

Medication Management in Primary Care

Cindy Ellis, MD







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At the time of this publication, Miriam Delphin-Rittmon served as Assistant Secretary for Mental Health and Substance Use and Administrator of SAMHSA. The opinions expressed herein are the views of the speakers and do not reflect the official position of the Department of Health and Human Services (DHHS), or SAMHSA. No official support or endorsement of DHHS, SAMHSA, for the opinions described in this presentation is intended or should be inferred.

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The MHTTC Network uses affirming, respectful and recovery-oriented language in all activities. That language is:

Inviting to individuals participating in their OWN JOURNEYS

PERSON-FIRST AND FREE OF LABELS

STRENGTHS-BASED AND HOPEFUL

NON-JUDGMENTAL AND AVOIDING ASSUMPTIONS

INCLUSIVE AND ACCEPTING OF DIVERSE CULTURES, GENDERS, PERSPECTIVES, AND EXPERIENCES

RESPECTFUL, CLEAR AND UNDERSTANDABLE

HEALING-CENTERED/ TRAUMA-RESPONSIVE CONSISTENT WITH OUR ACTIONS, POLICIES, AND PRODUCTS

Adapted from: https://mhcc.org.au/wp-content/uploads/2019/08/Recovery-Oriented-Language-Guide_2019ed_v1_20190809-Web.pdf

Announcements

• The webinar recording is here.

https://mhttcnetwork.org/centers/mid-america-mhttc/tele-behavioral-health-consultationtbhc-primary-care-webinar-series

Mid-America Mental Health Technology Transfer Center

Established to increase utilization of evidencebased mental health practices.

Missouri, Iowa, Nebraska, and Kansas.

- Free training and technical assistance.
- SAMHSA grant awarded to the Behavioral Health Education Center of Nebraska at University of Nebraska Medical Center.

(5 years, \$3.7 million, grant number: H79SM081769)



Nebraska Mental Health Access Grant

- 5-year, \$2.2 million HRSA grant through maternal and child health bureau
- Designed to improve timely access to behavioral healthcare for children in rural Nebraska
- The main goal is to provide primary care providers access to behavioral health supports



Goals

- Enhance early screening of behavioral health disorders
- Conduct a clinical demonstration project in a network of providers to <u>expand and diversify integrated</u> <u>behavioral health provision in PC</u> pediatric and family medicine practices, with a focus upon <u>rural</u> communities
- Evaluate the overall <u>effectiveness of increasing</u>
 <u>access to PCP's to behavioral health consultation</u>

https://www.unmc.edu/mmi/services/psychology/teleproviderconsult.html?mscl kid=77c12956b5f311ec8c21922c759e3b30

Tele-Behavioral Health Consultation (TBHC)

- Behavioral health providers or case managers on-site at primary care clinics
- Behavioral health/care managers determine need for consultation with psychiatry
- Consultant consults with PCP (audio or audio-visual) on the same day
 - Child Psychiatry
 - Developmental Medicine
 - Psychiatric Nurse Practitioner



Behavioral Health Consultation for Primary Care Providers

The UNMC Tele-Behavioral Health Consultation Team (TBHC) provides psychiatry support to primary care providers in Nebraska who are managing pediatric patients with behavioral health problems. Providers are available to offer guidance on diagnosis, medications, and psychotherapy interventions to assist primary care providers in better managing patients in their practices. Support is available through phone and synchronous audio/video teleconference consultations to referring primary care providers.

How Does it Work?

- 1. The participating provider or representative initiates a request to Dani Porter at (402) 559-3838 or through the website at unmc.edu/mmi/departments/psychology/ psych-patientcare/teleproviderconsult.html
- 2. A member of the TBHC team will contact the provider within the same business day to offer guidance.
- 3. The TBHC is not an emergency service. Emergencies will be routed to local emergency services.
- 4. The UNMC TBHC team does not prescribe medication. They provide support for prescribers.

Team Members



Psychiatric Nurse Practitioner





Cindy Ellis, M.D. Developmental-Behavioral Pediatrician





Scan me



Ryan Edwards, M.D.

Psychiatrist



Primary Care Providers (PCPs)

- PCPs can request a consultation three ways:
 - 1) Visit our website:

https://www.unmc.edu/mmi/services/psychology/teleproviderconsult.html

2) QR Code

3) Call 402-559-3838



Psychopharmacology in Primary Care

Cindy Ellis, M.D. Developmental/Behavioral Pediatrics

June 28, 2022



MUNROE-MEYER

DISCLOSURES

- I have no relevant financial relationships with the manufactures of any commercial products and/or commercial services discussed
- I DO intent to discuss off-label use of medications (drugs without current FDA approval will be identified)
- Brand names of some drugs might be used to differentiate new formulations



OBJECTIVES

- Discuss mental, behavioral, and developmental conditions for which medications ae appropriate
- Discuss basic best practices for treatment of common behavioral health conditions
- Identify misconceptions about common psychotropic medications for children and adolescents
- Describe the process for requesting expert behavioral health consultation to manage mild to moderate behavioral health concerns in primary care



Treatments for Psychiatric, Emotional and Behavioral Problems

Educational

Information

Behavioral

- Address functions
- External modifications

Biomedical

Target underlying neurological functioning



Biomedical Treatments

Focus on the potential links between:

- Symptoms of the disorder (expressed in behavior) and
- Neurobiologic systems involved in the etiology and pathogenesis of the symptoms (e.g., specific neurotransmitter systems)

Pharmacological or medication treatments

 Most widely used biomedical treatment for behavioral and emotional problems in children



Neurotransmitter Systems





Biomedical Treatment: Medication

Typically considered when problem or symptoms of the disorder:

- Significantly interfere with an individual's functioning
- Have not responded or shown suboptimal response to appropriate behavioral interventions, or
- Pose an acute safety risk



Psychotropic Medication

any drug prescribed to stabilize or improve mood, mental status, or behavior

- includes medications typically classified as antidepressants, antianxiety, etc.
- includes other medications not typically classified as psychotropic when such medication is prescribed to improve or stabilize mood, mental status or behavior (e.g., an antiepileptic medication prescribed for affective disorders)
- includes herbal or nutritional substances when such substances are used to stabilize or improve mood, mental status, or behavior



Role of Medication

Medication is:

- is a single component of a broad treatment plan
- is usually considered when behavior interventions have been unsuccessful or the behavior is presumed to be of organic origin
- use increases as the number and severity of the individual's behavior problems increase
- can be used to treat specific diagnoses as well as specific target symptoms



Principles of Medication Use

Standard diagnostic and medication management principles should be followed such as the Practice Parameters and/or Standard Practice Guidelines developed by the American Academy of Pediatrics or the American Academy of Child and Adolescent Psychiatry

Evaluation of the drug response using repeated assessment measures and monitoring of side effects is necessary to determine the effects of the treatment

Role of Medication

In pediatrics, generally used to treat psychiatric disorders, including:

ADHD Mood Disorders Anxiety Sleep Problems Psychiatric Disorders OCD



Role of Medication

In individuals with IDD / NDD, medications can be used to target specific challenging behaviors or psychiatric disorders, including:

aggression rigid behaviors self-injury inattention hyperactivity sleep problems mood disorders anxiety repetitive behaviors (stereotypies, compulsive actions, obsessive thinking)





Commonly used classes of medications to treat psychiatric and behavior problems include:

antipsychoticsstimulantsantidepressantsantimanicsanxiolyticsanticonvulsantsselective norepinephrine reuptake inhibitors

alpha adrenergic agonists



Specific Medications

Stimulants



Stimulants - Indications

Attention Deficit Hyperactivity Disorder

ADHD with comorbid disorders (including IDD/NDD, Fragile X Syndrome, Tourette Syndrome)
hyperactivity in neurodevelopmental disorders
narcolepsy

adjunctive treatment in refractory depression



Stimulant Medications

- Stimulant medications are the most studied, most commonly used first-line agents for ADHD treatment
- In ADHD, stimulant medications improve:
 - core symptoms: inattention, impulsivity, hyperactivity
 - associated symptoms: cognition, on-task behavior, academic performance, social function, defiance, and aggression
- Good response in preschoolers, school-age children, adolescents and adults



Stimulant Medications

• two primary classes of stimulants

- amphetamines
- methylphenidate (MPH)

• For ADHD:

- response rate for any one particular stimulant is approx.
 70%
- no predictors of response have been identified
- all stimulants are generally of comparable efficacy
- there is significant individual variability in response to a particular stimulant



Stimulants – Side Effects

- most side effects are transient and dose dependent
- common side effects include: insomnia, decreased appetite, mild increase in heart rate and BP, weight loss, headache, nausea
- rare side effects include: behavioral rebound, psychosis (inc risk w/ higher doses), anxiety or depression
- Pre-screen for patient or family hx of structural heart defect or fam hx of sudden cardiac death
- Monitor abuse potential (dec. w/ some formulations, e.g., Vyvanse and Concerta



Stimulants - methylphenidate

- immediate-release, extended-release, controlled-release, and delayed/extended-release forms
- oral (tablet/capsule, liquid, chewable) and transdermal patch
- includes methylphenidate and dexmethylphenidate
- numerous preparations and brands, including:

Ritalin (LA, SR) *Methylin (ER) *Concerta*Metadate (ER, CD)DaytranaCotempla XR-ODTFocalin (XR)*

QuilliChew ER Quillivant XR Aptensio XR Jornay PM



* generic available

Stimulants - amphetamine

- immediate-release and extended-release
- oral (tablet/capsule, liquid)

* generic available

- include amphetamine, dextroamphetamine, and lisdexamfetamine
- numerous preparations and brands, including:

<u>Mixed</u>	<u>amphetamine</u>	lisdexamphetamine	<u>dextroamphetamine</u>
Adderall *	Dynavel XR	Vyvanse	Dexedrine
Adderall XR*	Evekeo		Dextrostat
Mydayis	ProCentra *		Dexedrine spansules

Short-Acting Stimulant Preparations

Brand Name	Preparation	Duration	generic	FDA approval for
(dosing)				ADHD
Ritalin - 5, 10, 20 mg	tablet	3-4 hours	methylphenidate HCL	
Methylin - 5, 10, 20 mg	tablet	3-4 hours	methylphenidate HCL	≥6 years
Metadate - 5, 10, 20 mg	tablet	3-4 hours	methylphenidate HCL	
Focalin - 2.5, 5, 10 mg	tablet	4-6 hours	dexmethylphenidate HCL	≥ 6 years
Adderall - 5, 7.5, 10,	tablet	4-6 hours	mixed amphetamines	
12.5, 15, 20, 30 mg				≥ 3 years
Evekeo - 5, 10 mg	tablet	4-6 hours	amphetamine sulfate	
Dextrostat - 5, 10 mg	tablet	4-6 hours	dextroamphetamine	
			sulfate	
Zenzedi - 2.5, 7.5, 15, 20,	tablet	4-6 hours	dextroamphetamine	<u>></u> 3 years
30 mg			sulfate	
Procentra - 5mg/5ml	oral	4-6 hours	dextroamphetamine	
	suspension		sulfate	

Long-Acting Stimulant Preparations

brand name (dosing)	preparation	AM/PM effect	duration	generic	FDA approval for ADHD	
Concerta - 18, 27, 36, 54 mg	tablet	30% IR 70% next 8 hr	8-12 hours	methylphenidate HCL		
Metadate CD - 10, 20, 30, 40, 50, 60 mg	capsule	30% / 70%	8-10 hours	methylphenidate HCL		
Metadate ER - 20 mg	tablet		6-8 hours	methylphenidate HCL		
Methylin ER - 10, 20 mg	tablet		6-8 hours	methylphenidate HCL		
Ritalin SR - 20 mg	tablet		6-8 hours	methylphenidate HCL		
Ritalin LA - 10, 20, 30, 40 mg	capsule	50% / 50%	8-10 hours	methylphenidate HCL		
Daytrana - 10, 15, 20, 30 mg	transdermal patch	Continuous	Duration + 3 hrs	methylphenidate	≥6 years	
QuilliChew ER - 20, 30, 40 mg	chewable tab	20% /80%	8 hours	methylphenidate HCL		
Quillivant XR - 25 mg per 5 mL	oral suspension	20% /80%	12 hours	methylphenidate HCL		
Aptensio XR - 10, 15, 20, 30, 40, 50, 60 mg	capsule	40% / 60%	10-12 hours	methylphenidate HCL		
Cotempla XR-ODT - 8.6, 17.3, 25.9 mg	orally disintegrating tablet	25% / 75%	12 hours	methylphenidate HCL		
Jornay PM – 20, 40, 60, 80, 100 g	Capsules	Delayed and extended release		methlphenindate HCL		
Focalin XR - 5, 10, 15, 20, 25, 30, 35, 40 mg	capsule	50% / 50%	6-10 hours	dexmethylphenidate HCL	≥ 6 years	
Adderall XR - 5 10, 15, 20, 25, 30 mg	capsule	50% / 50%	8-12 hours	mixed amphetamines		
Dyanavel XR – 2.5 mg/ml	liquid		12 hours	amphetamine	≥6years	
Mydayis - 12.5, 25, 37.5, 50 mg	capsule	triplerelease	16 hours (onset at 2-4 hours)	mixed amphetamines	≥ 13 years	
Vyvanse - 10, 20, 30, 40, 50, 60, 70* mg (* cap only)	capsule OR chewable tab		12 hours	lisdexamfetamine dimesylate	≥6years	
Dexedrine Spansules - 5, 10, 15 mg	long-acting spansule		5-10 hours	dextroamphetamine sulfate	≥ 6 years	

Specific Medications

Selective Norepinephrine Reuptake Inhibitor



atomoxetine - Strattera



- FDA approved for treatment of ADHD in youth <u>></u> 6 years old
- Highly selective blockade of the norepinephrine transporter
- Several studies showed that once daily dosing strategy similar to twice-daily dosing
- May take up to 2-4 weeks to see optimal benefit



atomoxetine - Strattera

Formulation (mg)	Dosing	Side Effects
10, 18, 25, 40, 60, 80, 100 mg capsules	 < 70 kg: 0.5 mg/kg/d Inc to 1.2 mg/kg/d after 1-2 weeks Max: 1.4 mg/kg/d or 100 mg/d > 70 kg: Up to 40 mg/d Inc to 60-80 mg/d after 1-2 weeks Max: 100 mg/d 	 diastolic BP and heart rate increase (not clinically significant) 20% with decreased appetite (weight decrease usually seen only in first 9-12 weeks of treatment) dizziness/fatigue/mood swings headache no exacerbation of tics or anxiety *** need to watch for abn. liver function *** black box warning – may inc. suicidal thoughts



Specific Medications

Alpha-2 Adrenergic Agonists




Alpha-2 Adrenergic Agonists

These centrally acting antihypertensive agents have more recently been reported as primary or alternative / adjunctive treatments for:

- ADHD (FDA approved \geq 6 years old)
- Tourette Syndrome (tics)
- behavior disorders with severe agitation, self-injury, or aggression (IDD or TBI)
- adjunctive treatment of schizophrenia and mania
- opiate withdrawal



clonidine – Catapres, Kapvay

Formulation (mg)	Dosing	Side Effects
Tablet: 0.1, 0.2, 0.3 mg (q hs to QID) Patch: 0.1, 0.2, 0.3 mg/24 hr (daily) ER (Kapvay): 0.1, 0.2 mg (daily)	 Start with 0.05 to 0.1 mg (at time needed) Increase by 0.05 mg every 3-7 days Typical range 0.05 – 0.4 mg/day When d/c, taper over 1-2 weeks ** When Kapvay is added on to a stimulant, the dose of stimulant may be adjusted depending on 	 diastolic BP and heart rate increase (not clinically significant) – monitor at baseline, dose change and follow-up 20% with decreased appetite (weight decrease usually seen only in first 9-12 weeks of treatment) Sedation/dizziness/fatigue/mood swings Headache Rebound HTN or insomnia if stopped abruptly no exacerbation of tics or anxiety

guanfacine – Tenex, Intuniv

Formulation (mg)	Dosing	Side Effects
IR Tablet: 1, 2 mg (q hs to TID) ER (Intuniv): 1, 2, 3, 4 mg (daily)	 Start with .5 to 0.1 mg (at time needed) Increase by .5-1 mg per week Typical range 0.05 – 4 mg/day ** When Intuniv is added on to a stimulant, the dose of stimulant may be adjusted depending on response to Kapvay 	 More specific binding than clonidine, so less sedation diastolic BP and heart rate increase (not clinically significant) – monitor at baseline, dose change and follow-up Less sedation than clonidine, otherwise similar side effects Less risk for rebound HTN than clonidine no exacerbation of tics or anxiety

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents Mark L. Wolraich, Joseph F. Hagan Jr, Carla Allan, Eugenia Chan, Dale Davison, Marian Earls, Steven W. Evans, Susan K. Flinn, Tanya Froehlich, Jennifer Frost, Joseph R. Holbrook, Christoph Ulrich Lehmann, Herschel Robert Lessin, Kymika Okechukwu, Karen L. Pierce, Jonathan D. Winner, William Zurhellen and SUBCOMMITTEE ON CHILDREN AND ADOLESCENTS WITH ATTENTION-DEFICIT/HYPERACTIVE DISORDER *Pediatrics* 2019;144; DOI: 10.1542/peds.2019-2528 originally published online September 30, 2019;

Journal of Developmental Behavioral Pediatrics Official Journal of the Society for Developmental and Behavioral Pediatrics

Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder

Barbaresi, William J. MD (Guideline Panel Chair)^{*}; Campbell, Lisa MD[†]; Diekroger, Elizabeth A. MD[‡]; Froehlich, Tanya E. MD[§]; Liu, Yi Hui MD, MPH^I; O'Malley, Eva[¶]; Pelham, William E. Jr PhD, ABPP^{**}; Power, Thomas J. PhD, ABPP^{††}; Zinner, Samuel H. MD^{‡‡}; Chan, Eugenia MD, MPH^{*} **Author Information** ⊙

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doi: 10.1097/DBP.0000000000000770

American Academy of Pediatrics: ADHD Treatment Guidelines

Recommendations for treatment of children and youth with ADHD vary depending on the patient's age:

For preschool-aged children (4–5 years of age):

- prescribe evidence-based parent- and/or teacheradministered behavior therapy as the first line of treatment
- may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to severe continuing disturbance in the child's function
- If evidence-based behavioral treatments are not available, weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment



Wolraich et al., 2019

American Academy of Pediatrics: ADHD Treatment Guidelines

Recommendations for treatment of children and youth with ADHD vary depending on the patient's age:

For elementary school-aged children (6-11 years of age):

- prescribe US Food and Drug Administration—approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both
- titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects



American Academy of Pediatrics: ADHD Treatment Guidelines

Recommendations for treatment of children and youth with ADHD vary depending on the patient's age:

For adolescents (12–18 years of age):

- prescribe US Food and Drug Administration—approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both
- titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects



ADHD Medication Guide

www.ADHDMedicationGuide.com

	ADHD Medication Guide* Revised: January 1, 2022																	
Methylphenidate Formulations – Long Acting** (Capaules and tablets in this section are shown at actual size)																		
Adhansia XR® 🕈	6-17 Yrs: 25–70mg; SD: 25mg Adults: 25–85mg; SD: 25mg				25mg	(B	35mg	MLR-0	45mg	45 mg	55mg	S5 mg	70mg	70 mg	85mg	ILR-0. 85 mg		
Concerta®†	6-12 Yrs: 18-54mg; SD: 18mg 13-17 Yrs: 18-72mg; SD: 18mg >18 Yrs: 18-72mg; SD: 18mg or 36mg	G 18mg	atro 18	27mg	G 36mg	atra 36	G 54mg	one of	C 72mg	otza 36	+ atra 36)	Methy (bioequin	Iphenidate ER 72 ralent to 2 x 36 mg Con	mg certa tablets)			TL 710
Aptensio® XR‡	6 Yrs-Adult: 10-60mg; SD: 10mg (biphasic - 40/60)	10mg		15mg (1)	20mg	Notes to	30mg	(Mar	40mg	The second	50mg	tan ta	60mg	koten tomp				
Cotempla XR-ODT®\$ (grape flavor)	6-17 Yrs: 8.6-51.8mg; SD: 17.3mg	8.6mg	0		17.3mg	72	25.9mc	73	34.6mg	72).	+ 72	1	51.8mg	73	+ 73			
Focalin® XR [‡] (desmethylphenidate)	6-17 Yrs: 5–30mg; SD: 5mg 18 Yrs-Adult: 5–30mg; SD: 5mg (hiphasir – 50/50)	G 5mg	DE		G 10mg	-	G 15mg		G 20mg	(La contraction of the contracti	C 25mg		G 30mg		G 35mg	CED	G 40mg	
Quillivant XR® 25mg/5mL (5mg/mL) (banana flavor)	6 Yrs-Adult: 20-60mg; SD: 20mg	10mg 2mL	1 Bottle: 300mg 60mL		20mg 4mL	1 Bottle: 600mg 120mL	30mg 6mL	1 Bottle: 900mg 180mL	40mg 8mL	2 Bottles: 600mg 120mL	50mg 10mL	2 Bottles: 750mg 150mL	60mg 12mL	2 Bottles 900mg 180ml	2			
Quillichew ER®§ (cherry flavor)	6 Yrs-Adult: 20-60mg; SD: 20mg				20mg		30mg		40mg									
Ritalin® LA‡	6-12 Yrs: 10-60mg; SD: 20mg (biphasic - 50/50)	G 10mg	11		G 20mg		C 30mg	E BE	C 40mg				60mg					
Metadate® CD [‡]	6-17 Yrs: 10–60mg; SD: 20mg (biphasic – 30/70)	G• 10mg			G 20mg		G 30mg		G• 40mg	to mg	G 50mg		60mg	Some set				
Metadate® ER [†]	6 Yrs-Adult: 20–60mg; SD: 20mg	G 10mg			G 20mg													
Daytrana®	6-17 Yrs: 10-30mg; SD: 10mg						2											
	(Patches are shown at 90% of actual size. The color border around each patch reflects	_		Methylphenidate Pro-Drug Formulations - Long Acting** (Medicators in this section are shown at actual size)														
	the cost of site polosying, not the polosi itself.)	trana ** Iphenidate mal system mg/hr	n) tran	Azstarys®? 6-12 Yrs: 26.1/5.2 - 52.3/10.4; SD: 39.2/7.8 mg: 13 Yrs - serdexmethytphendate SD: 39.2/7.8 mg 26.1 mg SDX / 5.2 mg d-MPH (equivalent to 20 mg d-MPH) 39.2 mg SDX / 7.8 mg d-MPH (equivalent to 30 mg d-MPH) 52.3 mg SDX / 10.4 mg d-MPH (equivalent to 40 mg d-MPH)														
		Day	ytrana	Methylphenidate	e Form	ulations - L	ong A	Acting/Delaye	d On	set** (Medications)	in this cortinn am	thouse at artical size)						
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6	Daytrana Mat	a™ hylphen late idermal stem	(m n) tran	Methylphenidate	e Form	nulations – S	hort /	Acting** (Medic	ations in this	section are shown at actual	size)							
m) stem) transdem	transdermal syst t.5 mg/hr	2.2 mg/l	utrana	Focalin® (dexmethylphenidate)	6-17 Yrs	: Daily: 5–20mg, divid	ed BID; SD	D: 2.5mg BID			G 2.5mg		G 5mg		G 10mg	10		
	enidate (m. m.	neth	ermal syst	Ritalin®	6-12 Yrs Aduits: D	: Daily: 10–60mg; divi aily: 10–60mg, divided	ded BID o BID or TID	r TID; SD: 5mg BID D			C 5mg	0	G 10mg	()	@* 20mg	0		
	g/tu	3. hvlphen a ^{ra}	.3 mg/hr	Methylphenidate Chewables (grape flavor)	6-12 Yrs Adults: D	: Daily: 10–60mg; divi aily: 10–60mg, divided	ded BID o BID or TIE	r TID; SD: 5mg BID D	G* 2.5mg	2 - 5 CHEW	G• 5mg	CHE W	G• 10mg	10 CHEW				
10mg)avt	15mg phends 20mg	dermal 30m	ng (m	Methylin® Solution (grape flavor)	6-12 Yrs Adults: D	: Daily: 10–60mg; divi aily: 10–60mg, divide	ded BID o d BID or T	r TID; SD: Smg BID 1D			G 5mg/5mL	d	G 10mg/5	mL				
				G indicates a generic	formulation	n is also available; generi	c products	are not shown	G indic	ates a generic (but NOT a	a branded) form	ulation is available						
Administration I 9 Orally disintegrating † Must be swallowed	Compositive controls and the control of the co																	

§ Chewable

- ¥ Can be mixed with yogurt, orange juice, or water
- 2 Can open capsule and sprinkle medication on apple sauce

? Can open capsule and sprinkle medication into water or onto apple sauce

Can open capsule and spiniste included on into water or onto appresse Can open capsule and mix with apple sauce or yogurt medication. Although every effort has been made to depict the size and color of each medication, we cannot guarantee that there are not mixed distortions in the final mage. This Guide should not be used as an exclusive basis for decision-making. The user understands and accepts that if Northwell Health were to accept the risk of harm to the user from use of this Guide, it would not be able to make the Guide available because the cost to cover the risk of harm to all users would be too great. Thus, use of this ADBM directation Guide and the user's sole risk.

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ADHD Medication Guide

www.ADHDMedicationGuide.com

	ADHD Medication Guide* Revised: January 1, 2022																	
Amphetamine Formulations – Long Acting** (Medicators in this section are thesen at actual size)																		
Mydayis ^{™‡} (mixed amphetamine salts)	13–17 Yrs: 12.5–25mg; SD: 12.5mg Adults: 12.5-50mg; SD: 12.5mg	12.5mg				25mg				37.5mg	161			50mg	2 mg			
Dyanavel® XR (d-& I-amphetamine sulfate) 2.5mg/mL (bubblegum flavor)	6 Yrs-Adults: 2.5-20mg; SD: 2.5 or 5mg	2.5mg 1mL	(<u>111</u>)	5mg 2mL		7.5mg 3mL	-	10mg 4mL		12.5mg 5mL		15mg 6mL		17.5mg 7mL		20mg 8mL		
Adzenys XR-ODT®9 (d-& I-amphetamine) (orange flavor)	6–12 Yrs: 3.1–18.8mg; SD: 6.3mg 13–17 Yrs: 3.1–12.5mg; SD: 6.3mg Adults: 12.5mg			3.1mg	0	6.3mg	0	9.4mg	0	12.5mg	0	15.7mg	0	18.8mg	0			
Adzenys ER® (d-& I-amphetamine) 1.25mg/mL (orange flavor)	6–12 Yrs: 6.3–18.8mg; SD: 6.3mg 13–17 Yrs: 6.3–12.5mg; SD: 6.3mg Adults: 12.5mg			3.1mg 2.5mL	(11111)	6.3mg 5mL		9.4mg 7.5mL		12.5mg 10mL	-	15.7mg 12.5mL		18.8mg 15mL	CANARE -			
Adderall XR®‡ (mixed amphetamine salts)	6–17 Yrs: 5–30mg; SD: 10mg Adults: 5-30mg; SD: 20mg (biphasic – 50/50)			C Smg		C 10mg		C 15mg		C 20mg	T I	C 25mg		G 30mg	The second			
Dexedrine Spansule® (d-amphetamine sulfate)	6-17 Yrs: 10–60mg; SD: 5mg 1-2x/day			G• 5mg		G• 10mg	C	G 15mg										
Amphetamine	Pro-Drug Formulatio	ns – Lo	ong Acting*	(Medicat	lors in this section are she	wen at actual s	120)											-
Vyvanse ^{@y} (capsules) (lisdexamfetamine)	6 Yrs-Adults: 10-70mg; SD: 30mg	10mg	ten Auf	20mg	HE 24	30mg	(a) Xm	40mg		50mg	-	60mg	500 0 m	70mg	-			
Vyvanse ^{®§} (chewables) (isdexamfetamine) (strawberry flavor)	6 Yrs-Adults: 10-70mg; SD: 30mg	10mg	0	20mg	(2)	30mg	0	40mg	1.0	50mg	60	60mg	0					
Amphetamine	Formulations – Shor	t Actin	g** (Medications in	this section are	shown at actual size)		0											
Evekeo® (d- & I- amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day			5mg	0			10mg										
Evekeo® ODT (d- & I- amphetamine sulfate)	6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day			5mg	0			10mg	0			15mg	3	20mg	3			
Zenzedi® (d-amphetamine sulfate)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: S-40mg divided BID; SD: 5mg 1-2x/day	2.5mg	0	G Smg	0	7.5mg		C 10mg				15mg	(1)	20mg		30mg	0	
Adderall [®] (mixed amphetamine salts)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: S-40mg divided BID; SD: 5mg 1-2x/day			G Smg	0	G 7.5mg		G 10mg		G 12.5mg	0	G 15mg	0	G 20mg	-2 0-	G 30mg		
ProCentra [®] (d-amphetamine sulfate) (bubblegum flavor)	3–5 Yrs: SD: 2.5mg 1x/day 6–17 Yrs: 5-40mg divided BID; SD: 5mg 1-2x/day			G Smg/SmL	6													
Non-Stimulant	S** (Medications in this section are shown	at actual size	20			114												
Intuniv ^{®†} (guanfacine, extended release)	6-12 Yrs: 1-4mg; SD: 1mg 13-17 Yrs: 1-7mg; SD: 1mg Weight-based dosing: SD: 0.05-0.08 mg/ kg/day; may increase to 0.12 mg/kg/day	G 1mg	0	C 2mg		C 3mg	BHG	G 4mg	HHG									
Kapvay®† (clonidine, extended release)	6–17 Yrs: 0.1-0.2mg BID; SD: 0.1mg qHS	G 0.1mg	0	(only in dose pack) 0.2mg	9													
Strattera®† (atomoxetine)	s70kg: 0.5mg/kg x =3days, then 1.2mg/kg (max:1.4mg/kg, not to exceed 100mg) >70 kg: 40mg x =3days, then 80mg (max:100mg)	G 10mg	-	G 18mg		C 25mg	•••	G 40mg		G 60mg	-	G 80mg	(1) New	C 100mg	(in 1000)			
Qelbree ^{™‡} (viloxaszine)	6-11 Yrs: 100-400mg; SD: 100mg 12-17 Yrs: 200-400mg; SD: 200mg	100mg	SPN 100	200mg	SPN 200	300mg	SPN 150	+	8PN 150	400mg	SPN 200	+	SPN 200					
Discontinued ADHD M (though, in some cases, br capsules (40mg, 60mg); M Smg, 10mg); Dexedrine Sp LiquADD solution (Smg/Sm	edications: The following FDA-approv anded or generic equivalents are still a letadate ER tablet (10mg); Ritalin SR t varsules (Smg, 10mg); Dexedrine table 4), and Cylert (pernoline).	ved proprieta vvailable): Ri ablets (20m ets (5mg, 10	ary formulations are n talin LA capsule (60n g); Methylin Chewab Img); DextroStat tabl	o longer avail 19); Metadate 1 tablets (2.5 ets (Smg, 10)	able cD mg; mg); Cor	dated versio ninated cop ntact Dr. /	ons of the ADHD M pies of the ADHD Andrew Adesman w	Medication Medication vith any o	Guide can be viewe n Guide can be ob comments or sugges	i at: www tained at: tions: ADH	ADHDMedicationGuic www.ADDWarehous DMedGuide@Northw	de.com ie.com elLedu	**Important I approved preso age. Practitione Please note: n comparison; do	nformation ibing inform rs should ref redications sing equival	The age-specific d ation. "SD" refers to fer to the full prescrib have been arrange ence cannot be assu	osing inform the FDA-reco ing informati d on the A umed.	ation listed for each mmended starting do on for each medicatio DHD Medication Gu	medication reflects the FDA- se, which sometimes varies by n. ide for ease of display and

Initiating ADHD medications

stimulants

- Titrate over low-medium-high indicated dose range with 5-7 days at each dose for a 2-3 week medication trial
 - Generally begin with extended-release, providing pm IR of same medication as needed or consider use of agent with 16-hour duration of effect

atomoxetine

- Begin at 0.5 mg/kg for minimum one week then increase to 1.2-1.4 mg/kg as tolerated once daily or divided
- Wait at least 2-3 weeks on full target dose to assess potential full response



Initiating ADHD medications

alpha-agnoists

- Begin at lowest dose and titrate weekly as tolerated
 - Guanfacine-XR (Intuniv) 1, 2, 3, 4 mg tabs once daily to max 4 mg/day
 - Clonidine-XR (Kapvay) 0.1, 0.2 mg tabs once or twice daily to max 0.4mg/day



Stimulant Prescribing

Generic formulation	Starting Dose	Dose Titration	FDA Max (mg/d)	
MPH	0.25 – 1 mg/kg/d (IR: 5 mg TID)	 Inc. q 3-4 days to weekly 	72 mg/d or 2 mg/kg/d	
Dex-MPH	0.1 – 0.5 mg/kg/d (IR: 2.5 mg TID)	IR give BID to TIDAdequate trial is	30-40 mg or 1 mg/kg/d	
AMPH (mixed)	0.1 – 0.5 mg/kg/d (IR: 5 mg TID)	1 week at max dose	40-60 mg/d	
Dex-AMPH	0.1 – 0.5 mg/kg/d (IR: 5 mg TID)		40-60 mg/d	
L-Dex-AMPH	20-30 mg		70 mg/d	
May exceed	FDA approved	labelling		

Stimulant Prescribing

XR generic formulation	Starting Dose	Dose Titration	Max (mg/d)
MPH XR	20 mg/day OROS: 18 mg/day Transderm: 10 mg	 Inc. q 3-4 days to weekly Long-acting 	2 mg/kg/d
Dex-MPH XR	5-10 mg/day	give q am (may supplement with IR from	1 mg/kg/d
AMPH (mixed)	5-10 mg/day	5-10 mg/day after school) • Adequate trial	
L-Dex-AMPH	30 mg/day	is 1 week at max dose	70 mg/d

May exceed FDA approved labelling



New MPH-XR Prescribing

Brand	Release	Duration	FDA Max (mg/d)
Quillivant (Susp 25mg/5mg)	20:80	45 mins – 12 hrs	20-60 mg/d
QuilliChew ER (20, 30, 40 mg chewable tab)	20:80	45 mins – 8 hrs	20-60 mg/d
Cotempla XR-ODT (8.6, 17.3, 25.9 mg ODT [= 10, 20, 30 mg MPH-XR])	25:75	1-12 hrs	8.6-51.8 mg/d
Aptensio XR (10, 15, 30, 40, 50, 60 mg caps)	40:60	1-12 hrs	10-60 mg/d
Adhansia XR (25, 35, 45, 55, 70, 85 mg caps)	50:50	1-16? hrs	Max 55 mg Peds/100 mg Adults

ODD/Outbursts/Aggression

- <u>Irritable</u> is how one feels; <u>outbursts</u> are what one does (consider the frequency, severity, and duration of the outbursts). The more severe and persistent, the more difficult to treat.
- Irritability and outbursts are transdiagnostic; most children had ADHD complicated by other externalizing, internalizing, and learning/language disorders.
- Treatment consists of treating the primary disorder; teaching self-control skills and parent management – environmental factors are most important to change behavior
- Considering adding adjunctive medication when necessary
 - optimizing ADHD treatment and adding another medication where necessary (e.g.,stimulant + guanfacine/clonidine)
 - "mood stabilizers" beneficial only if mood component is separate from ADHD (phenotype of mania)
 - May consider 2nd treatment to address the mood (or aggression) symptoms (e.g., risperidone or aripiprazole)



Specific Medications

Antidepressants





Antidepressants - Indications

major depressive disorder enuresis **ADHD** anxiety disorders (e.g., school phobia, separation anxiety, panic disorder, and obsessivecompulsive disorder) sleep disorders (night terrors) some cases of self-injury in individuals with IDD



Depression/Anxiety

When medicating for MDD or anxiety:

Assess symptoms using screening tools and diagnose using DSM-5 criteria

Determine there is:

- significant impairment or distress
- recurrent or persistent symptoms despite therapy, or
- an inability to access psychosocial interventions

Prescribe medication for the few uncomplicated cases – otherwise, refer for therapy



Depression/Anxiety

Refer to mental health specialist if/when:

- longer duration or recurrent episodes
- lack of response to first line treatment
- significant impairment
- environmental stressors
- increasing number of comorbidities
- use of drugs and alcohol



Classes of Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs)

fluoxetine (Prozac) paroxetine (Paxil)* citalopram (Celexa) Vilazodone (Viibryd)* fluvoxamine (Luvox) sertraline (Zoloft) escitalopram (Lexapro)

Others

Tricyclics

bupropion (Wellburtin) venlafaxine (Effexor)* vortioxetine (Trintellix)* mirtazapine (Remeron) trazodone (Desyrel) desvenlafaxine (Pristiq)*

duloxetine (Cymbalta)

Monoamine Oxidase Inhibitors (MAOIs)

* limited data or not commonly used in children ALL HAVE BLACK BOX WARNING FOR SUICIDAL IDEATION



FDA-Approved Pediatric Age Ranges and Indications for Antidepressant Medications

generic/Brand	FDA approved age / indication
fluoxetine (Prozac)	 ≥ 7 y/o- OCD ≥ 8 y/o - MDD ≥ 10 y/o - Bipolar dep, in combo w/ olanzapine (Symbyax)
sertraline (Zoloft)	<u>≥</u> 6 y/o - OCD
excitalopram (Lexapro)	<u>></u> 12 y/o - MDD
fluvoxamine (Luvox)	≥ 8 y/o – OCD (immediate release only)
duloxetine (Cymbalta)	≥7 y/o – GAD > 13 y/o - fibromyalgia
clomipramine (Anafranil)	<u>></u> 10 y/o - OCD
imipramine	≥ 6 y/o childhood enuresis

Antidepressants – SSRIs

SSRIs:

- Selectively blocks the reuptake of serotonin
- Side Effects: irritability, headaches, insomnia, nervousness, drowsiness or fatigue, anorexia, nausea, or diarrhea (safer side effect profile)

** concerns regarding antidepressants and increased risk for suicidal ideation in children/adolescents (BLACK BOX)

FDA recommended visit frequency: weekly x 4 weeks; every 2 weeks for next month; and at the end of 12th week of taking the drug

Adequate trial: last 4+ weeks at optimal/max dose (highest tolerated dose)



Antidepressants - SSRIs

generic (Trade) name	Formulations (mg)	Dosing (mg/d)	Titration schedule
fluoxetine (Prozac)	tab: 10, 20, 60 cap: 10, 20, 40 weekly cap: 90 liq: 4mg/mL	Star: 5-10 mg/d Target: 20-60 mg/d (may need inc. for OCD)	5-10 mg q 2 weeks
fluvoxamine (Luvox)	tab: 25, 50, 100 mg	Start: 12.5-25 mg/d Target: 50-200 mg/d	25 mg q 2 weeks
paroxetine (Paxil)*	tab: 10, 20, 30, 40 er: 12.5, 25, 37.5 liq: 2mg/mL	Start: 5-10 mg/d Target: 10-40 mg/d	5-10 mg q 2 weeks
sertraline (Zoloft)	tab: 25, 50 ,100 mg liq: 20mg/mL	Start: 12.5-25 mg/d Target: 50-200 mg/d	25 mg q 2 weeks
citalopram (Celexa)	tab: 10, 20, 40 liq: 2mg/mL	Start: 5-10 mg/d Target: 20-40 mg/d	10 mg q 2 weeks
escitalopram (Lexapro)	tab: 5, 10, 20 mg liq: 1mg/mL	Start: 2.5-5 mg/d Target: 10-30 mg/d	5-10 mg q 2 weeks
Vilazodone (Viibryd)*	tab: 10, 20, 40, 10-20	Start: 10 mg/d Target: 40 mg/d	10 mg q 2 weeks

Antidepressants - Other

bupropion (Wellbutrin):

- exact mechanism of action in treating ADHD is unknown (not FDA approved)
- Side Effects**: irritability, anxiety, insomnia, reduced seizure threshold (with high doses)

venlafaxine (Effexor):

- strongly inhibits serotonin and norepinephrine reuptake
- several open-label studies in adults and children have shown promising results for ADHD
- Side Effects**: nausea, dry mouth, sweating, dizziness, nervousness, constipation, anorexia



Antidepressants - Other

mirtazapine (Remeron):

- Used to augment SSRI, treat anxiety or insomnia
- Side Effects**: stimulates appetite (weight gain)

trazodone (Desyrel):

- Used for insomnia
- Side Effects**: priapism

*** black box warning – may increase suicidal thoughts



Antidepressants - Other

generic (Trade) name	Formulations (mg)	Dosing (mg/d)	Titration schedule
mirtazapine (Remeron)	tab: 7.5, 15, 30, 45 dis: 15, 30, 45	Start: 7.5-15 mg/d Target: 15-30 mg/d	7.5 mg q 2 weeks
venlafaxine (Effexor)	ab: 25, 37.5, 50, 75, 100 er cap: 37.5, 75, 150 er tab: 37.5, 75, 150, 225	Start: 25-37.5 mg/d Target: 150-300 mg/d	25 mg q 2 weeks
trazodone (Desyrel)	tab: 50, 100, 150, 300 er: 150, 300	Start: 25 mg/d Target: 50-100 mg/d	25 mg weekly
bupropion (Wellbutrin)	tab: 75, 100 er: 100, 150, 174, 200, 300, 348, 450, 522	Start: 37.5-75 mg/d Target: 150-300 mg/d	37.5 – 75 mg q 2 weeks

Specific Medications

Anxioltyics





Anxioltyics - Indications

anxiety disorders seizure control night terrors and sleepwalking acute management of severe agitation adjunct treatment in mania and refractory psychosis **Tourette Syndrome**



Classes of Anxiolyics

Benzodiazepines

alprazolam (Xanax) diazepam (Valium) lorazepam (Ativan)

Antihistamines

diphenhydramine (Benadryl) hydroxyzine (Atarax)

Atypical anxiolytics

buspirone (BuSpar)

- start: 2.5-5 mg BID and titrate to 5-15 mg TID
- 3-6 weeks for effect
- NOT FDA approved for anxiety in children



Anxioltyics - Side Effects

headache

sedation and decreased cognitive performance behavior disinhibition gastrointestinal distress physical and psychological dependence (long-acting benzodiazepines) rebound or withdrawal reactions (short-acting benzodiazepines) blood abnormalities anticholinergic effects



Specific Medications

Antipsychotics





Antipsychotics - Indications

Behavior disorders with severe agitation, aggression, and selfinjury (IDD) – Irritability in ASD

Adjunctive treatment in depression and anxiety

Dyskinetic movement disorders (e.g., Tourette Syndrome)

Psychotic disorders

Schizophrenia (exacerbations and maintenance)

Mania (in conjunction with a mood stabilizer)

Bipolar disorder





Traditional antipsychotics

Low potency: chlorpromazine (Thorazine) thioridazine (Mellaril)

Intermediate potency: loxapine (Loxitane)

High potency: haloperidol (Haldol) thiothixene (Navane)



Antipsychotics

Newer or Atypical Antipsychotics

- clozapine (Clozaril)
- quetiapine (Seroquel)
- olanzapine (Zyprexa)
- risperidone (Risperdal)
- aripiprazole (Abilify)
- ziprasidone (Geodon)*

paliperidone (Invega)

asenapine (Saphris)

lurasidone (Latuda)

iloperidone (Fanapt)*

pimozide (Orap)

Brexpiprazole (Rexulti)*



* limited data or not commonly used in children

Antipsychotics

generic (Brand)	FDA approval / indication										
	Schizophrenia	Bipolar	Mania/mixed	Agitation (ASD)	Tourette's						
risperidone (Risperdal)	≥13 y/o		≥ 10 y/o	<u>≥</u> 5 y/o							
aripiprazole (Abilify)	≥13 y/o	≥ 10 y/o		<u>≥</u> 6 y/o	≥ 6 y/o						
olanzapine (Zyprexa, Zydis)	<u>≥</u> 13 y/o	≥ 10 y/o (adjunct)	≥ 10 y/o								
quetiapine (Seroquel)	≥13 y/o	≥ 10 y/o									
	paliperidone lurasidone	lurasidone asenapine Symbyax			pimozide						
Atypical Antipsychotics - Side Effects

Most common side effects include:

Sedation, constipation, disrupted sleep, increased appetite and weight gain, prolactin elevation, extrapyramidal symptoms, akathisia

Many of these common side effects are transient and may decrease after 2 to 4 weeks

Potentially more serious side effects include metabolic risks (inc. weight, lipids, HgA1c, fasting glucose), tardive dyskinesia, Neuroleptic Malignant Syndrome



Atypical Antipsychotics - Monitoring

	Baseline	q visit	@ 3 mos	q 6 mos	yearly
Weight	Х	Х			
BP/pulse	Х	Х			
HgA1c/Glc	Х		Х	Х	
Lipids	Х		Х	Х	
CBC	Х				Х
LFTs	Х				Х
AIMS	Х	Х			
lifestyle	Х	Х			

AIMS – Abnormal Involuntary Movement Scale or other screen for TD Lifestyle – diet, exercise, sleep hygiene, substance use



Metformin for Weight Gain

Recent Study: 16-week RCT 60 participants (6-17 years old) with ASD taking atypical antipsychotics

- >7% BMI increase in 12 months
- or >85%ile BMI + 5% weight gain / year
 Dose titration
- 250 mg at Dinner
- 250 Breakfast + Dinner
- 850 mg/day
- No significant difference in reported Aes (main AE is GI that can be minimized with slow dose titration)



P = 0.003





Specific Medications

Antiepileptics





Antiepileptics - Indications

seizure control

bipolar disorder – mood stability

most evidence for Depakote and Lamictal

adjunct treatment in major depressive disorder



Antiepileptics – Mood Stabilizers

None are FDA approved as *mood stabilizers* in children

Effective in PC-RT in ADULTS:

- sodium valproate (Depakote, Depakene)
- carbamazepine (Tegretol)

Positive results in child/adol trial(s)

- lamotrigine (Lamictal)
- topiramate (Topamax)

Positive results in child/adol case reports

• oxcarbazepine (Trileptal)



Antiepileptics - Side Effects

sedation, fatigue behavioral disinhibition, overexcitement blood abnormalities anticholinergic effects

- topiramate memory loss, difficulty concentrating
- valproate liver failure, pancreatitis
- lamotrigine Stevens-Johnson Syndrome
- carbamazepine blood dyscrasias



Specific Medications

Antimanics





Antimanics

lithium carbonate (Lithobid, Eskalith)

- Manic/mixed episodes of bipolar disorder 1
 - lithium is the only mood stabilizer FDA-approved for children (>7) and adolescents
- Side effects: weight gain, sedation, confusion, headache, electrolyte imbalances, gastrointestional distress, renal dysfunction (polydipsia, polyuria)
- Need to monitor drug levels, thyroid function, EKG and electrolytes every 1-3 months once stabilized



Sleep Medications - Insomnia

diphenhydramine (Benadryl)

- FDA approved > 12 y/o
- Side effects: Drowsiness, Dizziness, Dry mouth, Nausea, Nervousness, Blurred vision, Decreased mental alertness, Paradoxical excitation, May lower seizure threshold

melatonin

- Regulated by FDA as a dietary supplement
- Dosing: 0.05 0.15 mg/kg/day up to total dose of 5mg/day give 1-2 hrs before bedtime
- Side effects: sedation, may lower seizure threshold

clonidine (Catapres, Kapvay)

trazodone (Desyrel)

mirtazapine (Remeron)



Psychotherapeutic and pharmacologic treatment of pediatric insomnia



Skoch, S.H., et al (2022). Pediatric Insomnia: Treatment. Current Psychiatry, 21:1 (15-21).

Pharmacogenomic Testing

Genes important for drug response and metabolism

But..

Pharmacogenomic testing not yet proven helpful for routine care in child/adol psychiatry

Results generally no more informative than "start low, go slow...



Drug Combinations

- although it is not uncommon in clinical practice, there are few reports in the literature concerning the simultaneous use of more than one medication
- usually considered in treatment-resistant patients and patients with comorbid diagnoses
- use of two different medications may permit lower doses of each and decrease the potential for side effects
- further research is needed evaluating the overall safety and efficacy of various drug combinations





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