

PRINCIPLES IN USING PSYCHOTROPIC MEDICATION IN CHILDREN AND ADOLESCENTS

2019 edition

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Lack of adequate and fair access to pediatric mental health care has long been a sad and universal phenomenon. According to a 2003 WHO report, 44%-70% of youth with mental illness in high income countries did not receive mental health treatment in any given year. In low- and middle-income countries (LAMICs), this gap was closer to 90%. Over 90% of LAMICs had no mental health policies that included children and adolescents (WHO, 2003).

Notwithstanding the above generalizations, psychopharmacotherapy is practiced within the context of regional mental health care systems. Prescribing varies widely, both across and within countries. This variability cannot be fully explained by differences in nosology or illness prevalence, thus suggesting that cultural, geographic, economic, regulatory, and other factors play a major role in prescribing practices (Vitiello, 2008) (see Table A.7.1).

Relative to other areas of medicine, perception of psychiatric disorders appears to be more influenced by cultural values. For example, use of stimulants for ADHD in the US is greater among the white population than among children of African American or Hispanic background (Cohen et al, 2013). Stimulant medication use is lower in the US West Coast than in the rest of the country (Zuvekas & Vitiello, 2012) These ethnic differences appear to be independent of economic factors. Levels of parental concern about risks of adolescent addiction are

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Table A.7.1 Factors that may contribute to the variability of psychotropic prescribing

| Factor | Examples |
|------------------------------------|---|
| Geographic differences in nosology | Some EU countries rely on the ICD classification system while DSM is preferred in the US |
| Geographic variations in diagnosis | ADHD may be under-diagnosed in some areas and over-diagnosed in others |
| Prevalence of psychopathology | Completed suicides vary according to country |
| Cultural | Psychosocial interventions preferred over medication treatment in some cultures but not in others |
| Economic | Insufficient manufacturing capacity; limited personal finances |
| Differences in healthcare systems | Countries with a universal health care system have greater consistency of pharmacotherapy |
| Regulatory | Prohibition of some medications in some countries (e.g., stimulants, buprenorphine) |
| Racial disparity | Stimulant prescription for ADHD is greater for white relative to non-white youth in US |
| Marketing | Branded medications are marketed (especially in high income countries), while generics are not |

different across cultures with parents of African and Hispanic children expressing more concerns than parents of white children (Zhu et al, 2009).

Relative to other high-income countries, use of psychotropic medications is substantially higher in the US; for example, it has more than 80% of the world usage of psychostimulants. It is estimated that about 3.5% of US children are treated with stimulant medication for ADHD, and use has been consistently increasing over the years (Zuvekas & Vitiello, 2012). Likewise, antidepressant and antipsychotic use is many times greater in the US than in other countries (Fegert et al, 2006).

Differences in prescription rates appear to be influenced by economic factors also. For example, there is a significant variation among countries in prescriptions for the treatment of comorbidities associated with autism spectrum disorder, with a correlation between per capita gross domestic product and prescription rates (Hsia et al, 2014). It is likely that pharmaceutical industry's marketing efforts play a significant role in prescribing practices.

Overall, approaches to mental health care vary considerably based on cultural factors. The implications of this variability for disease outcome and patient prognosis are serious and yet to be understood.

HISTORICAL CONTEXT AND SOME CORE QUESTIONS

Medications to treat mental conditions (psychotropics) have become increasingly used in child and adolescent psychiatry around the world. From the serendipitous discovery by Bradley of the effects of amphetamines on child hyperactivity in 1937 to the multisite clinical trials of the 21st century, pediatric psychopharmacology has evolved from an area of research to a standard of clinical care (Vitiello & Davico, 2018). Nevertheless, the role of pharmacotherapy in pediatric mental health remains the object of debate and controversy. With the notable exception of medications for ADHD—which were first introduced in pediatric population and subsequently extended to adults—most psychotropic medications were first developed to treat psychiatric conditions in adults, and only later extended to children. Appropriate concerns have been raised about both the validity of applying adult diagnostic categories to children and the validity of extrapolating safety and efficacy information collected in adults to children.

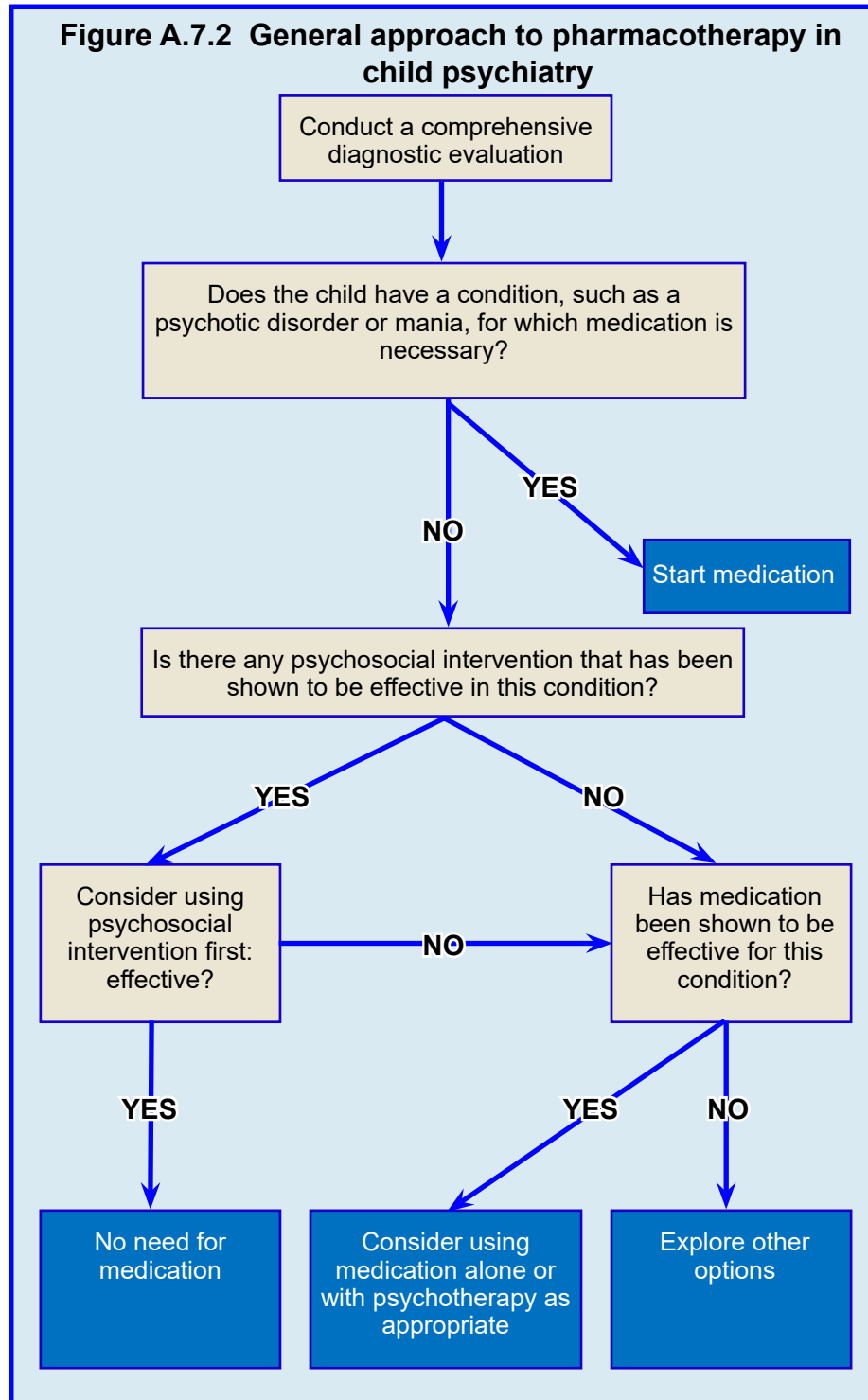
Growing research has provided a better understanding of the benefits and risks of the pediatric use of some psychotropics. For many others, however, the current knowledge base is incomplete. This inadequacy is especially evident with respect to their long-term use. In psychiatry, medications are seldom curative and long-term treatment is often required, thus raising concerns about both the persistence of the therapeutic effect and the safety of prolonged exposure to psychotropic agents at a time of rapid development. A related question is whether treatment in childhood will lead to better functional outcomes later in life. Unfortunately, controlled clinical trials are usually brief, and studying long-term treatment effects is methodologically difficult.

In this chapter, we hope to provide clinicians with key elements and a general framework for the pharmacotherapy of psychiatric disorders during development.

Use of psychotropic medications is substantially higher in the US than in other developed countries.



In 1937, Charles Bradley, a psychiatrist, administered d-amphetamine to “problem” children at the Bradley Home in Providence, Rhode Island (US), in an attempt to alleviate headaches. Bradley noticed an unexpected effect: improved school performance, social interactions, and emotional responses. Bradley’s studies went largely ignored for nearly 25 years. However, they proved to be an important precursor to studies on the use of amphetamines in ADHD (Strohl, 2011).



“But family and many friends were judgmental: How could we start a five-year-old on medication, especially one as smart as our son, who had taught himself to read before age four? They seemed to assume that he was different because he was so smart. Anyway, the logic went, a lot of boys are a handful at that age, and that’s not a reason to put a five-year-old on medication. They concluded that the problem was that I was a psychiatrist. Clearly, I was pathologizing a boy who was just being a boy. How else would you expect a mom who is a psychiatrist to handle a rambunctious, precocious five-year-old besides putting him on medication?” (Gold, 2010).

For detailed information on specific medications the reader is referred to the chapters covering the relevant disorders.

WHEN TO USE PSYCHOTROPIC MEDICATION IN YOUTH?

A comprehensive diagnostic evaluation and psychosocial formulation is the necessary first step (Figure A.7.2). Patients with psychotic disorders often

require pharmacological treatment as a first step to control symptoms and restore functioning. For more details on pharmacological treatment of psychosis, see [Chapter H.5.1](#).

Patients with non-psychotic disorders may often be successfully treated with non-pharmacological interventions first. For example, behavioral therapy can be an effective first step in the management of patients with mild major depression, OCD, and anxiety disorders. Not all children, however, improve with purely psychosocial interventions and, for them, medication may be necessary to improve their functioning. Of note, psychotherapy and medication are not mutually exclusive: in many conditions, such as depression and anxiety, combined use as been found to be more beneficial than monotherapy (Vitiello, 2009a).

A key consideration in choosing among therapeutic options is the strength of the evidence supporting the efficacy and safety of the treatment for the specific condition and the age of the child (Gray, 1997). Thus, the strongest level of evidence comes from at least one systematic review of multiple, well-designed, randomized controlled trials (Type I). A lower level of evidence comes from at least one randomized controlled trial (Type II).

Thanks to clinical research conducted since the 1990's, there is a growing body of evidence for the short-term efficacy of many medications (summarized in [Table A.7.3](#)). Much less strong is the evidence of their long-term effectiveness and safety. For more details on assessment of treatment evidence see [Chapter A.6](#) and [Figure A.6.8](#).

Several placebo-controlled discontinuation studies have shown that long-term treatment can be effective in maintaining improvement and preventing symptom recurrence. For example, in youth suffering from depression, continuing antidepressant treatment significantly reduces the risk of relapse (Emslie et al, 2008). Likewise, discontinuing risperidone in children with autism and severe behavioral disturbances increases the risk of recurrence of aggression, self-injury, and tantrums compared with continuing treatment (Research Units on Pediatric Psychopharmacology Autism Network, 2005a). In addition, a number of naturalistic follow-up studies provide useful information on the long-term outcome of youths treated for several years, even though treatment effects are difficult to determine due to the lack of a control condition.

Beyond the level of evidence for each medication, prescribers also need to understand their regulatory environment. Some psychotropics have received approval for pediatric indications by drug regulatory agencies (i.e., the FDA in the US or the EMA in the European Union), while others are used off-label.

In the US, many medications that have a high level of evidence also carry an FDA approval—for example, methylphenidate is FDA approved for ADHD in children aged 6 and older (see [Table A.7.3](#)). On the one hand there are medications that have a high level of evidence but do not have FDA approval—for example, sertraline has Type I level of evidence for efficacy in anxiety disorders in childhood, but no FDA indication. On the other hand, there are medications that have a low level of evidence, yet have FDA approval—for example, haloperidol has little evidence of efficacy among preschoolers, but it has an FDA indication for pediatric use starting at age 3.

Evidence of the long-term effectiveness and safety of pharmacological treatments in children and adolescents is largely lacking.

Table A.7.3 Selected psychotropic medications and level of evidence for efficacy in children (<18 years)

| Medication | Condition | Evidence for efficacy ¹ | US FDA-approved indication and age, in years, for which it is approved |
|---|--|------------------------------------|--|
| Methylphenidate and dexamethylphenidate | ADHD | Type I | 6 and older |
| Amphetamines | ADHD | Type I | 3 and older |
| Atomoxetine | ADHD | Type I | 6 and older |
| Clonidine | ADHD | Type I | 6 and older |
| | Tourette's disorder | Type I | |
| Guanfacine | ADHD | Type I | 6 and older |
| Fluoxetine | Major depression | Type I | 8 and older |
| | OCD | Type II | 7 and older |
| | GAD/SP | Type II | |
| Sertraline | OCD | Type I | 6 and older |
| | Major depression | Type II | |
| | GAD/SP | Type I | |
| Citalopram | Major depression | Type II | |
| Escitalopram | Major depression | Type I | 12 and older |
| Fluvoxamine | OCD | Type II | 7 and older |
| | GAD/SP | Type I | |
| Venlafaxine | Major depression | Type V | |
| Bupropion | ADHD | Type II | |
| | Major depression | Type V | |
| Clomipramine | OCD | Type II | 10 and older |
| Haloperidol | Tourette's disorder | Type I | 3 and older |
| | Psychosis | Type II | 3 and older |
| | Hyperactivity, severe behavioral problems, explosive hyperexcitability | Type II | 3 and older |
| Pimozide | Tourette's disorder | Type I | 12 and older |
| Risperidone | Schizophrenia | Type II | 13 and older |
| | Bipolar disorder | Type I | 10 and older |
| | Aggression | Type I | "Irritability" in autism: 5-16 years of age |
| | Tourette's disorder | Type I | |

Table A.7.3 (Continuation). Selected psychotropic medications and level of evidence for efficacy in children (<18 years)

| Medication | Condition | Evidence for efficacy ¹ | US FDA-approved indication and age, in years, for which it is approved |
|----------------------------|--------------------|------------------------------------|--|
| Quetiapine | Schizophrenia | Type II | 13 and older |
| | Bipolar disorder | Type II | 10 and older |
| Aripiprazole | Schizophrenia | Type II | 13 and older |
| | Bipolar disorder | Type II | 10 and older |
| | Aggression | Type I | "Irritability" in autism: 6 and older |
| Olanzapine | Schizophrenia | Type II | 13 and older |
| | Bipolar disorder | Type II | 10 and older |
| Lithium | Bipolar disorder | Type III | 7 and older |
| | Aggression | Type II | |
| Valproate ² | Bipolar disorder | Type II | |
| | Aggression | Type II | |
| Carbamazepine ² | Bipolar disorder | Type V | |
| Oxcarbazepine ² | Bipolar disorder | Type V | |
| Lamotrigine ² | Bipolar depression | Type V | |

ADHD: attention deficit hyperactivity disorder; OCD: obsessive compulsive disorder; GAD: generalized anxiety disorder; SP: social phobia.

¹Strength of the evidence: Type I: strong evidence from at least one systematic review of multiple well-designed randomized controlled trials. Type II: strong evidence from at least one properly designed randomized controlled trial. Type III: evidence from well-designed trials without randomization, single group, pre-post, cohort, time series or matched case-control studies. Type IV: evidence from well-designed non-experimental studies from more than one center or research group. Type V: opinions of respected authorities, based on clinical evidence, descriptive studies or reports of expert committees (Gray, 1997).

²Approved for the treatment of epilepsy from infancy.

Likewise, controlled clinical trials support the efficacy of methylphenidate in preschoolers (age 3-6 years) with ADHD but it does not have an FDA indication for use before the age of 6 years, while amphetamines, which have not been adequately evaluated in controlled studies under age 6, have FDA approval starting at age 3. Thus, the on-label *vs.* off-label status of medications results from evidence of effectiveness as well as other factors, including the historical and regulatory context of their introduction.

These inconsistencies are largely due to the fact that the FDA approval process was not designed to regulate clinical practice. Instead, it reflected the US legislative efforts to regulate the marketing and sale by pharmaceutical companies of new patented medications.

FDA approval processes underwent many changes since its inception in the 1940s. Older medications, such as haloperidol, had a much less transparent and

more expert-driven approval process with unclear impact of evidence. With respect to sertraline, it became “generic” (its patent duration expired) before the evidence for pediatric generalized anxiety disorder was shown. Once a medication becomes generic, applying for FDA approval (or “label”) no longer makes financial sense for the manufacturers since it carries great administrative costs with no returns for the pharmaceutical companies. As a result, the vast majority of medications used in clinical practice in both medicine and psychiatry, for both adults and children, are used “off-label.” Use of a medicine off-label is not in itself an inappropriate practice as it is often supported by considerable empirical evidence and may be consistent with treatment guidelines.

These concepts are important to understand and explain not only to parents, but also to policy-makers. For example, officials in many countries make decisions to purchase medications based on FDA approval status—or of its counterpart, the European Medicines Agency—and not on the overall evidence of efficacy and safety.

Availability (status of manufacturing, trade, etc) also impacts prescribing practice. Examples range from the transient intramuscular lorazepam shortages in the US due to supply chain problems to the virtual lack of psychostimulants in Ukraine due to the complexities of introducing a controlled substance into a developing democracy. Lack of effective medications can encourage growth of alternative treatments that either have no evidence of efficacy or have evidence of causing harm.

In another example, the WHO list of essential medicines for mental and behavioral disorders includes both medications that have a high degree of efficacy and safety (for example, fluoxetine for depression, anxiety, and OCD) as well as others that lack evidence for efficacy, safety, or both. For example, diazepam is not effective for the long-term treatment of pediatric anxiety and amitriptyline is not

BAP Position Statement: Off-label prescribing of psychotropic medication to children and adolescents

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If you want to learn more about the issues around off-label prescribing of psychotropic medication to children with an European focus click on the figure to access a position statement by the British Association for Psychopharmacology.

Table A.7. 4 WHO essential medicines for mental and behavioral disorders (2017)

| | |
|---|---|
| Medicines used in psychotic disorders | <ul style="list-style-type: none"> • Chlorpromazine • Fluphenazine • Haloperidol • Risperidone • Clozapine |
| Medicines used in depressive disorders | <ul style="list-style-type: none"> • Amitriptyline • Fluoxetine |
| Medicines used in bipolar disorders | <ul style="list-style-type: none"> • Carbamazepine • Lithium • Valproic acid (sodium valproate) |
| Medicines for anxiety disorders | <ul style="list-style-type: none"> • Diazepam |
| Medicines used for obsessive compulsive disorders | <ul style="list-style-type: none"> • Clomipramine |
| Medicines for disorders due to psychoactive substance use | <ul style="list-style-type: none"> • Nicotine replacement therapy • Methadone |

effective for pediatric depression (see Table A.7.4).

PHARMACOKINETICS

Drug absorption, distribution, metabolism, and excretion all change during child development. As a result, extrapolation of doses and frequency of administration for children based on data obtained from adults can lead to inappropriate treatment. Although children have smaller absolute body size, the relative mass of their liver and kidney tissue is greater than in adults when adjusted for body weight. Children also have relatively more body water, less fat, and less plasma albumin to which drugs can bind. Consequently, the volume of distribution of a medication tends to be greater in children than in adults. As a result of the above differences, children have greater drug extraction during the first pass through the liver, lower bioavailability, and faster metabolism and elimination. This means that simply decreasing adult doses based on child weight may result in under-treatment.

In adolescence, together with a marked growth in body size, there is a redistribution of the body compartments. In males, the percentage of total body water increases and that of body fat decreases, while the opposite occurs in females. For a summary of pharmacokinetic differences between children and adults (see Table A.7.5)

Once absorbed, most drugs undergo biotransformation (metabolism) that turn the parent compound into more polar, and therefore easier to eliminate, byproducts (metabolites). Typically, medications undergo first an enzymatic oxidative or hydrolytic transformation (phase I), and then are conjugated with glucuronic acid, sulfate, glutathione, or acetate to form products that are eliminated via the kidneys or bile.

The phase I oxidative processes are mediated by cytochrome 450 (CYP450) microsomal enzymes, which are concentrated primarily in the liver. The CYP450 system is immature at birth, but its metabolizing capacity increases rapidly, so that by one month of age it is already about 20% of the mature level, which is achieved by three years of age. Because children have proportionally more liver parenchyma than adults, they have greater weight-adjusted metabolic capacity.

The two most important CYP450 enzymes in pediatric psychopharmacology

Pharmacokinetics

What the body does to the drug: absorption, distribution, metabolism, and excretion.

Pharmacodynamics

What the drug does to the body: the biochemical and physiological effects of drugs on the body.

Half life

The time required to reduce the plasma concentration to one half of its initial value

Plasma steady state

Steady state occurs when the rate of drug absorption into the blood equals the rate of elimination from it. The time to reach steady-state concentrations is dependent on the half-life of the drug.

Table A.7.5 Pharmacokinetic characteristics in children relative to adults

| | |
|--|---------------|
| Liver & kidney mass adjusted for body weight | Greater |
| Metabolism and elimination | Faster |
| Dosing | Higher |
| Elimination half-life | Shorter |
| Plasma steady-state | Sooner |
| Withdrawal symptoms | More likely |
| Dosing | More Frequent |

are the CYP3A4 and the CYP2D6, which are involved in the metabolism of most psychotropics, as well as CYP2C9 and CYP2C19. For example, the 3A4 system metabolizes sertraline, citalopram, escitalopram, bupropion, mirtazapine, aripiprazole, quetiapine, ziprasidone, lurasidone, cariprazine, alprazolam, zolpidem, and oral contraceptives. The 2D6 system metabolizes fluoxetine, trazodone, atomoxetine, tricyclic antidepressants, risperidone, olanzapine, chlorpromazine, and haloperidol.

Some psychotropics can also act as inhibitors of these enzymes so that concurrent administration of another drug that is a substrate for the enzyme results in reduced metabolism and higher medication concentration in the body. For example, 3A4 metabolized enzymes can be inhibited by fluoxetine or fluvoxamine. Concomitant administration of fluvoxamine (inhibitor of 3A4) and quetiapine or aripiprazole (metabolized by 3A4) could lead to higher levels of quetiapine or aripiprazole and prolongation of the QTc interval.

An additional complexity is that some medications, such as carbamazepine and phenobarbital, can induce CYP3A4 activity, thus potentiating its metabolizing capacity. The concomitant administration of carbamazepine and a medication metabolized by CYP3A4 can result in lower blood levels of many anticonvulsants, antipsychotics, tricyclic antidepressants, clonazepam, and oral contraceptives. In females, use of oral contraceptives can also induce CYP enzymes and thus increase lamotrigine metabolism and elimination resulting in decreased lamotrigine serum concentration.

Genetic polymorphisms have been identified for CYP 450 enzymes. About 7-10% of Caucasians, 1-8% of Africans, and 1-3% of East Asians are poor CYP2D6 metabolizers of specific medications. Poor metabolizers have higher drug concentrations in plasma and other body tissues. For example, the mean elimination half-life of atomoxetine is about 5 hours in children or adults who are fast metabolizers, but 22 hours in poor metabolizers (Sauer et al, 2005). While these metabolic differences do not appear to be clinically significant for atomoxetine, some cases of toxicity have been reported with other psychotropics. For example, one case of death in a child with a 2D6 genetic deficiency was associated with unusually high plasma levels of fluoxetine (Sallee et al, 2000).

Technological advances in the 2010's have enabled affordable testing of genetic variants potentially relevant to medication metabolism and response. With direct-to-consumer advertising of commercially available pharmacogenomic testing. Many parents ask to use such tests for decision-making about prescription. While future advances are promising, the evidence to support this practice is insufficient at this time.

On November 1, 2018, the [FDA published the following warning](#): “The FDA has become aware of genetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic (DNA) variations and the medication’s effects has not been determined. For example, the FDA is aware of genetic tests that claim results can be used to help physicians identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications. However, the relationship between DNA variations and the effectiveness of antidepressant medication has never been established. Patients and health care providers should not make changes

to a patient's medication regimen based on the results from genetic tests that claim to predict a patient's response to specific medications, but are not supported by sufficient scientific or clinical evidence to support this use, because doing so may put the patient at risk for potentially serious health consequences. There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications." While testing for genetic polymorphism is not routinely done in current child psychiatry practice, it may be considered for individual patients who do not respond to adequate doses of medication, or present with unusual reactions to medications metabolized by enzymes with genetic polymorphism (e.g., 2D6 and 2C19).

The main route of drug elimination is through the kidneys. Absolute clearance is usually lower in children than in adults, but weight-adjusted clearance is greater. Because of the faster elimination, the drug plasma half-life can be shorter in children than in adults (Daviss et al, 2005). 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. In these cases, a more frequent administration is needed to maintain consistent therapeutic levels and prevent withdrawal symptoms between doses.

For some medications, the dose and duration of treatment can influence pharmacokinetics. After a single dose of sertraline 50 mg in adolescents, the mean half-life is about 27 hours but after repeated administration it decreased to about 15 hours (Axelson et al, 2002). Moreover, the steady-state half-life is longer (about 20 hours) after administration of higher doses (100-150 mg). Based on these data, lower doses (50 mg/day) of sertraline should be given twice a day to ensure consistent treatment and prevent withdrawal, while higher (100-150 mg) doses can be given once a day.

The pharmacokinetics of many psychotropics has been studied in children and adolescents. For escitalopram, aripiprazole, quetiapine, risperidone, and lithium, pharmacokinetics was found to be similar in youth and adults (Rao, 2007; Findling et al, 2008; Thyssen et al, 2010; Findling et al, 2010). However, considerable inter-subject variability was observed, so that major individual differences in the time-course of pharmacological effects can occur in clinical practice. For methylphenidate and amphetamines, whose short half-life results in short duration of action and in the need for multiple daily administrations, a variety of extended release formulations have been developed and require prescribers to continue to keep up their learning.

PHARMACODYNAMICS

Most psychotropics act through neurotransmitters, such as dopamine, serotonin, glutamate, GABA, and norepinephrine, whose receptors undergo major changes during development. Receptor density peaks in the preschool years and then gradually declines toward adult levels in late adolescence (Chugani et al, 2001). The impact of these developmental changes on drug activity, efficacy, and safety are still not well understood. However, observed differences between children and adults in efficacy and safety suggest that development can significantly

Assessing and monitoring medication effects is more complex and time consuming in children than in adults because clinicians must collect and integrate information from multiple sources.

Table A.7.6 Psychotropic drug groups: pharmacodynamic differences between children and adults

| Drug group | Children | Adults |
|-------------------------------------|---|--|
| Tricyclic antidepressants | Not effective for pediatric depression | Effective for adult depression |
| Serotonergic antidepressants | Increase the risk of suicidal ideation | Do not increase the risk after age 25 |
| Antipsychotics | Relatively greater metabolic side effects | Relatively lower metabolic side effects |
| Amphetamine-based stimulants | Less likely to induce euphoria | More likely to induce euphoria |
| Methylphenidate | Lower tolerability and efficacy in children with ADHD aged 3 to 5 years | Higher tolerability and efficacy in adults and children with ADHD above the age of 5 years |

influence the effects of psychotropics (summarized in Table A.7.6). For example, tricyclic antidepressants, though proven effective in adult depression, have no demonstrable antidepressant effect in children (Hazell et al, 1995); amphetamine-based stimulants are more likely to induce euphoria in adults than in children; antipsychotics have stronger metabolic effects in youth than in adults (Correll et al, 2009); and serotonergic antidepressants increase the risk for suicidal ideation in children, adolescents, and young adults, but not in the middle-aged or the elderly (Hammad et al, 2006; Stone et al, 2009).

The developmental stage influences the response to a number of psychotropics. This is evident also in the lower tolerability and efficacy of methylphenidate in children with ADHD between 3 and 5 years of age as compared with older children (Greenhill et al, 2006). Abnormal brain development, such as in autism, impacts medication response, as shown by the lack of benefit from SSRIs for compulsive and repetitive behaviors in autism (King et al, 2009). Thus, information derived from adolescents may not be applicable to younger children or to those who suffer from pervasive disorders of development. This underscores the need for research in specific patient populations.

EFFICACY

The term *efficacy* is used to describe treatments with a demonstrated therapeutic benefit when tested under controlled experimental conditions, usually involving carefully selected samples of patients. *Effectiveness* refers to treatments that have demonstrated benefit in non-experimental clinical settings with patients broadly representative of the population likely to receive the treatment. Often, however, these two terms are used interchangeably.

Double-blind trials are methodologically more persuasive than open studies because they control for placebo effects. A number of well-designed placebo-controlled clinical trials have been conducted in pediatric psychopharmacology. The results of these studies provide the foundation for evidence-based pharmacotherapy

Some adverse effects can be anticipated based on the mechanism of action of the medication, while others are completely unexpected, such as increased suicidality with antidepressant treatment.

in child psychiatry, summarized in evolving practice guidelines and treatment algorithms (e.g., National Institute for Health and Clinical Excellence, 2005 and 2008; Pliszka et al, 2007; Birmaher & Brent, 2007; McClellan et al, 2007). One critical element in evaluating the efficacy of a treatment is the chosen outcome. A treatment can be effective at:

- Decreasing symptoms (improvement)
- Eliminating the key manifestations of the disorder (remission, in the short-term, and recovery, if sustained over time)
- Restoring functioning (functional recovery)
- Decreasing the risk for relapse or recurrence of the symptoms.

Thus, when stating that a certain treatment is effective, one should also specify the particular outcome. Typically, medications are approved for clinical use based on studies showing that they decrease symptoms. Proving treatment effects on remission, recovery, or functioning requires longer-term controlled trials, which are more difficult and expensive to conduct.

There are, however, studies supporting efficacy and effectiveness for remission and recovery in some medications, such as stimulants in ADHD (Swanson et al, 2001) and serotonergic antidepressants in adolescent depression (Kennard et al, 2009; Vitiello & Davico, 2018).

The need to document symptom reduction and remission highlights the importance of measuring the behavioral, emotional, and functional manifestations of mental dysfunction. In the absence of direct biological markers of disease and treatment effects, clinicians must rely on symptoms and indirect signs to gauge treatment response. Rating scales have been developed for all of the conditions in child mental health (see Chapter A.5).

These scales can be divided into those that are completed by the clinician based on both direct observation and informants (clinician-rated), and those that are completed directly by informants (self, parent, teacher). A distinctive characteristic of pediatric psychopharmacology is that, in addition to the child, clinical information is usually derived from parents and teachers. Since clinicians must collect and integrate information from multiple sources, assessing and monitoring medication effects is more complex and time consuming in children.

When comparing treatments, it is useful to quantify the size of the treatment effect (see also Chapter A.6). Using data from controlled trials, the magnitude of the treatment effect relative to a control can be expressed in standard deviation units. The most commonly used ways of computing effect size are Cohen's *d* or Hedges' *g*—the difference in the means of the outcome measure between the study groups (active treatment and control) divided by the pooled standard deviation (Rosenthal et al, 2000).

Compared with placebo, stimulants have a large effect size (0.8 and above), while non-stimulants (clonidine, guanfacine, atomoxetine) have small to moderate effect sizes (0.25-0.5) in decreasing symptoms of ADHD (Greenhill et al, 2001). In trials that have detected a separation between SSRI and placebo, the SSRIs had a moderate effect size (0.5-0.7) in the treatment of major depression (TADS Team, 2004) or obsessive-compulsive disorder (Pediatric OCD Treatment Study, 2004). However, meta-analyses of all available clinical trials in pediatric depression (both positive and negative) indicated that the effect size of antidepressant medication vs.

Efficacy

A term used to indicate that a treatment has a demonstrated therapeutic benefit when tested in rigorous conditions, usually involving carefully selected samples of patients.

Effectiveness

Typically means that the treatment has shown to be beneficial in usual clinical settings for patients broadly representative of the population likely to receive that treatment.

placebo was small (0.25, 95% C.I. 0.16-0.34) (Bridge et al, 2007).

Effect size can also be used to quantify pre-post treatment difference within the same group of patients, rather than the difference between treatment and control groups. However, due to the lack of a parallel control group, the effect due to the treatment cannot be separated from the effect of the mere passage of time as well as of patient's expectations, classical conditioning, and other non-specific components of the placebo effect. For this reason, a within-group pre-post effect size is expected to over-estimate the effect of treatment and reflect the combined effects of placebo and specific treatment.

It is also useful to quantify the therapeutic benefit using the *number needed to treat* (NNT)—the number of patients who need to receive the treatment in order to add one more improved patient to those who improve in the control condition. NNT is a type of effect size and is the inverse of the absolute risk reduction (ARR). ARR is the difference between outcome incidence in the treated and control groups. Thus, in the Treatment for Adolescents with Depression Study (TADS), 61% of patients treated with fluoxetine improved at the at 12 weeks, compared with 35% of the placebo patients (TADS Team, 2004). Based on the absolute difference of 26% (ie, 61- 35) observed, the NNT for fluoxetine is 4 (i.e., $100/26 = 3.9$), which indicates that one needs to treat on average 4 patients to improve one patient more than the placebo condition.

The smaller the NNT the greater the efficacy of the treatment. The NNTs of psychotropic medications, though variable among studies, are often quite favorable when compared with other non-psychiatric drugs used in pediatrics. For example, NNT for antibiotics for pain reduction in case of acute otitis media in children is 16 (Sanders et al, 2004). Most of what is currently known about the effects of treatments is limited to the short- (i.e., weeks) and intermediate-term (i.e., months) (see also Chapter A.6).

Relatively few studies have addressed the long-term effectiveness of pharmacotherapy in childhood mental disorders (MTA Cooperative Group, 2004; TADS Team, 2007; Vitiello et al, 2011; Findling et al. 2010). More research is needed to determine whether reduction of symptoms leads to better prognosis. For example, it would be important to know if improved ADHD symptoms translate into a lower risk for motor vehicle accidents, higher academic and occupational achievement, and better social adjustment, in the same way that the control of hypertension has been found to decrease cardiovascular morbidity and mortality. Unfortunately, we have yet to obtain data to answer these questions. Studying the long-term effects of treatments poses many challenges from practical and methodological perspectives. Long-term randomized controlled trials are difficult to implement, while observational studies are insufficient to prove causality.

SAFETY

Ensuring safety is especially important when treating children. Pharmacological treatment during human development may result in toxicities that are not seen in adults. A general concern is that agents acting on neurotransmitter systems during rapid development may interfere with normal processes and result in unwanted long-lasting changes.

Studies in developing animals have been informative. For example, fluoxetine given to newborn mice transiently inhibits the serotonin transporter during early development; this is associated with behavioral abnormalities such as reduced exploratory behavior and slower adaptation to novel environments or stimuli in adult age (Ansorge et al, 2004). Even though the relevance of these data to children is unclear, a high level of concern is warranted when treating children with medication, especially when the treatment is at an early age (under age 6) or long-term.

Medications may cause a variety of adverse effects (Vitiello et al, 2003a). Some, such as dystonias with anti-dopaminergic agents or appetite suppression with stimulants, become evident after hours to days, while others, such as tardive dyskinesia or metabolic syndrome with antipsychotics, emerge slowly with treatment over months to years. Some adverse effects are related to elevated plasma concentrations, such as lithium-induced tremor, while others emerge after drug discontinuation, such as antipsychotic withdrawal dyskinesias. Some adverse effects can be anticipated based on the mechanism of action of the medication (e.g., sedation with antipsychotics). Other adverse effects are paradoxical, such as increased suicidality with antidepressant treatment.

Assessment of safety largely relies on monitoring and reporting by responsible adults. Identification of adverse effects is contingent on a thorough evaluation by a clinician. In recent years, more information has become available on the long-term safety of several psychotropics in children. For example, it is now recognized that stimulants, such as methylphenidate and amphetamines, can cause a dose-related delay in physical growth, in both weight and height. After 14 months of treatment, children treated with stimulant medication for ADHD grew on average 1.4 cm less in height than peers treated with behavior therapy (MTA Cooperative Group, 2004). A growth deficit was found to persist in future years in children who were medicated for three years (Swanson et al, 2007). The effect on height appears to be more evident in children who started stimulant treatment before the onset of puberty (Díez-Suárez et al, 2017). The mechanism underlying the interference of stimulants with skeletal growth is still unclear.

Because stimulants have adrenergic activity, concern has been raised about unwanted cardiovascular outcomes, including sudden death (Gould et al, 2009). However, analyses of large patient population data have not identified an association between therapeutic use of stimulants and increased cardiac death or cardiac events leading to emergency department visits (Cooper et al, 2011; Schelleman et al, 2011). Moreover, a prospective study of children treated for up to 10 years did not find an increased risk for hypertension, although stimulants have a small detectable acute effect on heart rate and blood pressure (Vitiello et al, 2012).

As stimulants have abuse potential, concerns have also been raised about the possibility that treatment in childhood may sensitize the brain and thus increase the risk of substance abuse in adulthood (Vitiello, 2001). The feasibility of mounting randomized, well-controlled studies to address this issue is questionable, and researchers have relied on naturalistically treated samples. Available prospective studies have not found increased risk of adult substance abuse associated with childhood treatment with stimulants (Volkow & Swanson, 2008; Biederman et al, 2008; Wilens et al, 2008).

Table A.7.7 Key steps in implementing pharmacotherapy in child and adolescent psychiatry

1. Complete a comprehensive diagnostic evaluation documenting the presence of a condition for which medication is indicated
2. Inform parents and child (to the extent allowed by developmental level and cognitive functioning) of the potential benefits and risks of medication as compared with alternative options
3. If the medication does not have a regulatory-approved indication for use in children with the condition, inform parents and child that the medication is being used “off-label”
4. Identify and measure the target symptoms and functions that medication is expected to improve
5. Based on the medication, obtain baseline clinical or laboratory parameters (e.g., weight, height, blood pressure, pulse rate, cholesterol level, renal function)
6. Start medication at a dose in the lower end of the usually effective dose range aiming at identifying the lowest possible dose that produces the desired outcome
7. Monitor effects, side effects and, if appropriate, plasma levels (e.g., lithium levels) in the first few weeks of treatment, and adjust the dose as appropriate
8. If there is improvement, optimize the dose aiming at maximum resolution of symptoms and improvement in functioning
9. Determine the maintenance dose and, based on the condition and medication, establish a tentative duration of treatment
10. As appropriate, periodically consider the need for continuous treatment vs. discontinuation
11. When discontinuing treatment, examine the need for gradual taper, which is recommended for most medications after chronic treatment (e.g., antidepressants, lithium, antipsychotics), vs. abrupt discontinuation, which can be appropriate for some medications (e.g., methylphenidate)

Differences in tolerability have been observed across age and type of development. Preschoolers with ADHD show lower tolerability to methylphenidate than older children (Greenhill et al, 2006; Wigal et al, 2006). Likewise, children with autism spectrum disorder and comorbid ADHD symptoms were more sensitive to the adverse effects of methylphenidate as indicated by an 18% treatment discontinuation due to adverse events (most commonly irritability) as compared with less than 5% in children with ADHD without ASD (Research Units on Pediatric Psychopharmacology Autism Network, 2005b).

Youth exposed to second generation antipsychotics are more prone to gaining weight than adults (Correll et al, 2009). Antidepressants have been found to increase the risk for suicide-related events, such as thoughts about suicide and suicidal behaviors, although an effect on completed suicide has not been determined (Hammad et al, 2006). In a meta-analysis including 13 placebo-controlled trials in children and adolescents with major depression, the suicidality

Preschoolers with ADHD show lower tolerability to methylphenidate than older children. Likewise, children with autism or other pervasive developmental disorders with ADHD symptoms are more sensitive to the adverse effects of methylphenidate.

rate (thoughts, attempts, and self-harm) was 3% on antidepressant and 2% on placebo (Bridge et al, 2007). A similar meta-analysis in adults documented an interaction between age and risk of suicidality with antidepressant use: risk was increased for individuals under age 25, not affected between 25 and 64 years, and actually decreased in patients over 64 (Stone et al, 2009). These data provide an example of interaction between development and pharmacological effect, even though the biological underpinning of this interaction remains unknown.

The mechanism through which antidepressants may trigger suicidality remains a matter of speculation. It is possible that some youth become abnormally activated by the antidepressant, with akathisia, agitation, anxiety, insomnia, and impulsivity. However, this explanation, based on anecdotal reports, remains a theory as systematic analyses of treated patients have not confirmed it (Vitiello et al, 2009b). A related explanation includes unmasking or triggering a bipolar disorder, but this also lacks experimental evidence.

Safety is a relative concept and the risks of pharmacotherapy must be weighed against the risks of an untreated illness. Decisions about prescribing medication must also take into account the availability of effective nonpharmacological interventions. Though generally found less effective at decreasing acute and severe symptoms in most conditions, psychotherapy should always be considered in lieu of, or in combination with medication. Psychotherapy, used either sequentially (i.e., start first with psychotherapy, then add medication if insufficient) or in combination (i.e., start both psychotherapy and medication concurrently), may be able to shorten time to recovery and reduce the total dose of medication needed to control symptoms (TADS Team 2007; MTA Cooperative Group, 1999).

ETHICAL AND REGULATORY CONSIDERATIONS

Children should be able to learn about their condition and the possible treatments to the extent allowed by their cognitive and emotional development. However, before the age of 14, 16, or 18 years (the legal age for consent to treatment varies according to country; see [Chapter A.1](#)), they cannot give legal permission for treatment, which must come from their guardians. It is the responsibility of the prescribing clinician to inform the parents of the expected benefits and risks of the medication. Parents are also instrumental for implementing pharmacotherapy by ensuring appropriate administration of prescribed medication and for reporting treatment-emergent adverse effects.

Research in children

Progress in pediatric psychopharmacology depends on the participation of children in research (see also [Chapter J.7](#)). In the US and some other countries, research involving children is subject to special regulations in addition to those for adults participating in research (United States Department of Health and Human Services; Food and Drug Administration, 2001). Only scientifically sound research that utilizes valid methodology and is posited to add new knowledge about important health issues may be ethically acceptable (Vitiello, 2003b).

Pediatric research can be divided into two broad categories based on whether it does or does not have the prospect of direct benefit to the individual participant. “Prospect of direct benefit” means that each participant has the potential of

A number of public and private websites provide detailed information about child participation in research and the process of determining if a particular project is ethically acceptable. Click on the picture below to access the website of the Office for Human Research Protection.



deriving a health benefit from participation. General acquisition of knowledge relevant to the child's condition does not satisfy the requirement of direct benefit. To be ethically acceptable, research with prospect of direct benefit must also have a favorable balance between anticipated benefits and foreseeable harms. Usually, studies of treatment efficacy have potential for direct benefit to the research participants. In these cases, the main criterion for determining ethical acceptability is the risk/benefit ratio. The inclusion of a placebo arm in randomized clinical trial is usually considered acceptable. Placebo does not necessarily mean absence of treatment and has been associated with substantial improvement, especially in the case of mood and anxiety disorders.

Pharmacological research that does not offer a prospect of direct benefit includes pharmacokinetic and pharmacodynamic studies. In order to be acceptable, such research must have potential for generating essential knowledge relevant to the disorder or condition of the participant. If the information is not relevant to the child's disorder or condition (e.g., a pharmacokinetic study in healthy children at no increased risk for the condition being targeted by the treatment), the research can be conducted only if it entails no more than minimal risk.

Minimal risk is defined as "risk for harm not greater than ordinarily encountered in daily life, or during routine physical or psychological examinations or tests" (section 46.102(i) in U.S. Department of Health and Human Subjects 1991). The prevailing interpretation is that the daily life exams and tests of a normal child is to be used as reference, but a precise quantification of risk in ordinary daily life is not easy and remains a matter of discussion.

If the study aims to acquire information relevant to the child's condition (e.g., pharmacokinetics of a medication for ADHD being studied in children with ADHD), the research risk cannot be greater than a minor increase of minimal risk.

The process of informing parents and children about the aims, procedures, potential risks and benefits of research participation, existence of alternative treatments, and the rights of research participants is critical for obtaining their informed consent and assent. In general, children age 7 and above are able to provide assent, which is often documented in writing within an appropriate "research participation assent form." By age 16, adolescents have a level of understanding similar to that of their parents (Vitiello et al, 2007).

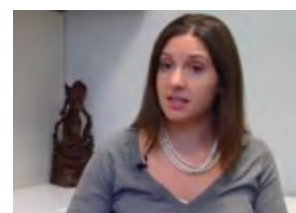
PEDIATRIC PSYCHOPHARMACOLOGY IN CLINICAL PRACTICE

Practicing evidence-based pharmacotherapy in child and adolescent psychiatry requires the integration of knowledge and expertise at different levels, including developmental psychopathology, pharmacology, current regulatory policies for prescribing—that vary from country to country—bioethics relevant to vulnerable patients, and at least enough familiarity with psychosocial interventions to allow an informed and balanced decision-making process.

Research typically provides information at the group level. This is certainly useful for preparing general practice guidelines and algorithms, but the information needs to be interpreted and adapted to the needs of the individual child, a process that relies on the skills of the clinician.

Children and youth who come to the attention of the child welfare system have disproportionately high rates of emotional and mental health challenges and are prescribed high rates of psychotropic medications. [Click here to access the Recommendations about the Use of Psychotropic Medications for Children and Adolescents Involved in Child-Serving Systems by the AACAP](#)

[Click on the image to view a short clip \(2:30\) about talking to children about psychotropic medication](#)



The first few weeks of treatment are devoted to determining if and at which dose the medication is effective and tolerated. During this phase (acute treatment), frequent monitoring is needed in order to titrate the dose based on clinical response (Table A.7.7). Depending on the type of medication, clinical response can take just a few days to emerge or may require several weeks. As previously discussed, the use of standardized rating scales is especially useful in this phase.

Even for the most effective medications, such as stimulants in ADHD, the chance that an individual patient will derive a clinically significant benefit is about 70%, thus leaving about a third of patients without sufficient improvement. This means that the clinician must be ready to recognize non-response and change the treatment plan accordingly. In many cases, a second-step medication should be considered. For example, if a child with ADHD has not improved from methylphenidate, an amphetamine product may be effective. Likewise, depressed adolescents who have not improved on one antidepressant have about a 50% chance to respond to another antidepressant (Brent et al, 2008).

Once a medication has been found to be of benefit and well tolerated by the patient, the treatment continues with the goals of optimizing it, achieving remission and functional recovery (continuation phase). After achieving recovery, the treatment typically continues with the purpose of maintaining improvement and preventing relapse or recurrence (maintenance phase). The duration of maintenance treatment depends on the condition being treated and the history of illness of the individual patient. For example, ADHD is a chronic condition, so that long-term treatment is usually indicated. However, the phenotypic manifestations of ADHD may change with time, as hyperactivity tends to decrease in adolescence or young adulthood, so that periodic reassessment of the need for pharmacological treatment is advisable on an annual basis or so.

In the case of MDD, it is recommended that effective treatment be continued for 6 to 12 months after reaching remission, after which a gradual tapering off of the medication over a 2-3 months period can be considered (Hughes et al, 2007). For patients who had had recurrent episodes of depression, a proportionately prolonged treatment is usually advisable.

CHALLENGES

While insufficient access to competent prescribers and integrated systems of care is virtually universal, countries across the globe also face great region-specific challenges. In high income countries, such as the US, polypharmacy practice has become increasingly prevalent even though evidence for its efficacy and safety is lagging. Shortage of prescribers and excessive reliance on medications in the absence of effective psychosocial interventions exacerbate this problem. There is a concern that insufficient training and team integration of “mid-level physician extenders” may lead to “over-prescribing.” Responsible approaches to deprescribing are still in early stages of development.

Another emerging challenge in high income countries has to do with the growing commercial use of pharmacogenomic testing before it has gathered sufficient scientific evidence. Conversely, low- and middle-income countries are facing a severe dearth of both medications and prescribers. Medications that are considered to be the standard of care in high income countries may not be available

in low- and middle-income countries.

Some countries have less than ten or no child psychiatrists at all. Other countries have questioned the need for child psychiatry as a specialty altogether. The growing practice of conducting clinical trials in low- and middle-income countries that will disproportionately benefit patients on high income countries presents both ethical and cross-cultural validity challenges. Finally, in the absence of effective public education in both high- and low- and middle-income countries, the use of sham treatments that have not been scientifically studied continues to be on the rise.

CONCLUSIONS

When properly used, medications have an important role in the treatment of youth with severe mental disorders. There is evidence that some medications can help not only manage symptoms, but also improve functioning and hasten recovery. A thorough and complete diagnostic evaluation before considering medication is critical, as well as the need for consistent monitoring during treatment. The therapeutic value of a number of psychotropics is now well documented in both the short and intermediate-term, while more research is needed to better understand the long-term impact of pharmacotherapy. Pediatric psychopharmacology continues to develop rapidly, and clinicians must remain informed as new data become available.

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Appendix A.7.1

SELF-ASSESSMENT EXERCISES

A.7.1 *Discontinuing risperidone in children with autism and severe behavioral disturbances:*

- A** Increases the risk of recurrence
- B** Results in an improvement of behavior
- C** Does not make any difference
- D** Lessens self-harming behaviors
- E** Improves learning

A.7.2 *Psychotropic medications were typically introduced to treat adult disorders and then extended to the pediatric population, with the exception of:*

- A** Chlorpromazine
- B** Psychostimulants
- C** SSRIs
- D** Lithium carbonate
- E** Clozapine

A.7.3 *When compared with adults and adjusted for body weight, the relative mass of children's liver and kidney tissue is:*

- A** Smaller
- B** Similar
- C** Greater
- D** Much greater
- E** Of no clinical relevance

A.7.4 *Using a medication "off label" means that it:*

- A** Lacks evidence of effectiveness
- B** Has not received approval for that indication by a regulatory agency (e.g., FDA)
- C** Has significant side effects
- D** Is not recommended by the WHO
- E** Is not recommended by clinical practice guidelines

A.7.5 *Some medications are included in the WHO list of essential medicines for mental and behavioral disorders in spite of:*

- A** Their price
- B** Their availability
- C** Being "of label"
- D** Lacking evidence of effectiveness in children
- E** Significant side effects

A.7.6 *Which one of the CYP450 enzymes listed below is most relevant in pediatric psychopharmacology?*

- A** CYP2C9
- B** CYP2C19
- C** CYP2B6
- D** CYP3B7
- E** CYP3A4

A.7.7 *When treating children, decreasing adult target dosage based on the child's weight:*

- A** Is a good practice
- B** Reflects pharmacodynamic principles
- C** Reduces side effects
- D** May result in under-treatment
- E** May result in over-treatment

A.7.8 *Tricyclic antidepressants for depression in children:*

- A** Should not be used
- B** Are effective
- C** Are better tolerated than in adults
- D** Require lower doses than adults
- E** Require higher doses than adults

A.7.9 *Effect size is the difference in the outcome measure between the study groups...*

- A** Multiplied by the pooled standard deviation at the end of treatment
- B** Divided by the pooled standard deviation at the end of treatment
- C** Subtracted from the pooled standard deviation at the end of treatment
- D** Added to the pooled standard deviation at the end of treatment
- E** Divided by the square of the pooled standard deviation at the end of treatment

A.7.10 *Which statements listed below are true or false:*

- A** The higher the number needed to treat (NNT) the lower the effectiveness of a treatment
- B** Even for the most effective medications, such as stimulants in ADHD, the chance that an individual child will derive a clinically significant benefit is about 70%
- C** Nowadays psychotropic medication should not be prescribed unless genetic testing has been carried out
- D** Psychotherapy should not be used concurrently with medication
- E** Antipsychotic drugs are better tolerated by children than by adults

ANSWERS

- A.7.1 Answer: A
- A.7.2 Answer: B
- A.7.3 Answer: C
- A.7.4 Answer: B
- A.7.5 Answer: D
- A.7.6 Answer: E
- A.7.7 Answer: D
- A.7.8 Answer: A
- A.7.9 Answer: B
- A.7.10 Answer: A, true; B, true; C, false; D, false; E, false