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

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Abstract

The use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression and anxiety in young people is increasing. However, we lack a good understanding of the effects of SSRIs in adolescence, a time when there are substantial changes in neural, cognitive and social functioning. Here we review evidence from clinical trials about the benefits and risks of SSRIs in young people and consider their mechanisms of action, as revealed through human experimental work and animal models. We highlight 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 critical that we 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 is based.

1 Introduction

The effective treatment of depression and anxiety in young people is a key public health priority. 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 long-term outcomes, with a sustained positive impact on functioning and life satisfaction into adulthood.[8,9] However, many young people experiencing 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 United States of America (USA), Europe and the World Health Organisation, suggest that the use of antidepressant medication should be reserved for young people with moderate to severe illness who do not respond to or who are unable to effectively engage with psychological therapies, although medication may be part of initial approaches in more severe depression.[15–19] Despite this, 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[22] (for further discussion see Appendix pg 1).

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 likely that the effects of antidepressants may be different from those in adults, in whom most of the scientific investigations have been conducted. Here, we review current evidence of the effects of selective serotonin reuptake inhibitors (SSRIs) for depression and anxiety disorders in young people (aged 14-24 years). OCD, acute stress disorder and post-traumatic stress disorder are outside of the scope of this review. 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 revealed through studies in humans and preclinical animal models. We outline the gaps in our knowledge, based on the literature and our consultation with young people with lived experience (see Boxes 1 & 2 and Appendix pg 2), which are critical to address in order to narrow the gap between the widespread use of SSRIs in youth and the science on which this is based.

2 The benefits and risks of antidepressant treatment in young people

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

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

Despite this, 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.[26] However, the estimated efficacy of antidepressants in young people needs to be interpreted in the context of the high placebo response rate seen in these trials. Younger age and shorter time since depression onset are known to be associated with high rates of remission to placebo.[27–29] Interestingly, placebo response rates are higher in industry-funded studies, which have also been shown to have a smaller effect size.[30] One proposed explanation for this is that a large number of industry funded studies were conducted quickly in response to a scheme launched by the US Food and Drug Administration (FDA) in the late 1990s, which was designed to encourage industry to conduct trials in children and adolescents. Unfortunately, this had the unintended consequence of incentivising a large number of poor quality studies, which were conducted over multiple sites and had a high placebo response rate (~50-60%). These studies introduce substantial variability in meta-analyses and may negatively distort the estimation of antidepressant efficacy for young people with depression.[31]

Within this context, high quality, large scale, publicly funded trials of antidepressant effects in young people give the most reliable estimate of antidepressant efficacy. The largest study of this kind, the US-based Treatment for Adolescents with Depression Study (TADS, N=439, 12-17 year olds), directly compared the efficacy of the SSRI fluoxetine and Cognitive Behavioural Therapy (CBT). Notably, this study demonstrated 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]

There is some evidence that combining SSRI treatment with evidence-based psychological therapy (such as CBT) gives an additional benefit to medication alone in young people. This evidence is perhaps strongest in anxiety, where the combination of SSRIs and CBT has been

shown to be more effective than either treatment alone.[32,33] In depression, the evidence is limited and mixed.[34] The TADS study demonstrated that CBT plus fluoxetine was superior to fluoxetine treatment alone;[21] however, there was no additional benefit of combined therapy over medication alone in the most severely depressed patients.[35] This is consistent with the findings from a trial of combination therapy for moderate to severe depression, which reported no benefit of CBT plus fluoxetine compared with fluoxetine alone.[36] A recent 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 those given combined treatment.[37] Interestingly, there was some evidence in this study that combined treatment was more effective for depression and anxiety symptoms in participants who were older than 18 years, which may have been driven by the poorer response to CBT alone seen in this age group.[37]

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[38] and improved treatment options for the substantial minority of young people who are treatment-resistant are needed.[39,40]

2.2 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[41], and concerns about side effects can be a barrier to antidepressant usage (Box 1, see Quote 1 in Appendix pg 2).

2.2.1 Side effects and physical adverse effects

Side effects such as headache, nausea and abdominal pain are commonly reported by young people initiating treatment,[42,43] although the low discontinuation rate for SSRIs suggests that these are typically manageable and decline over time[44]. Many side effects are similar to the somatic symptoms seen in untreated depression and anxiety, and placebo-treated patients also report treatment-emergent adverse events, making a true estimation of the rate of SSRI-related side effects challenging.[42,45] In adults, sexual side effects (such as erectile dysfunction, anorgasmia and decreased libido) are commonly associated with SSRI use, however this is less well understood in young people.[46] SSRI use in young people has also been associated with other physical adverse effects, including weight gain,[47] reduced growth,[48] reduced bone

mass density[49] and a small increase in risk of Type 2 diabetes,[50] which need to be considered carefully in the context of long-term antidepressant use.

2.2.2 Psychiatric adverse effects

SSRIs commonly cause insomnia and increased anxiety early in treatment. These and other adverse effects (irritability, agitation, impulsivity, emotional lability, hostility, restlessness and aggression) have been clustered together as symptoms of an 'activation syndrome', which is estimated to occur in 11-14% of children and adolescents[51] and is associated with high levels of treatment discontinuation.[41,52,53] Activation symptoms are particularly pronounced in the first weeks of treatment and are more common in children than adolescents.[54] 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 limited.[52,53] Some individuals may be more susceptible than others to SSRI-induced activation; for example, some small scale studies suggest polymorphisms in serotonergic genes may confer risk of such adverse effects.[55,56] Mania symptoms have also been reported in young people at high risk of bipolar disorder treated with antidepressants and particular care should be taken when treating this high-risk group, although this can be challenging given the lack of good markers of risk.[57]

2.2.3 Suicidality

In 2004, the FDA conducted a revew and meta-analysis of 24 placebo-controlled trials of antidepressant medication in children and adolescents. They found that relative to placebo, SSRIs significantly increased the risk of experiencing adverse events of suicidal ideation and behaviour (risk ratio 1.66, 95% CI, 1.0-2.7).[58] This led to a series of regulatory warnngs of an increased risk of suicidality in young people taking antidepressant medications. Interestingly, 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, while antidepressants might increase the risk of suicidal ideation and behaviour in children and young people, they are apparently increasingly protective against suicidality in those aged 30 years and over.[59,60]

The clinical trials from which these data are derived were not optimally designed to establish drug-related suicide risk; they generally excluded patients at high risk of suicidality, they were underpowered to detect rare events such as suicide, and had a limited follow-up period. The data from early trials was mainly based on adverse event reporting, rather than systematic measurement of suicidality, which is vulnerable to ascertainment bias, since those participants

reporting other antidepressant-related side effects may be more likely to be asked about other adverse events including suicidality.[58,61] More recent network meta-analyses of randomised trials, which include trials using structured clinician-administered suicidality measures, have reported that only selected antidepressants, notably venflaxine in depression[24] and paroxetine in anxiety[25], are associated with increased risk of suicidal ideation/behaviours. Interestingly, sertraline was associated with a lower incidence of treatment emergent suicidality in anxiety disorders compared with placebo.[25]

Generally, suicidal thinking and behaviour in young people diminish during the course of SSRI treatment.[45,62] In addition, ecological studies raise the important concern that suicide risk might actually increase when antidepressant prescriptions are limited due to the under-treatment of severe illness,[63–65] a concern that is supported by evidence that the use of antidepressants in young people who have died from suicide is rare.[66,67] Taken together, however, the available studies suggest that some young people may 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 which may underpin these effects.

2.3 Summary

SSRIs are a reasonably effective treatment for depression and anxiety in young people, and may 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 may prove a more efficacious 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 long-term effects of antidepressants on brain development, physical growth and sexual function/fertility are not well understood and were highlighted as key concerns by our YPAG (Box 2). While 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 currently remains a necessary tool in the armoury of clinicians treating young people, there is an ethical imperative

that careful scientific investigations are conducted in order to fully understand effects of antidepressant medications in this age group.

3 How do SSRIs work in young people?

Applying a mechanistic approach to characterize the effects of SSRIs in young people could resolve some of the outstanding questions emerging from clinical trials. Such an approach can help identify which patients will respond best to treatment, derive frameworks for combining different treatments, understand unwanted effects of treatment, and define targets for future treatment development.[68] 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 relatively few relevant mechanistic studies.

3.1 Serotonin mechanisms

The pharmacological effect of SSRIs on the developing brain is not well understood, and dosing is primarily based on information derived from adult studies. PET imaging studies demonstrate that in adults, minimal therapeutic doses of SSRIs occupy about 80% of brain serotonin transporters (the pharmacological target of SSRIs, see Appendix pg 1).[69] Analogous imaging data for young people are not available but they 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 compared to mature animals, however, there are strain and species differences in these studies.[70,71] It may 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 adult animals and an increase adolescence observed.[70] The latter effect could be associated with diminished pharmacological activity of SSRIs and a requirement for an increased dose to maintain suitable transporter occupancy. Whether such an effect occurs in humans is not known.[70]

3.2 Brain plasticity

Recent 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 brain derived neurotrophic factor (BDNF).[68] Generally, SSRI treatment appears also to stimulate synaptic plasticity in adolescent animals with increases in hippocampal neurogenesis, protein markers of cellular plasticity and BDNF[72,73] though there are some negative studies.[74]

Investigating plasticity in the human brain is challenging, although increases in human brain plasticity might be detectable through anatomical changes revealed by Magnetic Resonance Imaging (MRI). There are hints in adult studies that SSRI treatment increases hippocampal and cortical volumes[75] and that this is related to treatment response[76] but there are no analogous studies in adolescents. Peripheral measures of BDNF are increased by antidepressant treatment in some studies of adult depressed patients and may correlate with clinical response.[77] Conversely, in depressed adolescents one study suggested that therapeutic response to escitalopram was predicted by early decreases in serum BDNF.[78]

3.3 Corticolimbic circuitry and affective processing

Affective cognitive processes, such as emotion regulation and resistance to peer influence, show large developmental changes across adolescence.[79] Dramatic shifts in brain circuits supporting these processes are also evident, including changes in structure (reflecting changes from synaptic pruning and increased myelination), function (patterns of corticosubcortical connectivity), and neurochemistry (including changes in prefrontal neurochemistry). The relatively protracted development of the prefrontal cortical areas, which are important for emotion regulation, may increase risk for mood and anxiety disorders during this critical developmental period.[80] Consistent with this, functional MRI studies have reported lower functional connectivity between the prefrontal cortex and amygdala, as well as exaggerated (or unregulated) amygdala responses to negative stimuli in adolescent depression.[81]

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[82] and predictive of therapeutic effects[83]. There is relatively little mechanistic work in adolescents and developmental changes in this circuit undoubtedly complicate investigations by introducing high levels of between-subject heterogeneity. Treatment with fluoxetine over 8 weeks decreases amygdala and subgenual cingulate responses to negative faces in depressed adolescents.[84] A recent study showed a similar effect after a single dose of fluoxetine vs placebo, suggesting fast effects of SSRIs on limbic function in adolescent depression.[85] Decreases in limbic and/or increases in prefrontal response have been shown to be

associated with clinical response (both to SSRIs and CBT) in adolescents with depression and anxiety.[86–88] These preliminary findings suggest that changes in emotional processing may be important in the mechanism of SSRI treatment action in young people, as has been suggested in adults.[68]

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.[68] CBT works, in part, by challenging such automatic negative thoughts and mechanistic studies have demonstrated this is also a key mechanism of antidepressant action in adults.[68] In one study extending this to young adults, acute fluoxetine reduced the perception of angry, as well as sad facial expressions compared to placebo.[89] Increased sensitivity to angry facial expressions has been associated with irritability[90] and the effect of fluoxetine on the recognition[89] and neural processing of anger[85] may be relevant to its action in adolescent depression, which is particularly characterized by symptoms of irritability.[91]

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 which are associated with clinical response, although most studies use self-report measures making it difficult to understand the underlying mechanisms of change. These include improved emotional reappraisal,[92] enhanced problem solving ability,[93] decreased perfectionism,[94] decreased hopelessness,[95] improved coping efficacy,[96] decreased negative interpretative bias,[97] reduced somatic symptoms,[98] reduced social distress and behavioural avoidance[99] and improved sleep.[100,101]

3.4 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.[68] This can help explain the delay in clinical effects of antidepressants since a period of responding to and learning from this new perspective is required i.e. changes in emotional bias would be expected to improve social interactions and help deal with stress across time, leading to gradual improvements in mood (Figure 1). Indeed, studies in adults have suggested that environmental factors may moderate the effects of SSRIs, with the best response seen in those in supportive social environments.[102,103]

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 may be experienced more strongly.[79] The role of social, environmental and family influence may also be different across the adolescent period and require a finer grained analysis. Some studies have reported that low levels of family conflict are associated with better treatment response.[104–107] However, there has been little attention to the role of peers and social context moderating the effects of SSRI treatment. Further research is needed to explore interactions between SSRI treatment and social, emotional and sociodemographic factors since this may help reveal potential blocks to treatment success. This perspective also highlights the potential benefit of integrating mechanistic understandings of psychological and pharmacological treatment to allow cross talk between these approaches and the identification of optimal treatment combinations.

3.5 Using a mechanistic approach to understand the psychiatric adverse effects of antidepressants

The mechanisms by which SSRIs produce adverse effects such as anxiety and other actvation symptoms remain largely unknown. Most studies exploring this question have been conducted in animals, and may 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.[108] A similar time course of effect is often seen in adult patients receiving SSRIs. In two strains of juvenile mice, repeated fluoxetine treatment produced a persistent increase in anxiogenic behaviours.[109] A similar effect in humans could result in a greater risk of troublesome SSRI-induced anxiety in young people. However, work from our group reviewed above suggests that acute fluoxetine does not have anxiogenic-like effects in young adult volunteers, showing instead a profile more consistent with anxiolysis.[89,85] Individual differences are likely to be important here, and more work needs to be done to understand the exact mechanisms that could contribute to the experience of SSRI-induced behavioural activation and arousal, which are likely to occur in a subset of at-risk young people. Recent studies in adult depressed patients have shown a link specifically between irritability and suicidal ideation.[110] Hence SSRI-induced increases in irritability in a subgroup of young people could be an important mechanism in the development of treatment-related suicidality.[53]

3.6 Summary

Together this mechanistic focus suggests core processes which are affected by SSRI treatment in young people. Antidepressants may enhance emotion regulation and reduce anger processing, partly meditated by effects on corticolimbic neural circuitry, helping to reduce irritability and negative affect. While these effects of SSRIs occur quickly, the effect on symptoms of depression and anxiety take time. This work suggests, as also highlighted by our YPAG, that antidepressants are not an instant fix but rather that they provide tools to assist recovery (Box 1, see Quote 2 in Appendix pg 2),. There is huge potential to learn how to facilitate this process and to consider individual differences and environmental factors in the moderation of SSRI action, which may be partly unique within the adolescent context. Further mechanistic work is also needed to understand vulnerability to the negative effects of SSRI medication in young people.

4 What are key outstanding unknowns about SSRIs in young people?

4.1 Individual differences in treatment response

The effectiveness of SSRIs varies across individuals but there are currently no validated markers which can be used to inform clinical decision making. A number of potential moderating factors have been investigated in adolescents, including specific symptoms[98,111,112], symptom severity,[33,35,113–121] abuse or trauma history,[122,123] genetic polymorphisms,[55,124–129] neural structure and response,[88,130–134] family[104–106,119,121] and demographic[33,35,118,121,135] characteristics. However, studies have typically been small in scale and have not focussed on whether these factors are general markers of outcome, or specific to SSRI treatment. As such, our ability to translate this work into clinical application requires larger scale studies, focused on defining and validating core classifiers and considering predictors across traditional divisions (see Section 3.4). From a clinical perspective, markers which could be used to predict differential response to psychological and pharmacological treatments would be most transformative. This has started to be explored in adults and needs to be extended to young people, where selecting the best treatment earlier rather than later can have important implications for psychosocial development and well-being.[136] It is important to acknowledge that the vast majority of the research reviewed here has been conducted in high income countries. Future research should consider the impact of sociocultural and geographical context and extend this work to lower and middle income countries.

4.2 Inflammation

Raised levels of inflammatory markers (such as C-reactive protein (CRP), interleukin-6 (IL-6) and Tumour Necrosis Factor-α (TNFα))[137] have been associated with a poorer response to SSRIs in adults. In female adolescents, depression has been associated with increased levels of circulating CRP and IL-6 in those with a history of childhood adversity, but not in those without.[138] A systematic review confirmed that adolescent depression is associated with raised proinflammatory markers, though results are somewhat inconsistent.[139] Similarly, there is disagreement as to whether SSRI treatment lowers inflammatory markers in adolescents and whether raised baseline levels of CRP and IL-6 predict SSRI response.[140] Interestingly, recent evidence suggests that an increase in IL-6 levels may be a risk factor for SSRI-associated suicidality in young people with pretreatment suicidality.[141,142] This is an important area for future systematic research particularly in view of the connection between childhood adversity, SSRI-related adverse effects and raised inflammatory markers.

4.3 Cognitive symptoms

Depression in adolescence has been associated with impairments in cognitive function including attention, memory and planning.[143–145] To some extent, these cognitive impairments remain after SSRI treatment even in those whose affective symptoms have improved.[146] These results chime with concerns raised by our YPAG about the effects of treatment on cognition (Box 2, see Quote 3 in Appendix pg 2). This is critical, especially for this age group, where impaired attention or memory may affect ability to cope with school and everyday function. Characterizing the effects of SSRIs on cognitive function is therefore a priority and highlights the need for research focused adjunct treatment approaches.

4.4 Reward processing and anhedonia

Decreased responses to rewards have been described in adolescents with depression, potentially related to symptoms of low motivation and anhedonia.[147] It has been hypothesized that these impairments may be even more prominent in this age group because of changes in the dopamine system and reward function during adolescence.[148] However, the effect of antidepressant treatment on reward is far from clear. In young healthy volunteers (average age 25 years) short term SSRI treatment has been reported to have the paradoxical effect of decreasing response within reward-related neural circuitry.[149,150] Such effects highlight a potential mechanism underpinning poorer response to SSRI treatment in young people with high levels of anhedonia.[112]

4.5 Functional outcomes

The primary outcomes 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,[151] and it is important to elucidate whether this reflects measurement insensitivity or a failure of the treatment to address outcomes of relevance to young people.[152] There is some evidence that young people's self-reports of quality of life are improved by antidepressant treatment,[153] although this is not replicated across all studies[154]. Our YPAG highlighted 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 (Box 2, see Quote 4 in Appendix pg 2). However, the literature on the functional outcomes of antidepressant treatment in young people is very limited and this should be a priority for future research in this area.

4.6 Long term use and discontinuation

Withdrawal (or 'abstinence symptoms') on stopping SSRI treatment are a major concern in adults[155] but appear little researched in young people. Of the available SSRIs, because of its long half-life, fluoxetine is least likely to cause withdrawal symptoms; however, withdrawal and the possibility of dependence are certainly a concern of young people as highlighted by our YPAG (Box 2, see Quote 5 in Appendix pg 2). Apart from withdrawal symptoms, SSRIs do not produce the dose-escalation and drug-seeking behaviour characteristic of typical addictive drugs.[156] However, more systematic study is required to assess the effects of SSRI withdrawal in young people, both to identify withdrawal symptomatology as well as assess the impact of SSRI treatment on the longer-term course of anxiety and depressive disorders.

5 Conclusions

Antidepressant use in young people is rising but there is a corresponding lack of research on their effects and mechanisms in this age group. We need 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 may be. We have emphasized 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 which 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 conducted in this area suggests that SSRIs are effective for adolescent depression and anxiety. There are risks both 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 may be experienced as changes in negative bias and improved emotional regulation, which can ameliorate symptoms of depression and anxiety across time and experience. Importantly, there may be a role for environmental factors (such as stress, peer relationships and living circumstances) in moderating the effects of SSRIs.

SSRIs may 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, those patients with high levels of inflammation, cognitive dysfunction and/or anhedonia may require alternative or additional approaches.

Critically, the field may have avoided researching key questions about 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 highlights the more troubling conclusion that we are frequently using these treatments without fully understanding their effects in our children and adolescents. We need to know why, how and when they work to progress more effective treatments of the future.

Search Strategy and selection criteria

References for this review were identified through searches of MEDLINE (via Ovid), PsycINFO, Cochrane Database of Systematic Reviews, Web of Science (Core Collection) for articles published from 1st January 2000, to 6th July 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 review protocol: https://osf.io/rcth7/?view_only=690a33b27664457e9c0e63b480370ff9 We restricted the search to English language publications. Two independent reviewers independently reviewed titles and abstracts identified through the search strategy to determine whether studies were of relevance to the objectives of the review and recorded a justification for each excluded study. A third reviewer resolved disagreements between the two reviewers. The selected manuscripts were read in full and further assessed for relevance to the review. Further focussed searches on PubMed were performed on selected topics. Given the many references identified by these searches, this review provides representative rather than complete citations.

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

Themes that emerged from a workshop with our Young Person Advisory Group (YPAG, see Appendix pg 2 for further details):

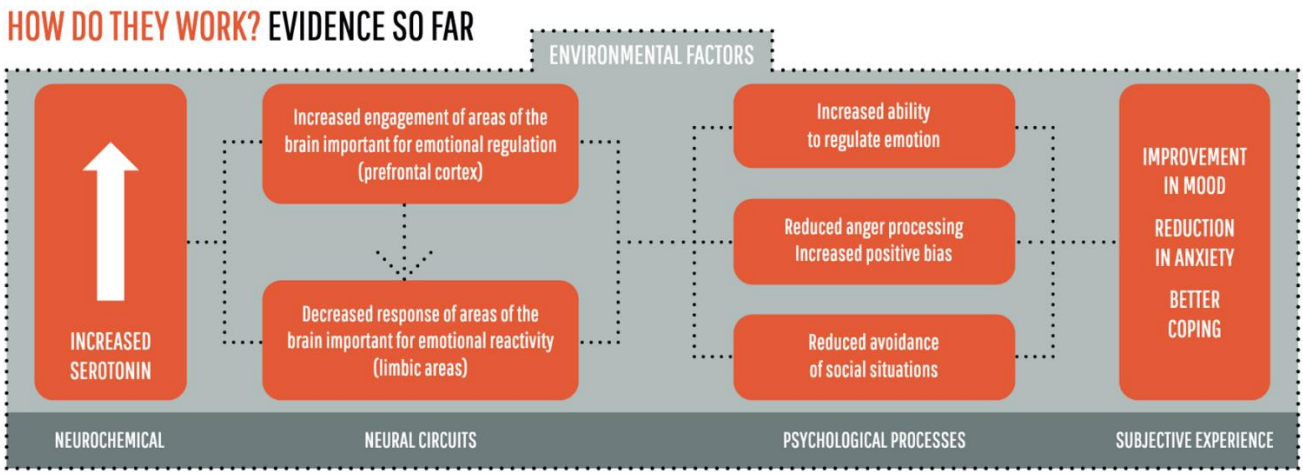
- Antidepressants are not an instant fix but can help give you the tools to work at getting better yourself. They may help an individual engage more fully with psychological therapy and interact better with others
- Antidepressants have side effects and the "net outcome" of symptoms needs to be considered, e.g. 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' one's diagnosis as a real illness.

Box 2: Key outstanding questions about SSRI treatment in young people identified by our YPAG

Questions that emerged from a workshop with our YPAG 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 may also impair their ability to think clearly.
- What are the long term effects of using antidepressants 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 certain individuals to react positively or negatively to different antidepressants? This could help understand how antidepressants work for young people and why some individuals may 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/alcohol? Young people should be given clear information about this rather than simply being told to avoid all drugs/alcohol when taking antidepressants.
- How do we reduce the stigma associated with taking antidepressants and the misrepresentation of some of the effects of antidepressants in the media (e.g. that they cause suicide)?
- Is there racial bias in the diagnosis of depression and anxiety in young people, and in the use of antidepressants?

Figure 1: Across levels of analysis - a mechanistic framework for SSRI action in young people



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Conflicts of Interest

Sophie Giles and Dr Capitão have nothing to disclose. Dr. Cowen reports grants from Wellcome Trust, during the conduct of the study. Dr. Murphy reports grants from Wellcome Trust, during the conduct of the study; grants from Janssen Pharmaceuticals, personal fees from Janssen Pharmaceuticals, grants from UCB Pharma, grants from Zogenix, personal fees from Zogenix, personal fees from Sumitomo Dainippon Pharma, outside the submitted work. Dr. Harmer reports grants from Wellcome Trust, during the conduct of the study; grants from Janssen Pharmaceuticals, personal fees from Janssen Pharmaceuticals, grants from UCB Pharma, grants from Zogenix, personal fees from Zogenix, personal fees from Sage Pharmaceuticals, personal fees from P1vital, personal fees from Lundbeck, personal fees from Pfizer, outside the submitted work. Dr. Stringaris reports fees from Cambridge and Oxford University Press, outside the submitted work.

Authors' contributions

CJH, SEM and LC developed the conceptulaisation and design of the review; SFG and LC conducted initial searches of the literature and set up the lived experience workshops. CJH, LC, SEM and SG developed and attended all youth workshops. All authors contributed to evidence synthesis and writing and revision of the review.

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. *Journal of Consulting and Clinical Psychology* 2002; **70**: 1224–39.

3 Kovacs M, Goldston D. Cognitive and Social Cognitive Development of Depressed Children and Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 1991; **30**: 388–92.

4 O'Neil 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. *Journal of Affective Disorders* 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. *The American Journal of 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. *Journal of Adolescent Health* 2016; **58**: 253–9.

9 Swan AJ, Kendall PC, Olino T, *et al.* Results from the Child/Adolescent Anxiety Multimodal Longitudinal Study (CAMELS): Functional outcomes. *Journal of Consulting and Clinical Psychology* 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. *Journal of pharmaceutical health services research* 2016; **7**: 53–62.

12 McHugh RK, Whitton SW, Peckham AD, Welge JA, Otto MW. Patient Preference for Psychological vs. Pharmacological 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 Mental Health Journal* 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. *Australian and New Zealand Journal of Psychiatry* 2005; **39**: 500–6.

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

16 World Health Organisation. mhGAP intervention guide for mental, neurological and substance abuse disorders in non-specialized health settngs: Mental health Gap Action Programme (mhGAP). 2010. https://www.who.int/mental_health/publications/mhGAP_intervention_guide/en/.

17 Dolle K, Schulte-Koerne G. The Treatment of Depressive Disorders in Children and Adolescents. *Dtsch Arztebl Int* 2013; **110**: 854+.

18 Walter HJ, Bukstein OG, Abright AR, *et al.* Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders. *Journal of the american academy of child and adolescent psychiatry* 2020. DOI:10.1016/j.jaac.2020.05.005.

19 Birmaher B, Brent D, AACAP Work Group on Quality Issues, *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. *The 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-Journal of the American Medical Association* 2004; **292**: 807–20.

22 Crenna-Jennings W, Hutchinson J. Access to child and adolescent mental health services in 2019. 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. *Journal of Clinical Psychiatry* 2019; **80**. DOI:10.4088/JCP.17r12064.

26 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.

27 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.

28 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**: 10–6.

29 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.

30 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.

31 Walkup JT. Antidepressant Efficacy for Depression in Children and Adolescents: Industry- and NIMH-Funded Studies. *AJP* 2017; **174**: 430–7.

32 Walkup JT, Albano AM, Piacentini J, *et al.* Cognitive Behavioral Therapy, Sertraline, or a Combination in Childhood Anxiety. *New England Journal of Medicine* 2008; **359**: 2753–66.

33 Ginsburg GS, Kendall PC, Sakolsky D, *et al.* Remission After Acute Treatment in Children and Adolescents With Anxiety Disorders: Findings From the CAMS. *JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY* 2011; **79**: 806–13.

34 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 of Systematic Reviews* 2014. DOI:10.1002/14651858.CD008324.pub3.

35 Curry J, Rohde P, Simons A, *et al.* Predictors and Moderators of Acute Outcome in the Treatment for Adolescents With Depression Study (TADS). *Journal of the American Academy of Child & Adolescent Psychiatry* 2006; **45**: 1427–39.

36 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 Technology Assessment* 2008; **12**: 1+.

37 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. *The Lancet Psychiatry* 2019; **6**: 735–44.

38 Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. 2020; **61**: 312–32.

39 Vitiello B. Prevention and treatment of child and adolescent depression: challenges and opportunities. *Epidemiology and Psychiatric Sciences* 2011; **20**: 37–43.

40 Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. 2020; **61**: 312–32.

41 Luft MJ, Lamy M, DelBello MP, McNamara RK, Strawn JR. Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and Management. *Current problems in pediatric and adolescent health care* 2018; **48**: 50–62.

42 Carolina Rojas-Mirquez J, Max Rodriguez-Zuniga MJ, Javier Bonilla-Escobar F, *et al.* Nocebo effect in randomized clinical trials of antidepressants in children and adolescents: systematic review and meta-analysis. *Frontiers in Behavioral Neuroscience* 2014; **8**. DOI:10.3389/fnbeh.2014.00375.

43 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. *Clinical Therapeutics* 2012; **34**: 113–23.

44 Gordon M, Melvin G. Selective serotonin re-uptake inhibitors--a review of the side effects in adolescents. *Australian family physician* 2013.

45 Emslie G, Kratochvil C, Vitiello B, *et al.* Treatment for Adolescents With Depression Study (TADS): Safety Results. *Journal of the American Academy of Child & Adolescent Psychiatry* 2006; **45**: 1440–55.

46 Deumic E, Butcher BD, Clayton AD, Dindo LN, Burns TL, Calarge CA. Sexual Functioning in Adolescents With Major Depressive Disorder. *Journal of Clinical Psychiatry* 2016; **77**: 957–62.

47 Cockerill RG, Biggs BK, Oesterle TS, Croarkin PE. Antidepressant use and body mass index change in overweight adolescents: A historical cohort study. *Innovations in Clinical Neuroscience* 2014; **11**: 14–21.

48 Nilsson M, Joliat M, Miner CM, Brown EB, Heiligenstein JH. Safety of Subchronic Treatment with Fluoxetine for Major Depressive Disorder in Children and Adolescents. *Journal of Child and Adolescent Psychopharmacology* 2004; **14**: 412–7.

49 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. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2017; **32**: 2367–74.

50 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* 2020; published online Sept 2. DOI:10.1001/jamapsychiatry.2020.2762.

51 Offidani E, Guidi J, Tomba E, Fava GA. Efficacy and Tolerability of Benzodiazepines versus Antidepressants in Anxiety Disorders: A Systematic Review and Meta-Analysis. *PPS* 2013; **82**: 355–62.

52 Vitiello B, Silva S, Rohde P, *et al.* Suicidal Events in the Treatment for Adolescents with Depression Study (TADS). *J Clin Psychiatry* 2009; **70**: 741–7.

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

54 Safer DJ, Zito JM. Treatment-Emergent Adverse Events from Selective Serotonin Reuptake Inhibitors by Age Group: Children versus Adolescents. *Journal of Child and Adolescent Psychopharmacology* 2006; **16**: 159–69.

55 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. *Journal of Child and Adolescent Psychopharmacology* 2007; **17**: 741–50.

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

57 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 Disorders* 2014; **16**: 523–30.

58 Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *ARCHIVES OF GENERAL PSYCHIATRY* 2006; **63**: 332–9.

59 Leon AC. The revised warning for antidepressants and suicidality: unveiling the black box of statistical analyses. *Am J Psychiatry* 2007; **164**: 1786–9.

60 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-BRITISH MEDICAL JOURNAL* 2009; **339**. DOI:10.1136/bmj.b2880.

61 Friedman RA, Leon AC. Expanding the black box - depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356**: 2343–6.

62 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-BRITISH MEDICAL JOURNAL* 2007; **335**: 142-146A.

63 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. *American Journal of Psychiatry* 2007; **164**: 1356–63.

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

65 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**. DOI:10.1136/bmj.g3596.

66 Dudley M, Goldney R, Hadzi-Pavlovic D. Are adolescents dying by suicide taking SSRI antidepressants? A review of observational studies. *Australasian Psychiatry* 2010; **18**: 242–5.

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

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

69 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. *AJP* 2004; **161**: 826–35.

70 Bowman MA, Daws LC. Targeting Serotonin Transporters in the Treatment of Juvenile and Adolescent Depression. *Front neurosci* 2019; **13**: 156.

71 Olivier JDA, Blom T, Arentsen T, Homberg JR. The age-dependent effects of selective serotonin reuptake inhibitors in humans and rodents: A review. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2011; **35**: 1400–8.

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

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

74 Cowen DS, Takase LF, Fornal CA, Jacobs BL. Age-dependent decline in hippocampal neurogenesis is not altered by chronic treatment with fluoxetine. *Brain Research* 2008; **1228**: 14–9.

75 Aydogan AS, Oztekin E, Esen ME, *et al.* Cortical thickening in remitters compared to non-remitters with major depressive disorder following 8-week antidepressant treatment. *Acta Psychiatrica Scandinavica* 2019; **140**: 217–26.

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

77 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. *Journal of Affective Disorders* 2015; **174**: 432–40.

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

79 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.

80 Powers A, Casey BJ. The Adolescent Brain and the Emergence and Peak of Psychopathology. *Journal of Infant, Child, and Adolescent Psychotherapy* 2015; **14**: 3–15.

81 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. *Developmental Cognitive Neuroscience* 2020; **42**: 100775.

82 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.

83 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. *Translational Psychiatry* 2016; **6**: e957–e957.

84 Tao R, Calley CS, Hart J, *et al.* Brain activity in adolescent major depressive disorder before and after fluoxetine treatment. *The American Journal of Psychiatry* 2012; **169**: 381–8.

85 Capitao LP, Chapman R, Murphy SE, *et al.* A single dose of fluoxetine reduces neural limbic responses to anger in depressed adolescents. *Translational Psychiatry* 2019; **9**. DOI:10.1038/s41398-018-0332-2.

86 Burkhouse KL, Kujawa A, Hosseini B, *et al.* Anterior cingulate activation to implicit threat before and after treatment for pediatric anxiety disorders. *Progress in neuro-psychopharmacology & biological psychiatry* 2018; **84**: 250–6.

87 Cullen KR, Klimes-Dougan B, Vu DP, *et al.* Neural Correlates of Antidepressant Treatment Response in Adolescents with Major Depressive Disorder. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2016; **26**: 705–12.

88 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.

89 Capitao LP, Murphy SE, Browning M, Cowen PJ, Harmer CJ. Acute fluoxetine modulates emotional processing in young adult volunteers. *Psychological Medicine* 2015; **45**: 2295–308.

90 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.

91 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. *Journal of the American Academy of Child & Adolescent Psychiatry* 2013; **52**: 831–40.

92 Carthy T, Benaroya-Milshtein N, Valevski A, Apter A. Emotional reactivity and regulation following citalopram therapy in children and adolescents with anxiety disorders. *Journal of Child and Adolescent Psychopharmacology* 2017; **27**: 43–51.

93 Gottlieb L, Martinovich Z, Meyers KM, Reinecke MA. Treatment for Depression Enhances Protection: Findings From the Treatment for Adolescents With Depression Study (TADS). *International Journal of Cognitive Therapy* 2016; **9**: 38–56.

94 Jacobs RH, Silva SG, Reinecke MA, Curry JF, Ginsburg GS, Kratochvil CJ. Dysfunctional Attitudes Scale Perfectionism: A Predictor and Partial Mediator of Acute Treatment Outcome among Clinically Depressed Adolescents. *Journal of clinical child and adolescent psychology* 2009; **38**: 803–13.

95 Joiner TE, Brown JS, Gordon KH, Rouleau MR, Wagner KD. Attributioual style, hope, and initial response to selective serotonin reuptake inhibitors in youth psychiatric inpatients. *Cognitive Therapy and Research* 2005; **29**: 691–704.

96 Kendall PC, Cummings CM, Villabo MA, *et al.* Mediators of Change in the Child/Adolescent Anxiety Multimodal Treatment Study. *Journal of Consulting and Clinical Psychology* 2016; **84**: 1–14.

97 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.

98 Hale AE, Ginsburg GS, Chan G, *et al.* Mediators of treatment outcomes for anxious children and adolescents: The role of somatic symptoms. *Journal of clinical child and adolescent psychology* 2018; **47**: 94–104.

99 Scharfstein LA, Beidel DC, Finnell LR, Distler A, Carter NT. Do Pharmacological and Behavioral Interventions Differentially Affect Treatment Outcome for Children With Social Phobia? *Behavior Modification* 2011; **35**: 451–67.

100 Alfano CA, Ginsburg GS, Kingery JN. Sleep-related problems among children and adolescents with anxiety disorders. *Journal of the american academy of child and adolescent psychiatry* 2007; **46**: 224–32.

101 Caporino NE, Read KL, Shiffrin N, *et al.* Sleep-related problems and the effects of anxiety treatment in children and adolescents. *Journal of clinical child and adolescent psychology* 2017; **46**: 675–85.

102 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. *International Journal of Geriatric Psychiatry* 2014; **29**: 1132–9.

103 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. *Translational Psychiatry* 2017; **7**: e1066–e1066.

104 Feeny NC, Silva SG, Reinecke MA, *et al.* An Exploratory Analysis of the Impact of Family Functioning on Treatment for Depression in Adolescents. *Journal of clinical child and adolescent psychology* 2009; **38**: 814–25.

105 Rengasamy M, Mansoor BM, Hilton R, *et al.* The Bi-Directional Relationship Between Parent-Child Conflict and Treatment Outcome in Treatment-Resistant Adolescent Depression. *Journal of the american academy of child and adolescent psychiatry* 2013; **52**: 370–7.

106 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. *American Journal of Psychiatry* 2009; **166**: 418–26.

107 Dardas LA. Family functioning moderates the impact of depression treatment on adolescents' suicidal ideations. *Child Adolesc Ment Health* 2019; **24**: 251–8.

108 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. *Biological Psychiatry* 2004; **55**: 1171–8.

109 Oh J, Zupan B, Gross S, Toth M. Paradoxical Anxiogenic Response of Juvenile Mice to Fluoxetine. *Neuropsychopharmacology* 2009; **34**: 2197–207.

110 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.

111 Emslie GJ, Kennard BD, Mayes TL, *et al.* Insomnia Moderates Outcome of Serotonin-Selective Reuptake Inhibitor Treatment in Depressed Youth. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2012; **22**: 21–8.

112 McMakin DL, Olino TM, Porta G, *et al.* Anhedonia Predicts Poorer Recovery Among Youth With Selective Serotonin Reuptake Inhibitor Treatment-Resistant Depression. *Journal of the american academy of child and adolescent psychiatry* 2012; **51**: 404–11.

113 Walkup JT, Labellarte MJ, Riddle MA, *et al.* Searching for moderators and mediators of pharmacological treatment effects in children and adolescents with anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* 2003; **42**: 13–21.

114 Wilkinson P, Dubicka B, Kelvin R, Roberts C, Goodyer I. Treated depression in adolescents: predictors of outcome at 28 weeks. *British journal of psychiatry* 2009; **194**: 334–41.

115 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. *BEHAVIOR THERAPY* 2014; **45**: 126–36.

116 Lorenzo-Luaces L, Rodriguez-Quintana N, Bailey AJ. Double trouble: Do symptom severity and duration interact to predicting treatment outcomes in adolescent depression? *BEHAVIOUR RESEARCH AND THERAPY* 2020; **131**. DOI:10.1016/j.brat.2020.103637.

117 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; : 1–13.

118 Cheung A, Mayes T, Levitt A, *et al.* Anxiety As a Predictor of Treatment Outcome in Children and Adolescents with Depression. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2010; **20**: 211–6.

119 Asarnow JR, Emslie G, Clarke G, *et al.* Treatment of Selective Serotonin Reuptake Inhibitor-Resistant Depression in Adolescents: Predictors and Moderators of Treatment Response. *Journal of the american academy of child and adolescent psychiatry* 2009; **48**: 330–9.

120 Compton SN, Peris TS, Almirall D, *et al.* Predictors and Moderators of Treatment Response in Childhood Anxiety Disorders: Results From the CAMS Trial. *JOURNAL OF CONSULTING AND CLINICAL PSYCHOLOGY* 2014; **82**: 212–24.

121 Curry J, Silva S, Rohde P, *et al.* Recovery and Recurrence Following Treatment for Adolescent Major Depression. *ARCHIVES OF GENERAL PSYCHIATRY* 2011; **68**: 263–70.

122 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). *Journal of the american academy of child and adolescent psychiatry* 2011; **50**: 293–301.

123 Nguyen LJ. The impact of childhood trauma on treatment response of depressed adolescents. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2007; **68**: 1316.

124 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. *AMERICAN JOURNAL OF PSYCHIATRY* 2010; **167**: 190–7.

125 Gasso P, Rodriguez N, Boloc D, *et al.* Association of regulatory TPH2 polymorphisms with higher reduction in depressive symptoms in children and adolescents treated with fluoxetine. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2017; **77**: 236–40.

126 Gasso P, Blazquez A, Rodriguez 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. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2018; **28**: 711–8.

127 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. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2013; **23**: 117–22.

128 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.

129 Joyce PR, Mulder RT, Luty SE, *et al.* Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta 3 subunit as predictors of response to fluoxetine and nortriptyline. *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY* 2003; **6**: 339–46.

130 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. *JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY* 2017; **58**: 546–54.

131 Burkhouse KL, Jagan J, 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**: 561–9.

132 Klimes-Dougan B, Schreiner MW, Thai M, Gunlicks-Stoessel M, Reigstad K, Cullen KR. Neural and neuroendocrine predictors of pharmacological treatment response in adolescents with depression: A preliminary study. *PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY* 2018; **81**: 194–202.

133 McClure EB, Adler A, Monk CS, *et al.* fMRI predictors of treatment outcome in pediatric anxiety disorders. *PSYCHOPHARMACOLOGY* 2007; **191**: 97–105.

134 Bunford N, Kujawa A, Fitzgerald KD, *et al.* Neural reactivity to angry faces predicts treatment response in pediatric anxiety. *JOURNAL OF ABNORMAL CHILD PSYCHOLOGY* 2017; **45**: 385–95.

135 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. *JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY* 2012; **22**: 37–47.

136 McGrath CL, Kelley ME, Holtzheimer PE, *et al.* Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder. *JAMA Psychiatry* 2013; **70**: 821–9.

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

138 Miller GE, Cole SW. Clustering of Depression and Inflammation in Adolescents Previously Exposed to Childhood Adversity. *Biol Psychiatry* 2012; **72**: 34–40.

139 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. *JNP-Journal for Nurse Practitioners* 2014; **10**: 149–56.

140 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. *Journal of Child and Adolescent Psychopharmacology* 2016; **26**: 727–32.

141 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. *European Neuropsychopharmacology* 2020; published online July 31. http://www.sciencedirect.com/science/article/pii/S0924977X20302315 (accessed Sept 26, 2020).

142 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, Behavior, and Immunity* 2020; **87**: 301–8.

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

144 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. *Journal of Affective Disorders* 2008; **106**: 1–27.

145 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.

146 Shehab AAS, Brent D, Maalouf FT. Neurocognitive changes in selective serotonin reuptake inhibitors-Treated adolescents with depression. *Journal of Child and Adolescent Psychopharmacology* 2016; **26**: 713–20.

147 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.

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

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

150 Abler B, Gron G, Hartmann A, Metzger C, Walter M. Modulation of Frontostriatal Interaction Aligns with Reduced Primary Reward Processing under Serotonergic Drugs. *Journal of Neuroscience* 2012; **32**: 1329–35.

151 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.

152 Krause KR, Bear HA, Edbrooke-Childs J, Wolpert M. Review: What Outcomes Count? Outcomes Measured for Adolescent Depression Between 2007 and 2017. *Journal of the American Academy of Child & Adolescent Psychiatry* 2019; **58**: 61–71.

153 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. *Noropsikiyatri Arsivi* 2014; **51**: 30–9.

154 Park SH, Song YJC, Demetriou EA, *et al.* Distress, quality of life and disability in treatment-seeking young adults with social anxiety disorder. *Early Intervention in Psychiatry* DOI:10.1111/eip.12910.

155 Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *The Lancet Psychiatry* 2019; **6**: 561–2.

156 Weller I, Ashby D, Brook R, *et al.* Report of the CSM Expert Working Group on the Safety of Selective Serotonin Reuptake Inhibitor Antidepressants. undefined. 2005. /paper/Report-of-the-CSM-Expert-Working-Group-on-the-of-Ivd.-Ashby/9f66a4029a30bd86bfc1d942ab72960bf12a124e (accessed Sept 28, 2020).