PRINCIPLES IN USING PSYCHOTROPIC MEDICATION IN CHILDREN AND ADOLESCENTS

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Medications to treat mental conditions (psychotropics) have become increasingly used in child and adolescent psychiatry. From the serendipitous discovery by Bradley of the effects of amphetamines in child hyperactivity in 1937 to the multisite clinical trials of the 2000s, pediatric psychopharmacology has gradually become both an active area of research and, at least in some countries, common clinical practice. It has also been the subject of debate and controversy in the general public and among mental health experts, especially with respect to the appropriateness and safety of using medication for treating emotional and behavioral problems during development. With the notable exception of medications for attention deficit hyperactivity disorder (ADHD), which were first introduced for pediatric use and then applied to adults, psychotropic medications were first developed to treat depression, anxiety, mania, or psychosis in adults, and then used also in children suffering from these conditions. Concern has been raised about both the validity of applying adult diagnostic categories to children and the safety of extrapolating information collected in adults to children.

In 1937, Charles Bradley, a psychiatrist, administered dl-amphetamine to "problem" children at the Emma Pendleton Bradley Home in Providence, Rhode Island, in an attempt to alleviate headaches. However, Bradley noticed an unexpected effect upon the behavior of the children: improved school performance, social interactions, and emotional responses. Bradley's studies went largely ignored in the field of child psychiatry for nearly 25 years. However, they proved to be an important precursor to studies on the use of amphetamines in conditions such as attention deficit hyperactivity disorder (Strohl, 2011).

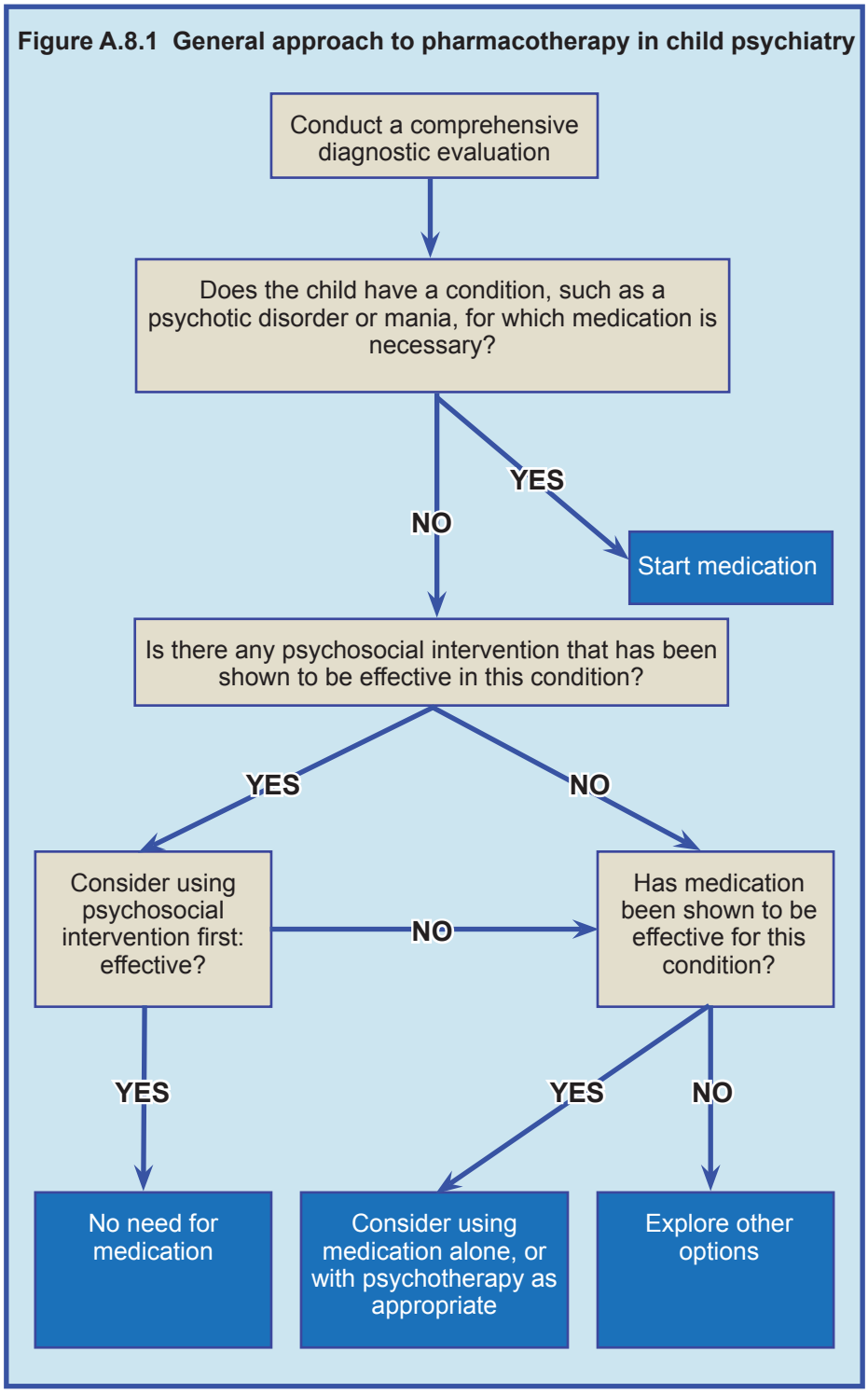
Pediatric pharmacology research has provided a better understanding of the benefits and risks of the pediatric use of several psychotropics, such as stimulants and antidepressants. For many other medications, however, the current knowledge base is still incomplete. The inadequacy is especially evident with respect to the long-term use. In psychiatry, medications are seldom curative and, since many disorders tend to persist or recur, 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 a better functional outcome and improve the ultimate prognosis. Unfortunately, controlled clinical trials are usually limited to just a few months of treatment, and documenting long-term treatment effects is methodologically very difficult.

The purpose of this chapter is to review the key elements relevant to the therapeutic use of psychotropic medications in children and adolescents. The aim is to provide clinicians with a general framework for approaching the pharmacotherapy of psychiatric disorders during development. For detailed information on specific medications, the reader is referred to the chapters covering the relative disorders.

WHEN TO USE PSYCHOTROPIC MEDICATION IN YOUTH?

A number of factors come into play when choosing a treatment. A comprehensive diagnostic evaluation is the necessary first step (Figure A.8.1). Patients with psychotic disorders typically require pharmacological treatment to control symptoms and restore functioning. Patients with other disorders, on the other hand, may be often successfully treated with non-pharmacological interventions, and medication is just one of several therapeutic options whose potential benefit and risks need to be considered by the treating clinician, the family, and, whenever possible, the young persons themselves. For example, psychotherapy can be effective in the management of patients with attention deficit/hyperactivity disorder (ADHD), major depression, and anxiety disorders. Not all children, however, improve on purely psychosocial interventions and, for

Figure A.8.1 General approach to pharmacotherapy in child psychiatry



"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).

them, medication may be necessary to improve mood, behavior, and functioning. It should be noted that psychotherapy and medications are not mutually exclusive treatment modalities: in some conditions, combined use was 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. As in other areas of medicine, also in child psychiatry the standards of evidence-based medicine apply (Gray, 1997). Thus, the

strongest level of evidence comes from at least one systematic review of multiple, well-designed, randomized controlled trials (Type I), followed by evidence from at least one properly designed randomized controlled trial (Type II). Thanks to clinical research conducted in the last decade, there is now evidence for the short-term efficacy of a number of medications in children (Table A.8.1).

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

Much less strong is the evidence of the long-term effectiveness and safety of treatments. There are, however, a few placebo-controlled discontinuation studies that have shown that long-term treatment can be effective in maintaining improvement and preventing symptoms recurrence. For example, in youth suffering for 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 as 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.

PHARMACOKINETICS

Drug absorption, distribution, metabolism, and excretion can be influenced by development, so that trying to determine doses and frequency of administration for children based on data obtained from adults can lead to inappropriate treatment. Although children have smaller body size than adults, the relative mass of liver and kidney tissue is greater 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 drug tends to be greater in children than in adults. In general, 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.

Once absorbed, most drugs undergo biotransformations (metabolism) that turn the parent compound into more polar, and therefore easier to eliminate, by-products (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 kidney or the bile. The Phase I oxidative processes are mediated by cythocrome 450 (CYP450) microsomal enzymes, which are concentrated primarily in the liver. The CYP 450 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 CYP 450 enzymes in pediatric psychopharmacology are the CYP3A4 and the CYP2D6, which are involved in the metabolism of most psychotropics. For example, the 3A4 system metabolizes sertraline, citalopram,

Table A.8.1 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 dexmethylphenidate	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.8.1 Selected psychotropic medications and level of evidence for efficacy in children (<18 years) (Continuation).

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: 5-16 years of age
Olanzapine	Schizophrenia	Type II	13 and older
	Bipolar disorder	Type II	10 and older
Lithium	Bipolar disorder	Type III	12 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.

[1]Strength 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).

[2]Aproved for the treatment of epilepsy from infancy.

escitalopram, bupropion, mirtazapine, aripiprazole, quetiapine, ziprasidone, alprazolam, and zolpidem. The 2D6 system metabolizes fluoxetine, atomoxetine, risperidone, olanzapine, 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, the 3A4 enzymes can be inhibited by fluoxetine or fluvoxamine. Concomitant administration of fluvoxamine (inhibitor of 3A4) and pimozide (metabolized by 3A4) could lead to high levels of pimozide and prolongation of the QTc interval. An additional complexity is that some medications, such as carbamazepine and phenobarbital, can induce the 3A4 activity, thus potentiating its metabolizing capacity. The concomitant administration of carbamazepine and a medication metabolized by 3A4 can result in lower levels of the medication. In sexually active female adolescents, use of oral contraceptives can induce CYP enzymes and thus increase drug metabolism and elimination.

Genetic polymorphism has been identified for CYP2D6. About 7-10% of Caucasians, 1-8% of Africans, and 1-3% of East Asians are poor metabolizers. 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 extensive metabolizers, but 22 hours in poor metabolizers (Sauer et al, 2005). While the clinical implications of these metabolic differences do not seem to be 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). Assay for genetic polymorphism is not routinely done in current child psychiatry practice, but 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 elimination is faster so that withdrawal symptoms upon discontinuation are more likely. In these cases, a more frequent dosing is needed to maintain consistent therapeutic levels and prevent withdrawal symptoms between doses.

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

The pharmacokinetics of many psychotropics has been studied in children and adolescents. For escitalopram, aripiprazole, quetiapine, risperidone, and lithium, the pharmacokinetics was found to be similar in youths than in 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 use.

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. The first generation of extended release formulations of methylphenidate consisted of tablets with different coatings of immediate and slower release medication. With these preparations, however, the onset of action was at times delayed in the morning or the therapeutic effect faded in the afternoon. Consequently, a second-generation of biphasic extended release formulations has been introduced. These formulations allow an initial bolus of medication to be absorbed immediately, followed by a second, more gradual release. The plasma pharmacokinetics curve thus shows an

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.

acute initial peak at about 1.5 hours after dosing, followed by a second peak about 3 hours later (Swanson et al, 2003). With these extended release preparations, only a once-a-day morning administration is needed to provide therapeutic effects up to 8-10 hours.

PHARMACODYNAMICS

Most psychotropics act through neurotransmitters, such as dopamine, serotonin, and norepinephrine, whose receptors undergo major changes during development (Rho & Storey, 2001). Receptor density tends to peak in preschool years and then gradually declines towards adult levels in late adolescence (Chugani et al, 2001). The impact of these developmental changes on drug activity and possible implications for efficacy and safety are still not well understood. However, differences between children and adults in efficacy and safety have been observed thus suggesting that development can significantly influence the effects of these medications. For example, tricyclic antidepressants, though proven effective in adult depression, have no demonstrable antidepressant effect in children (Hazell et al, 1995); amphetamine-like stimulants are more likely to induce euphoria in adults than in children; antipsychotics tend to cause stronger metabolic effects in youth than in adults (Correll et al, 2009); and serotonergic antidepressants were found to increase the risk for suicidal ideation and attempts in children, adolescents, and young adults, but not in the middle-aged or the elderly (Hammad et al, 2006; Stone et al, 2009).

Clearly 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). When brain development is abnormal, such as in autism, the effects of medication can be impacted, as shown by the lack of benefit from selective serotonin reuptake inhibitors for compulsive and repetitive behaviors in autism (King et al, 2009). Thus, information derived from data from adolescents may not be applicable to children who are younger or suffer from pervasive disorders of development. This underscores the need for research directly in the patient populations likely to be treated with these medications.

EFFICACY

The term *efficacy* is broadly used to indicate that a treatment has a demonstrated therapeutic benefit when tested in fairly tight experimental conditions, usually involving carefully selected samples of patients. The term *effectiveness* is typically applied to treatments that have shown to have benefit in usual clinical settings for patients broadly representative of the population likely to receive the treatment. Often, however, these two terms are used interchangeably.

The most convincing evidence of the efficacy of a treatment comes from controlled clinical trials showing the superiority of the treatment over a control in modifying a clinically meaningful outcome. Double-blind trials are methodologically more convincing than open studies because they control for expectation biases. 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 in child psychiatry,

which is currently summarized in a number of practice guidelines and treatment algorithms (National Institute for Health and Clinical Excellence, 2005 and 2008; Pliszka et al, 2007; Birmaher and 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*), or 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 being considered. Typically, medications are approved for clinical use based on studies showing efficacy at decreasing symptoms. In fact, proving treatment effects on remission, recovery, or functioning requires longer term controlled trials, which are more difficult and expensive to conduct. There are, however, a few studies showing effectiveness on remission and recovery for a number of medications, such as stimulants in ADHD (Swanson et al, 2001) or serotonergic antidepressant in adolescent depression (Kennard et al. 2006; Vitiello et al, 2006).

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.

The need to document symptom reduction and remission brings forward the importance of measuring the behavioral, emotional, and functional manifestations of mental dysfunction. In the absence of biological markers of disease and treatment effects, clinicians must rely on symptoms in order to gauge treatment response. Suitable rating scales have been developed for all the more common conditions in child mental health (e.g., Conners et al, 1998; Poznanski & Mokros, 1996; Birmaher et al,1997; March et al, 1997; Research Units on Pediatric Psychopharmacology Anxiety Study Group 2002; Bernstein et al, 2010; Shaffer et al, 1983; Wagner et al., 2007; see also Chapter A.5). These scales can be broadly divided into those that are completed by the clinician based on direct observation and informants (*clinician-rated scales*), and those that are completed directly by the informant (*self-administered scales*). Respect to adults, a distinctive characteristic of pediatric psychopharmacology is that, in addition to the child, the clinical information is usually derived from parents and teachers. Assessing and monitoring medication effects is therefore more complex and time consuming in children than in adults because clinicians must collect and integrate information from multiple sources.

When comparing treatments or making clinical decisions, it is useful to quantify the size of the treatment effect (see also Chapter A.6). Using data from controlled clinical trials, the magnitude of the treatment effect relative to a control can be expressed in standard deviation units. One of the most commonly used way of computing an effect size is the Cohen's *d* or the Hedge *g*, which is in the difference in outcome measure between the study groups divided by the pooled standard deviation at the end of treatment (Rosenthal et al, 2000). Compared with a placebo condition, stimulants usually have a large effect size (0.8 and above) in decreasing symptoms of ADHD (Greenhill et al, 2001). In the trials that have detected a separation between SSRI and placebo, the SSRI had a moderate effect size (0.5-0.7) when used in the treatment of major depression (TADS Team, 2004) or obsessive compulsive disorder (Pediatric OCD Treatment Study, 2004). However, meta-analysis of all available databases of clinical trials in pediatric depression indicate that the effect size of antidepressant medication vs. placebo is small (0.25, 95% C.I. 0.16-0.34) (Bridge at al, 2007).

The effect size calculation can be applied also for quantifying the pre-post treatment difference within the same group of patients, rather than the difference between treated group and control. In these cases, however, due to the lack of a parallel control, the effect due to the treatment cannot be separated from the effect due to the mere passage of time. For this reason, a within-group pre-post effect size cannot be taken as an estimate of the effect of treatment but rather of the combined effects of time and treatment.

It is also useful to express the strength of the therapeutic benefit using the *number needed to treat* (NNT), which is the number of patients who need to be given the treatment in order to add one more improved patient to the number of those who are expected to improve in the control condition. Thus, in the Treatment for Adolescents with Depression Study (TADS), 61% of fluoxetine-treated patients improved at the end of the 12-week treatment as compared with 35% of the placebo patients (TADS Team 2004). Based on these rates, the NNT for fluoxetine is 4 (i.e., 1/61-35), which indicates that one needs to treat on average 4 patients in order to improve one patient more than the placebo condition. The smaller the NNT, the greater is the relative efficacy of the treatment. The NNTs of psychotropic medications, though variable among studies, is often quite favorable and compares well with other non-psychiatric drugs used in pediatrics.

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.

Most of what is currently known about the effects of treatments is limited to the short- (i.e., a few weeks) and intermediate-term (i.e., a few months). Relatively few studies have addressed the long-term effectiveness of pharmacotherapy in child psychiatry (MTA Cooperative Group, 2004; TADS Team, 2007; Vitiello et al, 2011). More research is needed to see whether control of symptoms leads to long-term benefits and better prognosis. For example, it would be good to know if improvement in ADHD symptoms translates 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 still do not have the data for drawing this type of conclusions. Research on the long-term effects of treatments poses many challenges from a practical and methodological perspective. In fact, long-term randomized controlled trials are difficult to implement, and merely observational studies are usually insufficient for proving causality.

SAFETY

Ensuring safety is especially important when treating children. Pharmacological treatment during a period when the organism undergoes rapid development may result in toxicities that are not seen in adults. A general concern is that agents acting on neurotransmitter systems in rapid development may interfere with normal processes and result in unwanted long-lasting changes. Some studies in developing animals have been conducted. For example, administration of fluoxetine 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 suspicion is warranted when treating children with medication, especially when the treatment is at an early age (under age 6) or

prolonged in time.

Medications may cause a variety of adverse effects (Vitiello et al, 2003a). Some effects, such as dystonias with anti-dopaminergic agents or appetite suppression with stimulants, become evident acutely, after a brief period of drug exposure, while others, such as tardive dyskinesia or metabolic syndrome with antipsychotics, emerge slowly with chronic treatment. Some adverse effects are related to drug dose or 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, while others are completely unexpected, such as increased suicidality with antidepressant treatment. Like for efficacy, assessment of safety depends in large part on adult monitoring and reporting. Identification of adverse effects is contingent on a thorough and detailed evaluation by a clinician familiar with the medication.

In recent years, more information has become available on the long-term safety of several psychotropics in children. For example, it is now better recognized that stimulants, such a 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 are continuously medicated (Swanson et al, 2007). The mechanism underlying the interference of stimulants with skeletal growth is still unclear, but recent data suggest that chronic treatment with methylphenidate leads to transient inhibition of testosterone levels and delay in puberty (Mattison et al, 2011).

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.

Because stimulants have adrenergic activity, concern has been raised about unwanted cardiovascular outcomes, including sudden death (Gould et al, 2009). However, recent analyses of large patient population data have not identified any 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 detectable effect on heart rate even with chronic use (Vitiello et al, in press).

As stimulants are drugs of potential abuse, concerns have been raised about the possibility that treatment in childhood may sensitize the brain and thus make substance abuse and dependence more likely in adolescence and 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. Most of these studies have not found an increased risk of substance abuse after treatment with stimulants (Biederman et al, 2008; Wilens et al, 2008).

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 or other pervasive developmental disorders with ADHD symptoms are more sensitive to the adverse effects of methylphenidate as indicated by an 18% treatment discontinuation due to intolerable adverse events (most commonly irritability) (Research Units on Pediatric Psychopharmacology Autism Network,

2005b). Youths 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 certain suicide-related events, such as thoughts about suicide and suicidal attempts, although an effect on completed suicide could not be determined (Hammad et al, 2006). In a meta-analysis including 13 placebo-controlled trials in children and adolescents with major depression, the suicidality rate (suicidal thoughts, attempts and self-harm) was 3% on antidepressant and 2% on placebo (Bridge et al, 2007). Similar meta-analyses of clinical trials in adults have documented an interaction between age and risk of suicidality with antidepressant use: the risk was increased for individuals under age 25, not affected between 25 and 64 years, and actually decreased in older patients (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 youths become abnormally activated by the antidepressant, displaying akathisia, agitation, anxiety, insomnia, and impulsivity. However, this explanation remains a theory based on anecdotal reports as systematic analyses of treated patients have not confirmed it (Vitiello et al, 2009b).

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.

Safety is a relative concept and the possible risks of pharmacotherapy must be weighed against the possible risks of untreated psychopathology. Decisions about prescribing medication must also take into account the availability of effective non-pharmacological interventions. Though generally found less effective at decreasing symptoms of ADHD or depression in children and adolescents, psychotherapy can be considered in lieu of medication for mild depression, or in combination with medication for more severe cases. 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 reduce the dose of medication needed to control symptoms.

ETHICAL AND REGULATORY CONSIDERATIONS

Children should be explained about their condition and the choice of possible treatments to the extent allowed by their cognitive and emotional developmental stage. However, before the age of 14 or 16 years (the legal age for consent to treatment varies according to country; see also Chapter A.1) they cannot give legal permission for treatment, which must come from their parents. 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 direct participation of children in research (see also Chapter J.7). In the US and some other countries, child research is subject to special regulations that are in addition to those for adult research participation (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 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 the efficacy of treatments have potential for direct benefit to the research participants. In these cases, the main criterion for determining if the study is ethically acceptable is the risk/benefit ratio. The presence of a placebo arm in randomized clinical trial is usually considered acceptable in child psychiatry conditions. Placebo does not equal 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 pharmacokinetics and pharmacodynamics studies. In order to examine the acceptability of a study in this category, it must be determined whether such a study does or does not have the potential for generating essential knowledge relevant to the disorder or condition of the research participant. If the information is not relevant to the child's disorder or condition (e.g., a pharmacokinetics 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 are 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*. According to the current US regulations, a *minor increase over minimal risk* can be considered acceptable only if:

a) It presents "experiences to the subjects that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" and

b) The study has the potential to generate new knowledge considered of "vital importance" for understanding or treating the child's disorder or condition.

Research not approvable based on these criteria but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, can be referred to the Secretary of Health for further review under the HHS regulations at 45 CFR 46.407 (U.S. Department of Health and Human Subjects 1991) and FDA regulations at 21 CFR 50.56 (Food and Drug Administration 2001). Studies where psychotropic medications are given to normal children in order to better understand their mechanism of action on the brain usually fall into this category since non-therapeutic administration of a

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.

Click on the picture below to access the Children's Hospital Boston's interactive parents' guide to medical research.

psychotropic drug would generally be considered to pose more than minimal risk. Similar, although not identical, regulations are in place in the European Union and in other countries.

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 permission and assent. In general, children age 7 and above are able to provide assent, which is often documented in writing with an appropriate "assent form". With proper communication and explanation by researchers, parents can achieve a good understanding of both the research procedures and the rights of participant. By age 16, adolescents have a level of understanding similar to that of their parents (Vitiello et al, 2007).

A number of psychotropics have received approved pediatric indications by the drug regulatory agencies (the FDA in the US), but others are used *off-label*. Use of a drug *off-label* is not in itself an inappropriate practice as it is often supported by considerable empirical evidence and consistent with treatment guidelines. However, it is important for parents to be aware that a medication is going to be prescribed off-label so that they can make fully informed decisions about the treatment of their child.

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 drug regulatory policies, 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 guideline 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.

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.8.2). 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 can be especially useful in this phase. It should be noted that, 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 can 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 an antidepressant have about a 50% chance to respond to another antidepressant (Brent et al, 2008).

Table A.8.2 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)

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*). Finally, 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 or fade away in adolescence or young adulthood, so that a periodic reassessment of the need for pharmacological treatment is advisable on an annual basis or so. This can be accomplished by discontinuing treatment and monitoring for symptoms at home and in school. In the case of depression, it is recommended that effective treatment be continued for 6-12 months after reaching remission, after which a

gradual tapering off of the medication over a 2-3 month period can be considered (Hughes et al, 2007). For patients who had had recurrent episodes of depression, a more prolonged treatment is usually advisable.

CULTURAL AND ETHNIC INFLUENCES

The use of pharmacotherapy for children and adolescents with mental disorders varies widely across countries. This variability cannot be fully accounted for by differences in nosology or prevalence of psychopathology, thus suggesting that cultural, economic, regulatory, and other contextual factors play a major role in the decision by clinicians and parents to medicate children with emotional and behavioral disorders (Vitiello, 2008). Use of psychotropic medications is substantially higher in the US than in other developed countries. More than 80% of the world usage of stimulant medications occurs in the US. 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, in press). Likewise, antidepressant and antipsychotic use is many times greater in the US than in other countries (Fegert et al, 2006).

There are also differences within countries. For example, use of stimulants for ADHD treatment in the US is greater among the white population than among children of African American or Hispanic background. These ethnic differences appear to be independent of economic factors. Furthermore, stimulant medication use is lower in the US West Coast than in the rest of the country (Zuvekas & Vitiello, in press). One needs to recognize that approaches to mental health vary considerably based on cultural factors. The implications of this variability for disease outcome and patient prognosis are unclear.

CONCLUSIONS

When properly used, medications can have an important role in the treatment of children and adolescents with several mental disorders. There is evidence that some medications can help not only manage symptoms, but also improve functioning and speed up recovery. The critical role of a thorough and complete diagnostic evaluation before considering medication cannot be overemphasized, 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 is a field in rapid development and clinicians need to remain informed as new data become available.

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

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