Current issues in child and adolescent psychopharmacology. Part 2: Anxiety and obsessive–compulsive disorders, autism, Tourette's and schizophrenia

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Abstract This paper reviews the evidence base supporting the use of pharmacological treatments for child and adolescent psychiatric disorders. Recent advances in knowledge are highlighted, with some of the controversies. New evidence supports a role for selective serotonin reuptake inhibitors in the treatment of anxiety disorders and obsessive–compulsive disorder. Educational and behavioural approaches remain the mainstay of treatment for children and adolescents with autism, but there is evidence that adjunctive medication may be effective. Atypical antipsychotics have been investigated in the treatment of Tourette syndrome and early-onset schizophrenia. Many questions remain unanswered and further research is needed in all areas of paediatric psychopharmacology.

Part 1 of this two-part consideration of child and adolescent psychopharmacology focused on attention–deficit hyperactivity disorder (ADHD), depression and bipolar disorder (Coghill, 2003). This second paper concentrates on current pharmacological approaches to the treatment of anxiety disorders, obsessive–compulsive disorders, autism, Tourette syndrome and schizophrenia. The aim is to describe some recent advances in child and adolescent psychopharmacology in a format that will be of practical benefit to child and adolescent psychiatrists and will also highlight gaps in knowledge.

Anxiety disorders

Despite being the most common psychiatric illness in childhood, affecting between 5% and 18% of children, anxiety disorders remain poorly understood. They can cause serious disruption to children's lives and are often persistent over time, leading to increased risks of anxiety disorders, major depression, substance misuse and educational underachievement in later life (Pine *et al*, 1998). The use of drug treatments in the management of child and adolescent anxiety disorders remains contentious, with many clinicians arguing that these disorders are most appropriately treated with psychosocial interventions. However, as success rates for cognitive–behavioural psychotherapy fall in the range of 70–80%, significant numbers of children require further intervention.

The first drugs to be studied in the treatment of childhood anxiety were benzodiazepines and tricyclic antidepressants. Although the results of studies using a range of benzodiazepines were generally positive with respect to efficacy, they revealed a wide range of adverse events. These side-effects, together with the theoretical risk of tolerance, dependence and withdrawal symptoms, mean that benzodiazepines should be considered only when other pharmacological approaches have failed, and they should be prescribed for weeks rather than months, with dose adjustments being made gradually, both when starting and when tapering off treatment (Velosa & Riddle, 2000).

There have been several randomised controlled trials (RCTs) of tricyclic antidepressants in the treatment of paediatric anxiety. Unfortunately, the

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positive results from initial studies have not been sustained (Velosa & Riddle, 2000). This, allied to the relatively high rates of adverse events, the need to monitor electrocardiograms (ECGs) and blood levels and reports of sudden deaths, especially with desipramine, means that the tricyclics should not be considered as first-line treatments for these disorders (Bhangoo & Riddle, 1999).

Several open-label studies have shown buspirone, a non-benzodiazepine anxiolytic reported in adults to be comparable in efficacy to the benzodiazepines with fewer adverse events, in childhood anxiety disorders. No controlled data are available for either safety or efficacy, but side-effects are usually mild, with nausea, dizziness, headache and insomnia being the most common. Buspirone may lead to increased aggression and, in some cases, the development of manic symptoms. It is therefore important to enquire about a past or family history of bipolar disorder (Pfeffer *et al*, 1997). Suggested doses are given in Box 1.

The selective serotonin reuptake inhibitors (SSRIs) seem likely to become the first-choice pharmacological treatment for child and adolescent anxiety disorders. As in depression, their use increased before firm data on their efficacy were available. Although open trials with positive results were reported several years ago, it was not until 2001 that data from an RCT were published. The Research Unit on Pediatric Psychopharmacology Anxiety Study Group conducted a well-designed, large-scale RCT that compared fluvoxamine (up to a maximum dose of 300 mg/day) with placebo in 128 children and adolescents with social phobia, separation anxiety disorder or generalised anxiety disorder, all of whom had failed to respond to 3 weeks of psychological therapy (Research Unit on Pediatric Psychopharmacology Anxiety Study Group, 2001). Children in the fluvoxamine group

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Box 1 Buspirone dosage schedule (Coffey, 1990)

Children
Initial total daily dose of 2.5–5 mg, with increases of 2.5 mg every 3 to 4 days to a maximum of 20 mg/day

Adolescents
Initial total daily dose of 5–10 mg, with increases of 5–10 mg every 3 to 4 days up to a maximum of 60 mg/day

NB   Buspirone is not licensed for use in children. In the UK, the maximum adult dose is 45 mg/day.

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showed greater reductions on both the Pediatric Anxiety Rating Scale and the Clinical Global Impression of Improvement Scale than those receiving placebo. Few dropped out from either group as a result of adverse events, suggesting that fluvoxamine is an efficacious and safe treatment for anxiety in this population. A subsequent small RCT comparing sertraline at a dose of up to 50 mg/day and placebo in 22 children and adolescents with generalised anxiety disorder, also reported significant global improvements and a decrease in anxiety symptoms beginning after 4 weeks of treatment (Rynn *et al*, 2001).

Both studies were short-term trials, lasting 8 and 9 weeks, respectively, and concerns have been expressed that long-term prescribing of SSRIs for childhood anxiety should not be sanctioned until there is clear evidence to support it. The basis of these concerns arises from animal studies which have demonstrated that the administration of SSRIs to juvenile rodents may induce long-term changes in serotonergic transmission in the cortex and hippocampus. However, these concerns must be balanced against the finding that stress also causes long-term unwanted changes to neurochemistry and neuronal development. Future studies are required, investigating the long-term safety and effectiveness of SSRIs in childhood anxiety disorders and more research is needed to clarify the effects of both stress and SSRIs on human brain development.

Treating attention-deficit hyperactivity disorder with comorbid anxiety disorder

Many children with attention-deficit hyperactivity disorder (ADHD) present with comorbid anxiety disorders. There has been uncertainty as to whether these children respond as well to methylphenidate as children with ADHD alone. Initial studies suggested that anxiety may blunt the response to methylphenidate but several studies undertaken more recently question these findings. The initial analysis of the Multimodal Treatment Study of Children with ADHD (MTA Cooperative Group, 1999) reported that children with anxiety disorders showed enhanced responses to the behavioural intervention, both when given alone and when given in combination with medication. They did not, however, display a reduced response to medication when it was given alone. Secondary analyses of the data confirmed both the importance of psychosocial treatment for children with anxiety disorders and ADHD and that anxiety has no adverse effect on the response to stimulant medication (March *et al*, 2000). Children with combined ADHD, anxiety and either

oppositional–defiant disorder or conduct disorder seem to benefit particularly from combined psycho-social and medication treatment (Jensen *et al*, 2001).

Obsessive–compulsive disorder

There is a much stronger evidence base to support the use of drug treatments for early-onset obsessive–compulsive disorder (OCD). Current theories of OCD stress the role of dysregulation in central serotonin subsystems, with target areas of dysfunction including the basal ganglia and orbitofrontal cortex (Grados & Riddle, 2001). Recent work further proposes that a reversible, glutamatergically mediated, thalamo-cortical-striatal dysfunction is important in both the aetiology of paediatric OCD and response to treatment (Bolton *et al*, 2001; Rosenberg *et al*, 2001). It is therefore not surprising that serotonin-enhancing agents such as the SSRIs and clomipramine are efficacious treatments for this disorder. Clomipramine has been shown in several RCTs to be efficacious in treating child and adolescent OCD (Grados *et al*, 1999). This anti-obsessional effect is independent of antidepressant effect and is not seen with other tricyclic anti-depressants. As with other disorders, concern over the safety of the tricyclics has led recently to increased interest in the use of the SSRIs in early-onset OCD.

There are now six published RCTs comparing various SSRIs with placebo in early-onset OCD. These trials are of variable quality, but they include several large methodologically sound studies and it seems reasonable to conclude that the SSRIs are both safe and efficacious in the short-term treatment of paediatric OCD (March *et al*, 1998; Geller *et al*, 2001; Riddle *et al*, 2001). The time taken to respond to treatment varies between the studies and, even though Riddle *et al* reported significant responses after only 1 week of treatment, most authors suggest titration over 6 to 8 weeks to maximum doses in partial or non-responders.

Obsessive–compulsive disorder is recognised as a chronic condition that persists into early adult-hood in about 50% of early-onset cases. Several studies report that long-term treatment with SSRIs not only is well tolerated and effective at main-taining improvement but also results in continued improvement for up to 1 year (Cook *et al*, 2001; Thomsen *et al*, 2001). Treatment continued after this time appears to remain effective but does not result in further improvements. Obsessional symptoms may relapse on discontinuation of treatment but it is suggested that treatment should be withdrawn after 1–1.5 years but restarted if significant symp-toms reoccur. These results are encouraging, but it appears that, as a group, children and adolescents with OCD may not respond as well to some SSRIs as do adults. About 25% show no improvement after a trial of an SSRI; most cases report improvements in symptoms of between 20% and 50% and only 20–25% of those treated with medication alone are symptom-free at the end of a course of treatment (Thomsen, 2000). It has been suggested that early-onset OCD is a subtype of OCD that is more difficult to treat effectively (Thomsen & Leckman, 2000). It is therefore important that medication should not be regarded in isolation and should usually be given in combination with cognitive–behavioural therapy. Although there is not yet any strong empirical evidence to support this position, it is highly likely that such a combined approach would lead to a greater reduction in symptoms and might be associated with longer-term benefits.

In cases of non-response, it is important to assess compliance and to ensure that other factors, such as family discord, other psychosocial stressors and co-morbid disorders, have been adequately addressed. As individuals respond differently to particular SSRIs, it is recommended that a second SSRI should be introduced if there is no response to the initial one. In adults with OCD, augmentation strategies using antipsychotics have been demonstrated to be efficacious in cases of partial response. These strategies have not been studied in children and adolescents.

Autism

Although educational and behavioural treatments remain the mainstay of treatment for children and adolescents with autism, there has been much interest recently in the possible role of medication as an adjunctive therapy. This trend has been far more noticeable in the USA than in the UK. Although this might reflect differences in general attitudes towards the use of psychoactive medication in child psychiatric practice, it might also be related to differences in the provision and funding of psychiatric services.

The aim of drug treatments in autism is not to alleviate the core symptoms. Rather, it is to reduce specific troublesome behaviours such as hyper-activity, aggression, withdrawal and repetitive, ritualised, stereotyped or self-injurious behaviours that commonly, either alone or in combination, interfere with the child's ability to benefit from educational opportunities. It is therefore important that target behaviours are carefully selected and measured before treatment is started, so that response can be accurately monitored. If this is done, pharmacological treatments can, in some cases, add

considerably to a comprehensive and integrated treatment package.

Autism is a heterogeneous disorder and our understanding of its complex aetiology remains incomplete. There is, however, evidence to suggest that reduced serotonergic transmission and altered dopaminergic transmission are involved in its pathophysiology (Buitelaar & Willemsen-Swinkels, 2000; McDougle *et al*, 2000). Several drugs that act on these systems have been studied in children and adults with autism.

Drugs that primarily affect serotonergic neurotransmission

Fenfluramine was not found to be beneficial in double-blind trials, despite some promising open- and single-blind studies. It has also been shown to be potentially neurotoxic in animal models and should not be considered for clinical use.

Clomipramine has been shown to be superior to placebo and desipramine on ratings of autistic symptoms (including stereotypies), anger and compulsive, ritualised behaviours in children and adolescents with autism (Gordon *et al*, 1992, 1993). However, the adverse events associated with clomipramine in these studies, including prolongation of the corrected QT interval, tachycardia and *grand mal* seizure, mean that both drugs must be used with great care in this population.

There has been only one controlled trial of an SSRI in autism. McDougle *et al* (1996) reported positive results in a 12-week RCT comparing fluvoxamine and placebo in 30 adults with autism. Fluvoxamine was superior to placebo in reducing repetitive thoughts and behaviour, maladaptive behaviour and aggression. It also improved aspects of social relatedness, particularly language use. However, a similar but unpublished 1997 study by the same team (cited in McDougle *et al*, 2000) with children and adolescents found no significant differences between the treatment groups and reported high levels of adverse events in the fluvoxamine group, including significant behavioural activation. Since this study used doses of fluvoxamine similar to those in the OCD the trial by Riddle *et al* (2001) reported above, it suggests that the serotonergic system in children with autism may be more sensitive to the effects of the SSRIs. Thus, although the SSRIs show promise in adults with autism, they may be of less benefit in children and adolescents.

Drugs that affect the dopaminergic system

Haloperidol has been the most intensively studied of the dopaminergic drugs and it remains the most established psychopharmacological agent for children and adolescents with autism. Several controlled studies have demonstrated haloperidol to be efficacious in reducing a wide range of maladaptive behaviours in this group including hyperactivity, withdrawal, aggression and temper tantrums, stereotypies and mood lability. Increases in social relatedness and discriminant learning were also noted in several studies. In longer-term studies, these effects continued in 71.5% of children, with 20% remaining unchanged and 8.5% worsening. These positive effects need to be balanced against the frequent and disabling adverse reactions. Short-term adverse events, including excessive sedation, dystonic reactions, acute dyskinesia, parkinsonism and akathisia, are relatively common although much less frequent with low-to-moderate doses. About one-third of children show withdrawal dyskinesias and about 10% develop tardive dyskinesia (Campbell *et al*, 1997). Despite their proven effectiveness, many clinicians continue to remain wary about using haloperidol in autism.

Drugs that affect both serotonergic and dopaminergic neurotransmission

There has been much interest recently in the potential uses of the newer 'atypical' antipsychotics in autism. Published reports (some of which are mentioned below) now describe the use of clozapine, olanzapine, quetiapine and risperidone in the treatment of autism. There are several reasons for considering the use of atypicals in this area. They have a relatively high ratio of $5HT_{2A}$ to dopamine D_2 receptor antagonism and therefore affect both serotonergic and dopaminergic neurotransmission. They are sometimes effective in reducing both the positive and negative symptoms in schizophrenia and, in clinical and preclinical studies, they show positive effects on social interaction. As the social impairments seen in autism are similar to the negative symptoms of schizophrenia it is hoped that the atypicals may also enhance social interactions in autism. The atypicals, particularly risperidone, have been shown to reduce aggression in patients with dementia and schizophrenia and in children with learning disabilities and conduct disorder (e.g. Findling *et al*, 2000). As aggression is a common problem in autism, it is hoped that similar effects will be seen in this group of patients. Perhaps most importantly, the atypicals have a significantly better safety profile than the typical neuroleptics, with much lower rates of acute or long-term extra-pyramidal side-effects.

Case reports and open-label trials have been reported for clozapine, olanzapine and quetiapine

in the treatment of children and adolescents with autism. Clozapine is less attractive because of the risk of agranulocytosis and the need for regular blood tests (Zuddas *et al*, 1996). The reports of open-label quetiapine treatment have suggested that it is relatively ineffective and poorly tolerated (Martin *et al*, 1999). Using a 6-week open-label parallel-groups design Malone *et al* (2001) compared olanzapine and haloperidol in 12 children with autism. Both groups demonstrated reductions in symptoms, with five of the six patients receiving olanzapine and three of the six receiving haloperidol being rated as responders. Olanzapine was well tolerated, with weight gain being the main adverse effect. There is some suggestion from another open-label trial that olanzapine is more effective than risperidone in improving social withdrawal and relatedness (Potenza *et al*, 1999).

Risperidone has received the most attention. There are now four published open-label trials (Hardan *et al*, 1996; McDougle *et al*, 1997; Perry *et al*, 1997; Nicolson *et al*, 1998) and two placebo-controlled double-blind trials – one in adults (McDougle *et al*, 1998) and one in children (McCracken *et al*, 2002). Overall, the results from these studies have been very encouraging. In an RCT sponsored by the National Institutes of Health, McCracken and colleagues compared risperidone with placebo in 101 children with autism and serious behavioural problems. They concluded that risperidone (dose range 0.5–3.5 mg/day) was efficacious and well tolerated for the treatment of tantrums, aggression and self-injurious behaviour in these children, who were aged between 5 and 17 years (McCracken *et al*, 2002). A positive response was seen in 69% of those receiving risperidone compared with 12% of those receiving placebo. Two-thirds of those with a positive response at 8 weeks maintained this improvement for 6 months. It is too early to comment definitively on whether the atypicals also improve social related-ness. Increased appetite and weight gain, fatigue, drowsiness, dizziness and drooling were more common in the risperidone group. Unfortunately, the study was too short to comment on adverse effects such as tardive dyskinesia. Although the atypical antipsychotics do appear to be associated with fewer extrapyramidal side-effects than the typicals, there are now numerous reports (e.g. Cozza & Edison, 1004; Mandoki, 1995) demonstrating that they are not risk-free. Weight gain, hepatotoxicity and neuroleptic-induced dyskinesias are the most troublesome adverse events, with children and adolescents seeming to be more prone to these than adults, particularly when treatment is continued over the long term.

Critics of the use of these medications in children with autism suggest that they are being used merely as 'chemical straight-jackets', but this does not seem to be the case. The doses used are relatively small and, although drowsiness and fatigue are among the most commonly reported adverse events, the clinical improvements seem to be independent of these negative side-effects. Further controlled studies are needed to clarify issues of safety and effectiveness, but both risperidone and olanzapine show potential in contributing to the treatment of autism alongside more traditional behavioural interventions.

Drugs that affect other aspects of neurotransmission

Several other agents have been proposed for the treatment of autism. An anecdotal report regarding the efficacy of secretin, a gastrointestinal peptide, in treating a child with autism led to a surge of media and public interest in this treatment. However, controlled studies have failed to detect any benefit from a single dose of secretin. Similarly, the evidence to support the use of naltrexone is minimal and was not supported in a controlled trial (Feldman *et al*, 1999). There is some evidence that clonidine may be effective in reducing hyperactivity, impulsivity and irritability over the short term but tolerance to this effect may develop in many patients. Finally, although autism is an exclusion criterion for the diagnosis of ADHD, many children and adolescents with autism present with symptoms of hyperactivity, distractibility and impulsivity. It was initially thought that treatment with methylphenidate could produce a worsening of stereotypical behaviour in these children but more recent studies, including controlled trials, have shown methylphenidate to be efficacious and well tolerated without worsening pre-existing symptoms (Quintana *et al*, 1995).

Tourette syndrome

Although Tourette syndrome is defined by the presence of motor and vocal tics, it is often complicated by associated difficulties such as obsessions and compulsions, aggressive and oppositional behaviour, ADHD symptoms, mood instability, anxiety and depression. It is therefore important that the clinician considering pharmacotherapy for Tourette syndrome first identifies the target symptoms to be treated and then seeks to match the target symptom(s) with an appropriate medication. Here I concentrate on the treatment of tics, but I also mention the treatment ADHD symptoms in the context of Tourette syndrome.

It is important to take into account the natural history and course of Tourette syndrome, which

usually has its onset in early childhood, increases in severity at puberty, attenuates somewhat after puberty and stabilises in adulthood. Tics fluctuate in severity throughout this time with a cycle that lasts, on average, about 3 months. This waxing and waning of tics can make it very difficult to assess the effects of pharmacological interventions and highlights the need for careful recording of the base-line and monitoring of symptoms, both before a new medication is started and during treatment.

It is also important to acknowledge that, although tic severity is important when considering starting medication, there are several other factors to be taken into account, including the expectations of the child and the parents, the child's adaptive capacities, coping mechanisms, interpersonal relatedness, impulse control and affect regulation, together with the level of family and social support. These all have an impact on outcome that is at least as important as that of medication.

Treating tics

Although a wide range of medications has been used to treat tics, there have been relatively few published RCTs of their use. Until recently, haloperidol, pimozide and, in the UK, sulpiride, were the mainstays of treatment. In RCTs, all three have been shown to be efficacious in reducing tics. Haloperidol is the most efficacious, leading to improvement in approximately two-thirds of cases, with pimozide and sulpiride improving tics in just over one-half. However, haloperidol is associated with frequent adverse reactions including disabling extra-pyramidal effects. Pimozide, although associated with fewer adverse events than haloperidol, can lead to ECG abnormalities, particularly prolongation of the QT interval. Sulpiride is also associated with a lower, but not absent, rate of extrapyramidal side-effects.

Recently, there has been much interest in the potential use of the atypical antipsychotics in treating Tourette syndrome. The increase in their use outstripped the available evidence and was based on case reports and case series rather than RCTs. However, over the past 2 years, RCTs have begun to appear in the literature. Sallee *et al* (2000) demon-strated that ziprasidone was superior to placebo and, at a mean dose of 30 mg/day, was efficacious in reducing tics by an average of 35% in a group of 28 children and adolescents with moderate-to-severe tic symptoms. Dion *et al* (2002) found that risperi-done, at a median dose of 2.5 mg/day, was significantly superior to placebo in reduction of tics, with 60% in the risperidone group showing clinically significant improvements. Risperidone did not increase symptoms of obsessive–compulsive

disorder. Bruggeman *et al* (2001) compared risperi-done and pimozide in a comparative double-blind parallel-group study. At the end-point, 54% of the patients on risperidone and 38% of those taking pimozide were rated as having only very mild or no symptoms. Both treatment groups had improved significantly with regard to Global Assessment of Functioning and Clinical Global Impressions scale outcomes. Symptoms of anxiety and depressive mood had also improved significantly from baseline in both groups but improvement in obsessive–compulsive behaviour reached significance only in the risperidone group. Finally, Onofrj *et al* (2000) reported the results of a very small 52-week double-blind crossover study of olanzapine *v.* low-dose pimozide in four adult patients. Although the size of the trial prevents detailed conclusions being drawn, it suggested that olanzapine was as effi-cacious as pimozide, with all four patients opting for olanzapine at the end of the study. All studies reported that the atypicals were associated with few adverse events, but larger, longer trials are needed before firm statements on safety can be made. Clinical experience suggests that a significant number of patients are unhappy about the amount of weight they gain while taking these drugs, although many commentators believe that the atypicals will soon become the first-line treatment for tics.

Other pharmacological treatments for tics include: α-agonists such as clonidine and guanfacine; botulinum toxin; calcium antagonists such as nifedipine, flunarizine and verapamil; nicotine; and the selective androgen receptor antagonist, flutamide. All received some support in open use for decreasing tics. However, of these only flutamide has been shown in an RCT to reduce tics. The studies involving these drugs are helpfully summarised by Robertson & Stern (2000). Clearly, there still needs to be much more research into drug treatments of Tourette syndrome, including larger trials from which clinicians can truly plan treatment in an evidenced-based way.

Drug treatments for comorbid ADHD symptoms in Tourette syndrome

Children and adolescents with comorbid Tourette syndrome and ADHD are extremely challenging to treat. Clinical judgement is required to balance the relative impairment from ADHD symptoms and tics before deciding the best approach to treatment. This is particularly important as it has long been debated whether stimulant medications increase tics. Recent double-blind placebo-controlled studies (e.g. Castellanos *et al*, 1997) have demonstrated that stimulants are highly efficacious in the treatment of
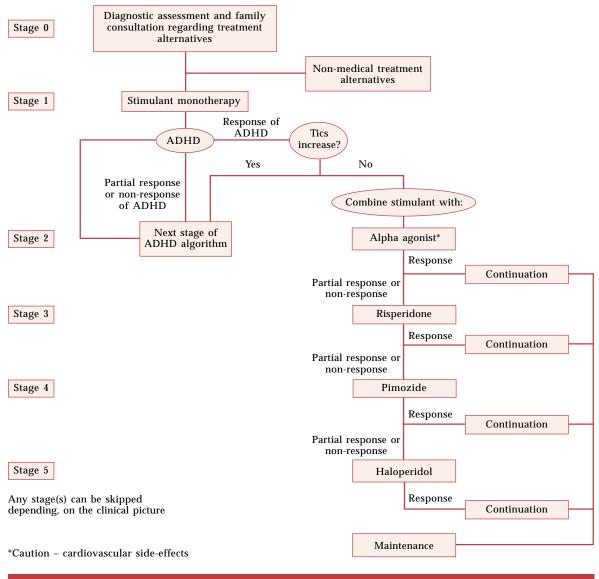
Stage 0 — Diagnostic assessment and family consultation regarding treatment alternatives

Non-medical treatment alternatives

Stage 1 — Stimulant monotherapy

ADHD

Response of ADHD

Tics increase?

Yes — No

Partial response or non-response of ADHD

Stage 2 — Next stage of ADHD algorithm

Combine stimulant with:

Alpha agonist*

Response — Continuation

Partial response or non-response

Stage 3 — Risperidone

Response — Continuation

Partial response or non-response

Stage 4 — Pimozide

Response — Continuation

Partial response or non-response

Stage 5 — Haloperidol

Response — Continuation

Any stage(s) can be skipped depending, on the clinical picture

Maintenance

*Caution – cardiovascular side-effects

Fig. 1 Strategies for the treatment of attention-deficit hyperactivity disorder (ADHD) with tics.

core ADHD symptoms in these patients and do not result in increase in tic severity or frequency in the majority of patients. It is, therefore, generally accepted that when the aim is to control ADHD symptoms, stimulants remain the first-line treatment. Methylphenidate appears to be better tolerated than dexamphetamine.

In cases where stimulant medication does lead to either the appearance of or an increase in tics, treatment with either a tricyclic antidepressant or clonidine may be considered. An advantage of tricyclics in this situation is that they may lead to improvement in both the tics and the ADHD symptoms (Spencer *et al*, 1993). Clonidine was initially thought to be effective in reducing tics but this has not been supported in more recent studies

(e.g. Singer *et al*, 1995). However, it does appear to be effective at reducing ADHD symptoms, irrespective of the presence or absence of tics. A helpful algorithm for the treatment of comorbid ADHD and Tourette syndrome is included in the algorithm for the treatment of ADHD in the Children's Medication Algorithm Project (Pliszka *et al*, 2000) (Fig. 1).

Schizophrenia

Early-onset schizophrenia, the development of psychotic symptoms before the age of 18 years, is associated with severe impairments and poor outcomes. It leads to loss of promise and fulfilment as well as frequent hospitalisations and usually

heralds the beginning of a long career as a psychiatric patient. The early identification and treatment of children and young people who are at an early stage of transition to frank psychosis or at the beginning of a first psychotic episode may not only facilitate aspects of normal development but also affect the course of the illness (Yung *et al*, 1998). Unfortunately, as early-onset schizophrenia is often insidious in onset, diagnosis and treatment are often delayed.

Pharmacological treatments should always be given within the context of a multi-disciplinary team which is also able to offer a range of supportive therapies. Although there are countless trials providing clear and unambiguous evidence that antipsychotics reduce symptoms in adults with schizophrenia, very few of these studies have included children or young people. This means that treatment of both the acute psychotic episode and the longer-term maintenance phase is currently based on experience and the extrapolated results of adult studies. Fortunately, there seems to be considerable continuity between early- and adult-onset schizophrenia. However, it is important that further studies are conducted to confirm both the effectiveness and safety of antipsychotics in early-onset schizophrenia, as this is often a life-long condition requiring long-term treatment.

Only two controlled trials have reported the efficacy of traditional antipsychotics in early-onset schizophrenia. Haloperidol was found to be clinically and statistically superior to placebo by Spencer *et al* (1992) and to be more efficacious than placebo and equally as efficacious as loxitane by Pool *et al* (1976). The traditional antipsychotics are, of course, limited in their use by the serious long-term side-effects, especially the extrapyramidal symptoms and tardive dyskinesia. In adult psychiatry they have, to some degree, been displaced by the atypical antipsychotics, which are at least as effective at treating positive symptoms, probably more effective at treating negative symptoms and less likely to lead to extrapyramidal symptoms. Clozapine is the best studied of the atypicals in adult-onset treatment-resistant schizophrenia, but its use is limited by its association with severe adverse events, including neutropenia, which necessitates regular blood testing.

Even though there are few studies examining their use, other atypicals (risperidone, olanzapine, quetiapine and ziprasidone) are beginning to be used in early-onset schizophrenia. This is largely due to the lower risk of extrapyramidal side-effects. They are, however, not free of side-effects and, indeed, it seems that children and adolescents are more prone to these than adults. There is little evidence relating to the long-term safety of the atypicals in early-onset

schizophrenia. In the only controlled study to examine the use of an atypical in treatment of this disorder, Kumra *et al* (1996) demonstrated clozapine to be more efficacious than haloperidol at treating both positive and negative symptoms. However, 5 of the 21 young people on clozapine developed significant neutropenia and 2 had seizures. None of the other atypicals have been studied systematically, although open-label studies of risperidone, olanzapine and quetiapine have reported positive results (Kumra, 2000; American Academy of Child and Adolescent Psychiatry, 2001). Large long-term systematic studies of their efficacy, effectiveness and safety are needed before clear evidence-based statements can be made about their use.

As there is no evidence, other than for clozapine, to suggest that any one antipsychotic is better than another in treating psychosis, the choice is generally made on the basis of potencies and side-effect profiles. When starting an antipsychotic, it is important to give an adequate trial (6 weeks) at an adequate dose. If there is no response after this time, a different antipsychotic should be tried. Clozapine should be reserved for patients who have failed to respond to at least two adequate trials of other antipsychotic agents, at least one of which was an atypical, or have experienced significant drug-induced side-effects (e.g. tardive dyskinesia). Strategies for treating early-onset schizophrenia are well discussed in a recent American Academy of Child and Adolescent Psychiatry practice parameter (American Academy of Child and Adolescent Psychiatry, 2001).

Conclusions

Although many unanswered questions remain, the evidence base for the pharmacological treatment of child and adolescent psychiatric disorders is growing. Psychological and psychosocial therapies remain the first-line treatments for some disorders (such as anxiety disorders and autism) and they are an important component of a comprehensive treatment package for others. It is important, however, that clinicians develop an understanding of the potential role which medication can play in such a package, especially when psychological treatments have been unsuccessful in reducing symptoms adequately. It is also important to recognise the limitations of the current evidence and to alert patients and their families of these uncertainties when suggesting the use of medication. More quality treatment trials are required. This will require collaboration between academics and clinicians across a wide range of settings and also support from funding bodies and managers within

health care, who need to ensure that these studies are recognised as an essential component of health care provision.

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Multiple choice questions

1 Selective serotonin reuptake inhibitors:

a   are of proven efficacy in the treatment of childhood autism

b   may cause significant behavioural activation in children with autism

c   often cause behavioural activation in childhood obsessive–compulsive disorder

d   have been demonstrated to be of benefit in paediatric social phobia

e   have been demonstrated to be safe in the long-term treatment of childhood anxiety disorders.

2 The following have been shown in RCTs to be efficacious and safe short-term treatments for childhood anxiety disorders:

a   risperidone

b   buspirone

c   benzodiazepines

d   tricyclic antidepressants

e   selective serotonin reuptake inhibitors.

3 Pathophysiological and/or pharmacological evidence suggests that:

a   obsessive–compulsive disorder is associated with dysregulation in central serotonin subsystems

b   glutamate is important in the aetiology but not treatment of paediatric obsessive–compulsive disorder

c   autism is a unitary condition associated with reduced serotonergic neurotransmission

d   autism is associated with reduced serotonergic transmission and altered dopaminergic transmission

e   the serotonergic systems of children with autism may be less sensitive to the effects of the specific serotonin reuptake inhibitors than` in adults with autism.

4 The following are considered effective treatments for reducing tics in Tourette syndrome:

a   sulpiride

b   botulinum toxin

c   clonidine

d   ziprasidone

e   haloperidol.

5 Risperidone:

a   has been demonstrated in RCTs to be effective in treating early-onset schizophrenia

b   is ineffective in treating childhood autism

c   is often associated with weight gain

d   is more likely to give rise to extrapyramidal side-effects in children than in adults

e   is effective in reducing tics in Tourette syndrome but often leads to an increase in associated obsessive–compulsive symptoms.

MCQ answers

1		2		3		4		5	
a	F	a	F	a	T	a	T	a	F
b	T	b	F	b	F	b	F	b	F
c	F	c	F	c	F	c	F	c	T
d	T	d	F	d	T	d	T	d	T
e	F	e	T	e	F	e	T	e	F

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