**Common practical questions - and answers - at the British Association for Psychopharmacology (BAP) child and adolescent psychopharmacology course**

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**ABSTRACT**

The British Association for Psychopharmacology (BAP)course on child and adolescent psychopharmacology has been run for more than 20 years and is currently a very popular course, attracting around 140 delegates/year from across the UK and abroad. As Faculty of recent sessions of the course, we have selected the most common questions we have been asked in recent years, and provided evidence-based and/or expert-informed answers. More specifically, we have included 27 questions and answers related to attention-deficit/hyperactivity disorder, anxiety and depressive disorders, autism spectrum disorder, bipolar disorder, eating disorders, epilepsy (in differential diagnosis or comorbid with mental health conditions), obsessive-compulsive disorder, personality disorders, psychotic spectrum disorders, and tics/Tourette syndrome in children and young people. We hope that this paper will be helpful for prescribers in their daily clinical practice and we look forward to further, high-level evidence informing the answers to these and other question in child and adolescent psychopharmacology.

**Keywords:** psychopharmacology; child; adolescents; young people; evidence; expert opinion

**INTRODUCTION**

Since 2001, the British Association for Psychopharmacology (BAP) has run a course (“clinical certificate”) on child and adolescent psychopharmacology, that has become more and more popular over the years and has attracted prescribers (around 140/year) from across the UK and abroad. As Faculty of the recent sessions of the course, we have reported here the most frequent clinical practice questions that we have been asked by the delegates, and our answers. In general, the questions were related to aspects/topics for which there is not a solid evidence base yet. Therefore, our answers reflect the available evidence alongside our clinical expertise and expert opinion. We have grouped the questions and answers by disorder to which they refer, in alphabetical order.

**ATTENTION-DEFICIT/HYPERACTIVITY DISORDER**

1. ***Can I use doses of psychostimulants beyond the maximum licensed or recommended ones?***

The maximum recommended doses of psychostimulants for the treatment of ADHD in guidelines or formularies may be higher than the maximum licensed doses by regulatory agencies such the Food and Drug Administration (FDA) or the European Agency (EMA). More specifically, the maximum licensed dose of methylphenidate for children (except for osmotic release and prolonged release formulations, see below) is 60 mg/day, while the British National formulary (BNF) (Joint Formulary Committee, 2022) recommends a dose of up to 90 mg/day, under the direction of a specialist. For osmotic-release (Concerta ® XL) and prolonged-release (e.g., Xaggitin ® XL and Delmosart ® prolonged-release tablet) formulations of methylphenidate, the maximum license dose is 54 mg/day, but the BNF mentions a maximum of 108 mg/day for Concerta ® XL, in line with other clinical guidelines, e.g., those from the Canadian ADHD Resource Alliance (CADDRA) (caddra.ca). For lisdexamfetamine, both the maximum licensed *and* the BNF recommended dose is 70 mg/day.

Many prescribers will use doses above the maximum licensed ones. Some of them will also use doses beyond the maximum recommended in guidelines/formularies. Currently, there is no solid, meta-analytic evidence to inform if, and to what extent, doses beyond the recommended ones are safe and bring additional efficacy/effectiveness. Some experts agree that, while it should not be a standard, routine practice, using doses beyond the maximum recommended ones could be considered when the patient has presented with a partial response, there is only some degree of improvement at the maximum recommended dose, tolerability is good, and the aim is to optimise the response (Cortese et al., 2021).

1. ***What shall I do if a patient does not respond to psychostimulants?***

Following poor response to two psychostimulants (methylphenidate, MPH and amphetamines, AMPH - including lisdexamfetamine, LDX), some clinicians would consider second- or third-line approved compounds, unlicensed medications for ADHD, or combinations of different agents. However, a number of factors should be considered before switching to alternative medications or using polypharmacy. Indeed, it should be highlighted that the vast majority of patients with ADHD respond to one or both classes of psychostimulants, when used properly. A comparative review found that ~41% of children treated with immediate-release stimulants responded equally well to AMPH or MPH, 28% responded better to AMPH, 16% had a better response to MPH, and 15% did not respond to either medication. A more recent review concluded that ~91% of individuals with ADHD respond to either or both class of stimulants (Hodgkins et al., 2012). Therefore, before considering alternative agents and/or polypharmacy, the following should be considered: a) Have I titrated properly? While some patients will respond well to low or moderate doses, others will need higher ones, regardless of their age and weight. Of note, meta-analytic evidence from flexible-dose trials for both MPH and AMPH demonstrated increased efficacy and reduced likelihood of discontinuations for any reason with increasing stimulant doses (Farhat et al., 2022); b) Is this drug/preparation working well at any times during the day or do I need to change the dose or preparation to get a more comprehensive coverage? Sometimes, poor response may be detected only in specific periods of the day, when the medication effect has worn off; c) Am I targeting the right symptoms? Psychostimulants are in general highly efficacious/effective on the core symptoms of ADHD (i.e., inattention, hyperactivity, impulsivity) (Cortese, 2020), not necessarily on other problems (e.g., oppositional behaviour/emotional dysregulation); d) Is the patient showing tolerance? It is not clear to which extent the phenomenon of tolerance occurs with psychostimulants. Some experts suggest decreasing the dose or temporarily (for a few weeks) stop the psychostimulant to overcome the tolerance issues; e) What else is going on in patient’s life/family life? A comprehensive formulation, beyond diagnosis, is key here; f) Have I missed any comorbidity? Some comorbidities, e.g., autism spectrum disorder, are associated with lower chances of response; g) Is the diagnosis correct?

Only after all these aspects have been assessed, the prescriber should consider: 1) second line medications (atomoxetine, guanfacine, clonidine); 2) augmenting agents (guanfacine or clonidine XR); 3) other agents, under specialistic advice/supervision, for which randomised controlled trial provide preliminary evidence of efficacy (e.g., bupropion) (Cortese et al., 2021).

1. ***Does the concomitant use of cannabis impact on the tolerability and effectiveness of ADHD medications?***

# The evidence on the tolerability of the combination psychostimulants- marijuana is limited. In a randomised controlled trial of OROS-methylphenidate and CBT in youths with substance use disorder, including marijuana, the tolerability of OROS-methylphenidate was not substantially different compared to what it would be expected with OROS-methylphenidate alone (Riggs et al., 2011). Another RCT showed addictive effects of MPH and tetrahydrocannabinol on heart rate, but not on systolic and diastolic blood pressure (Kollins et al., 2015). It should be noted that a subgroup of youths who use marijuana tend to misuse also other illicit substances, which may further impact on the tolerability of psychostimulants. Therefore, prescribers should comprehensively screen for the use of a variety of illicit drugs.

# Even though there is no solid evidence to support this, some experts would agree that the effects of psychostimulants may be decreased by the concomitant use of marijuana, and this should be discussed with the patient at the initial assessment and during the follow-up visits.

**ANXIETY AND DEPRESSIVE DISORDERS**

***4. What do I do if a young person has depression and has not responded to two Selective Serotonin reuptake inhibitors (SSRIs) and Cognitive Behavioural Therapy (CBT)?***

NICE guidelines currently recommend CBT as a first-line treatment for moderate to severe depression; and fluoxetine as a first-line antidepressant and if that is not effective, sertraline or citalopram (NICE 2009). There is limited evidence for other treatments beyond this, other than interpersonal psychotherapy (Zhou et al., 2015), which is often not available.

The first thing to do when a patient is treatment-resistant is to revisit the formulation and diagnosis. Is this really depression, or does the pattern of symptoms since you started seeing the patient suggest a personality disorder is a more appropriate diagnosis? Are there any social factors that have not been addressed?

Then review whether the patient has indeed had all the treatments they are ‘resistant’ to. Did they stop fluoxetine after a few days of mild side effects and would they be prepared to try again? Did they have a good number of sessions of evidence-based psychological therapy from a fully-trained and supervised therapist? If they stopped after a few sessions, was this due to a problem in the therapy or the therapist and would they consider trying a different therapist?

If the patient truly does have depression, and you have tried all the evidence-based treatments, there is no evidence to guide you. It would be reasonable to try two SSRIs up to the maximum tolerated dose, within BNF limits: although there is no evidence in favour of or against this, there is some evidence for a dose increase in adult depression; and there is plenty of safety data from paediatric OCD studies which use high doses of SSRIs. If the patient is nearly 18, it may be reasonable to try antidepressants shown to work in studies of 18-64 years old but not in studies of 12-17 years old, such as mirtazapine. It may be worth trying an augmenting agent such as lamotrigine or an atypical antipsychotic.

In all cases, it is important to discuss and document potential benefits and harms with patients and their families, and the lack of robust evidence or marketing authorisation for any drug treatment other than fluoxetine 20mg od. If you are unsure, it is important to discuss cases with your consultant peers and document this.

***5. If a patient has severe side-effects (such as suicidality) on one SSRI, is it safe to try a second SSRI?***

While the majority of adolescents given an SSRI have mild, transient side-effects, a small number of patients have rarer and more dangerous side-effects, including suicidal thoughts (Bridge et al., 2007), homicidal thoughts and clotting abnormalities (Lake et al., 2000). Many patients and their families (and their prescribers) will choose to stop the medication in this situation.

There is then the question of whether another SSRI should be used. There is no published evidence regarding this. However, in consensus discussions, several psychiatrists have tried the patient on a second SSRI and this has not led to the same side-effect. It is likely the patient will have increased risk of (eg) suicidality on a second SSRI compared to a patient who has never had an SSRI, but it could be worth trying, especially in more severe depression which itself carries significant suicide risk. As always, it is important to discuss potential benefits and risks with patients and families and make decisions jointly; and it is essential to document these discussions. It is also especially important to follow these patients up regularly when starting a second SSRI and have a clear plan in place for what to do if these side-effects recur. If unsure, discuss the case with consultant peers and document this.

It is also important to take into account pharmacological profile of the first and second SSRI. Sertraline and citalopram/escitalopram have significantly higher 5-HT specificity than fluoxetine. So, if sertraline caused dangerous side-effects, it would be better to try the more different fluoxetine than citalopram as second line.

***6. I see an adolescent with an anxiety disorder who a GP has started on propranolol. What should I do?***

SSRIs are by far the most effective medication for anxiety disorders in children, adolescents and adults (Ipser et al., 2009). GPs are often (and rightly) cautious about prescribing SSRIs in children and adolescents. This leads some GPs to prescribe propranolol (a beta blocker) instead for anxiety disorder. There are two problems with this: propranolol is not an effective treatment for anxiety disorders (Steenen et al., 2016); propranolol has significant side-effects and is particularly dangerous in overdose. Its use seems to have stemmed from the fact that it can reduce the physiological symptoms of anxiety – however in most cases, doing this does not reduce the feelings of anxiety. Therefore, it is much better to use SSRIs, which are both effective and safer. It may be better still to offer CBT, which has similar efficacy to SSRIs, but is more likely to keep the patient well long-term, and has no physical side-effects.

If we see a patient with an anxiety disorder who is taking propranolol, we should sensitively explain that it is not effective, and offer them an SSRI instead if they would like medication. If they have recovered from the anxiety by the time we see them, it is still worth stopping the propranolol as they may no longer need it. It is also important to educate the GP that propranolol is neither safe nor effective for anxiety disorders.

One possible exception is children/adolescents with Autism Spectrum Disorder (ASD) and anxiety. Some ASD experts report that children with ASD are much more sensitive to their internal environments, and if they have pronounced physical symptoms of anxiety, reducing these with propranolol may make a big difference and reduce overall anxiety. However, there is no clear evidence for this, and it is probably more appropriate to try an SSRI first.

**AUTISM SPECTRUM DISORDER**

***7. Can I use SSRI medication to manage repetitive behaviours in a child with a diagnosis of autism spectrum disorder*** ***(ASD)?***

Repetitive behaviours are a core diagnostic component of ASD, and, consequently, commonly observed among autistic individuals of all ages. These behaviours can take different forms: broadly speaking, whilst for some they comprise ‘functional’ behaviours, such as the pursuit of interests, for others they may be less purposeful, such as ritualistic and repetitive motor behaviours. The decision to treat is fundamentally determined by the degree to which the behaviour impacts on wellbeing and/or the ability to develop other skills.

Treatment of repetitive behaviours will largely be from a psychological/behavioural perspective. In some circumstances, however, these may be ineffective, or otherwise difficult to implement; in such cases, medication may be considered. The Cochrane Review of 2013, which considered the use of SSRIs in the management of ‘core’ symptoms of ASD, found no evidence to support their use for ritualistic behaviours (Williams et al., 2013). A more recent systematic review similarly concluded that there is no evidence for the use of SSRI or other medications in the management of ritualistic behaviours (Yu et al., 2020).

This notwithstanding, when examining individual studies, there is certainly some evidence to suggest that certain SSRIs (Carrasco et al., 2012), guanfacine (Politte et al., 2018), risperidone (McDougle et al., 2005) (D'Alo et al., 2021) and buspirone (Chugani et al., 2016b) may be effective. Given these data, it may be reasonable in the first instance to consider an SSRI given that these are used widely in clinical practice and so safety data are available. If inefficacious, or poorly tolerated, risperidone, guanfacine or buspirone may be considered as an alternative; however, particular caution is advised in relation to their use, which must be under specialist supervision.

At the outset it is essential that any trial of medication has (i) a clear titration schedule and (ii) well defined outcome measures. It is important to bear in mind that medication may take several months to alleviate symptoms. In accordance with the STOMP (Stopping The Over-Medication of children and young People with a learning disability, autism or both) and STAMP (Supporting Treatment and Appropriate Medication in Paediatrics (STAMP) frameworks (<https://www.england.nhs.uk/wp-content/uploads/2019/02/STOMP-STAMP-principles.pdf>), medication should be discontinued if it does not help, and among responders should be monitored and discontinued when appropriate.

***8. What are my options in the management of aggression in a child with ASD and an intellectual disability?***

Aggression is one of the most frequent reasons for referral to specialist services for a child with ASD. From the outset, a multidisciplinary approach is crucial in any such assessment to identify the relevant underlying factors so these can be managed (Volkmar et al., 2014b; Howes et al., 2018). Aggression is not a diagnosis; instead, it is a mechanism for the communication of need, discomfort or distress. The clinical team must identify the relevant biological, psychological and social predisposing, precipitating and perpetuating factors so that these can be managed accordingly. In rare instances, major life events, or factors such as constipation or pain, are key, but more commonly multiple factors are relevant. Despite the recommendations made below, it is always important to bear in mind that psychotropic medication can itself result in agitation, anxiety and mood disturbance, and so careful attention needs to be paid to the possibility that symptoms may be getting worse *as a result of* medication.

In the management of aggression, medication may be deemed an appropriate option in a number of different situations. For example, in the acute situation where it would be difficult or potentially unsafe to introduce behavioural therapy, medication can offer the possibility of reducing the severity of symptoms and thereby improving engagement in psychological interventions. Either risperidone (1-2 mg) or aripiprazole (2-3 mg) can be used for this purpose, both having shown efficacy and safety among autistic individuals (McCracken et al., 2002b; McQuire et al., 2015; Hirsch and Pringsheim, 2016b) at lower doses compared to when they are used as antipsychotics (of note, At these lower doses, serotonergic antagonism, rather than dopamine antagonism, predominates). Both have FDA approval for agitation in ASD. If used for this purpose, it is important that it is discontinued once behavioural work is underway. Less is known about the acute (and maintenance) use of other antipsychotics (D'Alo et al., 2021; McQuire et al., 2015). Similarly, benzodiazepines are sometimes used but there are no data.

In other situations, the consideration of medication may be raised when behavioural therapy has been unsuccessful or only partially successful. It is always important to consider the reasons for this lack of success, including revisiting the possibility of underlying medical causes (pain, constipation, metabolic, allergic and so forth). As in the acute situation, risperidone or aripiprazole may be introduced, with the expectation that the child is likely to remain on this over a period of 6 months or more. It is important that blood parameters are monitored on a regular basis, including liver function, lipids and glucose (Howes et al., 2018). This may not always be possible, in which case the decision to continue medication must be made in discussion with the decision maker and clearly documented. Other antipsychotics may also be used second line, but less is known about their use in this population. Similarly, benzodiazepines can have both a calming and anxiolytic effect, but there are no data on their use in this population. There is no evidence that SSRIs are effective for aggression, and no evidence for the use of mood stabilising treatments (unless of course a specific relevant diagnosis of bipolar disorder has been made). There is also no evidence for using different medications in combination.

Deciding on when to discontinue medication is also important, and a decision must be taken early in treatment. It may be reasonable to begin discontinuation at the 6-month point, or sooner for some. However, in reality other factors will influence this decision, such as whether or not the child has structure during the day (less likely during school holidays) and whether there is additional support available.

***9. What are my choices for the management of aggression in a child with ASD and ID when all options seem to have failed?***

For some children, behavioural interventions combined with ‘first line’ medications such as those suggested above fail to alleviate symptoms. There may be several reasons for this, and it is crucial at the outset that these are explored. The diagnostic formulation may have missed an important aetiological factor, or previously identified triggers or perpetuating factors may have been inadequately managed. For example, an environment with certain characteristics, such as routine, predictability and appropriate level of stimulation, may not be made available. Or there may be an absence of adequately trained support staff and staff may fail to follow behavioural recommendations. In these circumstances it is crucial that medication does not become the perceived ‘solution’. It is unethical for the psychiatrist to be expected to medicate where services are unable to meet needs.

On the other hand, there will be situations where challenging behaviour continues despite attention to all identified aetiological factors. Such situations are most likely to arise in the context of non-verbal autistic children who are severely or profoundly cognitively impaired. Whilst it remains important to continue to work towards a great understanding of the behaviour’s underpinning, this is often very challenging and medication may thus be considered as a least restrictive, best interest option in consultation with decision makers. Additionally, the psychiatrist should discuss treatment resistant cases with their peer group, and consider seeking a second option.

Other medications than those already discussed above have much less evidence for efficacy. Other antipsychotics such as quetiapine or olanzapine are certainly reasonable options, although have not been studied robustly in this population (Volkmar et al., 2014a; Hirsch and Pringsheim, 2016a; McQuire et al., 2015; D'Alò et al., 2021; Chugani et al., 2016a; Howes et al., 2018; McCracken et al., 2002a). Consequently, these medications must be used with caution, including low initial dose, slow titration and regular monitoring. Alternatively, benzodiazepines such as lorazepam, diazepam or clonazepam may be considered, but the same caution is advised. The combination of an antipsychotic with a benzodiazepine may also be considered, but the aim must always be to achieve symptomatic relief without sedation, such that the child can continue to engage in activities. If a benzodiazepine is prescribed it must always be only used in the short term.

SSRIs do not have a role to play in the management of aggression, and their use should be limited to the management of mood disorders, anxiety and, in some circumstances, repetitive and ritualistic behaviours as discussed above. There is no evidence for other agents, such as mood stabilisers or GABAergic agents (pregabalin).

**BIPOLAR DISORDER**

***10. How does one distinguish ADHD from Bipolar Disorder (BD)?***

As a neurodevelopmental disorder, the features of ADHD are usually present early in childhood and often cause functional impairment by the time a child is in primary school whereas BD usually presents in teenage years with peak onset described as between 15 and 19 years (NICE, 2014). Another factor that helps distinguish ADHD from BD is the course of symptoms as in ADHD the symptoms are pervasive in all settings (with some variation in severity), BD presents with an episodic course of symptoms with periods of euthymia interspersed. Lastly, ADHD is a disorder of attention, motor activity and impulsivity whereas BD is a disorder of mood. Of course these disorders may occur co-morbidly as well, and if this is the case appropriate management strategies should be employed.

***11. How does one distinguish Borderline Personality Disorder (BPD) from BD?***

BD is a disorder of mood characterised by discrete mood episodes. Periods between the mood episodes also described as euthymia are usually characterised by stable psychosocial functioning. BPD, also known as emotionally unstable personality disorder (EUPD), is a personality disorder characterised by a long-term pattern of unstable interpersonal relationships, distorted sense of self and marked affective instability. The affective instability is often triggered by environmental factors and usually lasts hours to days, unlike the mood episodes in BD which last weeks to months. Other clinical variables that help distinguish BD from BPD include: response to pharmacology in BD, a family history of BD. BPD is often associated with significant early life trauma.

***12. How does one distinguish antidepressant induced activation from antidepressant induced manic switch and what is the management?***

Both antidepressant-induced activation and switch occur quite early after the initiation of antidepressants (usually within a fortnight but not more than a month). In the activation syndrome, symptoms can include disinhibition, impulsivity, insomnia, restlessness, hyperactivity, and irritability, whilst on the other hand antidepressant-induced manic switch presents with symptoms of a manic episode. The treatment for a manic switch includes immediate discontinuation of the antidepressant (and possible use of antimanic agents) whereas a reduction of or discontinuation of antidepressants benefits the activation syndrome.

**EATING DISORDERS**
***13. What additional considerations are needed when prescribing in young people with eating disorders?***

There are considerations that relate to the physical complications of eating disorders. These include cardiac risks secondary to malnutrition and electrolyte abnormalities secondary to malnutrition or purging. Low weight can cause bradycardia and prolong QTc interval, thus increasing the risk of arrythmia (Giovinazzo et al., 2019), as can some psychotropic medications, in particular haloperidol. Studies suggest olanzapine has little effect on QTc interval (Jensen et al., 2015) but the UK manufacturer advises caution on the basis that other antipsychotics have QT prolonging effects. Purging causes potassium depletion, and low potassium can also arise secondary to severe weight loss. Hypokalaemia can further prolong QTc interval as well as causing arrythmia in its own right. It is therefore good practice to perform an ECG before prescribing.

Another consideration is patient engagement and adherence with prescribing. Anxiety about, and sensitivity to, side effects need to be addressed directly before initiating medication, in particular fear of weight gain secondary to antipsychotics. Patients should be reassured that the small doses of antipsychotics such as olanzapine typically used will have a minimal impact on appetite, that use of antipsychotics is short term (months rather than years), and that weight can be managed by adherence to meal plans during therapy. The primary purpose of prescribing antipsychotic medication in patients with anorexia nervosa is to reduce overwhelming arousal during meal times and not directly to cause weight gain.

***14. Should comorbidities in young people with eating disorders be treated separately?***

Comorbidities in eating disorders are common – up to 55% of children and adolescents presenting with an eating disorder have a comorbid disorder at presentation (Swanson et al., 2011; Simic et al., 2022). The commonest are depression, anxiety (especially social anxiety), obsessive compulsive disorder, and neurodevelopmental disorders such as ASD and ADHD. Three important considerations are warranted when considering whether to treat the comorbidity. Firstly, eating disorders can mimic or accentuate comorbidities, which are corrected as symptoms resolve. An example is the quasi-autistic effects that occurs in starvation syndrome, such as difficulties in set shifting and enhanced central coherence (Pender et al., 2014). Secondly, effective psychological treatments for eating disorders can result in improvements in other areas. For example, family-based treatment for anorexia nervosa, once malnutrition has been corrected, involves supporting dialogue around adolescent challenges and anxieties, such as difficulties in school or in interpersonal relationships, in a supportive family context. Clinical trials show resolution in anxiety and depression as well as the eating disorder at the end of treatment for the majority of subjects (Agras et al., 2014). Finally, studies suggest that some pharmacological interventions are ineffective during the acute phase. For example, antidepressants show limited efficacy in the context of malnutrition and it has been suggested that this decrease/loss of antidepressant efficacy is due to starvation-related structural and biochemical/pharmacologic changes in the brain (Marvanova and Gramith, 2018).

However, in some patients, the history clearly suggests that untreated or undiagnosed mental disorder may have preceded onset of the eating disorder and even that the eating disorder functioned as a ‘solution’ to these feelings of anxiety or other negative affect. For example, OCD may remerge as anorexia nervosa recedes. If a patient is not responding to competently delivered treatment as expected, re-evaluation of the diagnosis and formulation and consideration of additional treatment strategies for comorbidity should be considered.

***15. How might treatment approaches differ in young people with an eating disorder in the context of neurodevelopmental disorder?***

Neurodevelopmental disorders are common across mental disorders, and are especially associated with eating disorders. Studies report between 4 and 52.5% of participants with anorexia nervosa meet suggested clinical cut-off for autism spectrum disorder (ASD), with higher proportions in adult that in younger populations (Westwood and Tchanturia, 2017). ASD is also commonly comorbid with avoidant restrictive food intake disorder (ARFID). Treatment adaptations for comorbid ASD are in development (e.g., the PEACE pathway (Tchanturia et al., 2020)). The possibility of comorbid ASD is an important consideration when prescribing in terms of anticipated response, treatment duration, and side effect sensitivity. In general, people with ASD are more likely to remain on medication and to be prescribed polypharmacy.  What research there is suggests autistic people may be more likely to experience side effects such as drowsiness, irritability and reduced activity (Persico et al., 2021).

ADHD is commonly comorbid in the context of bulimic and binge eating disorder (BED) (Nazar et al., 2016). Identification, assessment and treatment of comorbid ADHD may be helpful in addressing difficulties in impulsivity and self-regulation common to both disorders. The potential appetite suppressing effects of ADHD treatment should also be a consideration in evaluating the treatment options. Trials of lisdexamfetamine show favourable results compared with placebo on remission, change in BMI and binge eating in adults with BED (NICE 2017). However, in trials more people withdrew due to adverse events in the active arm, and there was a trend towards higher depression scores in the lisdexamphetamine arm compared with placebo. Lisdexamfetamine is not licenced in the UK for treatment of BED, but is licensed for treatment of ADHD. No pharmacological trials in young people with BED have been conducted as yet.

**EPILEPSY (in differential diagnosis or comorbid with mental conditions)**

***16. What is the role of cannabidiol in the child with epilepsy and behavioural problems?***

There are now sufficient high-quality studies to confirm the efficacy of cannabidiol in treating seizures in both adults and children (Szaflarski et al., 2018; Devinsky et al., 2016; Lattanzi et al., 2018). The mode of action of cannabidiol as an antiseizure medication remains uncertain. The efficacy and adverse effects are not very different from those of other relatively new antiseizure medications. Overall, it is not notably more effective or less effective. With regard to either beneficial or adverse behavioural effects, there is currently conflicting evidence, although some suggestion of benefit (Arzimanoglou et al., 2020). A confounding factor is that seizure frequency can affect behaviour, implying that if the cannabidiol affects seizure frequency, it may be difficult to determine whether any change in behaviour is the result of a change in seizures or whether it is a direct result of the cannabidiol itself. There are also some important drug interactions; for example, cannabidiol raises clobazam blood levels. Further evidence will be required before definitive information on the effects of cannabidiol on behaviour in young people with epilepsy can be provided.

***17. If a child is having nocturnal episodes that are disturbing sleep, when should we be assessing for epilepsy as a possible cause?***

In the absence of a history of daytime seizures, the likelihood of undiagnosed nocturnal seizures is less. However, there are certain types of epilepsy that present with seizures that occur only or primarily at night.

In particular, nocturnal seizures of frontal lobe origin can present in a way that can be inconsistent with what most people would consider as being typical of epileptic seizures (Scheffer et al., 1995; Nobili et al., 2014). Nocturnal frontal lobe seizures typically present with brief episodes that can occur multiple times in a single night, often with non-rhythmical movements. They are frequently accompanied by vocalisation and, in contrast to the situation for most other focal-onset seizures, it is often possible for the individual to recall the seizures afterwards. The recollection can be disturbing, sometimes being associated with a subjective difficulty in breathing, which could be misdiagnosed as asthma. A careful history will usually distinguish nocturnal frontal lobe seizures from other nocturnal episodes. For example, the characteristics of nocturnal frontal lobe seizures can be distinguished clearly from night terrors, through careful history taking. A video of the nocturnal seizures, perhaps using an infrared camera, can assist in the diagnostic process. Nocturnal frontal lobe seizures classically respond to treatment with carbamazepine; they can also respond to other antiseizure medications, such as levetiracetam.

Children with nocturnal tonic (stiffening) seizures generally have a background history of epilepsy. Because they are brief, nocturnal tonic seizures may be difficult to distinguish from normal nocturnal movements but video EEG monitoring can be diagnostic. Brief tonic seizures can occur many times in a single night, sometimes more than 100 times. Such frequent seizures almost certainly affect daytime alertness and performance.

The other nocturnal epilepsy-related phenomenon that is of major importance, although rare, is electrical status epilepticus of slow-wave sleep (ESES), otherwise known as continuous spike-wave of slow-wave sleep (CSWS) (Tassinari et al., 2000). The definition of ESES requires that more than 85 percent of the slow-wave sleep be replaced by spike-wave epileptiform discharges. Although most cases present against the background of established epilepsy, some cases present with no history of overt seizures. ESES can be accompanied by profound loss of skills, especially profound loss of verbal auditory comprehension, which can lead to complete loss of speech, in some cases. ESES accompanied by loss of speech is known as the Landau-Kleffner syndrome (Landau and Kleffner, 1957) or acquired epileptic aphasia. Several medication treatments have been advocated, with some degree of success. If antiseizure medication, brief high-dose benzodiazepine treatment or treatment with steroids are not effective (Mikati and Shamseddine, 2005), then the surgical procedure of multiple sub-pial transection (Morrell et al., 1995) should be considered. Although reports of the efficacy of this procedure are variable, it can be highly successful in allowing the aphasic child to speak again. Any child who loses skills for no apparent reason deserves thorough investigation, including consideration of EEG monitoring during sleep. If this reveals ESES, then prompt treatment should follow. Children with acquired aphasia, understandably, may have major behavioural difficulties, including autistic features, emphasising the importance of effective, prompt, and appropriate management (Besag et al., 2016).

***18. If I have prescribed fluoxetine to a teenager with depression but no history of epilepsy and he or she has a seizure, what should I do?***

Both animal work and the landmark paper by Alper et al. (Alper et al., 2007) analysing data on people with depression, strongly suggest that SSRIs are protective against seizures rather than precipitating seizures. A cursory examination of the data could result in misleading, incorrect conclusions. Depression itself is a risk factor for having seizures. People taking SSRIs for depression are more at risk of having seizures than the general population, which might lead to the incorrect conclusion that the SSRIs have increased the risk of having seizures. This is because the comparison is the wrong one. If a group of people with depression taking SSRIs is matched with a group of people with depression not taking SSRIs, then those taking SSRIs have a very much lower risk of having seizures, as confirmed by the Alper et al. review.

In brief, if someone taking SSRIs for depression has a seizure, the situation should be discussed fully with the young person/family. It is unlikely that the SSRI will have precipitated the seizure and it is even possible that the SSRI might have some protective benefit against further seizures. The family should be provided with accurate information on which to make a decision. Usually, the recommendation will be to continue with the SSRI, unless there is a clear indication for not doing so.

**OBSSESSIVE COMPULSIVE DISORDER**

***19. What steps do you take in medicating Obsessive Compulsive Disorder (OCD) in Children and Young people?***

Much of the information held in NICE guidance for the initiation of treatment of OCD are still based on strong evidence (NICE 2005). When choosing to initiate medication, as part of stepped care, it is important to have a clear narrative for your patient and their family about the typical need to increase to a high dose of SSRI. Meta-analysis of OCD treatment trial, largely emanate from adult research but still emphasise the need to use a moderate to high dose of medication (Bloch et al., 2010). From clinical experience, most adolescents with OCD are able to tolerate weekly increments of medication, towards a high dose, e.g., fluoxetine 60mg daily. Understandably, young people with OCD are often very keen to see immediate effects of medication on their OCD symptoms. This is not realistic and a treatment trial for OCD should be around three months. It can be important to discuss the fact the SSRI may bring additional secondary benefits, such as improved mood and generalised anxiety, which are otherwise very common comorbidities. This can improve engagement and help longer terms commitment to the OCD treatment. These gains for the young person’s mental state are also individually important.
Ideally measuring response to treatment with a standardised measure can be helpful to track change. If there is little shift in the core OCD symptoms after three months at high dosage of an SSRI. At this point cross titrating to a second SSRI is recommended. A full three-month trial, again at high dosing is important. It would be after a second high dose trial that one would consider a trial of clomipramine, or more commonly to consider augmentation with low dose antipsychotic medication.

***20. What is the approach to the use of atypical anti-psychotics in OCD?***

Patients who fail to show a good treatment response to SSRI medication may respond to the addition of a low dose antipsychotic medication to the SSRI therapy (Kayser, 2020). It is important to note that the evidence for this intervention is purely as an augmenting agent and that OCD will not respond to treatment with atypical anti-psychotics alone. The research supporting this emanates from studies in adult age patients and of the obsessive-compulsive disorders, it is only OCD and not BDD that have been investigated.
In considering this intervention in children and young people, it is important that all the typical provisions and considerations be in place for prescribing and monitoring antipsychotics. It is also important to have a shared understanding with the young person and their family about the prospects for improvement. The data supports the use of low dose antipsychotic augmentation of an SSRI only. Approximately one third of treatment resistant cases of OCD will show an additional response to adding low dose anti-psychotics to the SSRI (Bloch et al., 2006). It is important when starting this intervention to adopt and open and transparent approach. Two thirds of patients will not show an improvement. It is therefore important to set a time limit for this intervention of around 2-3 month and then discontinue the intervention if there is no response. It is ideal that the intervention is monitored with an appropriate OCD measure, such as the Children’s Obsessive Compulsive Inventory (Shafran et al., 2003) or the Children’s Yale-Brown Obsessive Compulsive Scale (Scahill et al., 1997). Often clinicians can feel tempted to increase the dose of atypical antipsychotic, rather than being clear that if the patient is going to be in the minority that see this effect, it is likely to be with low dose atypical antipsychotic augmentation of the SSRI. It is often important to be clear to declare the trial of treatment as ineffective and to discontinue.

When treatment for OCD have been suboptimal, children, young people and their parents often ask for additional switches of medication. This can be an important moment in clinical practice, to discuss efforts around psychological therapy. Where medications have not brought about the required improvements, young people and their families need to understand that multiple further switches of psychopharmacology are unlikely to be helpful. It can be in these moments that one can renegotiate to redouble efforts around Cognitive Behavioural Therapy for OCD.

**PERSONALITY DISORDERS**

***21. What drug treatment should I use if a patient has Emotionally unstable personality disorder (EUPD)?***

Personality disorders can and do occur in people under 18 and no diagnostic criteria say they cannot. Patients can find having an accurate diagnostic label helpful, the correct diagnosis helps clinicians to give appropriate treatments and the correct diagnosis leads to a more realistic prognosis being given (Kaess et al., 2014). Making such a diagnosis is not straightforward given the complexity of adolescence, and is often better done over multiple assessments; it is also easier to do if the adolescent is older. The majority of evidence on personality disorders is for emotionally unstable/borderline PD.

There is no evidence that any medication is effective for the core symptoms of EUPD in adults or adolescents. There is limited evidence that medication is effective for co-morbid mental illness in adults with EUPD, and no evidence for this in adolescents. Instead the mainstay of treatment of EUPD (in all age groups) is complex and integrated psychological therapy programmes. In particular dialectical behaviour therapy and mentalization-based treatment have been found to be effective in adolescents with EUPD, although studies were limited by including mainly girls and only including the subset of patients with EUPD who were happy to be in a treatment trial (Rossouw and Fonagy, 2012; Wilkinson, 2018). It is also essential to address social factors (eg current abuse, educational issues, stability of placement) in helping these patients.

**PSYCHOTIC SPECTRUM DISORDERS**

***22. Can I diagnose and treat schizophrenia in adolescents who are consuming illicit drugs?***

Schizophrenia has a rise in prevalence during adolescence, which is also the time when drug consumption raises. Cannabis, particularly high-potency cannabis, is a common precipitant or contributor to psychosis in young people (Di Forti et al., 2019). Youth experiencing psychosis also frequently misuse substances, which makes the differential diagnosis between substance-induced psychosis and primary psychotic disorders challenging.

NICE guidelines advise to inquiry about the use of alcohol and illicit drugs when assessing a young person with psychosis and, if present, about particular substances and patterns of use (NICE 2011). Performing a drug urine test may be also useful in acute psychosis. In drug-induced psychosis, psychotic symptoms present in the context of acute intoxication or withdrawal from substances, with a gradual recovery and remission within one month of sustained abstinence (American Psychiatric Association, 2013), which may not always be possible to achieve. Regarding differential clinical features with primary psychotic disorders, later age of onset, fewer negative symptoms, greater insight, and less frequent family history of psychosis have been reported more frequently in drug-induced psychosis than in primary psychosis (Beckmann et al., 2020), although differential diagnoses with primary psychotic disorders cannot be made based solely on them.

If diagnostic criteria for schizophrenia are met in an adolescent with a substance use disorder, both diagnoses should be made. Integrated care, in which treatment for both disorders is provided simultaneously by the same clinician in community based mental health teams, should be provided (NICE 2011).  There is no evidence-based guidance on choice of antipsychotic on adolescents with schizophrenia and a co-occurring substance-use disorder. However, this comorbidity complicates management and prognosis, increasing relapse rates and worsening medication adherence (Beckmann et al., 2020). Long-acting injectable antipsychotics have shown some efficacy in adults with these conditions and may be an option in older adolescents (Coles et al., 2021). Antipsychotic treatment may also be considered if symptoms of psychosis persist in adolescents who are not able to maintain abstinence (Beckmann et al., 2020).

***23. How do I treat an adolescent with treatment-resistant schizophrenia?***

Treatment-resistant schizophrenia is defined by persistence of significant symptoms, despite adequate treatment in at least two (different) antipsychotic treatment trials lasting 6 weeks each, and during which there was no appreciable symptomatic or functional improvement, as measured by validated rating instruments (Howes et al., 2017). It can be present from the beginning of therapy or develop over time, often after relapses.

Before considering that a patient has a treatment resistant schizophrenia, we need to investigate possible causes of inefficiency of prescribed treatments (Abidi et al., 2017) (NICE 2013). After reviewing diagnosis, we should document adequate treatment adherence and make sure that optimal medication dosages have been used. In children and adolescents, antipsychotics should not be dosed according to weight, but rather using a “start slow, go slow” approach, raising the dose until reaching recommended maximum doses or until adverse events appear. If a trial cannot be completed at the adequate dose, then another treatment should be tried until two adequate trials of different antipsychotics are completed. Adequate treatment of medical and psychiatric comorbidities should also be implemented (medication or psychosocial interventions as needed), paying attention to potential drug interactions that may increase adverse effects or diminish efficacy of antipsychotic medication.

According to NICE guidelines, clozapine should be offered to children and young people with treatment- resistant schizophrenia (NICE 2013). This recommendation is based on evidence of clozapine being significantly more effective than other antipsychotics in children and adolescents (Krause et al., 2018). Clozapine monitoring trough plasma levels may help to guide dosing. Greatest efficacy is seen at levels ≥350 µg/L, although this level is not universal, and factors such as gender, inflammation or tobacco or caffeine consumption may alter clozapine plasma levels (Correll and Howes, 2021).

Initiation of clozapine requires a careful balance of the risk/benefit ratio and commitment to the increased monitoring requirements by patient, family and psychiatrist. Psychiatrists should adopt a proactive approach on assessment, intervention and reassurance for patients and families, as most side effects will appear during the first weeks of treatment and could be managed without discontinuation (Correll and Howes, 2021).

***24. How do I manage weight increase related to the use of antipsychotic medications in children and adolescents?***

Antipsychotics are associated with weight gain and adverse metabolic effects, particularly in children and adolescents, although mechanisms driving these effects are still largely unknown (Libowitz and Nurmi, 2021). However, not all antipsychotics carry the same risk. In randomized clinical trials clozapine, olanzapine and quetiapine showed the highest weight gain, while molindone, lurasidone and ziprasidone (which was not more efficacious than placebo) induced less wight gain (Krause et al., 2018). In observational studies, olanzapine and clozapine displayed the highest risk of weight gain, followed by risperidone, quetiapine and  aripiprazole, and  ziprasidone was associated with no weight gain (Pozzi et al., 2022). Longer time in treatment and being drug-naïve patients also increased risk, with a ceiling effect determined by higher baseline BMI values (Pozzi et al., 2022). Therefore, as there are not differences in efficacy (except for clozapine and ziprasidone), choosing an antipsychotic with less potential for weight increase, particularly if this is the first antipsychotic trial, together with education about strategies to enhance nutrition and physical activity, and regular weight monitoring (Barlow, 2007) may help diminish weight gain.

In case weight gain is established, treatment options could include switching to a less orexigenic/metabolically adverse antipsychotic, adjunctive behavioural treatments, and adjunctive pharmacologic interventions. The IMPACT trial (Correll et al., 2020), enrolled obese / overweight youth 8-19 years with psychotic disorders and with weight gain after treatment with antipsychotics, and randomized them to adjunctive metformin, antipsychotic switch or control intervention, with all arms receiving healthy lifestyle education. Both active interventions were significantly different compared to the control condition, with no differences between them, but with more gastrointestinal problems in the metformin group. However, weight reduction with aripiprazole and metformin was modest, highlighting the importance of considering potential risks and benefits prior to antipsychotic initiation. Switching strategy to newly FDA approved antipsychotics with better weight and metabolic profile such as lurasidone or brexpiprazole could be an option, although data supporting this option are still not available.

**TICS/TOURETTE’S SYNDROME**

***25. Is it best to replace methylphenidate with guanfacine or use it as adjunct when ADHD is present but tics require treatment as well?***

As both methylphenidate and guanfacine are licensed for the treatment of ADHD, both can be very helpful and effective treatments for this condition; however, the co-occurrence of tics is unlikely to be treated adequately using methylphenidate. Whilst treating ADHD with methylphenidate can have beneficial effects on associated symptoms that increase tics (frustration, impulsivity, emotional dysregulation etc), there does not appear to be a direct effect on tics.

The clinical decision whether to switch to guanfacine, or to argument methylphenidate with guanfacine is based on; i) the relative severity of ADHD and tic symptoms, ii) whether methylphenidate is effectively managing the ADHD symptoms, and iii) whether methylphenidate appears to be worsening tics. If methylphenidate is already effective in treating ADHD symptoms, but tics worsen and/or require treatment, guanfacine may be added. In cases of mild to moderate ADHD symptoms with co-existing tics, and/or if methylphenidate is only partially effective or poorly tolerated, discontinuation of methylphenidate and switching to guanfacine may be considered. If tics improve with guanfacine alone but ADHD worsens, then methylphenidate may be restarted. In the cases of mild to moderate ADHD with co-existing tics (where both require treatment) there is an argument to suggest that guanfacine monotherapy should be considered as the first line medication choice rather than methylphenidate. However, there remains clinical uncertainty about the best treatment choice in these circumstances, and in the UK the current HTA SATURN trial is examining this question in a head-to-head comparison of guanfacine versus methylphenidate for ADHD with co-existing tics.

In cases of moderate to severe ADHD with tics, ADHD symptoms are likely to require treatment with psychostimulants which are the first line treatment choice ADHD. Therefore, in cases such as this where tics are also present, augmenting methylphenidate with guanfacine to cover both the symptoms of both conditions seems preferable. Using guanfacine in this respect also may benefit ADHD symptoms as shown by McCracken et al (McCracken et al., 2016). Adverse events were generally mild to moderate, and combined treatment showed no differences in safety or tolerability.

Whilst appreciating that when prescribing for children and young people it is best for children to receive as few medications as possible at the lowest dose to achieve the desired clinical goals, when there is clear impairment from both disorders, it may be beneficial to combine treatment. Therefore, especially when ADHD symptoms are more severe and impairing, a combination of methylphenidate and guanfacine is worth considering.

The addition of guanfacine can also potentially benefit sleep difficulties and night-time settling and decrease the need for alternatives such as melatonin which may be beneficial to consider.

***26. When would I consider antipsychotics more appropriate than clonidine / guanfacine when treating tics in children and young people?***

In a recent prescribing survey among fifty-nine European expert clinicians who were members of the European Society for the Study of Tourette Syndrome (ESSTS) (Roessner et al. 2022) ~~(Hollis et al., 2016)~~ the most commonly used medications for tics in children and adolescents in descending order were aripiprazole, clonidine, tiapride (not available in the UK) and guanfacine. Newer (so called) antipsychotics (e.g., risperidone and aripiprazole) and noradrenergic agents (e.g., clonidine and guanfacine) have increasingly been favoured over the older antipsychotic drugs (e.g., pimozide, sulpiride and haloperidol). Although a recent systematic review and meta-analysis shows that the efficacy for tic treatment appears similar between noradrenergic and antipsychotic medications (Hollis et al. 2016, Whittington et al. 2016, the Maudsley prescribing guidelines (Taylor et al, 2021) state that because of the more serious adverse effects of antipsychotics, it is recommended that noradrenergic drugs (i.e. clonidine and guanfacine) are used first-line. The Maudsley guidelines go on to however recognise that the antipsychotic medications may be more beneficial in some individuals, although there is not clear guidance as to which group of children this might pertain to.

One possible advantage for using antipsychotic medications over other options is that medication such as risperidone or aripiprazole could have a more favourable effect on some of the behavioural symptoms associated with tic disorders and on the common comorbidities such as ASD and OCD. Risperidone particularly has proven to be useful in ameliorating aggressive behaviour (Sandor and Stephens, 2000) and therefore in the case of challenging behaviour either linked to autism spectrum disorder or ADHD, risperidone and aripiprazole are likely to have more significant effects on aggression than noradrenergic counterparts. It is worth noting though that noradrenergic options such as clonidine or guanfacine are likely to have much more of an effect on ADHD core symptoms, and noradrenergic drugs are recommended as the first-line option for tic disorders with co-morbid ADHD in the recent European Guidelines (Roessner et al. 2022).

Risperidone also has a greater affinity for 5HT receptors and is more likely to augment serotonergic agents in the treatment of obsessive-compulsive symptoms (OCS). Therefore, when a combined Tic and OCS presentation is present and obsessive and / or compulsive symptoms are equally problematic, antipsychotics have often been used alongside SSRI’s. This effect has also been shown to be present with aripiprazole and the partial agonist profile of this medication may point to it being more effective on mood and OCS difficulties. One of the potential side effects of noradrenergic agents is depression (Committee, 2022).

Typically, antipsychotic medications are also more sedating than noradrenergic alternatives. This might for example be beneficial to consider in young people who already using sedating medications such as promethazine.

Of note, noradrenergic agents are contraindicated in individuals who experience severe bradyarrhythmia secondary to second- or third-degree AV block or sick sinus syndrome. Antipsychotic medications are not contraindicated in this type of patients, although cardiology opinion would be essential to gain before prescribing antipsychotic medication in this client group. Aripiprazole has the least cardiac side effect profile of the antipsychotic medications especially related to QT prolongation.

***27. When clonidine is being used in higher doses is it best to go beyond treatment window or consider a switch to guanfacine? If switching, is it best to reduce and withdraw Clonidine before initiating Guanfacine or can you cross taper****.*

Recommended clonidine therapeutic doses are in the order of 3 to 5 mcg / kg /day. However, it is uncommon to use doses beyond 300mcg daily, due to the sedating and hypotensive effects of clonidine. However, some young people may be able to tolerate the cardiac effects of clonidine well and find that the sedation has additional benefits to sleep and comorbidities. Therefore, in these children, higher doses may be beneficial with regular monitoring of blood pressure and pulse. As clonidine can also be divided into two or three doses, quite often children who are sensitive to guanfacine side effects find that a BD or TDS regime of clonidine suits them more preferably than the once daily dosing of guanfacine.

Clonidine is 10 times more potent then guanfacine at alpha2 presynaptic receptors, whereas guanfacine appears to be more potent at post synaptic receptors, which translates into increased prefrontal activity and impulse control regulation and improvement in behaviour regulation (Cinnamon Bidwell et al., 2010). Therefore, in the case of comorbidities where behavioural modification is desired, guanfacine seems to have a better effect.

Guanfacine weight dosing guidelines indicate 0.05-0.08mg/kg/day suggesting that a rough equivalency is: Guanfacine 1mg = Clonidine 100mcg.

If it is clinically acceptable from a tic perspective to reduce and withdrawal clonidine first, before initiating guanfacine, this is likely to be best practise, as the side effects will be additive. Reducing Clonidine by 25 micrograms every three to five days is thought to be appropriate to facilitate this reduction.

However it may not be beneficial from a tic/ sleep/ behaviour perspective to reduce and withdraw clonidine completely before starting guanfacine. In these circumstances, cross-tapering is recommended (Elbe, 2020) by reducing clonidine to 100mcg daily before initiating Guanfacine at 1mg daily. Following on from this, all remaining clonidine doses are reduced and withdrawn at 25mcg every 3 days before guanfacine is increased as necessary.

**CONCLUSIONS**

We hope that this paper will be helpful for prescribers in their daily clinical practice. We also hope that in the near future, additional high quality evidence, applicable at the individual patient, rather than group, level, will inform the answers to these and other important questions, within a precision psychiatry approach (Cortese, 2021).

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**REFERENCES**

Abidi S, Mian I, Garcia-Ortega I, et al. (2017) Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth. *Can J Psychiatry* 62(9): 635-647.

Agras WS, Lock J, Brandt H, et al. (2014) Comparison of 2 family therapies for adolescent anorexia nervosa: a randomized parallel trial. *JAMA Psychiatry* 71(11): 1279-1286.

Alper K, Schwartz KA, Kolts RL, et al. (2007) Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. *Biological Psychiatry* 62(4): 345-354.

Arnold LE (2000) Methylphenidate vs. amphetamine: comparative review. *Journal of Attention Disorders* 3: 200-211.

Arzimanoglou A, Brandl U, Cross JH, et al. (2020) Epilepsy and cannabidiol: a guide to treatment. *Epileptic Disorders* 22(1): 1-14.

Association AP (2013) *Diagnostic and statistical manual of mental disorders (5th ed.).* Arlington, VA.

Barlow SE (2007) Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 120 Suppl 4: S164-192.

Beckmann D, Lowman KL, Nargiso J, et al. (2020) Substance-induced Psychosis in Youth. *Child Adolesc Psychiatr Clin N Am* 29(1): 131-143.

Besag F, Gobbi G, Aldenkamp A, et al. (2016) Psychiatric and Behavioural Disorders in Children with Epilepsy (ILAE Task Force Report): Subtle behavioural and cognitive manifestations of epilepsy in children. *Epileptic Disorders*. DOI: 10.1684/epd.2016.0816.

Bloch MH, Landeros-Weisenberger A, Kelmendi B, et al. (2006) A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry* 11(7): 622-632.

Bloch MH, McGuire J, Landeros-Weisenberger A, et al. (2010) Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Mol Psychiatry* 15(8): 850-855.

Bridge JA, Iyengar S, Salary CB, et al. (2007) Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *Jama* 297(15): 1683-1696.

Carrasco M, Volkmar FR and Bloch MH (2012) Pharmacologic treatment of repetitive behaviors in autism spectrum disorders: evidence of publication bias. *Pediatrics* 129(5): e1301-1310.

Chugani DC, Chugani HT, Wiznitzer M, et al. (2016a) Efficacy of Low-Dose Buspirone for Restricted and Repetitive Behavior in Young Children with Autism Spectrum Disorder: A Randomized Trial. *J Pediatr* 170: 45-53.e41-44.

Chugani DC, Chugani HT, Wiznitzer M, et al. (2016b) Efficacy of Low-Dose Buspirone for Restricted and Repetitive Behavior in Young Children with Autism Spectrum Disorder: A Randomized Trial. *J Pediatr* 170: 45-53 e41-44.

Cinnamon Bidwell L, Dew RE and Kollins SH (2010) Alpha-2 adrenergic receptors and attention-deficit/hyperactivity disorder. *Curr Psychiatry Rep* 12(5): 366-373.

Coles AS, Knezevic D, George TP, et al. (2021) Long-Acting Injectable Antipsychotic Treatment in Schizophrenia and Co-occurring Substance Use Disorders: A Systematic Review. *Front Psychiatry* 12: 808002.

Committee JF (2022) British national formulary 83. London: BMJ Publishing and the Royal Pharmaceutical SocietBritish national formulary 83. London: BMJ Publishing and the Royal Pharmaceutical Society.

Correll CU and Howes OD (2021) Treatment-Resistant Schizophrenia: Definition, Predictors, and Therapy Options. *J Clin Psychiatry* 82(5).

Correll CU, Sikich L, Reeves G, et al. (2020) Metformin add-on vs. antipsychotic switch vs. continued antipsychotic treatment plus healthy lifestyle education in overweight or obese youth with severe mental illness: results from the IMPACT trial. *World Psychiatry* 19(1): 69-80.

Cortese S (2020) Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder. *N Engl J Med* 383(11): 1050-1056.

Cortese S (2021) Setting the Foundations of Developmental Precision Psychiatry for ADHD. *Am J Psychiatry* 178(8): 677-679.

Cortese S, Newcorn JH and Coghill D (2021) A Practical, Evidence-informed Approach to Managing Stimulant-Refractory Attention Deficit Hyperactivity Disorder (ADHD). *CNS Drugs* 35(10): 1035-1051.

D'Alò GL, De Crescenzo F, Amato L, et al. (2021) Impact of antipsychotics in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Health Qual Life Outcomes* 19(1): 33.

D'Alo GL, De Crescenzo F, Amato L, et al. (2021) Impact of antipsychotics in children and adolescents with autism spectrum disorder: a systematic review and meta-analysis. *Health Qual Life Outcomes* 19(1): 33.

Devinsky O, Marsh E, Friedman D, et al. (2016) Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *The Lancet Neurology* 15(3): 270-278.

Di Forti M, Quattrone D, Freeman TP, et al. (2019) The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *Lancet Psychiatry* 6(5): 427-436.

Elbe D (2020) Switching from Clonidine Immediate-Release to Guanfacine Extended-Release. *J Can Acad Child Adolesc Psychiatry* 29(2): 121-123.

Farhat LC, Flores JM, Behling E, et al. (2022) The effects of stimulant dose and dosing strategy on treatment outcomes in attention-deficit/hyperactivity disorder in children and adolescents: a meta-analysis. *Mol Psychiatry* 27(3): 1562-1572.

Giovinazzo S, Sukkar SG, Rosa GM, et al. (2019) Anorexia nervosa and heart disease: a systematic review. *Eat Weight Disord* 24(2): 199-207.

Hirsch LE and Pringsheim T (2016a) Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev* 2016(6): Cd009043.

Hirsch LE and Pringsheim T (2016b) Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. Epub ahead of print 2016/06/28. DOI: 10.1002/14651858.CD009043.pub3.(6): CD009043.

Hodgkins P, Shaw M, Coghill D, et al. (2012) Amfetamine and methylphenidate medications for attention-deficit/hyperactivity disorder: complementary treatment options. *Eur Child Adolesc Psychiatry* 21(9): 477-492.

Hollis C, Pennant M, Cuenca J, et al. (2016) Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. *Health Technol Assess* 20(4): 1-450, vii-viii.

Howes OD, McCutcheon R, Agid O, et al. (2017) Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry* 174(3): 216-229.

Howes OD, Rogdaki M, Findon JL, et al. (2018) Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J Psychopharmacol* 32(1): 3-29.

Ipser JC, Stein DJ, Hawkridge S, et al. (2009) Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev*. Epub ahead of print 2009/07/10. DOI: 10.1002/14651858.CD005170.pub2.(3): Cd005170.

Jensen KG, Juul K, Fink-Jensen A, et al. (2015) Corrected QT changes during antipsychotic treatment of children and adolescents: a systematic review and meta-analysis of clinical trials. *J Am Acad Child Adolesc Psychiatry* 54(1): 25-36.

Kaess M, Brunner R and Chanen A (2014) Borderline personality disorder in adolescence. *Pediatrics* 134(4): 782-793.

Kayser RR (2020) Pharmacotherapy for Treatment-Resistant Obsessive-Compulsive Disorder. *J Clin Psychiatry* 81(5).

Kollins SH, Schoenfelder EN, English JS, et al. (2015) An exploratory study of the combined effects of orally administered methylphenidate and delta-9-tetrahydrocannabinol (THC) on cardiovascular function, subjective effects, and performance in healthy adults. *J Subst Abuse Treat* 48(1): 96-103.

Krause M, Zhu Y, Huhn M, et al. (2018) Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. *Eur Neuropsychopharmacol* 28(6): 659-674.

Lake MB, Birmaher B, Wassick S, et al. (2000) Bleeding and selective serotonin reuptake inhibitors in childhood and adolescence. *J Child Adolesc Psychopharmacol* 10(1): 35-38.

Landau WM and Kleffner FR (1957) Syndrome of acquired aphasia with convulsive disorder in children. *Neurology* 7: 523-530.

Lattanzi S, Brigo F, Trinka E, et al. (2018) Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. *Drugs* 78(17): 1791-1804.

Libowitz MR and Nurmi EL (2021) The Burden of Antipsychotic-Induced Weight Gain and Metabolic Syndrome in Children. *Front Psychiatry* 12: 623681.

Marvanova M and Gramith K (2018) Role of antidepressants in the treatment of adults with anorexia nervosa. *Ment Health Clin* 8(3): 127-137.

McCracken JT, McGough J, Shah B, et al. (2002a) Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347(5): 314-321.

McCracken JT, McGough J, Shah B, et al. (2002b) Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347(5): 314-321.

McCracken JT, McGough JJ, Loo SK, et al. (2016) Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study. *J Am Acad Child Adolesc Psychiatry* 55(8): 657-666.e651.

McDougle CJ, Scahill L, Aman MG, et al. (2005) Risperidone for the core symptom domains of autism: results from the study by the autism network of the research units on pediatric psychopharmacology. *Am J Psychiatry* 162(6): 1142-1148.

McQuire C, Hassiotis A, Harrison B, et al. (2015) Pharmacological interventions for challenging behaviour in children with intellectual disabilities: a systematic review and meta-analysis. *BMC Psychiatry* 15: 303.

Mikati MA and Shamseddine AN (2005) Management of Landau-Kleffner Syndrome. *Pediatric Drugs* 7(6): 377-389.

Morrell F, Whisler WW, Smith MC, et al. (1995) Landau-Kleffner syndrome. Treatment with subpial intracortical transection. *Brain* 118(Pt 6): 1529-1546.

Nazar BP, Bernardes C, Peachey G, et al. (2016) The risk of eating disorders comorbid with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *Int J Eat Disord* 49(12): 1045-1057.

National Institute for health and care Excellence (NICE) (2019). Depression in children and young people: identification and management. NG134. https://www.nice.org.uk/guidance/ng134

National Institute for health and care Excellence (NICE) (2017) Eating Disorders: Recognition and Treatment NG69. https://www.nice.org.uk/guidance/ng69

National Institute for health and care Excellence (NICE) (2014) Bipolar Disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. https://www.nice.org.uk/guidance/cg185

National Institute for health and care Excellence (NICE) (2013). Psychosis and schizophrenia in children and young people: recognition and management. Clinical guideline www.nice.org.uk/guidance/cg155.

National Institute for health and care Excellence (NICE) (2011) oexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings Clinical guideline Published: www.nice.org.uk/guidance/cg120.

National Institute for health and care Excellence (NICE) (2005) Obsessive-compulsive disorder and body dysmorphic disorder: treatment. https://www.nice.org.uk/guidance/cg31

Nobili L, Proserpio P, Combi R, et al. (2014) Nocturnal Frontal Lobe Epilepsy. *Current Neurology and Neuroscience Reports* 14(2): 424.

Pender S, Gilbert SJ and Serpell L (2014) The neuropsychology of starvation: set-shifting and central coherence in a fasted nonclinical sample. *PLoS One* 9(10): e110743.

Persico AM, Ricciardello A, Lamberti M, et al. (2021) The pediatric psychopharmacology of autism spectrum disorder: A systematic review - Part I: The past and the present. *Prog Neuropsychopharmacol Biol Psychiatry* 110: 110326.

Politte LC, Scahill L, Figueroa J, et al. (2018) A randomized, placebo-controlled trial of extended-release guanfacine in children with autism spectrum disorder and ADHD symptoms: an analysis of secondary outcome measures. *Neuropsychopharmacology* 43(8): 1772-1778.

Pozzi M, Ferrentino RI, Scrinzi G, et al. (2022) Weight and body mass index increase in children and adolescents exposed to antipsychotic drugs in non-interventional settings: a meta-analysis and meta-regression. *Eur Child Adolesc Psychiatry* 31(1): 21-37.

Riggs PD, Winhusen T, Davies RD, et al. (2011) Randomized controlled trial of osmotic-release methylphenidate with cognitive-behavioral therapy in adolescents with attention-deficit/hyperactivity disorder and substance use disorders. *J Am Acad Child Adolesc Psychiatry* 50(9): 903-914.

Rossouw TI and Fonagy P (2012) Mentalization-based treatment for self-harm in adolescents: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry* 51(12): 1304-1313.e1303.

Sandor P and Stephens RJ (2000) Risperidone treatment of aggressive behavior in children with Tourette syndrome. *J Clin Psychopharmacol* 20(6): 710-712.

Scahill L, Riddle MA, McSwiggin-Hardin M, et al. (1997) Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. *J Am Acad Child Adolesc Psychiatry* 36(6): 844-852.

Scheffer IE, Bhatia KP, Lopes-Cendes I, et al. (1995) Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. *Brain* 118 ( Pt 1): 61-73.

Shafran R, Frampton I, Heyman I, et al. (2003) The preliminary development of a new self-report measure for OCD in young people. *J Adolesc* 26(1): 137-142.

Simic M, Stewart CS, Konstantellou A, et al. (2022) From efficacy to effectiveness: child and adolescent eating disorder treatments in the real world (part 1)-treatment course and outcomes. *J Eat Disord* 10(1): 27.

Steenen SA, van Wijk AJ, van der Heijden GJ, et al. (2016) Propranolol for the treatment of anxiety disorders: Systematic review and meta-analysis. *J Psychopharmacol* 30(2): 128-139.

Swanson SA, Crow SJ, Le Grange D, et al. (2011) Prevalence and correlates of eating disorders in adolescents. Results from the national comorbidity survey replication adolescent supplement. *Arch Gen Psychiatry* 68(7): 714-723.

Szaflarski JP, Bebin EM, Comi AM, et al. (2018) Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsia* 59(8): 1540-1548.

Tassinari CA, Rubboli G, Volpi L, et al. (2000) Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. *Clinical Neurophysiology* 111 Suppl 2: S94-S102.

Taylor D; Barnes TRE YA (2021) The Maudsley Prescribing Guidelines in Psychiatry, 14th Edition.

Tchanturia K, Smith K, Glennon D, et al. (2020) Towards an Improved Understanding of the Anorexia Nervosa and Autism Spectrum Comorbidity: PEACE Pathway Implementation. *Front Psychiatry* 11: 640.

Volkmar F, Siegel M, Woodbury-Smith M, et al. (2014a) Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 53(2): 237-257.

Volkmar F, Siegel M, Woodbury-Smith M, et al. (2014b) Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 53(2): 237-257.

Westwood H and Tchanturia K (2017) Autism Spectrum Disorder in Anorexia Nervosa: An Updated Literature Review. *Curr Psychiatry Rep* 19(7): 41.

Wilkinson PO (2018) Dialectical Behavior Therapy-A Highly Effective Treatment for Some Adolescents Who Self-harm. *JAMA Psychiatry* 75(8): 786-787.

Williams K, Brignell A, Randall M, et al. (2013) Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. Epub ahead of print 2013/08/21. DOI: 10.1002/14651858.CD004677.pub3.(8): Cd004677.

Yu Y, Chaulagain A, Pedersen SA, et al. (2020) Pharmacotherapy of restricted/repetitive behavior in autism spectrum disorder:a systematic review and meta-analysis. *BMC Psychiatry* 20(1): 121.

Zhou X, Hetrick SE, Cuijpers P, et al. (2015) Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: A systematic review and network meta-analysis. *World Psychiatry* 14(2): 207-222.