The Evidence Base for the Assessment and Treatment of Attention-Deficit/Hyperactivity and Oppositional Defiant Disorder

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a common, often chronic, treatable childhood psychiatric illness, characterized by a pattern of developmentally inappropriate inattention, motor restlessness, and impulsivity that affects from 5% to 9% of school-aged children.[1] The incidence of ADHD has been estimated as high as 12% in child behavioral health outpatient populations, and 20% of inpatient populations. The predominantly inattentive type is relatively more common in females.

ADHD often goes unrecognized and untreated as demonstrated by a recent study, which found that among a community sample of 3,082 youngsters, only 52.1% of patients found to meet criteria for ADHD had been previously identified, and 68% of those identified had not received treatment.[2] ADHD has been associated with high levels of comorbidity, impairment, and persistence into adolescence and young adulthood.[1] Taken together, these characteristics make early recognition and treatment of ADHD of paramount importance. Treatment options include behavior management, medication alone, or a combination of the two.

Oppositional Defiant Disorder (ODD)

ODD is considered the less severe of the 2 major disruptive behavioral syndromes of childhood, the other being Conduct Disorder. ODD has been estimated to occur in about 3% -15% of children, with boys having only a marginally higher prevalence rate than girls.[3]

While some of the characteristics of ODD might be typically observed during toddlerhood or adolescence, the DSM criteria that specify both clinically significant symptomatology for a minimum of 6 months typically excludes these developmentally-appropriate behaviors.

Children with ODD demonstrate argumentative, disobedient, and defiant behavior, most commonly with authority figures such as parents or teachers, although such interactions can also be noted in relation to their own peers. They are sometimes portrayed as being stubborn and unnecessarily negativistic, often adopting a self-defeating stance with authority figures. For example, children with ODD are often willing to lose a privilege or toy, or accept a difficult consequence, rather than lose an argument or concede a previously adopted position of defiance. Children with ODD are experienced as being provocative, as they will often delay, procrastinate, or resort to sneaky or devious behavior to undermine an established rule or routine at home.

Etiology and Pathophysiology

ADHD

Genetic factors are implicated in ADHD, but their mechanisms of action are not completely understood. ADHD very likely results from a mixture of dominant and recessive major genes that act with complex polygenic transmission patterns.[4] Twin, family, and adoption studies of ADHD have supported a strong genetic contribution to the disorder, with heritability estimates ranging from 60%-90%.[4,5] Genetic studies

have demonstrated that ADHD symptoms are often associated with alterations in genes involved with catecholamine transmission.[6] More recent research highlighted genes involved with dopamine (DA) transmission, and found associations with the DA D1, D4, and D5 receptors, and the DA transporter.[7-9] Also reported are associations of ADHD with norepinephrine (NE) genes, including the synthetic enzyme for NE, dopamine-beta-hydroxylase, the NE transporter as well as the Alpha-2 Adrenergic (α2A) receptor, which is the site of NE's beneficial actions in the Prefrontal Cortex (PFC).[10-12] Such suboptimal catecholamine regulation in the PFC may contribute to the impaired attention, impulsiveness, and hyperactive behavior observed in patients with ADHD.[13]

There is increasing evidence that the frontostriatal network is a likely contributor to the pathophysiology of ADHD. This network involves the lateral PFC and its connections to the dorsal anterior cingulate cortex, caudate nucleus, and putamen. In subjects with ADHD, reductions in total cerebral and gray matter volume have been observed, particularly in the PFC, basal ganglia (striatum), dorsal anterior cingulate cortex, corpus callosum, and cerebellum.[14]

The PFC is important for sustaining attention over a delay, inhibiting distraction, and dividing attention. The PFC in the right hemisphere is especially important for behavioral inhibition. Lesions to the PFC produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. The PFC is very sensitive to its neurochemical environment, and either too little (drowsiness) or too much (stress) catecholamine release in the PFC weakens cognitive control of behavior and attention.[15,16] Other notable findings include evidence that norepinephrine enhances *signals* through postsynaptic α2A receptors in the PFC, while dopamine decreases *noise* (or distraction) through modest levels of D1 receptor stimulation.

Environmental influences have also been demonstrated to play in role in the etiology of ADHD; children exposed prenatally to alcohol can become hyperactive, disruptive, impulsive, and are at an increased risk for a range of psychiatric disorders.[17] Maternal smoking produces a 2.7-fold increased risk for ADHD,[18] and a dose-response relationship between maternal smoking during pregnancy and child hyperactivity has been reported.[19] This is hypothesized to be due to an effect on nicotinic receptors, which modulate dopaminergic activity.[20] Additional perinatal factors have also been implicated, with a 2-fold increase in ADHD in very low-birth weight children, and an increased rate of pregnancy and birth complications in mothers of children later diagnosed with ADHD.[21] Among postnatal factors, a role for malnutrition and dietary deficiency in ADHD has been proposed.[22]

ODD

Several psychosocial factors have been proposed in the genesis and perpetuation of ODD, in addition to neurobiological and temperamental characteristics. Parents with insufficient time and emotional energy may predispose the child to seek their attention in maladaptive ways. Inconsistent methods of limit setting, disciplining, and setting structure could contribute to deficient internal working models of social interaction.[23] A child identifying with a parent who is also stubborn, unpredictable, and negativistic in family and social interactions as a role model could be expected to demonstrate disobedient and defiant behavior.[24]

Langbehn et al[25] suggested that symptoms of ODD in high risk, adopted males may be linked to genetic traits leading to adult antisocial personality. In a sample of clinic-referred boys with ODD, 44% developed CD over a 3-year period.[26] Risk factors for progression to Conduct Disorder include poverty, young maternal age at first childbirth, and parental substance abuse.[26] Physical fighting, low socioeconomic status of the parent, ODD, and parental substance abuse have also been shown to predict the onset of CD. Attention-deficit hyperactivity disorder (ADHD) predicted an early onset, but not later onset, of CD.[27]

Differential Diagnosis and Comorbidity

ADHD

ADHD commonly co-occurs with other medical and psychiatric conditions.[28] Studies suggest that as many as 67% of children with ADHD have a coexisting condition such as an additional psychiatric problem, learning disability, or developmental delay.[29] The psychiatric conditions most likely to be found comorbid alongside ADHD include: ODD (prevalence of 35% in ADHD), conduct disorder (prevalence of 30% in ADHD), anxiety disorder (prevalence of 25% in ADHD),

and mood disorder (prevalence of 18% in ADHD).[28] Additionally, other genetic conditions often masquerade as ADHD and vice versa.[30] Acute and chronic psychosocial stressors may influence child behavior and functioning through mediation of hypothalamopituitaryaxis functioning, so all environmental systems connected to a child, including family and school, should be assessed.[31]

Dependent on both the specific definitions used and the research setting, 12% to 60% of children who have ADHD may have a coexisting learning or language delay.[32] A Disorder of Written Language is the most common disability found together with ADHD.[33] Because most children who have ADHD experience academic underachievement, it is important to distinguish whether a learning disability also is present.[34]

ODD

Common comorbidities with ODD include ADHD, learning disabilities, mood disorders (depression, or bipolar disorder), and anxiety disorders. The recognition and prompt treatment of such conditions is essential, as it may be difficult to improve the symptoms of ODD without treating the coexisting disorder; such delay may lead to rapid deterioration in the parent child relationship and preventable disciplinary issues in the classroom. A proportion of children with ODD may go on to develop conduct disorder.

Clinical Assessment

ADHD

The American Academy of Child and Adolescent Psychiatry's Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention Deficit/Hyperactivity Disorder[1] provides a detailed approach to assessment, which is briefly summarized here. Preliminary assessment for ADHD occurs via a clinical interview, which should involve the child and caregivers. Further screening for the number, severity, and settings of ADHD symptoms is commonly achieved through the collection of symptom checklist or rating scales that may be completed by the patients, caregivers, and teachers, depending on the instrument chosen. Information must be gathered from collateral sources to assess whether symptoms are evident, across raters and settings, as ADHD, which, by definition, presents pervasively. Because the DSM-5 symptoms for ADHD were not formulated via a scientifically rigorous process, and because there is a good deal of criterion overlap with other conditions, it is challenging to establish a rating scale or scoring symptom that can definitively ascertain whether or not a specific child has ADHD. Therefore, ADHD-specific rating scales are not diagnostic. However, they may be used to gather information about the child's behaviors from the parent, and/or teacher. These rating scales assess the core symptoms of ADHD, as specified in the DSM 5, and they are relatively easy to administer.[28]

The utility of the rating scales rests in the fact that they are comprised of DSM 5 symptoms.[35] Rating scales probably are most useful in documenting whether the rater sees the core symptoms as being present for a specific child compared with his or her same-age peers. The clinician also should recognize that ADHD-specific rating scales differ in their normative data.[35] For example, normative data for the Connors Scales and the Attention Deficit Disorder Evaluation Scale (ADDES-3) were formulated based on discrete age ranges (eg, comparing ages 3 to 5, and 6 to 8); whereas other scales, such as the ADHD-Symptoms Rating Scale (ADHD-SRS), established normative data based on broader age ranges (eg, 5 to 12 years, and 13 to 18 years).[32] Only the Connors Scales have normative data for preschool-age children. Normative data also may differ by race, sex, and geographic area. Therefore, when using a rating scale, it may be difficult to interpret the results if the clinician's particular patient sample is not represented in the scale's normative data.[36,37]

Rating scales also may be used to measure behavioral changes that occur over time or in response to treatment. However, few studies have been published describing their diagnostic utility in this context. Many of the ADHD rating scales also provide screening questions for comorbid conditions.[38]

Evidence-Based Interventions for ADHD and ODD

Psychosocial Treatments

There are several major factors to consider when making a choice about what intervention strategies to use with children who display disruptive behavior, including ADHD and ODD. These factors include the quality of the research base (including documented

treatment outcomes), the ease and practicality of implementation for the population to be served, and the type of training and infrastructure needed.[36,37] Dozens of psychosocial treatment protocols have been established as efficacious for disruptive behavior disorders. The following content focuses on the Triple P (Positive Parenting Program), Parent Management Training, and Parent Child Interaction Therapy, which are among the most widely deployed and well established.[39] The 2013 SAMA's publication provides a thorough, evidence-based overview of available psychosocial treatments when working with children with impulsive behaviors.

Triple P (Positive Parenting Program). Triple P is a multi-level system of parenting and family support programs that apply to prevention, early intervention, and treatment.[39] The developers are Mathew Sanders and his colleagues from University of Queensland in Australia. The program is used in a number of countries, including 9 states in the U.S. The intent of Triple P is to prevent or reduce behavioral, emotional, and developmental problems in children. This reduction in symptoms is accomplished by enhancing the skills, knowledge, and confidence of the key people in children's lives: their parents. It is designed to be used with children from birth to 16 years, and can be delivered by a range of professionals in primary care (nurses and physicians), mental health, and educational settings (family/parent liaisons, day care personnel, and school counselors). It is available in 10 different languages, and cultural adaptations can be made depending on the targeted population.[40]

The intervention offers 5 different levels of service that increase in intensity as a child and family's need increases. Level 1 is a prevention approach, and is more informational in nature. Level 2 begins using a brief elective intervention aimed at parents with specific concerns about their child's behavior and/or development. Level 3 begins to narrow the intervention to a very specific concern from the parents. The sessions become longer and more frequent at this level. By Level 4, there is a broadened parent training intervention for those who want to increase their positive parenting skills. Level 5 is the "Enhanced Triple P." The intervention at this level is intensive and tailored for families with increased problems and additional stressors (eg, parent depression or divorce).

Triple P has been studied extensively since 1977, and has a strong research base. There are 29 randomized clinical trials, 11 controlled single-subject studies, 9 effectiveness trials, and 6 dissemination trials. An interesting and innovative RCT was done looking at the culturally and ethnically diverse children in China.[39] The settings of implementation have also been diverse, spanning both mental health and community settings.

Parent Management Training-Oregon (PMTO). The PMTO model, based on social interaction therapy, was originally developed in the 1970's by Gerald Patterson, Marion Forgatch, and their colleagues at the Oregon Social Learning Center.[39] PMTO is both a behavioral prevention and clinical intervention model. It focuses on enhancing effective parenting, while reducing coercive parenting practices. The program is widely disseminated in Norway, the Netherlands, and in 13 sites in the U.S.

PMTO is designed for children aged 4 to 12 years old who display serious disruptive behaviors. The typical setting of implementation is the clinic, but it can also be delivered in the home. The intervention is delivered by trained providers (typically master's level-prepared professionals) over 20 sessions. However, the number of sessions can be modified to meet the needs of an individual family. The intervention requires participation of children and parents.

PMTO is a manual-based intervention with the following 5 essential components: (1) skill encouragement, which teaches pro-social development by breaking behaviors down into small steps and contingent positive reinforcement; (2) discipline, which decreases negative behavior using contingent and appropriate mild sanctions; (3) monitoring or supervision of activities, peers, and location of children and youth, which helps the parents ensure a safe environment for their children; (4) problem solving skills, which help the family to negotiate agreements and set rules; and (5) positive involvement, which assists parents with offering loving, positive attention. The infrastructure and staffing requirements are relatively modest, and training materials are readily available. The materials have been translated into 4 different languages, including Spanish. All materials can be found at Implementation Sciences International, Inc. (http://www.isii.net).

PMTO has been evaluated extensively in community settings. There are also a number of comparison

studies done using random assignment. Other studies using control groups have yielded promising results. Research to-date supports the claim that treatment effects may be generalized across settings, and effects are maintained for up to 2 years. There is also some evidence to suggest that the treatment effects extend to other deviant behaviors beyond those that are the primary focus of the treatment.

Parent-Child Interaction Therapy (PCIT). PCIT is a parent training/coaching program for families with children 2 to 7 years of age who are displaying disruptive behaviors. The program was originally developed in 1982 by Shelia Eyberg at the University of Florida, and was influenced by the earlier work of Constance Hanf and Diane Baumrind.[39] The intervention has been implemented in both the United States and in 3 other countries, in laboratory clinical settings, community mental health systems, Head Start programs, schools, and foster care settings.

PCIT is broken down into 2 phases, and its components are based on attachment and social learning theories. In the first phase—Child Directed Interaction—the parents learn how to strengthen their attachment through demonstrations of warmth, responsiveness, and sensitivity, in response to their child's behavior. The second phase—Parent Directed Interaction—involves the parents learning how to be effective authority figures by giving directions in age-appropriate, positive ways, while setting consistent limits and learning how to appropriately implement consequences (ie, time out).

The intervention is structured through 10 to 16 weekly, 60-minute sessions with either the parent alone or the parent and child dyad. Trained masters or doctoral-level therapists deliver the intervention. The treatment begins with an assessment of the family functioning, moves to teaching in the 2 phases mentioned above, and then to generalization, homework, and post-treatment assessment. The therapist monitors the client's progress through the treatment. In research settings the monitoring is done via a one-way mirror with a "bug" in the ear of the parent (ie, an earphone through which the therapist can assist the parent in the interaction with the child). In community settings, some adaptations have been made, such as a live observation in the families' home or in the child's school setting; it is not yet clear what impact those changes had on the fidelity of the intervention.

PCIT has been tested in a number of replication and follow-up studies and has been found to be effective in improving the interaction style of parents, and in improving behavior problems of children at home and in school.[41] This is in comparison to waitlist control groups, classroom control groups, and modified treatment groups.[41] There is also promising support for the culturally sensitive adaptations of PCIT.[42]

There are some noteworthy implementation challenges to consider when contemplating the use of PCIT as a primary intervention. First, it is recommended that the clinical setting be structured similarly to the conditions used in the research setting (eg, a one-way mirror and a bug in the ear).[43] There is also a considerable time and financial commitment from clinical staff. The estimated cost per clinician trainee is $3000, plus there is additional cost for the equipment needed to deliver the intervention. Training materials, workshops, on-going consultation as well as supervisor training is also available (http://pcit.phhp.ufl.edu/General_Workshop.htm).

Psychosocial Treatment Summary Tables

	Triple P-Positive Parenting	Parent Management Training-Oregon	Parent Child Interaction Therapy
Type of EBP	Prevention/Multilevel	Intervention	Intervention
Settings	Clinic, Home, School	Clinic, Home	Clinic
Ages	0-16	4-14	2-17
Training materials available	Yes	Yes	Yes
Outcomes	Increase in parental confidence, improvements in dysfunctional parenting style, reduction in child behavior problems	Significant reduction in child's behavior problems, reductions in coercive parenting, increases in effective parenting	Improvement in parent-child interaction style, improvement in child behavior problems

Table 1. Psychosocial Treatment Summary Tables.

Psychopharmacologic Treatments of ADHD

Rationale. Among the psychiatric conditions occurring in childhood, ADHD stands out as one with a relatively robust evidence base for pharmacologic interventions.[44] Stimulants have long been definitively established as first-line pharmacologic interventions for ADHD, with effect sizes averaging between .9-1.1.[45] Alpha adrenergic agents and the noradrenergic re-uptake inhibiter, atomoxetine, are regarded as second-line treatments for ADHD, with effect sizes ranging between .5-.7.

Data from the Multi-Modal Treatment of ADHD Study (MTA Cooperative Group, 1999),[46] functional and structural brain imaging,[47] and genetic and familial studies,[48] have increasingly demonstrated that this condition has significant heritability, along with clear neurophysiological or biological underpinnings. These findings, factored together with other variables, such as insufficient access to pediatric mental health specialty care and evidence-based behavioral treatments, have increasingly spurred a shift to medication strategies, as the primary and sometimes solo treatment for ADHD.[44]

Over 20 long-acting formulations of stimulant medication have evolved over the past few decades, not only leaving practitioners a multitude of options, but also necessitating a broadening of knowledge base and sophistication related to prescribing for ADHD.[49] The myriad and ever-expanding pool of varied formulations of stimulants and non-stimulants has led to increased confusion and errors in the prescribing and dispensing of these drugs. Knowing and understanding the advantages and disadvantages of the different formulations can facilitate optimal and customized treatment. Formulations like Concerta (OROS-methylphenidate), Adderall-XR (mixed amphetamine salts extended release), and Vyvanse (lisdexamfetamine) provide the convenience of once-daily dosing. Each of these formulations delivers a varied amount of stimulant at predictable time intervals throughout the day. Vyvanse has a unique delivery system that may lower the risk for patients abusing or diverting their medication. Daytrana (methylphenidate patch) can be given to patients who are unable to swallow pills and additionally confers flexibility over effect duration, via the choice of time when the patch is removed. For patients who cannot swallow tablets or capsules, the capsules of Focalin-XR (dexmethylphenidate extended release), Adderall-XR, Metadate-CD (methylphenidate extended release), and Ritalin-LA (methylphenidate LA) can be opened and sprinkled in applesauce or yogurt.

Stimulants. The stimulants can be divided into 2 broad categories: methylphenidate and amphetamine-derived products. There are currently over 20 long-acting stimulant formulations on the market, employing a myriad of technologies for medication administration, delivery, absorption, and metabolism. The products introduced during the past 1-2 decades have been specifically designed to overcome a phenomenon known as *tachyphylaxis*, which refers to an imme-

diate tolerance to stimulants that develops and must be overcome throughout the course of a given day, in order that the medication retain its efficacy for an extended period.[49] The first generation of sustained release stimulant products, which included Ritalin SR (methylphenidate sustained release) and Dexedrine Spansules (dextroamphetamine sustained release), predated the discovery of the tachyphylaxis phenomenon, and therefore were not inclusive of a delivery mechanism designed to overcome this impediment to prolonged duration of effect.

One strategy for overcoming tachyphylaxis involves the use of repeated doses of shorter-acting products delivered at distinct times, such as at the zero and 4-hour marks, using either regular, short-acting stimulants, or beaded formulations, which contain beads coated with short-acting and long-acting membranes. Examples of medications using this beaded, bimodal strategy include Ritalin LA, Focalin XR, Metadate CD, and Adderall XR. Another methodology for overcoming tachyphylaxis is the use of a capsule containing multiple layers of membranes and an osmotic pressure delivery system that generates an ascending dose curve, or increasing blood levels as the day transpires, an example of which includes Concerta. Vyvanse and Daytrana also produce pharmacokinetic profiles associated with an ascending dose curve as their mechanism for addressing tachyphylaxis.

	Onset of Action	Peak Clinical Effect Pharmacokinetic Profile	Duration of Action	Typical # Daily Doses
Short-Acting Preparations				
Regular MPH	20-60 minutes	~ 2 hours; range 0.3-4 hours	2-4 hours	2-3
AMPH	20-60 minutes	1-2 hours	3-6 hours	2
Regular MAS	30-60 minutes	1-2 hours	3-6 hours	2
First-Generation, Sustained-Release Preparations (Older Delivery Systems)				
MPH-SR *Metadate ER* *Methylin ER*	60-90 minutes	~ 5 hours; range 1.3-8.2 hours	4-6 hours	2
AMPHSpanulesSpansules	60-90 minutes	NA	4-6 hours	2
Second-Generation, Extended-Release Preparations (Newer Delivery Systems)				
MPHCD *Ritalin-LA*	30 minutes-2 hours	Bimodal pattern†	6-8 hours	1
OROS MPH	30 minutes-2 hours	Ascending pattern†	10-12 hours	1
MASXR	1-2 hours	Bimodal pattern†	10-12 hours	1
LAMPH	1-2 hours	Ascending pattern†	10-12 hours	1
MPH Patch	1-2 hours	Ascending pattern†	10-12 hours	1
DMPH XR	1-2 hours	Bimodal pattern†	6-8 hours	1

Table 2. Stimulant Medications Available for the Treatment of ADHD (adapted from Spencer[45] and Chavez[49]).

Legend: MPH=Methylphenidate, AMPH=Dextroamphetamine, MAS=Mixed Amphetamine Salts, DMPH=Dexmethylphenidate, LAMPH=Lisdexamfetamine, XR=Extended Release, SR=Sustained Release, CD=Continuous Delivery

Although there are a variety of long-acting stimulant products designed to be dosed once daily, there is substantial variation in the drug delivery mechanisms, along with the expected duration of effect and adverse event profiles. The bulk of these products are represented in the table below, with typical ranges for their expected onset, peak levels, duration, and number of daily doses.

Stimulant dosing is estimated based on the child or adolescent's weight in kilograms. Regardless of the duration of effect, mechanism of delivery, or number of daily doses, the total amount of *methylphenidate* administered can be calculated using an expected range of 0.5-2.0 mg/kg/day.[45] Exceptions include Focalin products and Daytrana, with Focalin's potency estimated to be roughly double that of regular methylphenidate products. Daytrana has a higher potency as well, roughly 1.5 times that of immediate release methylphenidate, with the following estimated equivalencies: 10 mg Daytrana = 15 mg Regular Ritalin (methylphenidate), 15 mg Daytrana = 22.5 mg Regular Ritalin, 20 mg Daytrana = 30 mg Regular Ritalin, and 30 mg Daytrana = 45 mg Regular Ritalin.[49] Generally, the *optimal* total daily amount of methylphenidate given will range between 0.6-1.0 mg/kg/day. Within this range, maximum benefit is generally achieved with concurrent excellent tolerability. Rarely would a child or adolescent require dosing of typical methylphenidate products in excess of a total of 1.0 mg/kg/day. Aggressive methylphenidate dosing above that benchmark has been associated with clinically significant adverse effects, including growth retardation, emotional lability, sleep disturbances, and even auditory hallucinations.[50,51]

Regardless of the duration of effect, mechanism of delivery, or number of daily doses, the total amount of *amphetamine* administered can be calculated using an expected range of 0.3-1.5 mg/kg/day.[45] An exception includes Vyvanse, whose potency is less than that of other amphetamine products. The estimated equivalences include the following: 30 mg Vyvanse = 10 mg Adderall (mixed amphetamine salts), 50 mg Vyvanse = 20 mg Adderall, and 70 mg Vyvanse = 30 mg Adderall. Aside from Vyvanse, amphetamine products are roughly 1.5 times as potent as methylphenidate products, so their dosing will be roughly two-thirds of what might be used with typical Ritalin products. Generally, the optimal total daily amount of amphetamine given to achieve significant benefit while minimizing side effects should range between 0.3-0.7 mg/kg/day. Rarely would a child or adolescent ever require dosing of typical amphetamine products in excess of a total of 0.8 mg/kg/day. Aggressive dosing above that benchmark has been associated with clinically significant adverse effects, including growth retardation, emotional lability, sleep disturbances, and even auditory hallucinations.[50,51]

Alpha Adrenergic Agents

Alpha Adrenergic Agents. The 2 alpha adrenergic agents commonly used as second-line monotherapy or adjunctive therapy, combined with stimulants for ADHD, include guanfacine and clonidine. These 2 medications have been widely used for many decades, based primarily on clinical lore. A dearth of data from controlled trials was available to establish their safety and efficacy for the indication of ADHD. However, in recent years, both agents were developed into extended release products, which have been well studied in controlled trials, and each new formulation received Federal Drug Administration (FDA) approval for the indication of ADHD.

Intuniv (guanfacine extended release) is available in the strengths of 1, 2, 3, and 4 milligrams (mg). Its safety and efficacy have been documented via at least 2 randomized, controlled trials, ranging from 8-9 weeks in duration, with subject pools of 345 and 324, aged 6-17 years. Intuniv was significantly effective for school-aged youth, but not for adolescents. However, the fixed-dose methodology, used in 25% of subjects, did not account for variability in subject size, age, and weight, which was conjectured as the probable explanation for failed demonstration of efficacy in the older cohort.

Kapvay (clonidine extended release) has been approved by the FDA as monotherapy for ADHD, as well as adjunctive therapy, with a stimulant. Its safety and efficacy were demonstrated via at least 2 randomized, controlled trials, with a subject pool of 236, aged 6-17 years. Two fixed doses, 0.2 mg and 0.4 mg, were found to be significantly impactful on ADHD symptoms, with roughly comparable tolerability and efficacy, and an effect size of 0.7.[45]

Atomoxetine. Atomoxetine's safety and efficacy are well established via over 20 randomized controlled trials involving several hundred subjects aged 6-17

years.[52] It has been studied as an adjunctive treatment, in combination with stimulants, and is recommended for patients who either cannot tolerate a full therapeutic dose of stimulants, or as monotherapy for children in whom stimulants might be contraindicated. A once-daily dosing regimen performed equivalently to a twice-daily dosing regimen, and the effect size ranged between.5-.7. The most common adverse effect is sedation, so preferred time of administration is before bed.

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