Chapter 18
Psychopharmacology of Neurodevelopmental Disorders in Children

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Abstract Recent advances in genetics and psychopharmacology have begun to illuminate the key players that contribute to neurodevelopmental disorders in children such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), Tourette's syndrome (TS) and rare diseases such as Rett syndrome (RTT). Clinical guidelines and data from clinical trials mainly focus on management of single disorders whilst most patients present with multiple, chronic, co-occurring developmental disorders. Neurodevelopmental disorders often present with a myriad of neuropsychiatric, emotional and behavioural problems and have neurochemical and neuro-circuitry problems underpinning this. Evidence from meta-analyses have indicated the efficacy of different treatments and some studies show benefit in improving co-occurring symptoms in children with ADHD, ASD or TS. It is increasingly being recognized that emotional, behavioural and autonomic dysregulation (EBAD) is central to difficult presentations in children and adolescents with rare diseases, and those with multiple co-occurring disorders. An incremental treatment approach should be adopted starting with non-pharmaceutical intervention followed by implementation of drug treatments. When drug treatments are used, a multimodal treatment strategy to neurodevelopmental disorders in children should be used in order to provide flexible medication regimens where one is able to select and adjust medication that achieves maximum benefit with the least possible side effects so that treatment can be personalized. Cross-lifespan approaches and web-based clinical and research medication-monitoring systems, such as the HealthTracker™, an e-health web-based platform, can assist in the triaging and management of cases across specialist and community clinics.

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Pharmacological management of neurodevelopmental disorders can present with challenges in Asia, where many of the commonly used medications such as stimulants are more difficult to access. Recent advances in the treatment of ADHD, ASD and TS in children are presented and when applicable discussed in line with experiences from Asia. Innovative strategies working with children and families such as the effective dosing with minimum side effects (EDMS) strategy, and the use of wearable sensor technology to assist in the management of a patient with RTT are described.

Keywords Attention deficit hyperactivity disorder (ADHD) · Autism spectrum disorder (ASD) · Effective dosing with minimum side effects (EDMS) strategy · Emotional behavioural and autonomic dysregulation (EBAD) · HealthTracker™ · Psychopharmacology · Rett syndrome (RTT) · Tourette's syndrome (TS) · Web-based health monitoring · Wearable sensor technology

18.1 Introduction

Neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and Tourette's syndrome (TS) are multifactorial disorders and some of their symptoms can be attributed to abnormalities in neurotransmitter pathways within the central nervous system. These abnormalities can manifest in impediments in social, personal and academic function. Research into ADHD, ASD and TS has proceeded at a geometric rate and whilst the precise molecular targets remain to be elucidated, recent genetic advances have paved the way for genetic variants that predispose certain individuals with an increased risk of neurodevelopmental disorders. Despite this, there is a general notion that phenotypically the clinical picture remains blurred and common molecular and genetic targets across disorders have not yet been identified. To broach this conundrum, some recent evidence has shed light on characterizing the genetic loci for complex neuropsychiatric disorders as was shown for schizophrenia and components of the complement cascade (Sekar et al. 2016).

In this chapter, the pertinent observations of neurodevelopmental disorders in children will be focused upon with an emphasis on the psychopharmacology of ADHD, ASD and TS in children. Increasingly, managing emotional, behavioural and autonomic dysregulation (EBAD) is becoming central to improving the quality of life in individuals with neuropsychiatric disorders such as Rett syndrome (RTT) (see Sect. 18.6.1). We describe novel strategies such as the effective dosing with minimum side effects (EDMS), and the use of wearable sensor technology to assist in managing a patient with RTT. The need for low-dose initiation with gradual increase of dosage, and frequent monitoring of impact of medication in children and adolescents will be emphasized. Specific issues that affect pharmacological and non-pharmacological interventions in Asia are highlighted as necessary.

18.2 The Art of Prescribing Medication

To begin with, apart from the chemical effect, the response to medication also depends on an inherent 'placebo response', as well as the 'therapeutic alliance' achieved by obtaining agreement and acceptance of why the medication is prescribed and what is the expected response. The role of the prescriber is to make the patient/parents/carers feel understood and jointly agree the treatment plan, that is, there is concordance between the world view of the clinician, patient, parents/carers, regarding the illness and its treatment. Treatment regimen(s) should be closely monitored with medication given in small doses, gradually increased and monitored for adverse effects regularly.

18.3 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (DSM-5 2013) or Hyperkinetic Disorder (HKD) according to the International Classification of diseases (ICD-10) [10th edition; ICD-10, World Health Organization (WHO 1992)] is a common condition characterized by inattention and hyperactivity/impulsivity, with a strong genetic component, that is present in the child population on a continuum of severity. Hyperkinetic Disorder is a narrower diagnosis, which requires the presence of inattention, impulsivity and hyperactivity, with symptoms starting before the age of 6 years and being present in more than one setting. The presence of another disorder, such as anxiety or depression, is in itself an exclusion criterion—the expectation is that most cases will have a single diagnosis. This restricted categorization makes HKD a subgroup of the broader ADHD group and could be considered as 'severe ADHD'. ADHD typically occurs with a prevalence of about 3–5 % and HKD around 1.5 %. Specific guidelines for the treatment of ADHD are presented elsewhere (National Institute for Health and Care Excellence [NICE] guidelines GC 72 2013) and in the following sections the key principles in managing ADHD will be described.

The complexity of ADHD is compounded as it frequently presents with one or more co-occurring conditions such as conduct disorder, oppositional defiant disorder, anxiety and/or depressive disorder and there is considerable symptom overlap between ADHD and comorbid disorders. Perturbations in synaptic plasticity within certain regions of the brain are thought to play a key role. Evidence has shown that patients with ADHD have a delay in regional cortical maturation within the prefrontal cortex (Shaw et al. 2007) and large-scale neural network analyses have revealed other important areas of the brain implicated in the pathogenesis of the disorder (Castellanos and Proal 2012). Others have indicated deficits in neural circuits in children with ADHD (Nagel et al. 2011; Cha et al. 2015). These brain regions and the associated neural connections are highly sensitive to modulations in neurochemical pathways, and it is highly likely that even relatively

benign fluctuations in catecholamine and serotoninergic signalling pathways can produce marked changes in attention, behaviour and emotion. The genetic heritability of ADHD symptoms is approximately 70 % in children and adolescents, and about 30 % in adults (Boomsma et al. 2010); however, other non-genetic factors, for example, pre-natal smoking and alcohol abuse, prematurity/low birth weight and other drug/environmental factors, are thought to increase the risk of ADHD (Purper-Ouakil et al. 2011). Epigenetic modulation is likely to be key factor in the causation of ADHD. Whether this is genetic and/or drug/environmental, it is probably likely that multiple epigenetic mechanisms coalesce and contribute to the complexity of ADHD resulting in differing degrees of severity and comorbidities that are often observed in individuals with ADHD.

18.3.1 Pharmacotherapeutic Strategy in Managing ADHD

In this section, we provide an overview of the pharmacotherapeutic strategy when managing ADHD in children.

- First-line Medication: methylphenidate (MPH) (immediate release MPH, Concerta XL, Medikinet XL, etc.), dexamphetamine (immediate release dexamphetamine; mixture of amphetamine salts—Adderall [immediate release and XR]); prodrug of dexamphetamine—Lisdexamfetamine [Elvance]); atomoxetine.
- Second-line Medication: guanfacine, bupropion, clonidine, imipramine, nortriptyline.
- Third-line Medication: carbamazepine, risperidone, aripiprazole, buspirone, venlafaxine.

18.3.1.1 Stimulants

In ADHD, the diagnosis and management NICE guidelines (NICE guidelines GC 72 2013), advocates group-based parent-training/education programmes as the first-line treatment for parents/carers of children and adolescents of school-going age with ADHD and moderate impairment. It is further recommended for older age cohorts that individual psychological treatment may be deemed acceptable if group behavioural or psychological approaches are found to be un-effective, or have been refused. Finally, drug treatment ought to be held in reserve for those with moderate impairment who have rejected non-drug interventions, or whose symptoms have not adequately responded to the first-line interventions (NICE guidelines GC 72 2013).

Medication is usually necessary when treating HKD or severe ADHD or if psychological treatments have been insufficient alone in managing symptoms. Greater hyperactivity, inattention and clumsiness in the absence of emotional disorder

predict greater positive response to MPH (Taylor et al. 1987). Similarly, those with HKD show greater response to MPH (Santosh et al. 2005). However, it has also been shown that symptoms in those with less severe ADHD improve more completely. NICE recommends drug treatment as the first-line treatment for school-aged children and young people with severe ADHD (hyperkinetic disorder) and severe impairment. Where drug treatment is considered appropriate, MPH, atomoxetine and dexamphetamine can be used. Of note, the choice of drug should be guided by comorbidities and adverse events. Specific issues that may affect compliance and whether there is a potential for drug diversion and/or substance misuse should also be considered. Finally, the wishes of the child/adolescent and their parent or guardian should also be taken into account (NICE guidelines GC 72 2013).

The literature on stimulant medications MPH, dexamphetamine, and lisdexamfetamine and their use in the treatment of ADHD is voluminous. In most cases a stimulant is the first choice medication. Its onset of action is rapid, the dosage easy to titrate and positive response(s) can often be predicted from a single dose. Delayed delivery systems, such as Diffucaps MPH system, spheroidal oral drug absorption system (SODAS) and osmotically controlled-release oral delivery system (OROS) for MPH and mixed amphetamine salts extended-release systems have allowed treatment without medication having to be dispensed in school, and have the potential to decrease the abuse potential of stimulant agents. Lisdexamfetamine dimesylate is an amphetamine prodrug that is inactive until ingested and metabolized (Gamo et al. 2010), and is an effective treatment for ADHD.

The multimodal treatment of ADHD (MTA) study was a 14-month longitudinal trial that compared the effectiveness of pharmacotherapy and behavioural therapy in children aged 7.0–9.9 years with combined ADHD (inattention and hyperactivity/impulsivity) (MTA Cooperative Group 1999). The findings from the MTA indicated that the combination of pharmacological and behavioural therapy did not confer additional benefit when compared to pharmacological treatment alone for core ADHD symptoms, but the combination or multimodal treatment offered some benefit with regards to associated symptoms such as academic achievement, conduct problems and parental satisfaction (Swanson et al. 2001; Conners et al. 2001). A re-analysis of the MTA data using the ICD-10 classification of HKD showed that the effect size of stimulants was significantly greater in those with a diagnosis of HKD, compared to those who had non-HKD ADHD (Santosh et al. 2005).

Stimulant medications are the most commonly prescribed medication for children and at present the most extensively studied treatment for ADHD. The use of MPH is based on a substantial evidence base, summarized by a recent Cochrane review that analysed 38 parallel group trials (n = 5111, median treatment duration 49 days) and 147 crossover trials (n = 7134, 14 days), with an average age across all studies of 9.7 years (Storebø et al. 2015). The analysis suggested a beneficial effect of MPH on teacher rated symptoms in 19 parallel group trials (standardized mean difference [SMD] −0.77, n = 1698), and teacher rated general behaviour (SMD −0.87, five trials, n = 668), and may improve parent-reported quality

of life (SMD 0.61, three trials, n = 514) (Storebø et al. 2015). There was no evidence that MPH was associated with an increase in serious adverse events (risk ratio 0.98, nine trials, n = 1532). MPH was associated with a small but increased risk of non-serious adverse events namely decreased appetite and poor sleep (risk ratio 1.29, 21 trials, n = 3132) (Storebø et al. 2015). They however rate the likelihood of bias as being high in most of the studies included in the analyses (Storebø et al. 2015).

A Cochrane review of the use of amphetamines in children and adolescents with ADHD (Punja et al. 2016) showed that amphetamines were effective. When comparing the effectiveness of stimulants such as MPH to amphetamines, a meta-analysis has shown that the effect size for amphetamines was greater than MPH (Charach et al. 2013). Furthermore, a more recent meta-analysis showed that the effectiveness of reducing ADHD symptoms in children and adolescents was the greatest for lisdexamfetamine followed by MPH, atomoxetine and bupropion (Stuhec et al. 2015).

Precautions with Stimulants

When managing the symptoms of ADHD in children, any treatment should be given with precaution and regular safety and tolerability monitoring should be routinely done. The main precautions are emphasized below.

- When children are started on stimulants, one needs to monitor pulse, blood pressure and heart rate (HR) at each dose increase and at every 6 months. Weight and height should also be monitored carefully using standardized charts at the minimum of 6-month intervals. Tics, depression, irritability, lack of spontaneity, withdrawal and excessive perseveration should be monitored at each visit. Routine haematological tests are unnecessary.
- Stimulants are contraindicated in schizophrenia, hyperthyroidism, cardiac arrhythmias, angina pectoris, glaucoma or a history of hypersensitivity to drug.
- There is no evidence that stimulants decrease seizure threshold. They can be used in well-controlled epilepsy. If seizures appear or worsen, change to dexamphetamine and avoid atomoxetine.
- Stimulants can reduce height and weight centiles over time. It is advisable not to start stimulants in children who are short or are biologically predisposed to short stature.
- Many anti-ADHD medications can increase HR and blood pressure and therefore electrocardiograms should be done and evaluated regularly. This is of particular importance in high-risk groups such as those with structural cardiac defects. Adderall should be avoided in cardiac high-risk groups.
- Stimulants can be abused by anyone with access to it. Self-initiated increase in dose by emotionally unstable patients with substance use disorders is possible, and should be monitored. Where substance abuse is suspected, atomoxetine, bupropion or Concerta XL (drug-delivery system makes it difficult to abuse) can be used, as they are safer in this scenario.

- Stimulants can induce or worsen psychotic experience. Therefore, stimulant use should be avoided in those who have first-degree relatives with a psychotic disorder or in children who have psychotic or quasi-psychotic experiences. Atomoxetine, tricyclic antidepressants, clonidine, bupropion, aripiprazole or risperidone can be used instead.

18.3.1.2 Atomoxetine

Atomoxetine was the first non-stimulant drug approved for the treatment of ADHD. Whilst the precise therapeutic effects of atomoxetine in the treatment of ADHD remain unclear, atomoxetine is thought to bring about its effect by acting as a selective norepinephrine inhibitor. The plasma half-life is usually about 4 h; an active metabolite, 4-hydroxyatomoxetine, is excreted in urine after glucuronidation. In 5–10 % of people, a polymorphism of the cytochrome enzyme P450 2D6 leads to a longer plasma half-life of up to 19 h. Randomized double-blind placebo-controlled trials in children and adolescents demonstrate atomoxetine's effectiveness in treating ADHD (Michelson et al. 2001, 2002; Bushe and Savill 2014). Atomoxetine was noted to be significantly more effective compared to placebo on both the parent and teacher scales. The primary adverse effects noted with atomoxetine were gastrointestinal upset, decreased appetite, fatigue, dizziness and mild increases in pulse and systolic blood pressure. Despite its relatively short half-life, atomoxetine can be used as either a once daily or twice daily dose and is generally quite safe. It produces minimal increase in blood pressure, HR and gastrointestinal symptoms (nausea and vomiting are possible especially during the early part of treatment). It may be useful in those with comorbid tics, anxiety/depression, or in those who have not responded to stimulants (although at present there have been no clear studies indicate this as yet). Symptoms take about 6 weeks to improve with atomoxetine (unlike stimulants), and hence parents have to be informed about this at start of treatment. Dosage can be initiated at half the required total dose in order to decrease the chances of side effects (especially upper gastrointestinal effects). Anecdotally, there have been some reports that suggest extremely rare, but serious liver dysfunction in patients treated with atomoxetine.

18.3.1.3 Clonidine and Guanfacine

Clonidine and Guanfacine are central acting alpha-2-adrenergic agonists commonly used as adjuncts in the treatment of pediatric ADHD. A meta-analysis summarizes the evidence base of clonidine in the treatment of ADHD (Connor et al. 1999). Several of these studies involved patients with ADHD and a comorbid psychiatric illness (conduct disorder, developmental disorder or tic disorder). Positive effects were reported on ADHD symptoms from all of these studies across parent, teacher and clinician raters. The effect size on ADHD symptoms was 0.58 ± 0.16,

which corresponds to a moderately positive clinical effect (Connor et al. 1999). In support of this finding, a recent meta-analysis of ADHD in youth has shown that clonidine XR (extended release) was more superior in comparison to placebo for total ADHD symptoms (Hirota et al. 2014). Seven prospective randomized controlled trials (RCTs) using guanfacine XR (extended release) for the treatment of ADHD in children and adolescents showed superiority over placebo on the primary outcome measure (Rizzo and Martino 2015). Based on this evidence, guanfacine, especially XR, appears to be an effective and safe treatment option in children and adolescents with ADHD (Rizzo and Martino 2015). There is no evidence to suggest a difference in efficacy between clonidine and guanfacine for total ADHD symptoms (Hirota et al. 2014).

Side effects frequently noted with these medications include sedation, hypotension, tachycardia and dizziness. Pulse and blood pressure should be monitored for bradycardia and hypotension in those treated with guanfacine (Ruggiero et al. 2014). Of note, when discontinuing clonidine, the dose needs to be carefully tapered rather than stopped all of a sudden to avoid rebound hypertension. Unpredictable compliance with clonidine elevates the risk of adverse cardiovascular events and this factor needs to be discussed with families. In general, the clinician needs to consider whether clonidine should be prescribed if it cannot be taken reliably. Depression and impairment of glucose tolerance can also occur.

18.3.1.4 Combination of a Stimulant and Non-stimulant

The problems presented by severe hyperactivity can be very severe and families may become desperate. Clinicians often feel pressed to prescribe unduly high dosages (for which there is no evidence base of value) and combinations of drugs, sometimes to target different aspects of the symptom complex. This can be justifiable in extreme cases, but the concurrent use of inadequately evaluated drugs can create hazards and warrants specialist advice and careful monitoring.

18.3.2 Developmental Trajectory and Medication Response

ADHD in Pre-schoolers: Behavioural interventions such as parent-training approaches are useful. Stimulants are less effective in school-going children and are associated with greater side effects. The evidence base is stronger for parent-based behaviour training interventions in comparison to MPH treatment in pre-schoolers at increased risk for ADHD (Charach et al. 2013).
ADHD in School-going Children: Medication is superior to behavioural interventions in this age group. Behavioural interventions are essential when treating comorbidity in ADHD.
ADHD in Adolescence: Non-compliance with medication is a greater problem in treatment of adolescents due to their desire to avoid taking medication during

school hours and the increased prevalence of stimulant-related dysphoria. The risk of misuse of stimulants is also elevated in adolescents. Giving or selling medication to peers is more common than abuse by the patients themselves. The drug interactions that could result from undisclosed substance misuse should always be borne in mind. Concerta XL or atomoxetines are good options in this group.

ADHD in Adults: It becomes difficult from a clinical perspective on how to manage adult ADHD without the necessary experience regarding the presentation of the disorder in childhood. Adult ADHD has a prevalence of about 5 % (Bonvicini et al. 2016) and evidence suggests that adult ADHD might be a distinct entity, i.e. without childhood ADHD (Moffitt et al. 2015). Nowadays, it is becoming more frequent for adult patients to seek treatment and management of their ADHD symptoms, and in this view clinicians are in the need for robust practice guidelines. An important factor to consider is that adult ADHD frequently presents differently from ADHD seen in childhood and can be comorbid with other disorders. When compared to children, adults with ADHD present with more inattentive symptoms and show less hyperactivity or impulsivity (Volkow and Swanson 2013). Hence, from this viewpoint it is important to recognize the different diagnoses. Physicians and other professionals should work with patients in a concerted manner in order to provide the most appropriate feedback about their symptoms, to empower them about ADHD, and to set realistic treatment goals. Both stimulants and atomoxetine are effective and well tolerated in adults with ADHD (Santosh et al. 2011) and RCTs using these treatments show favourable clinical effect sizes ranging from 0.4 to 0.7 (Asherson et al. 2016).

If hyperactivity is present only in one situation, i.e. at school or at home, then stresses in that situation should be sought and alleviated as the first line of management. With *school specific problems*, specific learning disabilities should be sought carefully through the assessment of a clinical or educational psychologist. If present, then adjustment of educational techniques and expectations should be given a try before anti-hyperactivity treatments. If hyperactive behaviour is *confined to the home situation*, then the possibility of adverse parenting influences should be considered, leading to a parent-training approach. In pervasive and severe cases, without autistic or affective comorbidity, a multimodal treatment approach will be needed. Medication should be initiated with proper monitoring of target symptoms. *Patients without hyperactivity (ADD)* may benefit from and tolerate lower doses of stimulants.

18.3.3 Experiences from the Indian Context

High-quality pharmacological research in neurodevelopmental disorders is currently sparse from Asia. Some studies exploring this topic from India have been highlighted here.

The significant lack of knowledge about the causes of academic impairments associated with ADHD and specific learning disorders (SLDs) among school-aged

children in India often goes unrecognized (Mukherjee et al. 2016). This is despite the prevalence of ADHD as assessed through questionnaire data in 6–11 year olds in India that shows rates of 16.33 % among the lower socio-economic group and 6.84 % among middle socio-economic group, highlighting the increased risk for ADHD from those at a socio-economic disadvantage (Venkata and Panicker 2013). This might have some significance because a case control study of newly diagnosed cases with ADHD has indicated that serum ferritin to be substantially lower in children with ADHD as compared to controls. Moreover, a statistically significant negative correlation between serum ferritin levels and oppositional sub-score on the Conners Rating Scale was observed (Juneja et al. 2010). This is important in countries with high rates of hookworm infestations and iron deficiency anaemia, often associated with poor socio-economic status. Despite this evidence, further work would be warranted in a much larger sample size before making any confirmatory claim(s) linking lower serum ferritin levels to ADHD causation and severity. The prevalence of ADHD and associated psychological problems among college students in Chandigarh, India showed that 5.48 % of the students fulfilled the criteria for adult ADHD. These students experienced significantly higher emotional instability and low self-esteem than those without ADHD but did not differ in the occurrence of depression, social problems and substance abuse (Jhambh et al. 2014).

Despite availability of effective treatments for ADHD in India, a substantial proportion of the patient population has unsatisfactory access to care or face protracted delays when seeking help (Arya et al. 2015). Patients with ADHD attending tertiary outpatient psychiatric services in India showed a mean delay of 3.96 years in seeking help for ADHD symptoms, due to a lack of recognition of ADHD by qualified practitioners (other than teachers), leading to delayed referral to Child and Adolescent Mental Health Services (CAMHS). Sociocultural beliefs of parents also influenced help seeking (Arya et al. 2015). There remains significant non-adherence to treatment in children with ADHD in India with 62.5 % being non-adherent and social factors contributing to non-adherence in 75.7 % (Antony 2016).

From a pharmacotherapy perspective, an open-label clinical trial of buspirone, a full 5HT1A agonist at the somatodendritic auto-receptor and a partial agonist at the post-synaptic 5HT1A receptors, conducted in a tertiary hospital setting in north India suggested that it can help to improve hyperactivity, impulsivity and oppositionality (Malhotra and Santosh 1998). The short-term efficacy and tolerability of MPH and atomoxetine in children with ADHD was explored using an open-label randomized parallel group clinical trial in a tertiary care hospital in north India using MPH (0.2–1 mg/kg/d) or atomoxetine (0.5–1.2 mg/kg/d) for 8 weeks. Methylphenidate and atomoxetine were both efficacious in Indian children with ADHD at lower doses than conventionally reported in the West. The dose needed was 0.45 mg/kg/d for MPH and 0.61 mg/kg/d for atomoxetine, and their efficacy and tolerability were comparable (Garg et al. 2014). In the subgroup with ADHD and oppositional defiant disorder (ODD) ($n = 37$), 80 % of the patients from MPH group and 64.3 % patients from atomoxetine group ceased to fulfil the

criteria for the presence of ODD at 8 weeks (Garg et al. 2015). In an interesting Indian study of 18 subjects recruited with early onset of substance dependence to at least two substances (alcohol, tobacco and other drug dependence), atomoxetine supplementation to treatment as usual led to significant reduction in externalizing symptoms, longer abstinence, shorter turnaround time and better quality of life (Benegal et al. 2013). Further work would be required in a much larger sample size to warrant generalization of these findings.

In summary, although some findings require confirmation in larger studies, in general, the following points should be considered in developing countries such as India:

- Psychoeducation regarding diagnosis and treatment of ADHD of professionals coming in contact with children and adolescents, parents and children should become a priority.
- Correction of iron deficiency should become an important component of the treatment package of ADHD in India.
- The difficulties associated in obtaining stimulants for treating ADHD have led to non-stimulants such as atomoxetine, tricyclic antidepressants, clonidine and non-allopathic medicines being used. Easing access to first-line treatments such as long-acting stimulants and making it affordable to patients should be aimed for in countries such as India.
- Non-adherence to treatment remains high and needs targeting.
- Lower doses of MPH and atomoxetine have been reported to produce comparable improvements in ADHD and ODD symptoms, suggesting that dose titration start at lower doses than suggested from studies conducted in the West.
- Screening high-risk groups such as adolescents and young adults with alcohol or substance misuse for ADHD (and treating it if present) should become part of holistic alcohol or substance misuse treatment programmes.

18.4 Autism Spectrum Disorder (ASD)

At its core, ASD is a disorder that impacts on the several aspects of socialization. The disorder is characterized by impairments in communication, social reciprocity, and by restrictive and repetitive patterns (DSM-5 2013). The mean prevalence of ASD is currently estimated as being 1 in 68 children (Wingate et al. 2014). Due to its inherent pleiotropic heterogeneity, teasing out the precise neurotransmitter receptor systems implicated in the pathophysiology of ASD makes it less tractable to pharmacological manipulation. Epigenetic dysregulation has been linked to a wide range of neurodevelopmental disorders (Petronis 2010) and it is likely that in ASD, modulation of epigenetic factors responding to internal and external environmental cues manifest in the disease and contribute to the divergent symptomology. Current evidence indicates that mid-foetal human cortical neurons (Willsey et al. 2013; Miller et al. 2014) are an important area for the co-expression

of candidate genes, and as described below, these candidate genes have a crucial role in the integrity of divergent synaptic pathways. Studies on candidate genes have provided valuable molecular insights into ASD. Defects in the gene encoding the adhesive junction-associated d-catenin protein (CTNND2) were shown to be associated with severe autism (Turner et al. 2015). Moreover, restoration of the gene *Shank3* that encodes SH3 and multiple ankyrin repeat domains 3 (SHANK3), a post-synaptic scaffold protein important for synaptic function and plasticity, and responsible of about 1 % of all ASD cases, rescued ASD like phenotypes in adult mice including certain behaviour abnormalities such as social interaction and repetitive grooming behaviour deficits (Mei et al. 2016). Despite these single-gene mutations providing important insight into molecular mechanisms, as mentioned above, the heterogeneity of ASD underscores the fact that the aetiology of about 70 % of ASD cases is still unknown (O'Roak and State 2008; Devlin et al. 2012). A recent study has shed light on possible epigenetic biomarkers associated with ASD and has implicated mutations of the gene *ERMN* that codes Ermin, an oligodendroglia-specific protein integral for myelinogenesis (Brockschnieder et al. 2006), in ASD susceptibility (Homs et al. 2016). Other studies in mice have shown that impairments in patched domain containing 1 (PTCHD1) within the thalamic reticular nucleus could have an important role in propagating the adverse symptomology across neurodevelopmental disorders such as ASD (Wells et al. 2016). Whilst promising, further work needs to be done in terms of how the findings conducted in animal models may extrapolate to humans. The road to clinical translation is beset with obstacles and data in animal models do not necessary yield the same outcomes as in clinical trials involving human subjects.

Whilst there is no established literature for prevention or cure, it is well agreed upon that defects in the core features of autism can be mitigated by focused behavioural interventions coupled with pharmacological treatments to reduce the co-occurring symptoms (Santosh and Singh 2016). In fact, ASD frequently presents with one or more comorbid problem (Simonoff et al. 2008). A number of different pharmacological treatments are used to treat the co-occurring disorders associated with ASD such as antidepressants, antipsychotics, anticonvulsants and stimulants. Despite their widespread use, there is paucity in the literature whether such treatment regimens can treat the underlying core symptoms in children with ASD.

18.4.1 Treatment Strategies in ASD

When planning treatment strategies in individuals with ASD, in particular children, an important factor to consider is compliance to medication. This is because individuals with ASD are likely to have cognitive rigidity and atypical sensory symptoms that can influence treatment compliance. Hence, medication may not be taken due to its smell or taste in those with ASD. In this scenario, prescribing needs to be individualized (Santosh and Singh 2016) to the patients' needs and the EDMS would be useful in this regard (Santosh 2014). In this context, the dose can

be titrated to provide maximum effectiveness with the minimum of side effects. In the UK, evidence-based guidelines inform clinicians and other healthcare practitioners' different ways of treating and managing children and adolescents with ASD (NICE guidelines GC 170 2013). An all-encompassing multimodal approach is essential for the treatment and management of ASD. This is particularly important in children. In children with ASD, medication should form only a part of a comprehensive treatment programme that also includes behavioural and psychological therapies. In the following sections, we discuss the treatments strategies when managing the frequent comorbidities seen in children with ASD.

In comparison to the UK and other developed countries, children in South Asia have little or if any access to treatment. The number of children with ASD is the highest in South Asia, and in particular, current estimates in India indicate that >5million children aged between 2–9 years of age have ASD (Rahman et al. 2016). Evidence has further emphasized the lack of an evidence base for treatment interventions that have been adapted from high-income countries and their practicability in countries such as India. Furthermore, the need for specialists to deliver these interventions, particularly for those in rural populations, where the treatment gap is nearly 100 % (Patel et al. 2013) also presents another barrier to treatment. Recent evidence has indicated that non-specialist interventions adapted from those used in high-income countries for children with ASD could be the way forward for countries such as India. Parent-mediated intervention was shown to be feasible and effective for the treatment of ASD in children in India and Pakistan (Rahman et al. 2016) and warrants the case for testing other non-specialist interventions in these and other regions of South Asia.

18.4.1.1 Treating Aggression, Irritability and Agitation

One of the most damaging comorbidities associated with ASD is aggression. Prevalence rates of aggression in children with ASD are variable. In one study involving 1380 children aged 4–17 years with ASD, it was reported that 56 % engaged in some form of aggression ranging from mild to severe towards caregivers and 32 % towards non-caregivers (Kanne and Mazurek 2011). Another study in 169 children aged 1.5–5.8 years with ASD, 22.5 % of children displayed aggression that was deemed to be clinically significant (Hartley et al. 2008). Despite these variations, it is clear that aggression and irritability can manifest as extreme non-compliance and socially inappropriate behaviours. This often leads to high risk and jeopardizes the core elements of ordinary personal experience for people with ASD such as living with their families, and attending local schools (Hodgetts et al. 2013).

The atypical antipsychotics risperidone and aripiprazole can be useful in treating aggression and irritability in ASD. In a study by McCracken et al. (2002), risperidone was safe, well tolerated and effective for treating aggression in 101 youth aged 5–17 years with ASD. Following on from this, in 2004, the effectiveness of risperidone for treating aggression and irritability was confirmed in 79 children

aged 5–12 years old with ASD in an 8-week placebo-controlled double-blind RCT (Shea et al. 2004). Another study has shown that risperidone was efficacious in reducing hyperactivity and aggression in children (Nagaraj et al. 2006). Similarly, studies have shown that aripiprazole was effective for the treatment of irritability in children with autistic and aggressive behaviour (Owen et al. 2009; Ching and Pringsheim 2012) and had positive effects on secondary outcome measures in individuals aged 6–17 years old with ASD (Findling et al. 2014). Taken together, these findings show that treatments with risperidone and aripiprazole are effective in reducing aggression and irritability in children and adolescents with ASD. Both risperidone and aripiprazole have been approved by the United States Food and Drug Administration for the treatment of irritability in youth with ASD. From a safety perspective, a systematic review has shown that aripiprazole has a more favourable metabolic safety profile than risperidone (De Hert et al. 2011); however, there is no evidence that risperidone or aripiprazole is more effective than the other (Ghanizadeh et al. 2014).

Some case reports have also suggested a positive safety and efficacy profile of clozapine when treating aggression in youth with ASD (Chen et al. 2001; Lambrey et al. 2010). In a recent meta-analysis, the effectiveness of pharmacological treatment for irritability and aggression in children and adolescents aged 2–17 years of age with ASD was evaluated (Fung et al. 2016). The primary outcome measure was the reduction in the Aberrant Behavior Checklist-Irritability (ABC-I) in the treatment group when compared to placebo. Forty-six (46) placebo-controlled RCTs were identified and in comparison to placebo, risperidone, aripiprazole followed by *N*-acetylcysteine showed the greatest improvement in ABC-I scores with effect sizes of 0.9, 0.8 and 0.7, respectively (Fung et al. 2016).

18.4.1.2 Treating Hyperactivity and Inattention

ASD presents with a plethora of symptoms and whilst not all will be described in this chapter, as with aggression, however, inattention and hyperactivity reflect symptoms that are frequently encountered in children with ASD. Indeed, evidence has suggested that in some cases, these symptoms are so severe that a diagnosis of ADHD is justified (Lee et al. 2014).

Although they might present as different disorders, recent evidence suggests that there is considerable aetiological overlap between the genes that cause ASD and those that cause ADHD (Smoller et al. 2013). That said, there are commonalities in the medication used for the treatment of hyperactivity and inattention in those with ASD comorbid for ADHD and those with ADHD. Good symptom reduction using MPH was observed in children and adolescents with ADHD comorbid for ASD in an open-label trial (Santosh et al. 2006). Moreover, MPH was shown to improve social communication and self-regulation in children aged 5–13 years old with pervasive development disorder and hyperactivity (Jahromi et al. 2009).

There is a dearth in the literature when assessing the effectiveness of amphetamines in children and adolescents with ASD. The evidence base suggests that amphetamines are useful for treating ADHD in children with ASD. Lisdexamfetamine dimesylate is useful in improving outcomes in children with ADHD (Coghill et al. 2013) and therefore its use in treating ADHD in ASD might be warranted; however, further work in studies of sufficient power and sample size would be needed to corroborate this.

In children with ASD, the overall strength of evidence for atomoxetine in improving hyperactivity and inattention is low. In children aged 6–17 years with ASD and ADHD, atomoxetine appears to have no effect on social functioning but might improve stereotyped behaviours and communication (Harfterkamp et al. 2014). Further work from this group showed no evidence of predictors of response to atomoxetine (Harfterkamp et al. 2015). Despite these findings, before making definitive claims on the effectiveness of atomoxetine in children with ASD, clearly there is a case that more RCTs of atomoxetine in children with ASD are needed.

Some studies have evaluated the efficacy of the alpha-2 adrenergic agonists clonidine and guanfacine in improving comorbid symptoms in children with ASD. In one double-blind placebo-controlled crossover study using transdermal clonidine, Fankhauser et al. (1992) showed that transdermal clonidine improved hyperactivity in autistic subjects aged 5–33 years old. Caution should be stressed when extrapolating this finding as the sample size was very small (nine males) and duration of the trial was short (4 weeks). Others have questioned the validity of clonidine for treating hyperactivity in individuals with ASD (Hazell 2007). Further work would be needed before confirming the effectiveness of clonidine in treating ADHD in those with ASD. Conversely, the evidence base for guanfacine is stronger. Recently, extended release guanfacine was shown to improve hyperactivity in children (mean age: 8.5 years) with ASD. Sixty-two (62) subjects were enrolled in a multi-site RCT and in the guanfacine treatment group; there was a 43.6 % decline in the ABC-hyperactivity score compared to a 13.2 % decrease in the placebo treatment group (Scahill et al. 2015). It is hoped that the advancement of treatments that aim to ameliorate core symptoms in ASD and ADHD will provide therapeutic inroads in not only combating the core deficits but also in addressing the associated psychiatric comorbidities.

18.4.1.3 Treating Anxiety and Depression

Elevated anxiety and depression are frequent occurrences in children with ASD. Anxiety ranges from 40 to 84 % for any anxiety disorder to 5–23 % for generalized anxiety and 13–29 % for social anxiety (Sukhodolsky et al. 2013). Parent-reported data has shown beneficial treatment effects of cognitive behavioural therapy (CBT) on anxiety in young adolescents aged 11–15 years of age with ASD (Wood et al. 2015). Treatment for anxiety would usually involve the use of serotonin reuptake inhibitors (SSRIs), and in this vein although, not specifically investigated in children with ASD, SSRIs together with CBT have been shown

to decrease the severity of anxiety in children (Walkup et al. 2008). Based on these data, it is likely that treatment for anxiety in children with ASD would follow a combined approach involving both medication and parent-led behavioural therapies.

18.4.2 Targeting the Core Symptoms of ASD

Currently, nearly all treatment strategies are directed towards managing the comorbid symptoms of ASD. No drug in routine clinical practice has as yet been found that is efficacious in improving the core impairments in ASD. Evidence from some preliminary studies indicates, however, that some might be useful in ameliorating the core symptoms of ASD. The molecules that aim to target core symptoms of ASD are quite broad and range from antibiotics that have been used previously for the treatment of tuberculosis, hormonal neuropeptides, to plant-based compounds.

The antibiotic D-cycloserine has been around for nearly 60 years for its use as a treatment in tuberculosis. More recently, it has emerged as a potential player in targeting core deficits in ASD and was shown to have positive effects on stereotypies and social deficits in patients aged 14–25 years old with ASD (Urbano et al. 2014, 2015). In another study, however, no differences between the placebo and D-cycloserine treatment groups were seen for the primary and secondary outcome measures in 34 children aged 5–11 years with ASD (Minshawi et al. 2016). Despite this finding, an improvement was seen for total raw scores in the social responsiveness scale from baseline to treatment end (Minshawi et al. 2016). These data warrant additional investigation before the role of D-cycloserine in ASD can be confirmed.

Oxytocin is a hormone secreted from the posterior pituitary gland and polymorphisms in the oxytocin receptor gene are thought to be associated with individual differences in social functioning observed in humans, including the social impairments seen in children with ASD (Parker et al. 2014). The potential of oxytocin for improving core deficits in ASD has garnered significant traction in recent years. In part, this momentum has been driven largely by single-dose studies of oxytocin that have yielded positive effects on core ASD symptoms in particular those related to social communication and interaction. In terms of single-dose studies, Hollander et al. (2003) was the first to show a significant beneficial effect following a single intravenous dose of oxytocin in 15 adults with ASD. Studies in children have shown that intranasal administration of single-dose oxytocin improved brain function for social stimuli in 17 children aged 8–16.5 years with high functioning ASD (Gordon et al. 2013). Further, in a crossover RCT, single-dose oxytocin administered for 5 weeks in 31 children aged 3–8 years with ASD led to significant improvement in caregiver-rated social responses when compared to placebo (Yatawara et al. 2015). Conversely, other studies using multiple doses

of oxytocin have shown less effectiveness in individuals with ASD. Intranasal oxytocin did not improve outcomes in adolescents aged 7–16 years of age when given over 4 days (Dadds et al. 2014) nor administered bid for 8 weeks in youth aged 12–18 years (Guastella et al. 2015) with ASD.

N-acetylcysteine is an antioxidant that has a key role in regulating extracellular glutamate levels (Deepmala et al. 2015). There is a strong evidence base suggesting that abnormalities in the glutamatergic neurotransmission system could play an important role in ASD (James et al. 2006; Canitano and Scandurra 2014). Modulators of extracellular glutamate levels such as *N*-acetylcysteine have shown some benefit in treating irritability in children with ASD (Hardan et al. 2012; Fung et al. 2016). Furthermore, together with risperidone, *N*-acetylcysteine showed a positive improvement in treating irritability in youth with ASD (Ghanizadeh and Moghimi-Sarani 2013; Nikoo et al. 2015). Despite these findings, recently it was shown in youth with ASD that *N*-acetylcysteine had no significant impact on social impairment (Dean et al. 2016; Wink et al. 2016). The small sample sizes, the doses used in the studies together with different instruments used to capture changes preclude definitive inferences on the effectiveness of *N*-acetylcysteine from being made. Further larger scale studies that are sufficiently powered and are able to predict treatment response are warranted to confirm the efficacy of *N*-acetylcysteine in the childhood ASD population.

Sulforaphane is an extract derived from broccoli and one recent study in 44 young men aged 13–27 years randomized roughly 2:1 and diagnosed with moderate to severe ASD, showed that sulforaphane derived from the consumption of broccoli sprouts at levels usually found in the diet for 18 weeks, significantly (and reversibly) improved core behaviour in comparison to patients on placebo (Singh et al. 2015). This improvement regressed upon cessation of treatment. The interest in sulforaphane has amplified following the extensive epidemiological evidence from many countries demonstrating that consumption of Brassica vegetables (such as broccoli and rocket) was associated with a lower incidence of several human cancers, in particular of the prostate and breast. It is thought that sulforaphane can do this in part by up-regulating antioxidant genes involved in control mechanisms through the Keap1-Nrf2 cyto-protective signalling pathway. Moreover, it is well documented that sulforaphane can counteract many of the molecular processes inherent to neurodevelopmental disorders including oxidative stress, mitochondrial dysfunction and neuro-inflammation (Liu et al. 2016a) which are critical for the integrity of synaptic transmission and plasticity (Hagerman et al. 2010, 2011).

These disorder modifying compounds in ASD show promise in improving the core symptoms in ASD, however, before they can realize their full potential as novel clinical treatments, certain challenges need to be addressed. First, optimizing the dose would be imperative as well as the length of drug administration. Second, there are no ‘gold standard’, outcome measures that can capture changes in the core symptoms of ASD. Third, larger studies of a sufficient sample size are needed.

18.5 Tourette's Syndrome

As with ADHD and ASD, Giles de la Tourette syndrome (TS) has a multifactorial aetiology. About 0.85–1 % of the pediatric population worldwide is affected by TS (Robertson 2009, 2015) and is more frequent in males (male to female ratio 3:1 or 4:1) (Robertson et al. 1988). Whilst the precise causes remain to be established, it is likely that multiple immunological, genetic and environmental factors combine and interact with one another to establish susceptibility. Some studies have identified candidate genes that although might only account for a small proportion of cases, can still provide important information on understanding the disease at the molecular level. One candidate gene is Slit- and Trk-like family member 1 (*SLITRK1*) and members of the *SLITRK* gene family have a key role in promoting neurite outgrowth and development (Whitford et al. 2002). SLITRK1 is a transmembrane protein that is highly expressed in neuroanatomical regions of the brain commonly associated with TS such as the cortical, thalamic and basal nuclei regions (Proenca et al. 2011). A loss of function in the *SLITRK1* gene is thought to be associated with TS (Abelson et al. 2005) and some have suggested that the role of *SLITRK1* in TS causation might have been under estimated (Karagiannidis et al. 2012). Others have suggested that mutations in the *HDC* gene that codes for an enzyme involved in histamine biosynthesis (L-histidine decarboxylase) links disordered histaminergic neurotransmission to TS (Ercan-Sencicek et al. 2010; Karagiannidis et al. 2011). At the neuroimaging level, the evidence base suggests that the decreased size of the caudate nucleus maybe responsible for TS symptomatology (Robertson 2015). In youth with TS, others have shown immaturity and anomalous patterns of functional connectivity in control networks mostly in the fronto-parietal network of the brain (Church et al. 2009).

Tourette's syndrome is referred to as a syndrome (Robertson and Eapen 2014) and for a diagnosis to be fulfilled multiple motor tics together with one or more vocal/phonic tics for a duration of more than 1 year are required to be present (DSM-5 2013). The mean age of onset is about 7 years and typically motor tics tend to appear sooner (~7 years) than vocal/phonic tics (~11 years) (Robertson 2015). The overall opinion is that TS lessens in severity with age but does not completely disappear. Despite this, the comorbidities and psychopathologies that are associated with TS remain, which can have an impact on the treatment trajectory of the patient.

Tourette's syndrome can be demarcated into those with (i) pure TS, i.e. patients who present with solely motor and vocal tics but without any other co-occurring conditions or (ii) those who present with co-occurring conditions. About 12–13.5 % of diagnosed patients have pure TS (Robertson 2015); however, patients with TS frequently present with comorbidities such as ADHD, obsessive–compulsive disorder (OCD) and depressive disorder. Findings from 3500 patients with TS demonstrated that 88 % of patients had comorbidities or other psychopathologies (Freeman et al. 2000). In this study, the most common comorbid disorder was ADHD, followed by OCD and males were more at risk of developing

comorbid disorders than females (Freeman et al. 2000). ADHD is present in about 60 % of individuals with TS (Rothenberger and Roessner 2013). TS and its associated comorbidities can have a disabling impact on the quality of life of the individual from both an academic and social functioning perspective (Eapen et al. 2016).

18.5.1 Treatment Strategies in TS

As with other neurodevelopmental disorders, medication should not be the only factor that is considered when offering care. In the UK, unlike ADHD and ASD, there are at present no NICE guidelines for the treatment and management of TS in children. The general opinion is that behavioural therapies should be used as first choice in children with TS. These include habit reversal training (HRT) and exposure and response prevention (ERP) therapies (Verdellen et al. 2011). In terms of management, comprehensive behavioural intervention in comparison to education and supportive therapy was shown to give greater improvement in tic severity in children with TS (Piacentini et al. 2010). Aripiprazole can be used to provide symptomatic relief in TS with few side effects (Davies et al. 2006) especially in refractory cases. A recent meta-analysis has indicated that aripiprazole was safe and effective in reducing tics in children and adolescents with TS (Liu et al. 2016b). Low-dose aripiprazole is increasingly considered as the first medication choice in TS. Others have shown clonidine and guanfacine should be considered as first-line treatments for tics in children and adolescents with TS (Whittington et al. 2016). In a systematic review, pooled analysis from four placebo-controlled RCTs favoured the use of clonidine and guanfacine for the treatment of tics in children with moderate effect sizes (SMD = −0.71; 95 % CI −1.03, −0.40; n = 164) (Whittington et al. 2016). Sulpiride is useful when managing the symptoms in patients with TS (Robertson et al. 1990), whilst fluoxetine has been shown to be beneficial in managing the obsessive symptoms (Eapen et al. 1996). In treatment refractory and severe cases, deep brain stimulation appears to be another treatment option available for TS (Deeb et al. 2016).

18.5.2 Cross-Cultural Perspectives

From an Asian perspective, TS and its associated features have been less well studied in comparison to Western populations. Nevertheless, TS exhibits remarkable similarity across cultures in terms of comorbidity, associated conditions and treatment outcomes (Staley et al. 1997). There are, however, some variations amongst cultures particularly with regards to associated features and comorbidities (Robertson et al. 2009). Less obsessive–compulsive behaviour was seen in 30 South Korean patients (Min and Lee 1986) and a higher incidence of TS in Japanese males has been documented (Nomura et al. 1992) when compared to

Western counterparts. The incidence of inappropriate and involuntary swearing (coprolalia) in TS might also vary across cultures, with broad occurrence rates ranging from 4 to 11 % in Japan (Nomura and Segawa 1979; Nomura et al. 1992) to 60 % in Hong Kong (Lieh-Mak et al. 1982). Moreover, in 39 case reports across cultures, the occurrence of coprolalia was 74 % (Staley et al. 1997). Despite these findings, it is unclear whether these variations across cultures are a true reflection of TS. Differences in diagnostic instruments, sample selection methods coupled with the small sample sizes used across studies hinder accurate comparisons across cultures from being made. At present, only one study has explored cultural differences in TS patients using the same diagnostic instruments (Eapen and Robertson 2008). In this study, 35 patients with TS of Arab heritage from the United Arab Emirates (UAE) where compared to age and gender matched 35 white Caucasian patients with TS from the United Kingdom (UK). Apart from rates of coprolalia being higher in the white Caucasian cohort, the clinical characteristics such as male preponderance, site of initial tic location and mean age of onset were similar amongst the UK and UAE cohorts (Eapen and Robertson 2008). Taken together, these findings suggest that when adopting treatment strategies for patients with TS, cultural factors and potential variations in TS symptomatology across populations must also be taken into consideration whenever applicable.

18.6 Neuropsychiatric Symptoms in Rare Diseases (for Example, Rett Syndrome [RTT])

Rett syndrome (RTT), a pervasive neurological disorder (Rett 1966; Hagberg et al. 1983), is characterized by compromised brain functions leading to language and learning disabilities, repetitive stereotyped hand movements and developmental regression. This condition is being discussed as an example of how one can manage neuropsychiatric symptoms accompanying many rare genetic diseases that present within developing countries.

Rett syndrome is predominantly found in young females with an incidence of 1: 20,000 live births (Kozinetz et al. 1993) although cases have been documented in males (Moog et al. 2003; Reichow et al. 2015). RTT presents with a complex clinical picture. Cianfaglione et al. (2015) provided evidence for a definable behavioural phenotype in individuals with RTT including hand stereotypies, breathing abnormalities, night-time unrest, anxiety and inappropriate fear. Hand stereotypies (hand wringing) appeared to be the most characteristic amongst individuals with RTT when compared to the contrast group that consisted of individuals with intellectual disability associated with a variety of genetic syndromes other than RTT.

The vast majority of patients with RTT have a loss of function in the methyl-CpG binding protein 2 (*MeCP2*) gene (Bienvenu et al. 2000), with some cases

of RTT arising from mutations in CDKL5 and FOXG1 genes (Evans et al. 2005; Philippe et al. 2010). More recently, others have identified novel candidate genes not previously associated with RTT such as those encoding ankyrin repeat containing proteins or neuronal acetylcholine receptor subunit alpha 5 subunits (Lucariello et al. 2016). MeCP2 is a highly conserved nuclear protein that is expressed widely in the mammalian brain (Lewis et al. 1992). Loss of MeCP2 does not result in neuronal cell death as the phenotype is reversible in mice models of RTT (Guy et al. 2007) and in *MECP2* duplication syndrome (Sztainberg et al. 2015).

Literature evidence suggests that MeCP2 is a critical epigenetic modulator in the brain, controlling mechanisms such as DNA methylation and post-translational mechanisms (see Katz et al. 2016). These processes regulate gene expression without altering DNA sequences, and in mature neurons others have suggested that the role of MeCP2 is to dampen transcriptional noise (Skene et al. 2010). Most likely, dysfunction in MeCP2 causes defective transcriptional repression mechanisms, possibly in part governed by differential post-translational modification of MeCP2 at serine 164 (Stefanelli et al. 2016). MeCP2 also appears to be critical loci for other proteins. Recently, mutation in the gene *switch-insensitive 3 family member A* (*SIN3A*), a MeCP2 interactor and transcriptional repressor that has an important role in cortex development, causes intellectual disability and ASD (Witteveen et al. 2016). Moreover, the $MeCP2^{R306C}$ mutation prevents it from interacting with the NCoR/histone deacetylase 3 (HDAC3) complex which causes impairments in social and cognitive functioning in animal models (Nott et al. 2016).

The general consensus is that MeCP2 dysfunction causes deleterious gene expression which in turn has a marked impact on post-natal neuronal development and contributes to the disease pathophysiology in individuals who present with the classical RTT phenotype. Recently, it was shown that mutations in MeCP2 cause neurological dysfunction by specifically disrupting long gene expression within the brain (Gabel et al. 2015). Phenotypically, RTT is quite heterogeneous in nature and it is likely that post-translational modifications of long genes implicated in neuronal development regulate the functional and developmental versatility of MeCP2 (Bellini et al. 2014; Gabel et al. 2015). In RTT, the clinical picture ranges from individuals who are high functioning, to those who are severely disabled. Individuals with RTT appear to develop normally up to 6–18 months of age. However, this is followed by a period of developmental stagnation and regression with significant loss of speech and social interaction.

At the neuronal level, the architecture of brains in patients with RTT is altered, with dysfunction and general paucity in dendritic branching and spines, which contribute to the abnormal synaptic morphology (Armstrong et al. 1995; Chapleau et al. 2009). In support of these findings, there is also likely to be altered expression of both excitatory and inhibitory synaptic receptors in the brain of RTT patients, supporting the premise that disordered homeostasis of excitatory (Meng et al. 2016) and inhibitory (Ure et al. 2016) signaling coupled with perturbations in neuronal architecture contribute to disordered modulation and maintenance of critical synaptic pathways in RTT brains (Dani et al. 2005; Chao et al. 2010).

Pre-clinical animal models provide a window of opportunity to explore the complex facets of RTT. Recently, SUMOylation, a type of post-translational modification, of MeCP2 was shown to restore behavioural abnormalities in an animal model of RTT (Tai et al. 2016) and deep brain simulation can rescue cognitive dysfunction (Hao et al. 2015) and hippocampal circuit impairment (Lu et al. 2016) in RTT mice. Furthermore, using different pharmacological agents, defects in synaptic architecture and breathing have been restored in MeCP2 null mice (Bittolo et al. 2016; Gogliotti et al. 2016; Patrizi et al. 2016). Others have shown in mouse models of RTT that some of the core features of RTT related to social interaction and anxiety-like behaviour might be caused by abnormal neuronal wiring of the peripheral nervous system (Orefice et al. 2016). Taken at face value, these studies provide very important therapeutic gateways into clinical trials. However, as was shown for Fragile X (Berry-Kravis et al. 2016), which shares some commonalities with RTT such as intellectual disability and ASD, how effectively these animal models translate into studies involving RTT patients remains unclear.

18.6.1 Emotional, Behavioural and Autonomic Dysregulation (EBAD)

Autonomic dysregulation also known as dysautonomia refers to an imbalance between the sympathetic and parasympathetic elements of the autonomic nervous system (ANS) or more broadly speaking refers to any abnormality of the autonomic nervous system. Some examples are vasovagal syncope, neuroleptic malignant syndrome and autonomic dysreflexia but also effects due to medication such as serotonin syndrome (Schwantes and O'Brien 2014). There are several medical conditions that present with ANS imbalances (Baguley 2008); however, what are not readily obvious are the emotional and behavioural components of autonomic dysfunction. Emotional and behavioural dysregulation is common across diagnostic groups and occurs in children with early maltreatment, multiple co-occurring neurodevelopment disorders (such as borderline personality disorder, bipolar disorder, ASD, ADHD and disorders of mixed emotional conduct), acquired brain injury and many rare disorders (Dvir et al. 2014; McLaughlin et al. 2015; Mandavia et al. 2016; Shaw et al. 2014; Li and Liu 2013). Despite this evidence base, there is a scarcity in the literature in terms of evaluating the impact of the autonomic component on these disorders. Autonomic dysregulation has implications for treating and managing the sympathetic and parasympathetic disequilibrium in patients alongside behaviour and emotional dysregulation. Clinically, this situation is often found in treatment non-responders and those with significant functional disability. When emotional and behavioural dysregulation co-occurs in the context of autonomic dysregulation, the term EBAD (**E**motional, **B**ehavioural and **A**utonomic **D**ysregulation) has been coined.

It has become increasingly clear at the Centre for Interventional Paediatric Psychopharmacology and Rare Diseases (CIPPRD), a National Specialist Child and Adolescent Mental Health Service based at the Maudsley Hospital, London, UK, that managing EBAD is central to reducing impairment in complex neuropsychiatric disorders (Santosh et al. 2016), such as those encountered in many rare diseases. When dealing with rare diseases with a limited patient population, it is important that patients can be stratified using phenotype and biomarkers (such as those obtained through wearable sensor monitoring). Ideally, responsive adaptive clinical trial designs using Bayesian approaches that boost the statistical power and reduce the number of patients required for a rare-disease trial should be used (Hampson et al. 2015). Using rare-disease-specific outcome measures as primary end-points and surrogate biomarkers as secondary outcomes will improve the identification of compounds that produce an improvement in this emerging field of research.

When managing rare diseases, EBAD is important to consider as impairments occur in multiple overlapping body systems which can give rise to abnormal physiological responses. RTT can be considered as a congenital dysautonomia (Julu et al. 2001). Genes that are important in regulation of the ANS are likely to be effected in RTT and in these children, understanding the individual physiological reactions (biomarkers of EBAD) would be a critical part when planning treatment strategies, using web-based health monitoring and wearable sensor technology. In Sect. 18.6.1.3, a case will be presented to demonstrate how wearable sensor technology in conjunction with treatment with the 5HT1A partial agonist buspirone can be used to manage EBAD in a 15-year-old girl with RTT who presented with significant emotional and behavioural dysregulation, and autonomic dysfunction. We show that treatment with buspirone improved the autonomic dysfunction and EBAD in this patient.

18.6.1.1 Autonomic Function in RTT

Dysautonomia, i.e. a dysregulation of the parasympathetic and sympathetic components of the ANS, occurs in as much as 75 % of patients with RTT (Sansom et al. 1993) and the subsequent sympathovagal imbalance is thought to be a unique to individuals with RTT (Halbach et al. 2016). Dysautonomia is a leading cause of sudden death (Guideri and Acampa 2005) in RTT. Typically, the autonomic dysregulation can manifest as palpitations, panic attacks and diaphoresis. Evidence has indicated that brainstem immaturity (Julu and Witt Engerström 2005; Julu et al. 1997, 2001) in particular underdevelopment of nascent serotoninergic neurotransmission pathways (Guideri et al. 2004; Paterson et al. 2005) is a major underlying component causing the autonomic dysregulation in those with RTT. Autonomic dysfunction has been explored previously in patients with RTT (Naidu 1987; Paterson et al. 2005) and HR variability has been used as a tool for assessing sympathovagal imbalance in RTT (Dotti et al. 2004; Guideri and Acampa 2005). HR variability provides an indirect measure of autonomic regulation and

is usually signified by the low frequency (LF) and high frequency (HF) ratio (LF/HF). However, the relationship between the sympathetic and parasympathetic components of the ANS and their effect on LF/HF (i.e. HR variability) is nonlinear and therefore not entirely obvious (Billman 2013). Nevertheless, although, having some opponents (Hopf et al. 1995; Eckberg 1997; Houle and Billman 1999; Billman 2013), the LF/HF ratio has been used widely as an index for the assessment of autonomic regulation of the cardiovascular system, whereby increases in LF/HF are thought to reflect a shift towards sympathetic activity and conversely decreases signify a shift towards parasympathetic activity (Billman 2013). In RTT, breathing dysrhythmia is one of the characteristic clinical features (Halbach et al. 2016), with forceful, feeble or apneustic breathing (Julu et al. 2008; Smeets et al. 2006; Julu and Witt Engerström 2005), with some having defective control of carbon dioxide metabolism (Halbach et al. 2011). These factors are important when assessing EBAD in RTT given the premise that it has been widely documented that respiratory parameters can modify HR variability (i.e. LF/HF) independent of changes exerted by the ANS (Billman 2013) and that carbon dioxide levels through interaction with chemoreceptors can also modulate in parallel sympathetic and parasympathetic components of the ANS (Eckberg 1997).

18.6.1.2 Using Web-Based Health Monitoring and Wearable Sensor Technology

The rates of development of digital health platforms and risk stratification strategies have rapidly increased in recent years and are widely adopted in medicine to assist in clinical decision-making. The CIPPRD uses a suite of instruments to monitor outcomes using the web-based HealthTracker™ health-monitoring platform—the HealthTracker™ (Santosh et al. 2016). The HealthTracker™ is a web-based health monitoring platform that allows for routine capture of symptoms, side effects, quality of life (QoL), patient experience and life-time response to individualized treatment episodes, using a multi-informant, multimodal methodology. It allows tracking of ongoing medical treatments and assists in optimal shared treatment decision-making and longitudinal patient centred outcome monitoring. The HealthTracker™ provides clinicians with baseline and longitudinal overview of symptom, side effects, QoL, patient experience and treatment response for each patient (Santosh and Singh 2016). Advances in wearable sensor technology have allowed it to be used by children with complex neurodevelopmental disorders such as in RTT. The technology is non-invasive, child-friendly, and allows real-time monitoring of biometric physiological data (heart rate [HR], skin conductance, blood volume pressure, perspiration and temperature) and how they might relate to medication use as well as external factors. In subjects with intellectual disability, poor communication and EBAD, mapping the physiological responses using sensor technology allows for a biometric proxy measure to assist in improving the dysregulation in EBAD.

The CIPPRD is pioneering the use of wearable sensor technology and uses real-time biometric physiological data obtained from different devices in patients with RTT and uses the captured biometric measures as biomarkers to assist in patient management. Once the physiological dysregulation has been identified, the clinician teaches parent/carer(s) to use the wearable sensor technology to track changes that require intervention and, for example, to understand what activities produce physiological stress and what activities/interventions help to normalize the physiological state. The sensor technology allows for colour-based alerts which show whether the HR is too high for the child in question, leading to parents/carers understanding that the child might be experiencing distress and so can use calming strategies for the patient. We have been able to help parents, carers and teachers who become aware of the situation sooner (often before behavioural meltdowns) via the biometric signals from the wearable sensor technology so that timely therapeutic action, i.e. stress-reducing strategies, can be taken (Santosh and Singh 2016).

18.6.1.3 Case

The subject was a 15-year-old girl with a clinical and genetic diagnosis of RTT who presented with significant emotional and behavioural dysregulation with concomitant autonomic dysfunction. Wearable sensor technology was used to monitor biometric physiological biomarker (HR variability and electro-dermal activity [EDA]) and the data for pre-treatment and post-treatment (30 mg/day buspirone) is presented in Fig. 18.1A1–A4 [pre-treatment] and B1–B4 [post-treatment]).

EDA at 1-h time intervals of pre- and post-treatment was analysed using Excel and SPSS software, and as described by Benedek and Kaernbach (2010). Whilst at pre-treatment there was significant variability in EDA (Fig. 18.1A1), this variability reduced significantly with buspirone treatment (Fig. 18.1B1). Heart rate (HR) variability at given time sessions was analysed with Kubios software (version 2.2) (http://kubios.uef.fi.) using time-domain, frequency-domain and nonlinear methods as described in Tarvainen et al. (2014). As noted in the time-domain histogram (Fig. 18.1A2), at pre-treatment, the average HR was 99.67 ± 18.79 beats/min. Following 30 mg/day buspirone, the average HR decreased to 82.20 ± 12.35 beats/min (Fig. 18.1B2).

Evaluable literature supports the premise that the HF component is associated solely with cardiac parasympathetic activity, whilst the LF component, although more complex, is thought reflect a more dominant sympathetic profile (Berntson et al. 1997; Billman 2011). Increases in LF/HF are thought to reflect a shift towards sympathetic activity and conversely decreases signify a shift towards parasympathetic activity (Billman 2013).

The data presented in Fig. 18.1 show a tendency to a shift towards parasympathetic dominance following treatment with buspirone. At 30 mg mg/day buspirone, the HR variability is far less (Fig. 18.1B2). This finding is further corroborated by the width of the Poincaré plot (Fig. 18.1B4) as this is greater than when compared

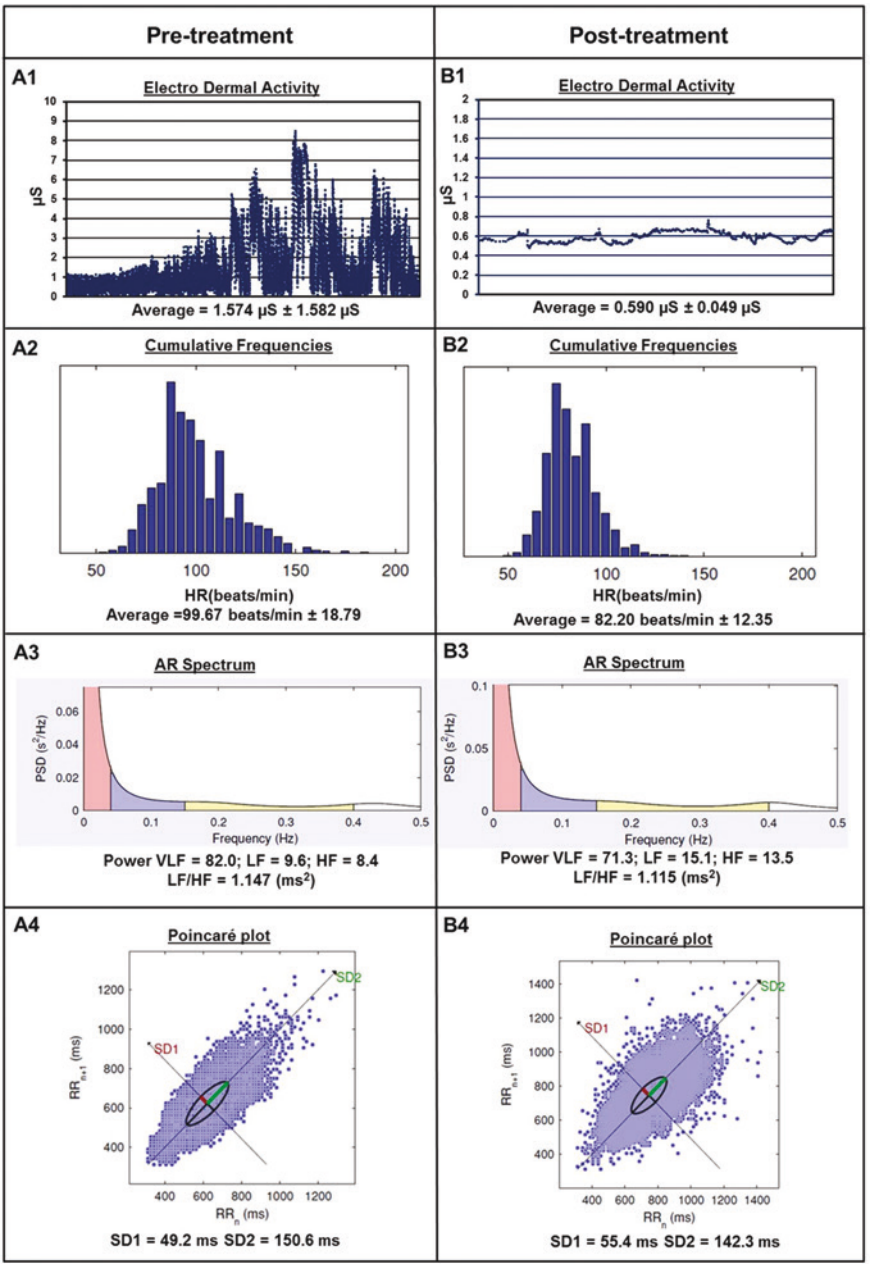

Fig. 18.1 Wearable sensor based biometric physiological data in a 15-year-old girl with Rett syndrome. *Notes* For frequency-domain results, spectral factorization was not used for the AR spectrum (AR model order = 16). Results were calculated from the non-detrended selected RR series. In panel A1, A2, B1 and B2, the data is presented as averages ± standard deviation (SD). *Abbreviations* Autoregressive (AR); High Frequency (HF); Low Frequency (LF); Standard Deviation (SD); Very Low Frequency (VLF)

to the Poincaré plot at baseline (Fig. 18.1A4). The width of the Poincaré plot can be used as a useful quantitative visual index of parasympathetic activity (Kamen et al. 1996). Taken together, these findings show that there was a recalibration of the autonomic equilibrium from pre-treatment to post-treatment. Buspirone 30 mg/day reduced the HR variability and EDA variability (measures of autonomic dysregulation), alongside emotional and behavioural symptoms—that is, an improvement in EBAD. This case represents an example, whereby monitoring and understanding the physiological responses is important when managing EBAD. This strategy is currently being tested in the CIPPRD and needs to be validated in other routine clinical settings.

18.7 Concluding Remarks

Neurodevelopmental disorders persist through development across the age range. It is necessary to combine pharmacological and non-pharmacological interventions together in order to optimize treatment outcomes. At present most treatments focus on symptomatic management, for example, hyperactivity and inattention; irritability, aggression and agitation; anxiety and low mood; tics; mood lability; psychotic symptoms; etc., rather than treatments being disorder-specific. The core symptoms of ASD have not shown response to pharmacological treatments till recently. These studies have shown some improvement of core symptoms (see Santosh and Singh 2016) and it would be of value to build upon the pertinent findings.

It is suggested that emerging technologies can provide biomarkers that can be useful in determining which subjects are most likely to respond and provide early detection of treatment effectiveness. Neuroimaging-based biomarkers would also be a useful adjunct to consider. Neuroimaging-based biomarkers developed using machine learning algorithms can help to unravel and identify pertinent neural phenotypes. Recently, this approach was used to show that a small number of abnormal brain connections were predictive for adult ASD (Yahata et al. 2016). Advancement of optogenetic tools may also shed light on pin-pointing circuit-level understanding of neuronal activity in neurodevelopmental disorders and may help to unravel complex neural mechanisms especially during social interaction (Gunaydin et al. 2014). It is also important to consider a balanced safety and efficacy profile in treatments that are used. In this regard, the EDMS strategy should be adopted to achieve the most acceptable improvement of symptoms with the least minimal side effects (Santosh and Singh 2016). Managing EBAD using wearable sensor technology would also be useful in the management of complex neuropsychiatric disorders especially in the case of individuals with rare diseases.

When treating neurodevelopmental disorders, it is likely that cross-cultural differences between Asian and Western cultures exist. From an Asian perspective, medication might not be readily available and cost of medication per patient would also need to be taken into account. Other factors that need to be considered are

the lack of evidence base, in particular the paucity in the number of randomized placebo-controlled double-blind trials conducted in Asia. This coupled with the insufficient numbers of child psychiatrists and behavioural pediatricians for the populations served makes managing patients less straightforward in comparison to Western counterparts.

To summarize, in children and adolescents, a holistic approach should be adopted for managing care. Pharmacology should be used as an adjunct together with psychosocial, language and behavioural intervention therapies. Careful monitoring of pharmacological treatment is paramount and EDMS strategy together with wearable sensor technologies are important avenues for consideration. Research in the neurodevelopment field is expanding quickly and the heterogeneity of these disorders is an important obstacle that requires careful consideration. There is hope, however, that having opened up new inlets, researchers might soon provide ways to overcome such obstacles. Epigenetic strategies would be a useful foil to adopt. Targeting epigenetic dysregulation of neurodevelopmental disorders would be an important step when navigating forward and can help to bridge the gap in our understanding of genetic and environmental basis of disease mechanisms.

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Informed consent was obtained from the parent of the child with Rett syndrome.

Declaration of Interest: Dr. Paramala Santosh is the Head of the Centre for Interventional Pediatric Psychopharmacology and Rare Diseases (CIPPRD), Maudsley Hospital, London and is also the co-inventor of the HealthTracker™ and is a Director and shareholder in HealthTracker Ltd.

Dr. Jatinder Singh has no conflicts of interest to declare.

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