Introduction

Psychotropic medications have a vital role in the treatment of psychiatric disorders among children and adolescents (Strawn et al., 2022). However, using these medications effectively and appropriately demands a deep understanding of pediatric pharmacokinetics and pharmacodynamics alongside the nuanced findings from double-blind, placebo-controlled trials. Within the context of developmental psychopharmacology, this Introduction highlights general principles that apply to the medication monographs that follow. Beyond this, we introduce you to specific changes that we have made in the *Second Edition* to help you understand how metabolism, drug–drug interactions, and pharmacogenetics are relevant to specific medications.

Not Just Little Adults: Developmental Pharmacology

The landscape of pharmacokinetics and pharmacodynamics in children and adolescents diverges significantly from that of adults, thereby necessitating differences in dosing and producing differences in response patterns and tolerability. It is crucial to recognize the interplay between pharmacokinetic and pharmacodynamic factors, as these factors influence one another and differ from adults. Such differences include variations in side effects (e.g., akathisia and drug-induced parkinsonism, hyperprolactinemia, weight gain) (Correll et al., 2010; Maayan and Correll, 2011; Koch et al., 2023), dosing (e.g., lithium) (Findling et al., 2011), and efficacy (e.g., benzodiazepines) among children, adolescents, and adults (Dobson et al., 2019).

Pediatric Pharmacokinetics

At birth, metabolic capacity in children is lower than in adults, gradually reaching adult levels by around 2 years of age (Strawn and Ramsey, 2024). However, near puberty, metabolism may surpass the levels observed in adults. In addition to developmental differences in hepatic metabolism, changes in renal function and fat distribution during childhood and adolescence influence the pharmacokinetics of various medications in the pediatric population. Furthermore, children and adolescents possess a greater total body water content and relatively less adipose tissue compared to adults, impacting the distribution of many medications and the accumulation of lipophilic substances and their metabolites.

Absorption and Bioavailability: The Journey Within

The route of administration greatly influences the absorption of drugs, with oral medications being particularly influenced by gastric pH and the presence of food in the stomach (Strawn and Ramsey, 2024). Bioavailability, on the other hand, represents the fraction of a drug that enters systemic circulation, which can be influenced by concomitant medication use and first-pass metabolism. Young children may also absorb some drugs faster than adults do, leading to higher peak drug levels and peak-related side effects. For this reason, once-a-day drugs for adults may occasionally have to be given twice or three times a day in children.

Drug Distribution: Mapping the Pathways

As drugs travel through the blood, they distribute throughout the body, with the distribution to their site of action being influenced by protein binding and how they

cross the blood–brain barrier (Strawn and Ramsey, 2024). The volume of distribution (V_D) serves as an indicator of the extent to which a drug is distributed within bodily tissues rather than remaining in the plasma. Higher V_D values signify greater tissue distribution, whereas lower V_D values indicate a more plasma-centric concentration. The V_D is influenced by factors such as high lipid solubility (e.g., certain benzodiazepines), low rates of ionization, and low plasma protein binding. Moreover, the V_D varies across development, and age-related changes in body composition can further influence drug distribution. Prepubertal children have more body water and less fat (where lipid-soluble drugs are stored) compared to adults. Prepubertal children also tend to have less protein binding of drugs compared to adults, leaving a greater proportion of the biologically active drug in the plasma.

Metabolism: Unraveling the Enzymatic Pathways

Hepatic enzyme activity develops early, and the rate of drug metabolism is related to liver size, which is proportionately larger in children than in adults. Because the liver parenchyma is also larger in children than in adults relative to body size, children may require a larger dose per kilogram of body weight of drugs that are primarily metabolized by the liver.

Various psychotropic medications undergo metabolism mediated by cytochrome P450 enzymes, namely CYP3A4, CYP2C19, or CYP2D6, within the liver (Hicks et al., 2015). While CYP2D6 activity remains relatively constant from the age of 1 through adulthood, CYP2C19 and CYP3A4 activities may be increased in children compared to adults (Strawn et al., 2018; Ramsey et al., 2019). Drug–drug interactions can occur through the inhibition or induction of these enzymes. Furthermore, younger children may exhibit increased hepatic clearance due to greater liver blood flow in relation to total body mass, resulting in a larger first-pass effect for certain drugs.

Excretion: Bid Farewell to the Medication

The renal and hepatic pathways serve as the primary routes for the excretion of drugs and their metabolites. Renal clearance is substantially higher in pediatric populations compared to adults and experiences a decline from ages 2 to 20 (Strawn and Ramsey, 2024) and this has implications for several medications, including lithium.

Pharmacogenetics in Children and Adolescents: Deciphering Genetic Variability

Variations within genes encoding metabolizing enzymes, such as *CYP2C19* and *CYP2D6*, influence the activity of these enzymes, including in children and adolescents (Ramsey et al., 2019). Consequently, patients can fall into different metabolizer groups, including poor metabolizers (with minimal to no enzyme activity), intermediate metabolizers, normal metabolizers, rapid metabolizers, or ultrarapid metabolizers (with increased enzyme activity). Dosing recommendations tailored to these metabolizer types are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) (Hicks et al., 2015), the Dutch Pharmacogenetics Working Group, and some are incorporated within US Food and Drug Administration (FDA) labels. The systemic concentration of a medication can be influenced by the activity of CYP2C19 and CYP2D6 enzymes, requiring dose adjustments. Poor metabolizers may require lower doses, while ultrarapid metabolizers may necessitate higher doses. It is imperative to focus on individual genes for medication dosing adjustments, avoiding the temptation of employing pharmacogenetic testing for medication selection.

While pharmacogenetic tests offer valuable insights, certain limitations must be acknowledged. First, these tests may overpromise by asserting the ability to predict

medication effectiveness and optimal drug concentrations. Second, the strength of evidence for gene–drug associations may vary across different tests, with limited or absent data available for certain pharmacogenetic variants in the pediatric population. Hence, caution is advised when applying such tests to children and adolescents without empirical grounding (Ramsey et al., 2020). Moreover, numerous clinical factors must be taken into account when selecting appropriate medications for individual patients, considering developmental effects on pharmacokinetically related enzymes (Ramsey et al., 2020). While we discourage relying solely on pharmacogenetics for medication selection, dismissing clinical factors or the evidence base for medications is equally problematic (Ramsey et al., 2020).

No consensus has yet been reached regarding the utility of pharmacogenetic testing in child and adolescent psychiatry. Nevertheless, dosing recommendations based on pharmacokinetic genes are included in FDA labels and Clinical Pharmacogenetics Implementation Consortium (CPIC) consensus guidelines (Bousman et al., 2023), and these guidelines are employed in many institutions across adult and child and adolescent psychiatry. However, it is crucial to exercise caution when extrapolating pharmacokinetic models from adults to youth, considering the influence of developmental factors on medication metabolism. Prospective and retrospective pediatric studies have provided insights into the impact of variation in these pharmacokinetic genes on drug concentration, tolerability, and response for several classes of medication metabolized by these enzymes (Aldrich et al., 2019; Strawn et al., 2020). Dose adjustments based on CYP2C19 metabolizer status are supported by modeling studies in adolescents for citalopram, escitalopram, and sertraline (Strawn et al., 2019), as well as by CPIC recommendations. Similarly, dose adjustments for atomoxetine, fluvoxamine, and paroxetine based on CYP2D6 metabolizer status are also supported by evidence.

The FDA recommends dosing based on product insert information for CYP2C19 for citalopram and CYP2D6 for aripiprazole and atomoxetine. These dosing recommendations aim to balance exposure levels (area under the concentration–time curve) and hold the potential to mitigate side effects associated with high exposure or treatment failures associated with low exposure to these medications. However, establishing a clear relationship between medication blood levels and efficacy can be challenging, as it may be confounded by tolerability and other factors. In certain cases, increased metabolism observed in rapid and ultrarapid metabolizers may lead to patients appearing "treatment resistant" due to sub-therapeutic medication blood concentrations. This phenomenon was observed in the Treatment of SSRI-resistant Depression in Adolescents Study (TORDIA) concerning fluoxetine and sertraline (Sakolsky et al., 2011). Finally, it is worth noting that a boxed warning in carbamazepine's product insert advises screening patients with ancestry in genetically at-risk populations (Asians) for the presence of HLA-B*1502 prior to initiating treatment. Due to the high risk of severe dermatological reactions, including Stevens–Johnson syndrome, carriers should refrain from receiving carbamazepine unless the benefits clearly outweigh the risks.

These insights into pharmacogenetics should not overshadow the importance of thorough clinical evaluations and the consideration of various clinical factors when deciding on medication usage. The choice of medication should be based on available evidence, and when pharmacogenetic testing is conducted, it should inform dosing adjustments, monitoring levels, or the selection of medications within the evidence-based class for a specific condition.

Hold On to Your Seat: What Is Different About Treating Children and Adolescents Compared to Adults?

Diagnoses in children and adolescents can be less stable than in adults; thus, at each follow-up visit, clinicians should look for morphing from one diagnosis to another and for emerging comorbidities that have changed since the last visit. In reality, there are at least two patients when treating a child/adolescent: the child/adolescent and the caregiver, each involved in different ways in the diagnosis and treatment of the patient, and each with different needs for information and explanation. Family dynamics, school environment, and social interactions with peers can also affect symptoms and behaviors.

Even more so than in adults, there is a need for "triangulation" of information when treating children and adolescents, particularly to assess improving or deteriorating symptoms, that is, not only the child or adolescent's perspective and any of the clinician's perspective at the time of the visit, but also a third observer who can confirm what the clinician observes or what the child says (particularly the primary caregiver, but also a teacher or other family members). Clinicians should be even more prepared to change/adjust/discontinue dosage of medications in children as diagnosis and symptoms change, as side effects occur, and as development progresses.

Additionally, clinicians should be alert to how the disorders that are the focus of treatment as well as the treatments change over the course of development. For example:

Attention Deficit Hyperactivity Disorder (ADHD) Medications:

- More hyperactivity may be observed in younger patients
- In younger patients, ADHD may be seen as irritability, aggressive behaviors, and school refusal instead of inattention, potentially resulting in diagnosing/treating inattention
- Clinical presentation in children with inattention without hyperactivity may be dismissed as immaturity or "spaciness," especially in young girls
- Younger children tend to be more sensitive to the effects of stimulants
- Since young children may absorb drugs faster than adults, immediate-release formulations may need to be given several times (3–4) a day. And because intestinal transit times are faster in younger children and absorption differs, the "actual" duration of action of some medications may differ in younger children compared to older ones.

Antidepressant Medications:

- Clinical presentation of depression in children and adolescents may be different than in adults, that is, with irritability, and school refusal
- For selective serotonin reuptake inhibitors (SSRIs), children can have a two- to threefold higher incidence of vomiting than adolescents, who have a somewhat higher incidence than adults (Strawn et al., 2023)
- Treatment-emergent activation syndrome (TEAS) may be more common in children compared to adolescents and adults (Luft et al., 2018)

Practical Notes

Conduct a thorough diagnostic evaluation and consider utilizing evidence-based psychosocial and behavioral interventions prior to psychotropic medications, especially in milder cases and when available and practical. However, the majority of children who receive psychosocial treatments that are not evidence-based interventions do not demonstrate improvement and may deteriorate.

Whenever possible, treat with one medication at a time and have clear goals and expectations. Align expectations for improving grades with the child/adolescent's strengths, empowering them to improve. Be cognizant of excessive pressure from some parents to improve grades that can lead to low self-esteem. Consider use of objective rating scales with special attention to teacher comments. These rating scales can be employed to assist in screening and diagnosing certain psychiatric disorders. However, it is crucial to note that these scales should not replace a comprehensive clinical assessment conducted by trained professionals. Standardized measures typically offer normative data that enable clinicians to compare a patient's symptoms to those of children of similar age. Be cautious in refilling medications without seeing patients. Integrate information from the child, parent, and teachers. In most cases, don't have the child/adolescent take medication at school to prevent stigma and avoidance of medication and in the case of stimulants, diversion. Suicide is one of the leading causes of death in the child/adolescent age group, especially for those without treatment of an underlying mental health disorder, so be vigilant to the onset of depression in patients with comorbid psychiatric conditions. Surveys by the Centers for Disease Control and Prevention (CDC) show that 15–20% of high school students in the past year have had serious thoughts of suicide and that 8–10% made a suicide attempt.

Comorbid Psychiatric Disorders / Managing Comorbidity

When it comes to children, psychiatric comorbidity is the rule rather than the exception (Masi et al., 2004, 2006; Ghuman et al., 2007; Cardoso et al., 2017), and comorbidity may be more common in children and adolescents compared to adults. For these reasons, it is essential to collect a current symptom portfolio at each visit and re-diagnose or add diagnoses as necessary. It is important to treat each individual symptom, as well as the diagnosis as a whole. Summarized in the accompanying table are some common psychiatric comorbidities in children and adolescents.

Disorder	Common comorbidities
ADHD	Mood and anxiety disorders, substance use and nicotine dependence
Depressive / Mood Disorders	Anxiety disorders, substance abuse, eating disorders, autism spectrum disorders, and ADHD
Psychotic Disorders	Mood and anxiety disorders, substance abuse, and ADHD

Comorbid Intellectual / Developmental Disabilities / Brain Injury

Patients with intellectual and developmental disabilities are almost always excluded from clinical trials. The administration of medications in this population is based on expert consensus and clinical expertise rather than on controlled trials. Modern pediatric psychopharmacology requires adequate diagnosis and treatment of specific symptoms of that diagnosis. Psychotropic medications should be used with caution in this population and be vigilant about reduced tolerability compared to other children. As many psychotropic drugs reduce the seizure threshold, be aware of possible induction of seizures in at-risk patients and in those with known seizure disorders. In this population, common sense and experience suggest "start low; go slow."

Antipsychotic Medications in This Population:

- Meta-analysis suggests that short-term antipsychotic use can help reduce challenging behaviors in children with intellectual disabilities, but the quality of existing evidence is low and significant side effects have also been reported

- Second generation antipsychotics (particularly risperidone) show moderate to large effects in decreasing irritability, disruptive behaviors, and aggression in children with and without autism spectrum disorders and developmental disabilities for short-term treatment
- Use of antipsychotics in this population in the past was encouraged by approval of a related drug, haloperidol, for severe behavior problems in children of combative, explosive hyperexcitability, symptoms common in this population
- No new atypical antipsychotics are approved for "severe behavior problems in children of combative, explosive hyperexcitability"
- Use of antipsychotics for nonspecific tranquilization in this population is not consistent with best medical practices

"Highly Vulnerable" Population / Foster Children

According to the World Bank, a "highly vulnerable" child refers to a child who faces a significant risk of inadequate care and protection. It is estimated that approximately 20% of children in the United States fall into this category. Foster care data suggest that around half of these children have psychiatric diagnoses, while two-thirds of children in juvenile detention centers and foster care settings also have psychiatric diagnoses. Among children with developmental disabilities, about 40% have comorbid psychiatric diagnoses, particularly depression, ADHD, and anxiety disorders. Psychological trauma is prevalent among approximately 90% of children in residential treatment centers. To address the needs of highly vulnerable populations more effectively, interventions should focus on improving living and educational environments, reducing repetitive stress, poverty, abuse, and neglect, and minimizing exposure to community violence and extreme poverty. Implementing trauma-informed care can be especially beneficial for these children and adolescents.

To avoid irrational polypharmacy, it is important to simplify medication regimens whenever possible instead of adding more medications. Highly vulnerable children enrolled in Medicaid are prescribed psychotropic medications at a rate 2–5 times higher than other children. Furthermore, a significant proportion of low-income children and those in foster care or with disabilities are prescribed two or more psychotropic medications. For children with autism spectrum disorders covered by commercial insurance, one-third receive two or more psychotropic medications, and 15% receive three or more. Even infants under the age of 1 with autism are being prescribed psychotropic medications. Vulnerable children, who often have more psychiatric disorders, are seldom the focus of research, resulting in standards of care being established based on the practices of those currently treating such children without the benefit of sufficient studies or research on similar populations.

The diverse and severe symptoms experienced by maltreated youth may lead caregivers to employ treatment strategies that result in significant polypharmacy. In a recent retrospective evaluation of Medicaid-enrolled or foster care children, up to one-third receive "high-level psychotropic polypharmacy" (Keeshin and Monson, 2022), which involved taking at least four psychotropic medications for a duration of at least 30 days. The majority of children with high-level polypharmacy had "disruptive behavior disorders," along with other comorbid diagnoses. These disruptive behavior disorders often include ADHD, oppositional defiant disorder, and conduct disorder, which have been associated with or speculated to be misdiagnosed as traumatic stress (Keeshin and Monson, 2022). Such prescribing patterns are not isolated incidents, as elevated prescribing rates have been observed in groups exposed to childhood maltreatment or at high risk for traumatic stress.

We must understand the underlying pressures influencing these prescribing practices and develop strategies for safe and effective de-prescribing when possible. However, in addressing polypharmacy in these populations and de-prescribing, it is crucial to consider the needs of each individual and recognize that the goal is not necessarily to discontinue all medications but to prioritize thoughtfully and reduce or discontinue medications with limited efficacy or high risk. Contextual factors such as the current medication regimen, access barriers to alternative treatments, and the perspectives of the patient and other stakeholders should also be considered.

Polypharmacy may arise from pressure to deviate from guidelines due to unrealistic expectations or the need for quick solutions from stakeholders such as parents or schools. It can also result from inadequate access to evidence-based treatments or insufficient mental health resources. Recent attention has been directed toward de-prescribing in this population, as described by Keeshin and Monson (2022). They outline a process that involves:

- collecting a comprehensive medication history,
- prioritizing medications with high risks or unclear rationales,
- developing and implementing a specific plan for reduction or discontinuation, and
- using a stepwise approach with sufficient observation time for adverse effects or symptom reemergence.

Comorbid Medical Conditions and Substance Use

Many children and adolescents with chronic medical conditions may be depressed or anxious or have other comorbid psychiatric conditions and need to take psychotropic medications. For antidepressants such as SSRIs, no dose adjustment is needed for patients with mild to moderate renal impairment but should be used cautiously in patients with severe renal impairment. When patients have hepatic impairment, SSRIs should be given at a lower dose (perhaps by half dose). Preliminary research suggests that most SSRIs are safe in patients with cardiac impairment, although some have been associated with QT prolongation in pediatric populations. When prescribing SSRIs, exercise caution if the patient is taking drugs for medical conditions that are metabolized by CYP2D6, CYP2C9/CYP2C19, or CYP3A4, and these effects are now highlighted throughout the *Second Edition* (Figure 1).

For patients taking ADHD medications, dose adjustment is not generally necessary for renal impairment. For patients with moderate liver impairment, the dose of ADHD medications should be reduced to 50%; for those with severe liver impairment, the dose should be lowered to 25% of the normal dose. Some ADHD medications can increase heart rate and blood pressure, so use with caution in patients with cardiac impairment and do not use in patients with structural cardiac abnormalities.

When prescribing antipsychotics, use this class of medication with caution if patients have renal, hepatic, or cardiac impairment, particularly with QT prolongation with this class of medication. For all psychotropic medications, for guidelines during pregnancy and breast feeding consult the adult prescriber's guide (*Stahl's Essential Psychopharmacology: Prescriber's Guide*).

Substance use, and in particular cannabis use, is increasing in adolescents (Weinberger et al., 2020) and has important treatment implications. For example, cannabis, which inhibits CYP2C19 in addition to other cytochromes, has been shown to increase concentrations of some antidepressant medications in youth (Vaughn et al., 2021) (Figure 2) and across disorders has been associated with reduced treatment response, raising the possibility that substance use needs to be treated independently from the

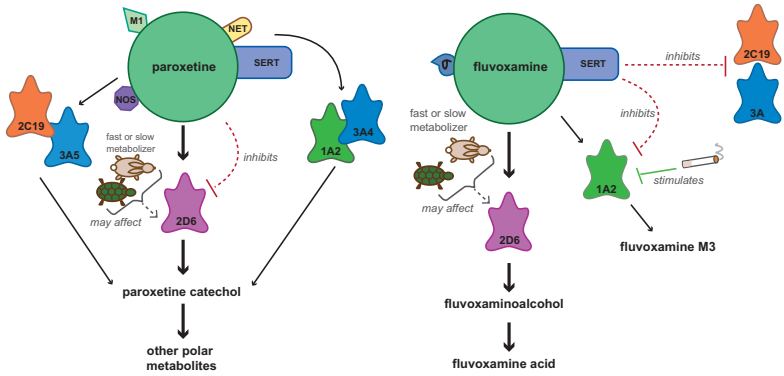

Figure 1 Examples of pharmacogenetic and environmental (e.g., smoking) factors influencing medication and the effects of medication on cytochromes that are highlighted in the Second Edition.

primary mood or anxiety disorder that is often the focus of our psychopharmacological interventions.

Potential Ethical Issues and Informed Assent

Children should have their condition explained to the extent that they can understand. Consent for medication in children and young adolescents can be made more difficult if the parents are in conflict, such as in custody disputes and divorce; it is recommended to obtain consent from both legal guardians, no matter the percentage breakdown of custody or who has "medical decision-making authority." Informed consent and assent are an ongoing, iterative process, a dynamic conduit. Regularly review the treatment plan, documenting the review process and accommodating any modifications that may prove necessary, ensuring the treatment remains aligned with the patient's evolving needs. Finally, try to get children and adolescents to agree to go along by respecting their input and, whenever possible, gaining their informed "assent," as legally, they cannot give informed consent under the age of 18. In doing this, ask questions such as "What would you want this medicine to help with?" or "What things make you worried about taking medicine?"

When engaging in the informed consent process with patients and their families, it is paramount to imbue the discussion with clarity, transparency, and comprehensive information. To facilitate this, we recommend incorporating the following components:

- **Target symptoms, prioritized:** Discuss specific symptoms that will serve as the focal point of the treatment, ensuring patients and families grasp the objectives of the proposed intervention.
- **Proposed medication plan:** Present a cogent outline encompassing the medication name, dosage, timing, and any intended adjustments that may arise during the course of treatment.
- **Specific rationale and risks:** Offer justification for the chosen medication plan, highlighting its anticipated benefits. Simultaneously, describe the potential risks and side effects, including any pertinent boxed warnings.
- **Alternatives to medication:** Engage in a thoughtful exploration of alternative treatment options, embracing the possibility of nonpharmacological approaches and engaging patients and families in the decision-making process.

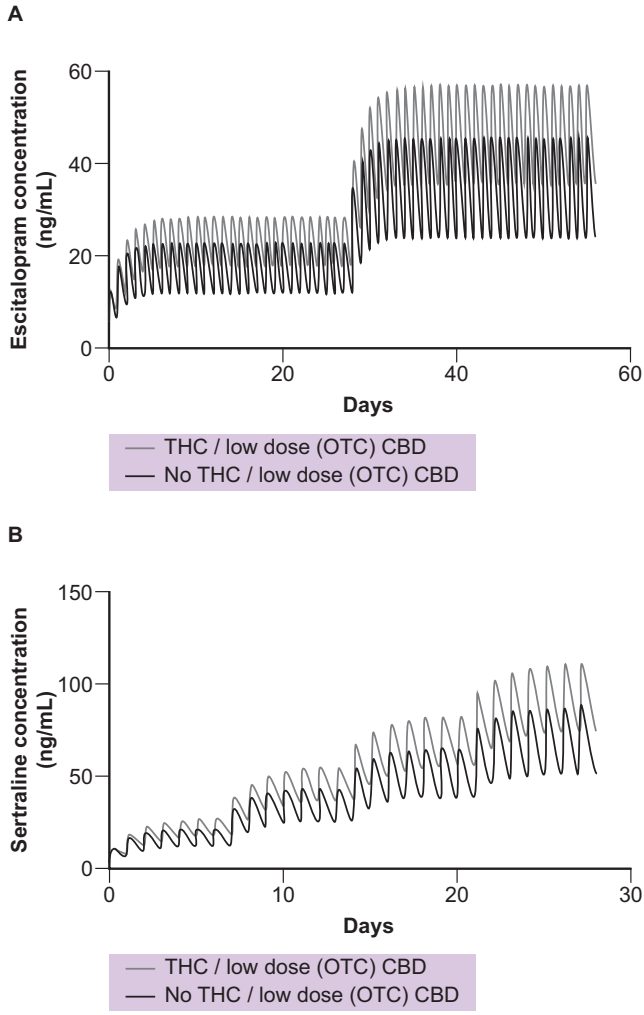

Figure 2 Simulated concentrations of escitalopram and sertraline in adolescents using and those not using cannabis (adapted from Vaughn et al., 2021).

- **FDA-approved use versus off-label use:** Distinguish between FDA-approved usage and off-label use. Articulate how medical professionals, while granted leeway in prescribing practices, may venture beyond the confines of FDA endorsement, often driven by empirical evidence and clinical rationale. Provide a glimpse into common off-label applications, bolstered by supportive research, and outline strategies to manage any potential challenges that may arise.
- **Cost of care:** Address the financial aspect of treatment, including the choice between brand names and generics, follow-up visits, and potential cost-saving measures.
- **Monitoring plan:** Establish a monitoring framework, delineating the necessary laboratory tests and the frequency of follow-up visits to ensure a vigilant and adaptive approach to treatment.

- **Concurrent treatment and intervention:** Emphasize the importance of a holistic treatment paradigm, integrating complementary therapies, school plans, and other interventions to maximize therapeutic outcomes.

Throughout these discussions, it is crucial to bear in mind the following considerations:

- Check state laws pertaining to the age of consent for mental health care, particularly in relation to medication treatment, ensuring legal compliance and ethical practice.
- Extend the conversation to include the child's perspective, fostering their assent and encouraging their participation as valued partners in the decision-making process, with due consideration to their age and cognitive development.
- Establish an ongoing communication channel, unequivocally conveying your availability and providing clear instructions on how patients or their families can reach you or designated coverage in the event of inquiries or concerns.

When children or adolescents refuse to take medications:

- Make sure the problem is not something manageable like side effects or problems swallowing or even the taste of the medication.
- Monitor what the patient actually does, not what they say or complain about; many children complain, yet they take their medication.
- Most families are not "democracies," so enlist the help of caregivers to explain and when it's necessary to exert some influence on getting the patient to take the medication.
- Giving medication in food without the patient's knowledge is unethical and should be discouraged.

Engaging Primary Care with Mental Health Professionals

More psychotropic drugs are prescribed for children and adolescents by primary care clinicians than by mental health clinicians, especially stimulants. Get written consent to mutually share information with the primary care clinician and make sure they are aware of the diagnosis and the medications. Make sure you know all the diagnoses and medications being managed in primary care or specialty care. Once the patient is stable, the primary care clinician can often take over from a mental health practitioner as the prescriber and refer back if problems emerge. If recommending the discontinuation of psychotropic drugs being prescribed by primary care and changing to something else, it is best to inform the clinician directly rather than through the parents to facilitate communication, reduce misunderstandings, and foster collaboration.

Summary

In sum, for psychiatric disorders and symptoms in children and adolescents, conducting thorough and developmentally sensitive assessments is critical before and throughout psychopharmacological treatment. Treatment plans should stem from comprehensive and accurate diagnostic evaluations, taking into account comorbidity, sub-syndromal symptoms, family factors, personality/temperament, and learning issues, including learning disorders and weaknesses. Addressing these factors may enhance the benefits of pharmacotherapy and decrease the incidence of "medication treatment resistance."

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