Pediatric Pharmacotherapy

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Hyperactivity Disorder

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Pharmacology Literature Reviews

Attention deficit hyperactivity disorder (ADHD) occurs in 3-5% of the pediatric population (1). The primary care provider must be adept at identifying and treating this disorder. This article will summarize the use of stimulant medications most commonly prescribed by primary care physicians.

ADHD is a clinical diagnosis based on DSM IV criteria. A trial of stimulant medication has no role in diagnosis because children without ADHD can have improvements in attention on these medications.

After a child is diagnosed with ADHD, the first step is educating the parents about the medical basis of their child's behavior. Stimulant medication is then presented as one component of a treatment plan that includes behavioral

modification and environmental adjustments. With this approach 60-90% of children respond to therapy (2). Improvements have been documented in attention span, conduct, social interaction, impulsive behavior, self control and aggression. Improvements have not been demonstrated in academic skills. However, studies to date have lacked the duration of follow up necessary to measure this outcome successfully (3). Some highly motivated families may decline medication and choose to treat using behavioral and environmental techniques. These parents should understand that stimulants may make it easier for the child to respond to their efforts (4).

Methylphenidate and dextroamphetamine have been first line therapy for many years. Pemoline and clonidine are being used with increasing frequency by the primary care provider. The mechanism by which these drugs modulate their effects is not fully understood. It is presumably through their effects on multiple catecholamine neurotransmitters (5). No clinical data clearly predict the medicine to which a particular child is most likely to respond. The presence of a comorbid diagnosis and parental preference best dictates the choice of medication. The advantages and disadvantages of each medication are listed in Table 1. Other agents (e.g., tricyclic antidepressants, carbamazepine) are used primarily in patients with complicating factors or if symptoms are resistant to first line agents. These medications are used infrequently in the primary care setting and are not discussed in this review.

Table I: Drug Therapy of ADHD

EDICATION	ADVANTAGES/ DISADVANTAGE	AVAILABILITY	STARTING DOSE	ONSET OF ACTION	DURATION OF ACTION	DOSE ADJUSTMENT	MAXIMUM DOSE
METHYLPHENI DATE (RITALIN®)	Extensive clinical experience	5mg,10mg ,20mg1 20mg SR	5mg qam (at breakfast)	15-30 min	2-4 hrs	Increase 5mg every 3-5 days until effect observed. When a theapeutic effect achieved, a second dose of the same amount can be given at lunch to control afternoon symptoms. An occasional child with severe symptoms may need a 3:30pm dose to control evening symptoms. Once the regimen has been adjusted the child, can be switched to the long acting form at the same total dose.	0.8mg/kg/ dose

DEXTRO- Extensive 5mg,10mg 5mg q am 15-30 2-6 hrs Increase 5mg every 3-5 days 1.5mg/kg/
clinical 5,10,15mg (at min until effect observed. day
AMPHETAMINE experience SR breakfast When therapeutic effect
) achieved, a second dose can
Longer half be added to control
(DEXADRINE®); life--- afternoon symptoms--usually
less slightly less than the am
likely to dose
need An occasional child with
afternoon severe symptoms may need a
dose. 3:30pm dose to control
evening symptoms.
Once the regimen has been
adjusted the child, can be
switched to the sustained
release form in the same
total dose.2

PEMOLINE Once a day 18.75mg 37.5mg q 1-2 N/A Increase 18.75mg every one 112.5mg/d
(CYLERT®) dosing. 37.5mg am weeks to two weeks until effect ay
Must 75mg for observed.
monitor (W/breakf maximal
LFTs. ast)
Contraindica effect
ted if
liver
dysfunction.

CLONIDINE May Tablets 0.05mg 1-2 N/A Increase to TID after 3-5 0.025mg/k
suppress 0.1mg,0.2mg. BID weeks days. g/day
(CATAPRES®) tics. 0.3mg for Then increase by 0.05mg/day
Preferred maximal every 3-5 days.
if Transdermal Monitor blood pressure and
aggressive Patch effect heart rate with each
or increase in dose.
hyperaroused 0.1,0.2,0.3m
behaviors g/day
Rebound HTN (Lasts 7
if days)
stopped
rapidly
Somnolence
may limit
use but
often
resolves
with time.

Anorexia, abdominal discomfort, insomnia and weight loss are common adverse effects associated with stimulant medications, but appear to resolve in most patients with continued therapy (Table 2). In addition, the potential for growth

suppression with stimulant medications continues to be a concern. Patients may show a temporary decrease in linear growth and weight gain; however, there is no evidence that these medications affect ultimate adult stature or weight (6,7). Stimulant medications are now considered safe in children with seizure disorders if the child's seizures are well controlled (8). Dextroamphetamine and methylphenidate have sympathomimetic effects and may elevate blood pressure and heart rate. Clonidine may lower blood pressure or cause rebound hypertension if stopped rapidly (9). Hepatic dysfunction has been reported with pemoline including liver enzyme elevation, clinical hepatitis and jaundice. These reactions are reversible on stopping the drug.

Table II: Managing Side Effects of Drugs used for ADHD

Decreased Appetite, Nausea or Growth Impairment	Take medication with meals. Do not force meals but encourage foods with high caloric density or nutritional supplements Encourage evening/bedtime snack Change from long acting to short acting preparation Check LFTs if using pemoline If severe, consider drug holiday or different agent
Sleep Disturbances	Administer doses earlier in the day If using a sustained-release product, consider changing to a short -acting preparation Discontinue afternoon/evening dose
Rebound Phenomena	If using a short-acting preparation, consider changing to a long acting preparation Overlap stimulant dosing
Irritability	Assess timing of symptoms -peak-reduce dose or try long acting formulation -withdrawal-change to long acting formulation Evaluate for comorbid diagnosis
Dysphoria, moodiness, agitation, dazed or withdrawn behavior	Decrease dose or change to long acting formulation Consider comorbid diagnosis
Dizziness	Monitor blood pressure Encourage fluid intake Lower dose or change to long- acting formulation to reduce peak effects

Development or increase in Tic disorder	Stop stimulant Consider trial of clonidine Consider referral

The risk of unmasking or exacerbating a tic disorder with methylphenidate, dextroamphetamine and pemoline is only 1.3% (10). This risk may be higher if there is a family history of a tic disorder. Clonidine is the preferred initial medication for children with tics because it suppresses tic disorders (11). The presence of a tic disorder or a postive family history for tics are not absolute contraindications to other stimulants, but these patients should be monitored closely for an exacerbation of tics. This effect is reversible with discontinuation of the drug.

Treatment with stimulant medications should be initiated with a low dose and slowly titrated to minimize adverse effects. A liaison at the school should be identified to give feedback on the child's progress. This may be a teacher, counselor, school nurse or principal. Dose adjustments can be made by phone every three to five days. The child can be seen in the office for evaluation of behavioral improvement and adverse effects every two to three weeks. When on a stable effective dose, visits can be every three months. Formal rating scales (e.g., Connor's questionnaires) can be invaluable in measuring the effectiveness of therapy, particularly if it is unclear from the subjective feedback. A baseline rating scale should be done to allow for future comparison.

Medication should be given seven days a week initially so that parents can monitor for effectiveness and side effects. The dose may then be slowly increased (Table 1) until a therapeutic effect is achieved. If a therapeutic effect does not occur despite maximal dosing or if side effects are troublesome, the medication should be stopped and the process repeated with a different agent. After the dosage has been optimized, parents can choose whether to give the methylphenidate or dextroamphetamine on weekends and holidays. If the child's behavior is not a problem in the home; parents may choose not to medicate on nonschool days. They may want to medicate on occasions (traveling, family gatherings and outings) where the child's behavior may be more problematic. Stopping medication for summer vacation should be approached with the same rationale. Pemoline and clonidine require weeks for maximization of effect and should not be stopped on the weekends. They can be stopped for the summer if the parents desire but must be restarted several weeks before the next school year. Clonidine should be weaned over one week because of the potential for rebound hypertension. If there are concerns about a child's growth, a drug holiday may allow for some catchup to occur. There is no absolute reason the child must go on a drug holiday, and medication may be given every day if it is the best therapeutic option.

The importance of using a multi-modal approach for treatment of ADHD should be stressed. The family's and school's efforts to use behavioral modification techniques and appropriately structure the child's surroundings should be

discussed at each contact. Behavioral and academic gains should not be attributed entirely to the stimulant medication.

Up to 30% of children with ADHD will respond to a placebo.2 After a child is on an effective stimulant regimen, the pediatrician may consider a brief placebo control trial to confirm that this is a drug and not placebo effect. A placebo-controlled trial also may clarify side effects and reinforce the benefit of the medication (12). At the University of Virginia, the pharmacy department prepares two identical bottles for these studies. One bottle is filled with gelatin capsules containing a placebo and the other with gelatin capsules containing medication. Capsules are given from each bottle on alternating weeks and Connor's questionnaires completed each week. After four weeks the trial is finished and the forms are returned to the pediatrician for review. UVA pediatricians are currently developing a computerized system to simplify this process in the primary care setting.

Increasingly, adolescents and adults are being diagnosed with ADHD and beginning stimulant medication. Parents should understand that this is a disorder that may be life long. With advancing age and the development of coping mechanisms some children can stop stimulant medication. Other patients may require treatment into adult life. Medications can be held for a brief period every two years to decide if therapy should continue. If medications are stopped, the family and school should continue the behavioral and environmental interventions that they have made. The physician should continue to monitor the child's adjustment at yearly visits (13).

The majority of children with ADHD can be managed by their primary health care provider. The treatment process requires a significant initial time investment as well as a long-term commitment by both the family and medical provider. Therapy can be highly effective, and for the child and family the rewards can be immense. Due to the complexity of their treatment regimens, children with comorbid disorders are best managed in consultation with a child psychiatric or developmental specialist. These disorders include Tourette's syndrome, oppositional defiant, conduct and obsessive/compulsive disorders, anxiety or depression and pervasive developmental delay. In addition, children who have failed a trial of several medications and younger, preschool-age children may benefit from referral to these professionals.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders IV. Washington, DC: American Psychiatric Association, 1994.
2. Barkley RA. A review of stimulant drug research with hyperactive children. J Child Psychol Psch 1977;18:137-65.
3. Ottenbacher KJ, Cooper HM. Drug treatment of hyperactivity in children. Develop Med Child Neurol 1983;25:358-66.
4. Wolraich ML. Behavior modification therapy in hyperactive children: Research and clinical implications. Clin Pediatr 1979;18:563, 565-6,568-70.

5. Stevenson RD, Wolraich ML. Stimulant medication therapy in the treatment of children with attention deficit hyperactivitiy disorder. Ped Clin North Am 1989;36:1183-96.
6. American Academy of Pediatrics, Committee on Children with Disabilities and Committee on Drugs. Consensus Statement. Medication for children with attention deficit disorder. Pediatrics 1987;80:758-60.
7. Roche AF, Lipman RS, Overall JE et al. The effects of stimulant medication on the growth of hyperkinetic children. Pediatrics 1979;63:847-50.
8. McBride MC, Wang DD, Torres CF. Methylphenidate in therapeutic doses does not lower seizure threshold. Ann Neurol 1986;20:428 (Abstract #130).
9. Leckman JF, Detlor J, Harcherik DF et al. Acute and chronic clonidine treatment in Tourette's syndrome: A preliminary report on clinical response and effect on plasma and urinary catecholamine metabolites, growth hormone, and blood pressure. J Amer Acad Child Psych 1983;22:433-40.
10. Denckla MB, Bemporad JR, Mackay MC. Tics following methylphenidate administration: A report of 20 cases. JAMA 1976;235:1349-51.
11. Steingard R, Biederman J, Spencer T et al. Comparison of clonidine response in the treatment of attention-deficit hyperactivity disorder with and without comorbid tic disorders. J Amer Acad Child Adol Psych 1993;32:350-3.
12. McBride MC. An individual double-blind crossover trial for assessing methylphenidate response in children with attention deficit disorder. J Pediatr 1988;113:137-45.
13. Wilens TE, Biederman J. The stimulants. Psych Clin North Am 1992;15:191-222.

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Pharmacology Literature Update

Antibiotic Allergies

For health care providers who need a quick tool to help them assess the probability of an allergic response being related to an antibiotic, this article may be a useful resource. The author presents a concise description of the incidence, mechanisms, and clinical presentation of antibiotic-associated allergic reactions. Skin testing and desensitization procedures are also described. Boguniewicz M. Adverse reactions to antibiotics: Is the patient really allergic? **Drug Safety 1995;13:273-80.**

Antiepileptic Pharmacokinetics

This is the first of a two part series reviewing the pharmacokinetic studies performed in children receiving antiepileptics. Section I includes: phenobarbital, primidone, valproic acid, ethosuximide, and mesuximide. The review of these agents alone incorporates 119 trials. Of note, particular attention is given to the information available on phenobarbital pharmacokinetics in neonates. The paper is well-written and would make a useful addition to any primary care provider's files. Battino D, Estienne M, Avanzini G. Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Part I. **Clin Pharmacokinet 1995;29:257-86.**

Effect of Maternal Drugs During Breastfeeding

The authors present a unique study of the effects of maternal medication use on the hepatic function of breastfeeding infants. The effects of levo-norgesterel (birth control pills) and the combination of ethambutol and isoniazid (TB treatment) were evaluated. Levo-norgesterel use by breastfeeding mothers resulted in a stimulation of hepatic metabolism in their infants, while maternal TB treatment blocked metabolic function. This preliminary study may stimulate further research into the long-term effects of maternal mediation use during lactation. Todywalla VS, Patel SB, Betrabet SS et al. Can chronic maternal drug therapy alter the nursing infant's hepatic drug metabolizing enzyme pattern? **J Clin Pharmacol 1995;35:1025-9.**

Lamotrigine Update

Another extensive review of lamotrigine, a new antiepileptic, has been published to provide readers with information gathered from clinical experience. Health care professionals working with children who receive lamotrigine may be interested in new information on adverse effects, particularly the potential for severe dermatologic effects. In addition, the authors review the literature regarding the extended use of this medication in children with refractory seizure disorders, including those with mixed seizure types. Fitton A, Goa KL. Lamotrigine: An update of its pharmacology and therapeutic use in epilepsy. **Drugs 1995;50:691-713.**

Midazolam Compatibility

Although the need to infuse multiple medications into a single IV site is a frequently encountered problem in pediatrics, compatibility information for many medications is not well documented in the medical literature. The visual compatibility of midazolam with 25 common pediatric medications is addressed in this paper. At 24 hours, using a simulation of Y-site exposure, the medications found to be incompatible with midazolam were: ampicillin, ceftazidime, cefuroxime, dexamethasone, dobutamine, furosemide, nafcillin, and sodium bicarbonate. Medications found to be compatible with midazolam included: calcium gluconate, cefazolin, cefotaxime, cimetidine, clindamycin, digoxin, dopamine, fentanyl, gentamicin, methylprednisolone, metronidazole, nitroglycerin, sodium nitroprusside, theophylline, tobramycin, and vancomycin. Mantong ML, Marquardt ED. Visual compatibility of midazolam hydrochloride with selected drugs during simulated Y-site injection. **Am J Health-Syst Pharm 1995;52:2567-8.**

Moricizine in Children

The pharmacokinetic properties of moricizine, an antiarrhythmic, were studied in four male children between the ages of 7 to 18 years. All four patients had refractory supraventricular tachycardia. Samples were obtained after a single 2-3 mg/kg oral dose. Peak levels ranged between 200 to 4,000 ng/ml, occuring within the first hour after administration. The average elimination half-life was 2 hours, similar to adult values. However, three of the patients exhibited a biphasic elimination with a slowing of elimination within four hours of the dose. The authors suggest further study before adopting a standardized dosing regimen for moricizine in children. Rice PJ, LeClair IO, Stone WL et al. Pharmacokinetics of moricizine in young patients. **J Clin Pharmacol 1995;35:1016-9.**

Propofol Use in Intensive Care

While focusing primarily on adult patients, this new review of propofol's use in the ICU includes basic information that may be of interest to pediatric intensive care clinicians as well. The authors have provided tremendous detail in their description of the pharmacodynamic properties of propofol, including not only its beneficial sedative effects but also its adverse effects. Fulton B, Sorkin EM. Propofol: An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. **Drugs 1995;50:636-57.**

Valproate Pharmacokinetics

The authors of this study present a NONMEM (nonlinear mixed effects pharmacokinetic model) method for determining valproate clearance. Ninety-seven serum samples were obtained from a heterogenous population of children to create the model. The authors found that weight and the concomitant use of carbamazepine were the two factors most influencing valproate clearance. The average clearance of the children studied was 0.21 L/kg/hr, slightly more rapid than previous reports. Botha JH, Gray AL, Miller R. A model for estimating individualized valproate clearance values in children. **J Clin Pharmacol 1995;35:1020-4.**

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