Chapter 17
Pediatric Psychopharmacology: Perspectives from Low Resource Countries

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Abstract Systematic research and evidence to guide prescribing practices for children and adolescents with psychiatric disorders, have seen tremendous growth in the last two decades. Despite the lack of trained personnel and capabilities for multidisciplinary care in low resource countries, use of psychopharmacological treatments in children has seen wide dissemination. Mostly guided by data from the West, there are a few contributions in the field of pediatric psychopharmacology from India. For a rational prescriber, the most sought-after knowledge would be regarding proper diagnosis, selection of the right medicine, pharmacokinetics, pharmacodynamics, proper dosage, dose titration schedule, side effects, and drug interactions of the relevant drugs. Better characterization of childhood psychiatric disorders; advances in developmental neurobiology; cellular and molecular mechanisms of neuronal functions; and advent of newer and more specifically targeted psychotropic drugs have contributed to the advancements in pediatric psychopharmacology.

Keywords Pediatric psychopharmacology · Challenges low resource countries · Pharmacokinetics pharmacodynamics · Drug interactions · Psychiatric disorders · Pharmacotherapies

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17.1 Introduction

Historically, pediatric pharmacology in general, and pediatric psychopharmacology in particular, have received much less research interest and funding than their adult counterparts. As a consequence, relatively few drugs are licensed for use in child and adolescent populations (Coghill and Sinita 2014). There is growing evidence that the use of psychopharmacological agents in children and adolescents has increased manifold and gained widespread acceptance (Zito et al. 2008; Huline-Dickens 2014). Alongside this, the debate whether this trend may be truly beneficial or harmful in the long run, still rages on (Rapoport 2013).

Childhood and adolescence, being a period of key biological, psychological and social growth, renders individuals more vulnerable to disruptions in healthy development. It has been reported that nearly 50 % of all adult psychiatric disorders manifest as early as age 14, and 75 % manifest by age 24 (Kessler et al. 2005). Nearly two-thirds of mental disorders that have their onset in childhood or adolescence are likely to be moderate to severe, and most of them continue into adulthood (Kessler et al. 2012). Thus, it is crucial that these disorders are identified and treated early, so as to minimize disruptions in the individual's developmental trajectory and hence reduce suffering (Correll et al. 2013).

17.2 The Chronology of Progress

A number of developments in the treatment of psychiatric disorders in children and adolescents have occurred, especially in the last two decades, which have been groundbreaking. Psychological and behavioral interventions were once the mainstay of treatment in child psychiatric disorders. But psychopharmacological approaches have provided important biological management tools. In recent years, child psychopharmacology is thus becoming more important day by day.

To promote research in the field of child psychopharmacology, the US Congress in 1997 authorized the United States Food and Drug Administration (US FDA) to grant an additional 6 months of drug exclusivity in return for conducting specific studies in children. Also, the US FDA, by its ''Best Pharmaceuticals for Children Act'' mandates that clinical trials are to be conducted in pediatric population by the pharmaceutical industry, especially when there is a possibility that the drugs may be of use in the children and adolescents. Research Units on Pediatric Psychopharmacology (RUPPs) under the leadership of the National Institute of Mental Health (NIMH) have formed. These measures have contributed to the remarkable increase in research relevant to child psychopharmacology since the last two decades (Vitiello 2006).

17.3 Low Resource Countries—The Challenges Faced

(1) **Paucity of Psychiatrists with Specialized Training in Child and Adolescent Psychiatry**

Mental health issues are being recognized more and more at an earlier age. The shortage of psychiatrists with specialized training is always the main constraint in case of developing countries. Current models that rely on psychiatrists to deliver direct care are unsuitable for low and middle income countries, where number of mental health professional is limited. A shift to a collaborative care model has been proposed, wherein the role of a psychiatrist is to provide training, supervision, and tertiary-level care. The majority of the service delivery, which comprises of treating common mental disorders, is to be provided by primary care professionals and community health workers, who would receive training and supervision from the tertiary care centers (Becker and Kleinman 2014; Malhotra and Padhy 2015).

(2) **Lack of Professionals to Aid in Psychosocial Interventions**

There is a huge dearth of personnel trained to provide evidence-based psychological, social, and educational therapies, which are essential to holistic treatment and rehabilitation of psychiatric illnesses especially in children. Very few centers have an infrastructure to provide multidisciplinary care, which is a basic standard in most high-income countries. The burden of providing, or coordinating these also rests upon the psychiatrist.

The increasing prevalence of childhood psychiatric disorders, along with constraint of resources makes work difficult in real-life situation, and may necessitate some practical changes. In order to cope with large numbers of patients in need of psychiatric treatment with acutely deficient manpower, clinical work-up has to be brief; therapeutic sessions may have to be cut down to simpler modules involving counseling; and parents and families have to become therapeutic allies as well as co therapists Medication thus assumes a more critical role in treatment, with possibly involving the nonspecialist psychiatrists/pediatricians; and a tendency to over-rely and over-prescribe medications. This partly also stems from clinicians' wish to be helpful with whatever resources available at hand. Judicious evidence-based prescribing, slow titration and never, ever, overprescribing, needs be emphasized to improve treatment outcomes in children.

(3) **Availability and Regulation of Psychotropics**

Most antipsychotics, antidepressants, mood stabilizers, and benzodiazepines are easily available in most low resource countries. This is partly due to measures by the World Health Organization to include these as "essential medications," and mostly due to the pharmaceutical industry. Even stimulant medications, though not as readily available as other psychotropics, are generally within reach of most populations and at affordable costs. The main challenge in developing countries,

however, has been poor regulation of prescription and sale of psychotropics. Polypharmacy, off-label use of medications, is rampant. Along with the lack of training and resources for monitoring adverse effects, the onus on clinicians to use more discretion in treating children is thus much larger.

(4) **Cultural Factors, Knowledge, and Attitudes of Parents and Teachers**

On the one hand, there are problems of lack of knowledge and failure of timely referral for psychiatric consultation. Furthermore, spiritual and magico-religious beliefs lead parents to take their children to faith healers for psychological problems causing treatment delays. All too often, a psychiatric consultation is sought only when there is an acute deterioration of clinical status, such as catatonic symptoms or suicide, or when the patient or family starting to lose hope in other treatments and turns to medications "as a last resort" (Shrivastava et al. 2013). Educating patients and families that prolong the duration of untreated symptoms and waiting for the illness to become more severe may decrease the likelihood of response or remission of symptoms, which is part of the clinician's overall responsibility (Stroeh and Trivedi 2012).

On the other hand, stigmatization and criticism of certain diagnoses and treatments (especially attention-deficit hyperactivity disorder [ADHD]) and stimulant medications in particular) in media and in the internet infusing negative attitudes amongst people, and reluctance of families to expose children to "mind altering drugs" in middle and upper socioeconomic groups is equally strong.

In summary, caregivers need to be educated to bring children early for assessment, adopt a more rational and informed approach to acceptance of psychopharmacology in children.

17.4 Treatment Gap and Need for an Indigenous Service Model

Children and adolescents with psychiatric illness in developing economies is a grossly under-cared section of population. By rough estimates, 6–20 % of children and adolescents have a diagnosable mental health disorder (Malhotra and Patra 2014). Very few have access to specialist services. The treatment gap is huge.

An indigenous service delivery model needs to be developed. More than in developed economies, training general psychiatrists, pediatricians, and family physicians may be required to bridge the gap. The bare minimum skills that they need to be sensitized about are proper identification of childhood psychiatric disorders, evidence-based medication choice and dosing, monitoring for adverse effects, along with basic counseling and psychoeducation abilities.

Transmitting information in this collaborative model has to be specifically very restricted and simple. General physicians and pediatricians have to be acquainted with a restricted number of medicines. In the case of antipsychotics, possible

drugs are risperidone, aripiprazole, and quetiapine; in case of antidepressants, fluoxetine, sertraline, and escitalopram; among mood stabilizers, lithium, and divalproex and among drugs for ADHD, methylphenidate, and atomoxetine.

An innovative model that has been studied in the Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh is the use of automated clinical decision support system through telepsychiatry services to facilitate diagnosis, treatment at the primary care level along with collaboration, and referral for more complicated cases (Malhotra et al. 2015) can be a viable option.

17.5 The Research Gap

Owing to the above-mentioned factors, research in child psychopharmacology from low resource countries has been minimal (Malhotra and Padhy 2015; Malhotra and Kate 2015a, b), though studies have started to emerge over the last few years (Malhotra and Kate 2015a, b; Malhotra and Banerjee 2009a, b). Much of the available research is in the form of case reports or open-label trials. Clinicians have to rely almost exclusively on evidence from studies in western populations to guide their selection of drugs, dosages, interactions, etc. There are likely to be differences in pharmacokinetic and dynamics owing to various genetic, biological factors, which may affect treatment. Other factors, such as treatment seeking and adherence also need to be addressed, as they also have a significant impact on management.

Below is a brief review of the available evidence in pediatric psychopharmacology, including research from lower-resource countries (mostly India), wherever available.

17.6 General Principles of Prescribing for Children

It is not easy or straightforward to formulate principles of prescribing psychotropic medications in children. Many a times, illnesses do not fully evolve, such that "syndromic" diagnosis may be difficult to make. Thus, more often than not, it is "symptoms" that are targeted, rather than underlying disease processes. Also, as presence of comorbidity is a "rule rather than an exception," diagnoses become more complicated.

The dictum for prescribing psychotropics in children has always been "begin with less, go slow and be prepared to end with more." The ideal way to decide the dose is mg/kg per day, but this should be child-specific data and not one extrapolated from adults. Also, even though monotherapy is preferred, polypharmacy may often be required. Off-label use of medications may quite often be necessary. Whether it is monotherapy, polypharmacy, or off-label use of medication, the rationale for including a drug in treatment plan, has to be based on a sound scientific basis.

In addition, regular monitoring of treatment in childhood and adolescence is very important. Ample time for an adequate trial of treatment should be considered, and wherever possible, only one drug at a time has to be changed or modified. Outcomes are better monitored in more than one setting, like home, school, and the playground.

As the aphorism goes, "children are not half, quarter or one-tenth adults," they need to be studied separately for their own data. One cannot just extrapolate data from adults to children. Simple body weight basis of drug dose fixation is not adequate. Pharmacodynamics and pharmacokinetic considerations are important. Most importantly, the possibility that long-term use of certain medications may cause deleterious effects on the developing brain have to be kept in mind, and need to be studied further (Karanges and McGregor 2011; Marrus et al. 2014).

17.7 Pharmacodynamics

Serotonin, dopamine, norepinephrine, and GABAergic networks are the main targets of most currently used psychotropic medications. These neurotransmitter systems undergo numerous developmental changes (Rho and Storey 2001; Chugan et al. 2001), the impact of which may have major implications on the efficacy and tolerability of psychotropics in children. This is evident from various studies, which have shown in children that tricyclic antidepressants have no antidepressant effect (Hazell et al. 1995); stimulants are less likely to produce euphoria; susceptibility to the metabolic side effects of antipsychotics is much higher (Correll et al. 2009); serotonergic antidepressants may induce suicidal ideations and attempts (Hammad et al. 2006; Stone et al. 2009). The relative lack of efficacy and tolerability of methylphenidate in pre-school age children (between 3 and 5 years of age), as compared to older children (Greenhill et al. 2006) also highlights this fact. It is also well known that first-generation antipsychotics produce acute dystonic reactions much more commonly in children and adolescents, especially males, than in adults. This clearly elucidates the need for separate drug trials in younger age groups. Only such evidence can inform rational, safer, and better prescribing and hence better treatment outcomes for children with psychiatric illnesses (Vitiello 2014).

17.8 Pharmacokinetics

Beginning from absorption of the drug till the process of excretion, there are numerous differences between adults and children, which need to be kept in mind while prescribing for children.

Absorption:

Although the extent of drug absorption for most medications is similar in children and adults, the rate of absorption may be faster in children and peak levels are reached earlier. Absorption is also dependent on the form in which it is administered, i.e., liquid versus tablet, and levels peak faster for liquid preparations (Santosh 2009). Ionized drugs (many of which are weak acids) may be less well absorbed from a child's less acid stomach (Taylor 2015).

Metabolism:

The normal rate of hepatic metabolism is high in children until the time of puberty. The result is that most medications are aggressively metabolized in the liver and rapidly excreted. Because what ultimately matters is how much of the drug enters the bloodstream, treatment of pre-pubertal children may require dose that approach or equal those for adults. The use of seemingly high doses for young children may seem counterintuitive to many parents, and thus it will be helpful for clinicians to explain the role of increased rate of drug metabolism.

During the entry into puberty, the rate of hepatic metabolism significantly slows down. For this reason, young children who have been on long-term maintenance doses of psychiatric medications and were tolerating it well may start to have worsening adverse effects around the time of puberty when this lowering of the hepatic metabolic rate occurs. Dosage adjustments may then be required, to minimize side effects (Preston et al. 2015a).

Distribution:

Children differ from adults in the proportions of extracellular water volume and body fat. The proportion of extracellular water decreases substantially from birth through early adolescence, resulting in a relatively larger distribution volume for water-soluble drugs in younger children, who therefore require a relatively higher dose to achieve a comparable plasma concentration (Johnson et al. 2015).

Blood—brain barrier:

The blood–brain barrier is possibly more permeable in children than in adults (Benedetti and Baltes 2003). The greater permeability of the blood–brain barrier in children may mean a greater proportion of the drug reaches the brain in a shorter duration of time, thus leading to greater than predicted efficacy or adverse reactions with smaller dosages (Taylor 2015).

Excretion:

Most psychotropics are eliminated mainly through the kidneys, biliary excretion; and excretion through skin and lungs account for a smaller proportion. It should be noted that although the absolute clearance is usually lower in children than in adults, the weight-adjusted clearance is greater. This is possibly because children have greater renal and liver parenchymal volumes relative to the body size as compared to adults. As the drugs are eliminated faster, plasma half-lives are often of

shorter durations in children than in adults. A shorter elimination half-life means that plasma steady state is reached sooner during repeated administration, and that withdrawal symptoms upon discontinuation are more likely. Thus, in children, a more frequent dosing may be needed in order to maintain stable therapeutic levels and avoid withdrawal symptoms between dosing (Vitiello 2014).

17.9 Clinical Guidelines

Unlike in adults, there are very few evidence-based practice guidelines for children. The practice parameters provided by the American Academy of Child and Adolescent Psychiatry (AACAP) are perhaps the most widely used and quoted. The National Institute of Clinical Excellence (NICE) also provides clinical guidelines for most child psychiatric disorders.

The numerous above-mentioned complexities of pharmacokinetic and pharmacodynamic factors always have to be taken into account. In every case, it is necessary that the dose be very gradually titrated against the desired clinical response. Wherever possible, blood levels should be monitored, especially of those medications that have an unpredictable or a narrow therapeutic window. Some of these drug levels, e.g., lithium and anticonvulsants, are very useful in monitoring the optimum dose of the drugs. Maintenance level for lithium is 0.6–1.2 mEq/L. Therapeutic level for carbamazepine is 8–12 ng/ml and for valproic acid is 50–125 μg/ml (Cobert 2013a).

17.10 Preventive Measures to Avoid Drug Interactions

It is important to obtain a detailed medication history including over-the-counter (OTC) drugs and compounds from alternative approaches than modern medicine. As young patients constitute high-risk group, usage drugs with minimum interaction potential is preferred.

Avoid polypharmacy, whenever possible. Educate patient and their families, include written instruction, when appropriate, and keep detailed, updated references on important potential drug interactions (Konar 2005).

17.11 Common Conditions Requiring Pharmacotherapies

Common pharmacotherapies for some of the common pediatric psychiatric disorders are covered here. Readers are also referred to the next chapter in this book written by Dr. Jatinder Singh and Dr. Paramala J. Santosh, which is an excellent review of treatment of neurodevelopmental disorders in children.

Anxiety Disorders

Both cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) are effective treatments for anxiety disorders in children and adolescents. Studies of tricyclic antidepressants (TCAs) have not shown efficacy (Chrzanowski et al. 2014). There is little evidence to support the use of non-antidepressant medication (Vallance and Fernandez 2014). Benzodiazepines should be prescribed only when other pharmacological approaches have failed, or to cover for the latency of onset of action of SSRIs when anxiety is severe. They should be prescribed only for weeks, and not months. Buspirone, a nonbenzodiazepine anxiolytic (5-HT$_{1A}$ partial agonist), has been found to be of comparable efficacy to the benzodiazepines, with fewer adverse events, in several open-label trials in children with anxiety disorders. However, no controlled data are available for either safety or efficacy (Sinita and Coghill 2014).

Obsessive Compulsive Disorder (OCD)

Several randomized controlled studies have established the efficacy of serotonin reuptake inhibitors (clomipramine, fluoxetine, sertraline, fluvoxamine) in the treatment of OCD in children, with no demonstrable superiority of any particular agent apart from clomipramine (Geller et al. 2003; Preston et al. 2015b). The Pediatric OCD Treatment Study (POTS) showed that combined treatment (CBT + sertraline) was superior to either CBT or sertraline alone, there was no treatment emergent suicidality in the study (Franklin et al. 2011).

There are a few studies from India on the clinical profile, course, and outcome of juvenile-onset OCD (Reddy et al. 2010). However, as of yet, there are no studies evaluating its pharmacotherapy.

Autism Spectrum Disorders

A wide range of medications have been tried in autism to improve various target symptoms such as aggression, comorbid disorders such depression and OCD, and also core features such as deficient social communication and stereotypies. These medications include psychotropics (antipsychotics, antidepressants, stimulants) and naltrexone, oxytocin and nutritional supplements just to name a few.

Children who were taking risperidone showed significant improvement in behaviors including aggression, self-injury, and tantrums, and 87 % of risperidone-treated subjects showed global improvement in their conditions, compared to 40 % of subjects treated with placebo. Mean dosage: 1.17 mg/day. Maximum allowable dose: 0.06 mg/kg/day (King and Bostic 2006). As such, risperidone and aripiprazole are the only drugs currently approved by the US FDA for this target symptom domain in children and adolescents with autism (Stigler 2014).

In a double-blind randomized placebo-controlled trial using risperidone in children with autism (Nagaraj et al. 2006), it was found that children in risperidone group showed improvement in the symptoms of social responsiveness, nonverbal communication, hyperactivity, and aggression with few side effects. Another study from India compared 40 children diagnosed with autism randomized to a 16-week trial of either risperidone or fluoxetine. The risperidone group showed significant improvement in irritability and hyperactivity, while the fluoxetine group showed

significant improvement in speech deviance, social withdrawal, and stereotypy (Desousa 2010).

Attention-Deficit Hyperactivity Disorder (ADHD)

Neurochemical dysfunction in ADHD is in the dopaminergic and adrenergic systems. Mainstay of treatment is psychostimulants and atomoxetine. Bupropion, modafinil, and TCAs have secondary role in treatment. Clonidine is useful in ADHD with comorbid conduct or oppositional defiant disorder, tic disorders, and sleep disturbances (Prince 2006).

Usual range for methylphenidate is 0.3–0.7 mgs per kg per dose rounded to nearest 2.5 or 5 mgs. In some cases, the dose may need rise to as high as 15 mg of methylphenidate three times a day, before response is seen. Dexamphetamine often has a longer duration of action than methylphenidate, permitting less frequent doses but its disadvantages include greater risk of growth retardation, appetite suppression, compulsive behavior, and higher potential for abuse by the patient's peer and family.

Clonidine is initiated at a dose of 25–50 mcgs at bedtime and the dose is titrated gradually over several weeks up to 150–300 mcg per day in 3–4 divided doses. Pulse and blood pressure should be monitored for bradycardia and hypotension (Santosh 2005).

Atomoxetine is a potent NAergic-specific reuptake inhibitor; is not a stimulant and not a controlled substance (no-abuse). 0.5–1.8 mg/kg/day once daily or bid is the usual dose. The best response in child and adolescents is seen with 1.2–1.8 mg/kg/day. It is well tolerated in long-term follow up of 1 yr. Severe liver injury and failure, has been reported though rare; so the drug must be discontinued if there is jaundice or an increase in liver function parameters. Increased risk of suicidal thinking and behavior in child and adolescents has been reported; weigh risks/benefits before starting; monitor closely for worsening depression or emergence of suicidal thoughts/behaviors especially early in treatment or after increased dose. Monitor for anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, mania, and hypomania. Expect mild increase in pulse and diastolic BP and mild decrease in appetite (Cobert 2013b).

Indian research on pharmacological management in ADHD is surprisingly very sparse. Malhotra and Santosh (1998) showed that buspirone had a favorable side effect profile and significantly reduced the symptoms of ADHD. Another study comparing effects of methylphenidate and atomoxetine showed that treatment response was observed in 90.7 % patients from methylphenidate group and 86.2 % patients of atomoxetine group at an average dose of 0.45 and 0.61 mg/kg/d, respectively (Garg et al. 2014).

Conduct Disorder or Oppositional Defiant Disorder

A crucial part of assessment in children with conduct or oppositional defiant disorder is to determine whether there is an underlying comorbid disorder, especially one of the following: significant situational stress, bipolar disorder, major depression, ADHD, emotional dyscontrol secondary to neurological injury, or substance abuse. The pharmacological treatments used for pure CD only target

symptoms such as aggression, irritability, and impulsivity. These medications include atypical antipsychotics such as risperidone, SSRIs, stimulants, clonidine, etc. (Preston et al. 2015c).

Childhood-Onset Schizophrenia (COS)

There is strong evidence for continuity between childhood-onset and adult-onset forms: it is assumed that many treatments used in adults will also apply to children. Typical antipsychotics, like, haloperidol and chlorpromazine can be used. Dystonia, extrapyramidal symptoms (EPS) and akathisia and tardive dyskinesia are the main side effects, which children are likely to be more susceptible to as compared to adults. Atypical antipsychotics, like, risperidone, olanzapine, quetiapine, aripripazole, and clozapine can also be used. With these drugs, tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS) are rare. Metabolic syndrome and increased prolactin could be some of the important concerns. Investigations are to be routinely pursued (Cobert 2013c). With clozapine, total white blood cell and differential count has to be done at prescribed interval. Evidence has been emerging that clozapine's superiority to other antipsychotics especially in COS may outweigh the risks, and that early initiation of clozapine may lead to better outcomes in COS.

Though research from low resource countries on pharmacological management of COS is sparse, a few studies from India are worthy of a mention. An early study by Bassa (1961) demonstrates the efficacy of trifluoperazine to treat psychosis in children with cerebral palsy. In a 6-week trial of olanzapine in children diagnosed with acute and transient psychotic disorders, 61 and 35 % of children showed marked and good improvement, respectively. (Agarwal and Sitholey 2006). An open trial of clozapine was carried out in five patients with childhood-onset schizophrenia in which it was found that there was improvement in positive symptoms, but not negative symptoms and ritualistic behavior. No side effects such as seizures or leukopenia were encountered in any of the patients (Malhotra et al. 2000). An open-label trial comparing aripiprazole to haloperidol and found both to be equally efficacious, with aripiprazole having significantly lower rates of extrapyramidal symptoms and weight gain (Banerjee et al. 2007).

The Schizophrenia Prodrome

Schizophrenia prodrome can be identified with certain clinical presentations such as:

1. Attenuated positive symptoms
2. Fully psychotic but very brief and intermittent positive symptoms
3. A substantial recent fall in functioning along with genetic risk

Drug treatment of prodromal schizophrenia is controversial. Omega-3 fatty acid or psychotherapies could potentially benefit these children. Atypical antipsychotics in doses lower than those employed for chronic schizophrenia are used sometime. Additional research is needed before the balance of long-term risks and benefits can be decided in support of drug treatment of schizophrenia (Thomas and Woods 2006).

Major Depressive Disorder and Dysthymia

Dysthymia, major depressive disorder in children is usually treated with SSRIs. Though most SSRIs have been studied, fluoxetine and escitalopram are the only ones that are approved by the US FDA for use in children. For psychotic depression, an atypical antipsychotic may be added. SSRIs and suicidality have been one of the most talked about issues in child psychiatry during recent times. In February 2004, the US FDA held meeting with parents. On October 15, 2004, the FDA issued the "Black Box:" warning regarding use of SSRI. Finally on February 9 2005, this warning was made milder (Rey and Martin 2006).

Three important trials of depression in children, TADS (Treatment of Adolescents with Depression Study), TORDIA (Treatment of SSRI-Resistant Depression in Adolescents), and ADAPT (Adolescent Depression and Psychotherapy Trial) found that a combination of medication with CBT was always more efficacious than either treatment alone. The TORDIA study, did not find any difference in efficacy between Venlafaxine and a switch to another SSRI (Brent et al. 2008).

TCAs, on the other hand, have been largely found to be inefficacious for managing depression in pre-adolescent children. Even in adolescents, there might be only marginal efficacy, despite robust evidence in adults (Hazell and Mirzaie 2013).

There again is a lack of data with respect to efficacy and effectiveness of antidepressants in patients with depression from India. One double-blind randomized controlled trial evaluated the usefulness of loading dose of imipramine in treatment of depression in adults, where high bolus doses of imipramine led to reduction in depressive features within 72 h (Malhotra and Santosh 1996). However there is no such data on children and adolescents.

Mania and Bipolar Disorder

Currently available antimanic medications intended to reduce symptoms of, and to prevent the occurrence of, hypo/mania include: (i) lithium, (ii) second-generation antipsychotic medications (SGAs) and (iii) antiepileptic medications (AEDs, for example, valproate and carbamazepine). Recent RCTs support the following conclusions: (i) SGAs are effective, and potentially superior to other antimanic agents, in the treatment of bipolar disorder (BD). However, such medications are associated with significant side effects, most notably impairing weight gain and metabolic abnormalities: (ii) lithium's role in BD children is less clear than in BD adults, though further study is warranted, given studies showing its efficacy in pediatric patients with extreme aggression; and (iii) AEDs may be less efficacious than other antimanic agents for children with BD. For an individual, a stepwise approach is often needed, involving trying different antimanic agents if initial attempts are unsuccessful. The treatment of acute mania may require augmentation with anxiolytic medications for short-term (Leibenluft and Dickstein 2015).

Usual mood stabilizers are lithium carbonate, divalproex sodium, carbamazepine when mania is predominant and lamotrigine when depression is predominant. Atypical antipsychotics are also used as mood stabilizer. Combining is possible (Kowatch and DelBello 2006).

Tic Disorders and Tourette's Syndrome

Some less severe and transient ones will not need medication. Atypical and typical antipsychotics, α-adrenergic agents and brief treatment with clonazepam have been found useful. Haloperidol, olanzapine, risperidone, all in small dose, may be useful. Alpha 2 receptor agonists are less effective, possible adverse effects are drowsiness, headache, irritability, and hypotension. Clonidine and guanfacine both are in use (Cobert 2013d).

Sleep Disorders (Insomnia, Hypersomnolence, Parasomnia)

Insomnia:

Although behavioral interventions should be the primary intervention and have a robust evidence base, exogenous melatonin is now the 'first-line' medication prescribed for childhood insomnia. The effect size for sleep latency is much greater than that for total sleep time, confirming that melatonin is of most use for sleep initiation, rather than sleep maintenance. Though melatonin is a hormone that is produced by the pineal gland in a circadian manner, its therapeutic use is not without side effects. Common side effects include headache, depression, restlessness, confusion, nausea, tachycardia and pruritus. The common dose is between 500 μg and 5 mg. Increasing doses above 5 mg is likely to involve the sedative effects for melatonin, rather than its sleep-phase shifting properties (Jan et al. 1999).

Parasomnias:

Sleep terror disorder and sleepwalking disorder occur in the transition from deep delta-wave sleep to light sleep. Benzodiazepines may be effective in these disorders. They work by reducing both delta-wave sleep and arousals between sleep stages. The medications should be used temporarily and only in severe cases, because tolerance to the medications develops. Cessation of these medications can lead to severe rebound worsening of the disorders, and reducing delta sleep in children may have deleterious effects (Sadock et al. 2015a, b).

Parasomnias like sleep walking, sleep talking, and night terrors are usually treated with benzodiazepines and tricyclic antidepressant (Santosh 2005).

Hypersomnolence:

Modafinil and stimulants can be used for hypersomnolence (Stahl 2014).

Enuresis

Patients can be treated with medicine when behavioral treatments fail. Imipramine and DDAVP (1-desamine-8-D-arginine-vasopressin) are commonly used in enuresis. Imipramine and amitriptyline have been used in the treatment of encopresis (Cobert 2013e). Two open-label trials from India evaluated the usefulness of imipramine in enuresis (Chatterjee and Khandpur 1965) and behaviorally disturbed children (Mahendru et al. 1970) and reported positive results with few side effects.

Substance Use Disorders in Adolescents

Psychopharmacological interventions for adolescent alcohol and drug users are still in their early stages (Sadock et al. 2015a, b). The mainstay of treatment of substance use disorders in adolescence, as in adults, continues to be non-pharmacological treatment. However, medication can play an important role. It should be noted that medications for substance abuse have been studied almost exclusively in adults, so that suggested uses are based on extrapolation from adult data and must be viewed with caution (Preston et al. 2015c).

17.12 Common and Useful Pharmacotherapies

In order to be a good practitioner of child and adolescence psychiatry, some of the more useful drugs for children need to be understood in greater detail.

Stimulants and Other ADHD Medications

Stimulants are sympathomimetic drugs that act by enhancing dopaminergic and noradrenergic transmission in the prefrontal cortex. Methylphenidate is the most commonly used stimulant in India, while Dexmethamphetamine and Lisdexmethamphetamine are not available in the market. As pharmacokinetics plays a key role in the effectiveness of stimulants, there is a range of formulation options (plain, sustained release and extended release) with half-lives ranging from four to about 12 h. Commonly reported side effects are anorexia, insomnia, headaches, dysphoria, and gastrointestinal upset. There is also controversy that long-term use of stimulants may cause a delay or stunting of growth. Other rare side effects include arrhythmias, seizures, worsening of tics, hallucinations, etc. Although rare, in some specific individuals sudden cardiac death has been reported when using stimulants. However, currently, no routine pretreatment cardiology evaluation is indicated unless the patient has a cardiac disorder and/or symptoms.

Atomoxetine, selective inhibitor of presynaptic norepinephrine transporters, also increases dopamine and norepinephrine in prefrontal cortex. Despite a plasma half-life of just four hours, it is effective in treating ADHD for 24 h. Though not as efficacious as stimulants (effect size 0.9), atomoxetine has an effect size of 0.6–0.7, with a latency of around 6–8 weeks to its onset of action (Banaschewski et al. 2006). Sedation, fatigue, somnolence, and dizziness, along with anorexia, weight loss, nausea and gastrointestinal symptoms are the common side effects. Nonclinical elevations in heart rate and blood pressure have also been seen. Treatment emergent suicidal thinking has also been reported, for which the FDA has issued a black box warning.

The α–adrenergic agents (clonidine and guanfacine) are presynaptic adrenergic agonists that appear to stimulate inhibitory presynaptic autoreceptors in the central nervous system. Although most commonly used in Tourette's disorder and ADHD, these agents may be useful in controlling aggression, particularly in patients with developmental disorders. Sedation, hypotension, dry mouth, depression,

and confusion are potential side effects. Abrupt withdrawal can result in rebound hypertension. Guanfacine appears to be less sedating and to have a longer duration of action than clonidine (DeMaso and Walter 2011).

Antidepressants

Antidepressant drugs act on pre- and post-synaptic receptors affecting the release and reuptake of brain neurotransmitters, including norepinephrine, serotonin, and dopamine. Major depressive disorder, anxiety disorders, and obsessive compulsive disorders are the three main indications.

SSRIs are generally the first-line of antidepressants used for most patients, as on the whole they have a favorable safety profile and minimal cardiovascular effects. Common side effects include gastrointestinal symptoms, headaches, irritability, restlessness insomnia, appetite changes and diaphoresis. Withdrawal or ''discontinuation'' symptoms are more common in short-acting SSRIs such as paroxetine and fluvoxamine. Reports of behavioral activation along suicidal thoughts warrant close monitoring for these adverse effects, especially in the first few weeks of treatment.

The TCAs have a broader mechanism of action, blocking both serotonin, and norepinephrine reuptake (e.g., clomipramine is primarily serotonergic; imipramine is both noradrenergic and serotonergic), along with anticholinergic and antihistaminic effects. The use of TCAs in children has declined significantly after the advent of SSRIs, and meta-analyses showing lack of efficacy studies (particularly in depression). They have a narrow therapeutic index, with overdoses being potentially fatal. Anticholinergic symptoms (e.g., dry mouth, blurred vision, and constipation) are the most common side effects. TCAs can have cardiac conduction effects in doses higher than 3.5 mg/kg. Blood pressure and electrocardiographic monitoring are indicated at doses above this level. The few common indications in children for which TCAs are used nowadays are obsessive compulsive disorder (clomipramine), enuresis (imipramine), and certain pain disorders (amitriptyline and nortriptyline).

The atypical antidepressants include bupropion, venlafaxine, and trazodone; they are second-line medications for anxiety and depressive disorders. Bupropion has also been used for smoking cessation and ADHD. Bupropion appears to have an indirect mixed agonist effect on dopamine and norepinephrine transmission. Common side effects include irritability, nausea, anorexia, headache, and insomnia. Venlafaxine has both serotonergic and noradrenergic properties. Side effects are similar to SSRIs, including irritability, insomnia, headaches, anorexia, nervousness, dizziness, and blood pressure changes (DeMaso and Walter 2011).

Anxiolytic Agents

Anxiolytic agents (including lorazepam, clonazepam, buspirone, and hydroxyzine) have all been effectively used for acute situational anxiety. Their efficacy as chronic medication is poorer, particularly when used as a monotherapy agent (DeMaso and Walter 2011).

Antipsychotics

Based on their mechanism of action, antipsychotic medication can be divided into typical (blocking dopamine D2 receptor) and atypical (mixed dopaminergic and serotoninergic activity) agents.

Atypical antipsychotics have lesser binding at the D2 receptors but relatively strong antagonistic effects with 5-HT2 receptors. Variable activity at central adrenergic, cholinergic, and histaminic sites account for the varying side effects noted among these agents. These medications have an evidence base for the treatment for psychotic disorders, moderate to severe agitation, and increasingly for monotherapy in bipolar disorder. The most commonly used medications of this class are risperidone, olanzapine, quetiapine, amisulpiride, aripiprazole, and clozapine. Common side effects of these medications include sedation, weight gain, and metabolic syndrome, extrapyramidal symptoms (e.g., restlessness and dyskinesias), hyperprolactinemia. Rare side effects include hematologic adverse effects (e.g., leukopenia or neutropenia), seizures, hepatotoxicity, neuroleptic malignant syndrome, and cardiovascular effects (QTc) prolongation. Monitoring metabolic profile, which includes weight, body mass index and waist circumference, blood pressure, fasting blood glucose, fasting lipid profiles, is essential while using atypical antipsychotics.

Typical (first-generation) antipsychotics that are still in use are haloperidol, chlorpromazine, trifluoperazine, and pimozide. The most commonly used amongst these is haloperidol, which is a high-potency butyrophenone. Its main indications are psychosis, Tourette's syndrome, and severe agitation. Side effects are drowsiness and extrapyramidal symptoms (dystonia, rigidity, tremor, and akathisia) and NMS. There is a risk of tardive dyskinesia with chronic administration (DeMaso and Walter 2011). As earlier mentioned, children are much more susceptible to both EPS and tardive dyskinesia, so these agents are preferably avoided or used with extreme caution.

Mood Stabilizers

Several medications have been shown to be potentially helpful in children experiencing significant mood instability and/or mania, although the evidence base is again sparse.

Lithium's mechanism of action is not well understood, though proposed theories relate to neurotransmission, endocrine effects, circadian rhythm, and cellular processes. Common side effects include polyuria and polydipsia and central nervous system symptoms (tremor, somnolence, and memory impairment). Periodic monitoring of lithium levels along with thyroid and renal function is needed. Lithium serum levels of 0.8–1.2 mEq/L are targeted for acute episodes and 0.6–0.9 mEq/L are targeted for maintenance therapy.

Valproic acid is an anticonvulsant with some evidence supporting its use in the treatment of mania. The therapeutic plasma concentration range is 50–100 μg/ml. Common side effects include sedation, gastrointestinal symptoms, and hair thinning. Idiosyncratic bone marrow suppression and liver toxicity have been reported, necessitating monitoring of blood counts as well as liver and kidney function.

Lamotrigine is another anticonvulsant that may be useful in the treatment of adolescent bipolar depression. It has been associated with potentially life-threatening Stevens-Johnson syndrome (DeMaso and Walter 2011).

17.13 Specific Issues Related to Pediatric Pharmacology

A few pertinent issues in the treatment of children and adolescents need discussion. First is the diagnosis versus target symptom approach. Though a categorical approach to diagnosis is easier to use; a dimensional approach by rating target symptoms that are functionally impairing may be a better approach to deal with the clinical situation. In child psychiatry, two common encountered circumstances favor a target symptom approach, when the disorder is poorly defined or when there are several comorbid conditions. Effective pharmacotherapists should be mindful of this, and should as much as possible, use medication to treat underlying disease states while regularly monitoring target symptoms as an index of progress (Bostic and Rho 2006). One cannot over emphasize the need for a good diagnosis, to the best of our understanding and ability, keeping differential diagnoses in mind and giving careful attention to comorbidities. These are a must in tailoring a rational prescription for the child.

Therapeutic alliance is a bit more complicated in the context of child psychiatry. Clinicians should strive to include both the child and his or her parents/guardian into the working alliance, and involve all of them in treatment plan (Joshi 2006). One should also keep in mind the need for autonomy in older children and adolescents, and be respectful of the same.

Children's concept about medications is also to be acknowledged and addressed. They may be concerned about "physical properties" of the medication itself like name, form, size, color, taste, etc. This may lead to certain wrong kind of notions about medicine. They may also harbor beliefs that only children who are "sick" or "bad" have to be on medications. Dosing schedules (like, morning, evening or during school dosage) also have to be kept in mind (Joshi 2006), to ensure availability of parents or guardians.

As earlier mentioned, comorbidity is more a rule than exception in children. For example, intellectual disability, autism, ADHD, ODD, epilepsy, anxiety disorders, depression, all come in different combinations of one another. Greater awareness of this has led to a dramatic increase in the use of polypharmacy in children. One has to be more cautious, look at drug interactions because children have a much higher propensity for seizure and EPS.

Adverse events are more likely when multiple drugs are used, and interactions can be unpredictable. Combining drugs from the same pharmacological class is rarely indicated, except when cross-tapering when switching drugs. Combining drugs can be rational when their pharmacological actions are complementary, although the side effect burden is usually higher. Examples include quetiapine augmentation of SSRIs to treat depression where there is good RCT evidence or a

second antipsychotic with clozapine for poor response in treatment resistant schizophrenia. If a second drug is added to counteract an adverse effect, strong justification is needed for not swapping drug if drugs are from the same broad class (e.g., aripiprazole to reduce raised prolactin caused by another antipsychotic). A careful weighing of risks and benefits is required if they are from different classes (e.g., antimuscarinic drugs for EPSE on antipsychotics). Polypharmacy requires pharmacological expertise and should usually be supervised by a specialist (Haddad and Wieck 2016).

17.14   Conclusion

Our basic commitment is to the patient, whom we should be treating "as a whole" and not just the disease or symptoms. We must remember, pharmacotherapy, no matter how effective, should only be a part of a larger, multimodal treatment plan.

Equal consideration must be given to all aspect of child's life-like psychosocial, educational, and family interventions. Almost every major clinical trial and practice guideline has shown that combination treatments are more effective. Though this may not be feasible in most settings in low resource countries, clinicians should work toward equipping themselves or developing an infrastructure for the same.

There is great concern today that children are being over treated with medication, especially in the US (Rapoport 2013). By contrast, many countries make so little use of medications, that it very likely that many children who could profit have no access to it or do not receive it. Undertreatment is perhaps a bigger problem globally than overmedication.

Great international differences in the use of psychopharmacological agents stem from differences in professional and cultural attitudes. In the light of these differences, clinicians need to always try and formulate treatment plans that are empirically informed and evidence based. As research in the field of pediatric psychopharmacology has been expanding rapidly over the last decade, it has become more important for clinicians to stay apace with the latest developments. In addition, pediatric pharmacovigilance for psychotropic agents are essential and more studies on efficacy in this population is necessary (Santosh 2009).

Research from low resource countries in this area has been very meager, though is likely to emerge in the next few years. With limited availability of professionals, the developing economies need to keep their focus on training professionals, developing infrastructure to enhance service delivery to reach to the widest population.

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