development of treatment-related suicidality.[51]

Summary

Together, this mechanistic focus suggests core processes that are affected by SSRI treatment in young people. Antidepressants can enhance emotion regulation and reduce anger processing, partly mediated by effects on corticolimbic neural circuitry, helping to reduce irritability and negative affect. Although these effects of SSRIs occur quickly, the effect on symptoms of depression and anxiety take time. This work suggests, as also emphasised by our Young Person Advisory Group, that antidepressants are not an instant fix but rather that they provide tools to assist recovery (panel 1, appendix p 2).

Huge potential exists to learn how to facilitate this process and to consider individual differences and environmental factors in the moderation of SSRI action, which can be partly unique within the adolescent context. Further mechanistic work is also needed to understand susceptibility to the negative effects of SSRI medication in young people.

What are key outstanding unknowns about SSRIs in young people?

The effectiveness of SSRIs varies across individuals, but no validated markers exist to inform clinical decision making. A number of potential moderating factors have been investigated in adolescents, including specific symptoms,[96,109,110] symptom severity,[32,34,111–119] abuse or trauma history,[120,121] genetic polymorphisms,[53,122–127] neural structure and response,[86,128–132] family,[102–104,117,119] and demographic characteristics.[32,34,116,119,133] However, studies have typically been small in scale and have not focused on whether these factors are general markers of outcome or specific to SSRI treatment. As such, the ability to translate this work into clinical application requires large-scale studies that are focused on defining and validating core classifiers and considering predictors across traditional divisions (eg, interactions with the environment). From a clinical perspective, markers that could be used to predict differential response to psychological and pharmacological treatments would be most transformative. These markers have started to be explored in adults and need to be extended to young people, where selecting the best treatment earlier rather than later can have important implications for psychosocial development and wellbeing.[134] It is important to acknowledge that most of the research reviewed here was done in high-income countries. Future research should consider the effects of sociocultural and geographical context and extend this work to low-income and middle-income countries.

Raised concentrations of inflammatory markers (eg, CRP, IL-6, and TNF)[135] have been associated with a poor response to SSRIs in adults. Depression has been associated with increased concentrations of circulating CRP and IL-6 in female adolescents with a previous history of childhood adversity but not in female adolescents without this history.[136] A systematic review supported that adolescent depression is associated with increased concentrations of proinflammatory markers, although results are somewhat inconsistent.[137] Similarly, there is disagreement as to whether SSRI treatment lowers the concentrations of inflammatory markers in adolescents and whether increased baseline concentrations of CRP and IL-6 predict SSRI response.[138] Evidence suggests that an increase in IL-6 concentration can be a risk factor for SSRI-associated suicidality in young people with pretreatment suicidality.[139,140] Inflammation is an important area for future systematic research, particularly in view of the connection between childhood adversity, SSRI-related adverse effects, and increased concentrations of inflammatory markers.

Depression in adolescence has been associated with impairments in cognitive function, including attention, memory, and planning.[141–143] To some extent, these cognitive impairments persist after SSRI treatment, even in adolescents whose affective symptoms have improved.[144] These results concur with concerns that were raised by our Young Person Advisory Group about the effects of treatment on cognition (panel 2, appendix p 2). Consideration of these effects is crucial, especially for this age group, where impaired attention or memory can affect ability to cope with school and everyday function. Characterising the effects of SSRIs on cognitive function is therefore a priority and emphasises the need for research-focused adjunct treatment approaches.

Decreased responses to rewards have been described in adolescents with depression and are potentially related to symptoms of low motivation and anhedonia.[145] Forbes and Dahl hypothesised that these impairments might be even more prominent in this age group because of changes in the dopamine system and reward function during adolescence.[146] However, the effect of antidepressant treatment on reward is far from clear. In young, healthy volunteers (mean age 25 years) SSRI treatment in the short term has been reported to have the paradoxical effect of decreasing response within reward-related neural circuitry.[147,148] Such effects emphasise a potential mechanism underpinning poor response of depression to SSRI treatment in young people as a function of anhedonia.[110]

The primary outcomes that are reported in trials of antidepressants almost exclusively rely on clinician reports of symptomatic improvement. The positive effect of antidepressants on symptomatology as assessed by clinicians and parents is not always reflected in youth reports,[149] and it is important to clarify whether this disparity reflects that the measurement is insensitive or that the treatment does not address outcomes of relevance to young people.[150] Some evidence exists that young people's self-reports of quality of life are improved by antidepressant treatment,[151] although this effect is not replicated across all studies.[152] Our Young Person Advisory Group emphasised that the effect of antidepressants on functional outcomes, such as quality of friendships and ability to engage with school, were key priorities when considering the use of antidepressants (panel 2, appendix p 2). However, the literature on the functional outcomes of antidepressant treatment in young people is scarce, and future research in this area should be a priority.

Withdrawal symptoms (or so-called abstinence symptoms) on stopping SSRI treatment are a major concern in adults[153] but appear under-researched in young people. Of the available SSRIs, because of its long half-life, fluoxetine is the least likely to cause withdrawal symptoms; however, withdrawal and the possibility of dependence are a concern of young people, as emphasised by our Young Person Advisory Group (panel 2, appendix p 2). Apart from withdrawal symptoms, SSRIs do not produce the dose-escalation and drug-seeking behaviour characteristic of typical addictive drugs.[154] However, systematic study is required to assess the effects of SSRI withdrawal in young people, both to identify withdrawal symptomatology and to assess the effect of SSRI treatment on the long-term course of anxiety and depressive disorders.

Search strategy and selection criteria

References for this Series paper were identified through searches of MEDLINE (via Ovid), PsycINFO, Cochrane Database of Systematic Reviews, and Web of Science (Core Collection) for articles published from Jan 1, 2000, to July 6, 2020. Search terms included "adolescent" AND "antidepressant" OR "SSRI" AND "depression" OR "anxiety" and common variations of these terms. A full list of search terms are listed in the Series paper review protocol. We restricted the search to papers that were published in English. SLCG and another reviewer independently reviewed titles and abstracts that were identified through the search strategy to decide whether studies were of relevance to the objectives of the Series paper and recorded a justification for each excluded study. A third reviewer (LPC) resolved disagreements between the two reviewers. The selected manuscripts were read in full and further assessed for relevance to the Series paper. Further focused searches on PubMed were done for selected topics. Given the many references that were identified by these searches, this Series paper provides representative rather than complete citations.

For more on the **review protocol** see https://osf.io/rcth7/?view_only=690a33b27664457e9c0e63b480370ff9

Conclusions

Antidepressant use in young people is rising, but there is a corresponding scarcity of research on their effects and mechanisms in this age group. It is important to know if the effects of SSRIs depend on stage of neural, cognitive, and social development; why some people benefit more than others; and what the long-term benefits and risks of treatment in adolescence might be. We have emphasised the importance of an experimental mechanistic approach as a way of identifying targets for treatment, predictors of response, and a framework to understand core processes that are affected by current treatment strategies. This approach can also offer insight into how to combine treatments and reduce the division between pharmacological and psychological approaches in theoretical perspectives and practice.

Research in this area suggests that SSRIs are effective for adolescent depression and anxiety. There are risks to treating and not treating these conditions, which should be given due consideration. Evidence suggests that SSRIs enhance processes underlying neural plasticity and improve the balance between limbic and prefrontal circuits in emotional response and regulation. These neural differences might be experienced as changes in negative bias and improved emotional regulation, which

can ameliorate symptoms of depression and anxiety across time and interactions with the environment. Importantly, there might be a role for environmental factors (eg, stress, peer relationships, and living circumstances) in moderating the effects of SSRIs.

SSRIs might not work on some core components of depression and anxiety, which has relevance for how they are used and how we identify potential targets for future treatment development. In particular, patients with high levels of inflammation, cognitive dysfunction, or anhedonia, or a combination, might require alternative or additional approaches.

Crucially, the field might have avoided researching key questions about the use of antidepressants in young people because of the disquiet about drug treatment in this age group. However, clinical need and use of SSRIs in this age group emphasises the troubling conclusion that these treatments are often used without fully understanding their effects in children and adolescents. Knowing why, how, and when these treatments work is crucial to progress effective treatments of the future.

Contributors

CJH, SEM, and LPC developed the conceptulaisation and design of the Series paper; SLCG and LPC did the initial searches of the literature and set up the lived experience workshops. CJH, LPC, SEM, and SLCG developed and attended all youth workshops. All authors contributed to evidence synthesis and writing and revision of the Series paper.

Declaration of interests

SLCG and LPC declare no competing interests. PJC reports grants from Wellcome Trust, during the conduct of the study. SEM reports grants from Wellcome Trust, during the conduct of the study; and grants from Janssen Pharmaceuticals, UCB Pharma, and Zogenix and personal fees from Janssen Pharmaceuticals, Zogenix, and Sumitomo Dainippon Pharma, outside the submitted work. CJH reports grants from Wellcome Trust, during the conduct of the study; and grants from Janssen Pharmaceuticals, UCB Pharma, and Zogenix and personal fees from Janssen Pharmaceuticals, Zogenix, Sage Pharmaceuticals, P1vital, Lundbeck, and Pfizer, outside the submitted work. AS reports fees from Cambridge and Oxford University Press, outside the submitted work.

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References

1 Pitchforth J, Fahy K, Ford T, Wolpert M, Viner RM, Hargreaves DS. Mental health and well-being trends among children and young people in the UK, 1995-2014: analysis of repeated cross-sectional national health surveys. *Psychol Med* 2019; **49:** 1275–85.

2 Armstrong TD, Costello EJ. Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *J Consult Clin Psychol* 2002; **70:** 1224–39.

3 Kovacs M, Goldston D. Cognitive and social cognitive development of depressed children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1991; **30:** 388–92.

4 Rodriguez KA, Kendall PC. Suicidal ideation in anxiety-disordered youth: identifying predictors of risk. *J Clin Child Adolesc Psychol* 2014; **43:** 51–62.

5 Swan AJ, Kendall PC. Fear and missing out: youth anxiety and functional outcomes. *Clin Psychol Sci Pract* 2016; **23:** 417–35.

6 Brent DA, Perper JA, Moritz G, Baugher M, Schweers J, Roth C. Suicide in affectively ill adolescents: a case-control study. *J Affect Disord* 1994; **31:** 193–202.

7 Zisook S, Lesser I, Stewart JW, et al. Effect of age at onset on the course of major depressive disorder. *Am J Psychiatry* 2007; **164:** 1539–46.

8 Peters AT, Jacobs RH, Feldhaus C, et al. Trajectories of functioning into emerging adulthood following treatment for adolescent depression. *J Adolesc Health* 2016; **58:** 253–59.

9 Swan AJ, Kendall PC, Olino T, et al. Results from the Child/Adolescent Anxiety Multimodal Longitudinal Study (CAMELS): functional outcomes. *J Consult Clin Psychol* 2018; **86:** 738–50.

10 Salaheddin K, Mason B. Identifying barriers to mental health help-seeking among young adults in the UK: a cross-sectional survey. *Br J Gen Pract* 2016; **66:** e686–92.

11 Soria-Saucedo R, Eisen SV, Cabral HJ, Kazis LE. Receipt of pharmacotherapy and psychotherapy among a nationally representative US sample of privately insured adults with depression: associations with insurance plan arrangements and provider specialty. *J Pharm Health Serv Res* 2016; **7:** 53–62.

12 McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *J Clin Psychiatry* 2013; **74:** 595–602.

13 Bradley KL, McGrath PJ, Brannen CL, Bagnell AL. Adolescents' attitudes and opinions about depression treatment. *Community Ment Health J* 2010; **46:** 242–51.

14 Dudley AL, Melvin GA, Williams NJ, Tonge BJ, King NJ. Investigation of consumer satisfaction with cognitive-behaviour therapy and sertraline in the treatment of adolescent depression. *Aust N Z J Psychiatry* 2005; **39:** 500–06.

15 National Institute for Health and Care Excellence. Depression in children and young people: identification and management (NICE guideline NG134). June 25, 2019. https://www.nice.org.uk/guidance/ng134 (accessed May 11, 2020).

16 WHO. mhGAP intervention guide for mental, neurological and substance abuse disorders in non-specialized health settngs: mental health Gap Action Programme (mhGAP). June 24, 2019. https://www.who.int/publications/i/item/9789241549790 (accessed July 21, 2021).

17 Dolle K, Schulte-Körne G. The treatment of depressive disorders in children and adolescents. *Dtsch Arztebl Int* 2013; **110:** 854–60.

18 Walter HJ, Bukstein OG, Abright AR, et al. Clinical practice guideline for the assessment and treatment of children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2020; **59:** 1107–24.

19 Birmaher B, Brent D, Bernet W, et al. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 2007; **46:** 1503–26.

20 Zhou X, Teng T, Zhang Y, et al. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. *Lancet Psychiatry* 2020; **7:** 581–601.

21 March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; **292:** 807–20.

22 Crenna-Jennings W, Hutchinson J. Access to child and adolescent mental health services in 2019. Jan 10, 2020. https://epi.org.uk/publications-and-research/access-to-child-and-adolescent-mental-health-services-in-2019 (accessed May 11, 2020).

23 Boaden K, Tomlinson A, Cortese S, Cipriani A. Antidepressants in children and adolescents: meta-review of efficacy, tolerability and suicidality in acute treatment. *Front Psychiatry* 2020; **11:** 717.

24 Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet* 2016; **388:** 881–90.

25 Dobson ET, Bloch MH, Strawn JR. Efficacy and tolerability of pharmacotherapy for pediatric anxiety disorders: a network meta-analysis. *J Clin Psychiatry* 2019; **80:** 17r12064.

26 Meister R, Abbas M, Antel J, et al. Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: a systematic review and meta-regression analysis. *Eur Child Adolesc Psychiatry* 2020; **29:** 253–73.

27 Shinohara K, Tanaka S, Imai H, et al. Development and validation of a prediction model for the probability of responding to placebo in antidepressant trials: a pooled analysis of individual patient data. *Evid Based Ment Health* 2019; **22:** 10–16.

28 Nelson JC, Zhang Q, Deberdt W, Marangell LB, Karamustafalioglu O, Lipkovich IA. Predictors of remission with placebo using an integrated study database from patients with major depressive disorder. *Curr Med Res Opin* 2012; **28:** 325–34.

29 Locher C, Koechlin H, Zion SR, et al. Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric disorders among children and adolescents: a systematic review and meta-analysis. *JAMA Psychiatry* 2017; **74:** 1011–20.

30 Walkup JT. Antidepressant efficacy for depression in children and adolescents: industry- and NIMH-funded studies. *Am J Psychiatry* 2017; **174:** 430–37.

31 Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *N Engl J Med* 2008; **359:** 2753–66.

32 Ginsburg GS, Kendall PC, Sakolsky D, et al. Remission after acute treatment in children and adolescents with anxiety disorders: findings from the CAMS. *J Consult Clin Psychol* 2011; **79:** 806–13.

33 Cox GR, Callahan P, Churchill R, et al. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev* 2014; **11:** CD008324.

34 Curry J, Rohde P, Simons A, et al. Predictors and moderators of acute outcome in the Treatment for Adolescents with Depression Study (TADS). *J Am Acad Child Adolesc Psychiatry* 2006; **45:** 1427–39.

35 Goodyer IM, Dubicka B, Wilkinson P, et al. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess* 2008; **12:** iii–iv, ix-60.

36 Davey CG, Chanen AM, Hetrick SE, et al. The addition of fluoxetine to cognitive behavioural therapy for youth depression (YoDA-C): a randomised, double-blind, placebo-controlled, multicentre clinical trial. *Lancet Psychiatry* 2019; **6:** 735–44.

37 Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual research review: defining and treating pediatric treatment-resistant depression. 2020; **61**: 312–32.

38 Vitiello B. Prevention and treatment of child and adolescent depression: challenges and opportunities. *Epidemiol Psychiatr Sci* 2011; **20:** 37–43.

39 Luft MJ, Lamy M, DelBello MP, McNamara RK, Strawn JR. Antidepressant-induced activation in children and adolescents: risk, recognition and management. *Curr Probl Pediatr Adolesc Health Care* 2018; **48:** 50–62.

40 Rojas-Mirquez JC, Rodriguez-Zuñiga MJ, Bonilla-Escobar FJ, et al. Nocebo effect in randomized clinical trials of antidepressants in children and adolescents: systematic review and meta-analysis. *Front Behav Neurosci* 2014; **8:** 375.

41 Anderson HD, Pace WD, Libby AM, West DR, Valuck RJ. Rates of 5 common antidepressant side effects among new adult and adolescent cases of depression: a retrospective US claims study. *Clin Ther* 2012; **34:** 113–23.

42 Gordon M, Melvin G. Selective serotonin re-uptake inhibitors—a review of the side effects in adolescents. *Aust Fam Physician* 2013; **42:** 620–23.

43 Emslie G, Kratochvil C, Vitiello B, et al. Treatment for Adolescents with Depression Study (TADS): safety results. *J Am Acad Child Adolesc Psychiatry* 2006; **45:** 1440–55.

44 Deumic E, Butcher BD, Clayton AD, Dindo LN, Burns TL, Calarge CA. Sexual functioning in adolescents with major depressive disorder. *J Clin Psychiatry* 2016; **77:** 957–62.

45 Cockerill RG, Biggs BK, Oesterle TS, Croarkin PE. Antidepressant use and body mass index change in overweight adolescents: a historical cohort study. *Innov Clin Neurosci* 2014; **11:** 14–21.

46 Nilsson M, Joliat MJ, Miner CM, Brown EB, Heiligenstein JH. Safety of subchronic treatment with fluoxetine for major depressive disorder in children and adolescents. *J Child Adolesc Psychopharmacol* 2004; **14:** 412–17.

47 Calarge CA, Mills JA, Janz KF, et al. The effect of depression, generalized anxiety, and selective serotonin reuptake inhibitors on change in bone metabolism in adolescents and emerging adults. *J Bone Miner Res* 2017; **32**: 2367–74.

48 Sun JW, Hernández-Díaz S, Haneuse S, et al. Association of selective serotonin reuptake inhibitors with the risk of type 2 diabetes in children and adolescents. *JAMA Psychiatry* 2021; **78:** 91–100.

49 Offidani E, Guidi J, Tomba E, Fava GA. Efficacy and tolerability of benzodiazepines versus antidepressants in anxiety disorders: a systematic review and meta-analysis. *Psychother Psychosom* 2013; **82:** 355–62.

50 Vitiello B, Silva SG, Rohde P, et al. Suicidal events in the Treatment for Adolescents With Depression Study (TADS). *J Clin Psychiatry* 2009; **70:** 741–47.

51 Amitai M, Chen A, Weizman A, Apter A. SSRI-induced activation syndrome in children and adolescents—what is next? *Curr Treat Options Psychiatry* 2015; **2:** 28–37.

52 Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. *J Child Adolesc Psychopharmacol* 2006; **16:** 159–69.

53 Kronenberg S, Apter A, Brent D, et al. Serotonin transporter polymorphism (5-HTTLPR) and citalopram effectiveness and side effects in children with depression and/or anxiety disorders. *J Child Adolesc Psychopharmacol* 2007; **17:** 741–50.

54 Amitai M, Kronenberg S, Carmel M, et al. Pharmacogenetics of citalopram-related side effects in children with depression and/or anxiety disorders. *J Neural Transm (Vienna)* 2016; **123:** 1347–54.

55 Strawn JR, Adler CM, McNamara RK, et al. Antidepressant tolerability in anxious and depressed youth at high risk for bipolar disorder: a prospective naturalistic treatment study. *Bipolar Disord* 2014; **16:** 523–30.

56 Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006; **63:** 332–39.

57 Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. *Am J Psychiatry* 2007; **164:** 1786–89.

58 Stone M, Laughren T, Jones ML, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009; **339:** b2880.

59 Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356:** 2343–46.

60 Goodyer I, Dubicka B, Wilkinson P, et al. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. *BMJ* 2007; **335:** 142–46A.

61 Gibbons RD, Brown CH, Hur K, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007; **164:** 1356–63.

62 Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons—prescription trends and toxicological analyses. *Acta Psychiatr Scand* 2014; **129:** 296–302.

63 Lu CY, Zhang F, Lakoma MD, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ* 2014; **348:** g3596.

64 Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. *Australas Psychiatry* 2010; **18:** 242–45.

65 Søndergård L, Kvist K, Andersen PK, Kessing LV. Do antidepressants precipitate youth suicide?: a nationwide pharmacoepidemiological study. *Eur Child Adolesc Psychiatry* 2006; **15:** 232–40.

66 Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New perspectives for refining future treatment approaches. *Lancet Psychiatry* 2017; **4:** 409–18.

67 Meyer JH, Wilson AA, Sagrati S, et al. Serotonin transporter occupancy of five selective serotonin reuptake inhibitors at different doses: an [11C]DASB positron emission tomography study. *Am J Psychiatry* 2004; **161:** 826–35.

68 Bowman MA, Daws LC. Targeting serotonin transporters in the treatment of juvenile and adolescent depression. *Front Neurosci* 2019; **13:** 156.

69 Olivier JDA, Blom T, Arentsen T, Homberg JR. The age-dependent effects of selective serotonin reuptake inhibitors in humans and rodents: a review. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35:** 1400–08.

70 Navailles S, Hof PR, Schmauss C. Antidepressant drug-induced stimulation of mouse hippocampal neurogenesis is age-dependent and altered by early life stress. *J Comp Neurol* 2008; **509:** 372–81.

71 Song T, Wu H, Li R, et al. Repeated fluoxetine treatment induces long-lasting neurotrophic changes in the medial prefrontal cortex of adult rats. *Behav Brain Res* 2019; **365:** 114–24.

72 Cowen DS, Takase LF, Fornal CA, Jacobs BL. Age-dependent decline in hippocampal neurogenesis is not altered by chronic treatment with fluoxetine. *Brain Res* 2008; **1228:** 14–19.

73 Saricicek Aydogan A, Oztekin E, Esen ME, et al. Cortical thickening in remitters compared to non-remitters with major depressive disorder following 8-week antidepressant treatment. *Acta Psychiatr Scand* 2019; **140:** 217–26.

74 Arnone D, McKie S, Elliott R, et al. State-dependent changes in hippocampal grey matter in depression. *Mol Psychiatry* 2013; **18:** 1265–72.

75 Polyakova M, Stuke K, Schuemberg K, Mueller K, Schoenknecht P, Schroeter ML. BDNF as a biomarker for successful treatment of mood disorders: a systematic & quantitative meta-analysis. *J Affect Disord* 2015; **174:** 432–40.

76 Lee J, Lee KH, Kim SH, et al. Early changes of serum BDNF and SSRI response in adolescents with major depressive disorder. *J Affect Disord* 2020; **265:** 325–32.

77 Andrews JL, Ahmed SP, Blakemore S-J. Navigating the social environment in adolescence: the role of social brain development. *Biol Psychiatry* 2021; **89:** 109–18.

78 Powers A, Casey BJ. The adolescent brain and the emergence and peak of psychopathology. *J Infant Child Adolesc Psychother* 2015; **14:** 3–15.

79 Rakesh D, Allen NB, Whittle S. Balancing act: neural correlates of affect dysregulation in youth depression and substance use—a systematic review of functional neuroimaging studies. *Dev Cogn Neurosci* 2020; **42:** 100775.

80 Murphy SE, Norbury R, O'Sullivan U, Cowen PJ, Harmer CJ. Effect of a single dose of citalopram on amygdala response to emotional faces. *Br J Psychiatry* 2009; **194:** 535–40.

81 Godlewska BR, Browning M, Norbury R, Cowen PJ, Harmer CJ. Early changes in emotional processing as a marker of clinical response to SSRI treatment in depression. *Transl Psychiatry* 2016; **6:** e957–957.

82 Tao R, Calley CS, Hart J, et al. Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. *Am J Psychiatry* 2012; **169:** 381–88.

83 Capitão LP, Chapman R, Murphy SE, et al. A single dose of fluoxetine reduces neural limbic responses to anger in depressed adolescents. *Transl Psychiatry* 2019; **9:** 30.

84 Burkhouse KL, Kujawa A, Hosseini B, et al. Anterior cingulate activation to implicit threat before and after treatment for pediatric anxiety disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **84:** 250–56.

85 Cullen KR, Klimes-Dougan B, Vu DP, et al. Neural correlates of antidepressant treatment response in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol* 2016; **26:** 705–12.

86 Kujawa A, Swain JE, Hanna GL, et al. Prefrontal reactivity to social signals of threat as a predictor of treatment response in anxious youth. *Neuropsychopharmacology* 2016; **41:** 1983–90.

87 Capitão LP, Murphy SE, Browning M, Cowen PJ, Harmer CJ. Acute fluoxetine modulates emotional processing in young adult volunteers. *Psychol Med* 2015; **45:** 2295–308.

88 Stoddard J, Sharif-Askary B, Harkins EA, et al. An open pilot study of training hostile interpretation bias to treat disruptive mood dysregulation disorder. *J Child Adolesc Psychopharmacol* 2016; **26:** 49–57.

89 Stringaris A, Maughan B, Copeland WS, Costello EJ, Angold A. Irritable mood as a symptom of depression in youth: prevalence, developmental, and clinical correlates in the Great Smoky Mountains Study. *J Am Acad Child Adolesc Psychiatry* 2013; **52:** 831–40.

90 Carthy T, Benaroya-Milshtein N, Valevski A, Apter A. Emotional reactivity and regulation following citalopram therapy in children and adolescents with anxiety disorders. *J Child Adolesc Psychopharmacol* 2017; **27:** 43–51.

91 Gottlieb L, Martinovich Z, Meyers KM, Reinecke MA. Treatment for depression enhances protection: findings from the Treatment for Adolescents With Depression Study (TADS). *Int J Cogn Ther* 2016; **9:** 38–56.

92 Jacobs RH, Silva SG, Reinecke MA, et al. Dysfunctional attitudes scale perfectionism: a predictor and partial mediator of acute treatment outcome among clinically depressed adolescents. *J Clin Child Adolesc Psychol* 2009; **38:** 803–13.

93 Joiner TE Jr, Brown JS, Gordon KH, Rouleau MR, Wagner KD. Attributioual style, hope, and initial response to selective serotonin reuptake inhibitors in youth psychiatric inpatients. *Cognit Ther Res* 2005; **29:** 691–704.

94 Kendall PC, Cummings CM, Villabø MA, et al. Mediators of change in the Child/Adolescent Anxiety Multimodal Treatment Study. *J Consult Clin Psychol* 2016; **84:** 1–14.

95 Makover HB, Kendall PC, Olino T, et al. Mediators of youth anxiety outcomes 3 to 12 years after treatment. *J Anxiety Disord* 2020; **70:** 102188.

96 Hale AE, Ginsburg GS, Chan G, et al. Mediators of treatment outcomes for anxious children and adolescents: the role of somatic symptoms. *J Clin Child Adolesc Psychol* 2018; **47:** 94–104.

97 Scharfstein LA, Beidel DC, Finnell LR, Distler A, Carter NT. Do pharmacological and behavioral interventions differentially affect treatment outcome for children with social phobia? *Behav Modif* 2011; **35:** 451–67.

98 Alfano CA, Ginsburg GS, Kingery JN. Sleep-related problems among children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2007; **46:** 224–32.

99 Caporino NE, Read KL, Shiffrin N, et al. Sleep-related problems and the effects of anxiety treatment in children and adolescents. *J Clin Child Adolesc Psychol* 2017; **46:** 675–85.

100 Shiroma PR, Thuras P, Johns B, Lim KO. Emotion recognition processing as early predictor of response to 8-week citalopram treatment in late-life depression. *Int J Geriatr Psychiatry* 2014; **29:** 1132–39.

101 Chiarotti F, Viglione A, Giuliani A, Branchi I. Citalopram amplifies the influence of living conditions on mood in depressed patients enrolled in the STAR*D study. *Transl Psychiatry* 2017; **7:** e1066.

102 Feeny NC, Silva SG, Reinecke MA, et al. An exploratory analysis of the impact of family functioning on treatment for depression in adolescents. *J Clin Child Adolesc Psychol* 2009; **38:** 814–25.

103 Rengasamy M, Mansoor BM, Hilton R, et al. The bi-directional relationship between parent-child conflict and treatment outcome in treatment-resistant adolescent depression. *J Am Acad Child Adolesc Psychiatry* 2013; **52:** 370–77.

104 Brent DA, Emslie GJ, Clarke GN, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *Am J Psychiatry* 2009; **166:** 418–26.

105 Dardas LA. Family functioning moderates the impact of depression treatment on adolescents' suicidal ideations. *Child Adolesc Ment Health* 2019; **24:** 251–58.

106 Burghardt NS, Sullivan GM, McEwen BS, Gorman JM, LeDoux JE. The selective serotonin reuptake inhibitor citalopram increases fear after acute treatment but reduces fear with chronic treatment: a comparison with tianeptine. *Biol Psychiatry* 2004; **55:** 1171–78.

107 Oh JE, Zupan B, Gross S, Toth M. Paradoxical anxiogenic response of juvenile mice to fluoxetine. *Neuropsychopharmacology* 2009; **34:** 2197–207.

108 Jha MK, Minhajuddin A, Chin Fatt C, et al. Association between irritability and suicidal ideation in three clinical trials of adults with major depressive disorder. *Neuropsychopharmacology* 2020; **45:** 2147–54.

109 Emslie GJ, Kennard BD, Mayes TL, et al. Insomnia moderates outcome of serotonin-selective reuptake inhibitor treatment in depressed youth. *J Child Adolesc Psychopharmacol* 2012; **22:** 21–28.

110 McMakin DL, Olino TM, Porta G, et al. Anhedonia predicts poorer recovery among youth with selective serotonin reuptake inhibitor treatment-resistant depression. *J Am Acad Child Adolesc Psychiatry* 2012; **51:** 404–11.

111 Walkup JT, Labellarte MJ, Riddle MA, et al. Searching for moderators and mediators of pharmacological treatment effects in children and adolescents with anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 13–21.

112 Wilkinson P, Dubicka B, Kelvin R, Roberts C, Goodyer I. Treated depression in adolescents: predictors of outcome at 28 weeks. *Br J Psychiatry* 2009; **194:** 334–41.

113 Beidas RS, Lindhiem O, Brodman DM, et al. A probabilistic and individualized approach for predicting treatment gains: an extension and application to anxiety disordered youth. *Behav Ther* 2014; **45:** 126–36.

114 Lorenzo-Luaces L, Rodriguez-Quintana N, Bailey AJ. Double trouble: do symptom severity and duration interact to predicting treatment outcomes in adolescent depression? *Behav Res Ther* 2020; **131:** 103637.

115 Norris LA, Olino TM, Gosch EA, et al. Person-centered profiles among treatment-seeking children and adolescents with anxiety disorders. *J Clin Child Adolesc Psychol* 2019; published online Jan 1. https://doi.org/10.1080/15374416.2019.1602839.

116 Cheung A, Mayes T, Levitt A, et al. Anxiety as a predictor of treatment outcome in children and adolescents with depression. *J Child Adolesc Psychopharmacol* 2010; **20:** 211–16.

117 Asarnow JR, Emslie G, Clarke G, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry* 2009; **48:** 330–39.

118 Compton SN, Peris TS, Almirall D, et al. Predictors and moderators of treatment response in childhood anxiety disorders: results from the CAMS trial. *J Consult Clin Psychol* 2014; **82:** 212–24.

119 Curry J, Silva S, Rohde P, et al. Recovery and recurrence following treatment for adolescent major depression. *Arch Gen Psychiatry* 2011; **68:** 263–69.

120 Shamseddeen W, Asarnow JR, Clarke G, et al. Impact of physical and sexual abuse on treatment response in the Treatment of Resistant Depression in Adolescent Study (TORDIA). *J Am Acad Child Adolesc Psychiatry* 2011; **50:** 293–301.

121 Nguyen LJ. The impact of childhood trauma on treatment response of depressed adolescents. *Diss Abstr Int B Sci Eng* 2007; **68:** 1316.

122 Brent D, Melhem N, Ferrell R, et al. Association of FKBP5 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. *Am J Psychiatry* 2010; **167:** 190–97.

123 Gassó P, Rodríguez N, Boloc D, et al. Association of regulatory TPH2 polymorphisms with higher reduction in depressive symptoms in children and adolescents treated with fluoxetine. *Prog Neuropsychopharmacol Biol Psychiatry* 2017; **77:** 236–40.

124 Gassó P, Blázquez A, Rodríguez N, et al. Further support for the involvement of genetic variants related to the serotonergic pathway in the antidepressant response in children and adolescents after a 12-month follow-up: Impact of the HTR2A rs7997012 polymorphism. *J Child Adolesc Psychopharmacol* 2018; **28:** 711–18.

125 Rotberg B, Kronenberg S, Carmel M, et al. Additive effects of 5-HTTLPR (serotonin transporter) and tryptophan hydroxylase 2 G-703T gene polymorphisms on the clinical response to citalopram among children and adolescents with depression and anxiety disorders. *J Child Adolesc Psychopharmacol* 2013; **23:** 117–22.

126 Poweleit EA, Aldrich SL, Martin LJ, Hahn D, Strawn JR, Ramsey LB. Pharmacogenetics of sertraline tolerability and response in pediatric anxiety and depressive disorders. *J Child Adolesc Psychopharmacol* 2019; **29:** 348–61.

127 Joyce PR, Mulder RT, Luty SE, et al. Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. *Int J Neuropsychopharmacol* 2003; **6:** 339–46.

128 Burkhouse KL, Kujawa A, Klumpp H, Fitzgerald KD, Monk CS, Phan KL. Neural correlates of explicit and implicit emotion processing in relation to treatment response in pediatric anxiety. *J Child Psychol Psychiatry* 2017; **58:** 546–54.

129 Burkhouse KL, Jagan Jimmy, Defelice N, et al. Nucleus accumbens volume as a predictor of anxiety symptom improvement following CBT and SSRI treatment in two independent samples. *Neuropsychopharmacology* 2020; **45:** 561–69.

130 Klimes-Dougan B, Westlund Schreiner M, Thai M, Gunlicks-Stoessel M, Reigstad K, Cullen KR. Neural and neuroendocrine predictors of pharmacological treatment response in adolescents with depression: a preliminary study. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **81:** 194–202.

131 McClure EB, Adler A, Monk CS, et al. fMRI predictors of treatment outcome in pediatric anxiety disorders. *Psychopharmacology (Berl)* 2007; **191:** 97–105.

132 Bunford N, Kujawa A, Fitzgerald KD, et al. Neural reactivity to angry faces predicts treatment response in pediatric anxiety. *J Abnorm Child Psychol* 2017; **45:** 385–95.

133 Forbes EE, Stepp SD, Dahl RE, et al. Real-world affect and social context as predictors of treatment response in child and adolescent depression and anxiety: an ecological momentary assessment study. *J Child Adolesc Psychopharmacol* 2012; **22:** 37–47.

134 McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry* 2013; **70:** 821–29.

135 Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 2016; **16:** 22–34.

136 Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biol Psychiatry* 2012; **72:** 34–40.

137 Mitchell AM, Davies MA, Cassesse C, Curran R. Antidepressant use in children, adolescents, and young adults: 10 years after the food and drug administration black box warning. *J Nurse Pract* 2014; **10:** 149–56.

138 Amitai M, Taler M, Carmel M, et al. The relationship between plasma cytokine levels and response to selective serotonin reuptake inhibitor treatment in children and adolescents with depression and/or anxiety disorders. *J Child Adolesc Psychopharmacol* 2016; **26:** 727–32.

139 Amitai M, Taler M, Lebow M, et al. An increase in IL-6 levels at 6-month follow-up visit is associated with SSRI-emergent suicidality in high-risk children and adolescents treated with fluoxetine. Eur Neuropsychopharmacol 2020; **40:** 61–69.

140 Amitai M, Taler M, Ben-Baruch R, et al. Increased circulatory IL-6 during 8-week fluoxetine treatment is a risk factor for suicidal behaviors in youth. *Brain Behav Immun* 2020; **87:** 301–08.

141 Han G, Klimes-Dougan B, Jepsen S, et al. Selective neurocognitive impairments in adolescents with major depressive disorder. *J Adolesc* 2012; **35:** 11–20.

142 Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lönnqvist J. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J Affect Disord* 2008; **106:** 1–27.

143 Maalouf FT, Brent D, Clark L, et al. Neurocognitive impairment in adolescent major depressive disorder: state vs. trait illness markers. *J Affect Disord* 2011; **133:** 625–32.

144 Shehab AAS, Brent D, Maalouf FT. Neurocognitive changes in selective serotonin reuptake inhibitors-treated adolescents with depression. *J Child Adolesc Psychopharmacol* 2016; **26:** 713–20.

145 Forbes EE, Hariri AR, Martin SL, et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry* 2009; **166:** 64–73.

146 Forbes EE, Dahl RE. Research Review: altered reward function in adolescent depression: what, when and how? *J Child Psychol Psychiatry* 2012; **53:** 3–15.

147 McCabe C, Cowen PJ, Harmer CJ. Neural representation of reward in recovered depressed patients. *Psychopharmacology (Berl)* 2009; **205:** 667–77.

148 Abler B, Grön G, Hartmann A, Metzger C, Walter M. Modulation of frontostriatal interaction aligns with reduced primary reward processing under serotonergic drugs. *J Neurosci* 2012; **32:** 1329–35.

149 Albano AM, Comer JS, Compton SN, et al. Secondary outcomes from the Child/Adolescent Anxiety Multimodal Study: implications for clinical practice. *Evid Based Pract Child Adolesc Ment Health* 2018; **3:** 30–41.

150 Krause KR, Bear HA, Edbrooke-Childs J, Wolpert M. What outcomes count? A review of outcomes measured for adolescent depression between 2007 and 2017. *J Am Acad Child Adolesc Psychiatry* 2019; **58:** 61–71.

151 MemIk NC. Karakaya I, Yildiz O, Sismanlar S, Caglayan C, Agaoglu B. The effect of sertraline on the quality of life for children and adolescents with anxiety disorder. *Noro Psikiyatri Arsivi* 2014; **51:** 30–39.

152 Park SH, Song YJC, Demetriou EA, et al. Distress, quality of life and disability in treatment-seeking young adults with social anxiety disorder. *Early Interv Psychiatry* 2021; **15:** 57–67.

153 Ruhe HG, Horikx A, van Avendonk MJP, Groeneweg BF, Woutersen-Koch H. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6:** 561–62.

154 Weller I, Ashby D, Brook R, et al. Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants. December, 2004. https://study329.org/wp-content/uploads/2015/01/CSMReportonSSRISafety1.pdf (accessed July 21, 2021).