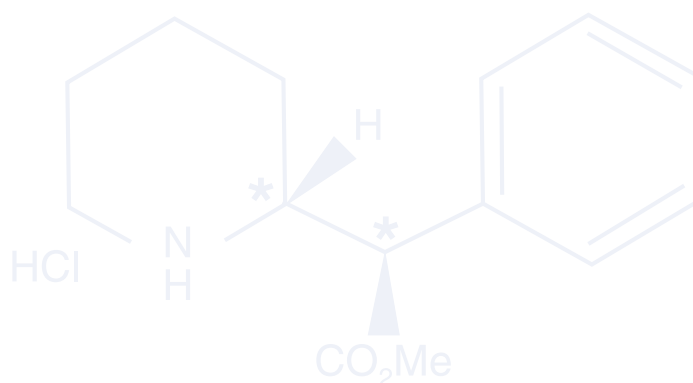
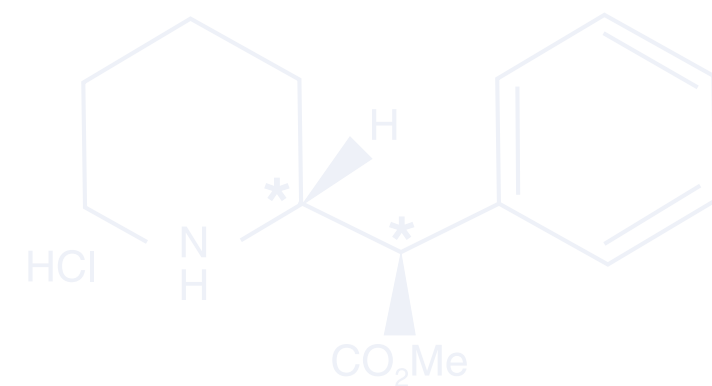


FOCALIN™ PRODUCT MONOGRAPH



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INTRODUCTION

Dexmethylphenidate hydrochloride (Focalin™), a twice-daily central nervous system stimulant, is a chemically refined form of *dl-threo*-methylphenidate hydrochloride (Ritalin®) indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

The efficacy of Focalin in the treatment of ADHD was established in 2 controlled trials of patients aged 6 to 17 years who met ADHD criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.¹

Background of Focalin

Focalin is the single-isomer form of *dl-threo*-methylphenidate hydrochloride, or Ritalin, which is manufactured by Novartis Pharmaceuticals Corporation (East Hanover, New Jersey). Ritalin has been available in the United States since 1955 and has been indicated for the treatment of ADHD since 1961.² Taken 2-3 times daily or in multiple doses, Ritalin has demonstrated efficacy in the management and treatment of ADHD, and its safety in ADHD populations is well established.³

Methylphenidate is the most studied and currently is the most prescribed medication for the management of ADHD.⁴ For many, Ritalin is considered the drug of choice.⁵

The Need for a Refined Drug

Ritalin is an asymmetric molecule made up of isomers that are mirror images of each other.² Stereoisomers have essentially identical physical and chemical properties, yet often different pharmacokinetic properties (absorption, distribution, biotransformation, and excretion). In 1992, the Federal Food and Drug Administration (FDA) highly encouraged the development of single-isomer drugs.⁶

Single-Isomer Drugs. The resulting transition to single isomers from racemic drugs clearly illustrates how drugs that are good enough to gain drug approval can still be further improved. In some cases, the effects of an isomer can be even more pronounced than those of its racemate. For example, esomeprazole magnesium for gastroesophageal reflux disease and the antibacterial, levofloxacin, are single-isomer products.

In the case of Ritalin, the isomers do not have equal activity. The *l* isomer is rapidly metabolized and degraded following oral administration and has little, if any, pharmacologic activity, whereas the *d* isomer is primarily responsible for the pharmacologic activity of Ritalin and other standard methylphenidate formulations.⁷

Benefits of Focalin

Focalin is a commercially available preparation that contains only the *d* isomer of methylphenidate—consistent with the FDA’s call to action. Because this chemically refined form of Ritalin only contains the active isomer, it provides efficacy at half the dose of the racemic drug, methylphenidate (Table 1). Like other short-acting methylphenidate preparations, Focalin has a rapid onset of effect.² It is recommended that individual daily doses be administered at least 4 hours apart. Favorable efficacy, safety, and tolerability profiles have been demonstrated in well-controlled trials of Focalin (see Focalin Prescribing Information, Efficacy and Safety).

Table 1. Recommended Conversion Doses

Methylphenidate Dose	Focalin
5 mg	2.5 mg
10 mg	5 mg
20 mg	10 mg

The Importance of Comprehensive Treatment

Focalin is indicated as an integral part of a total treatment program for ADHD in children 6 years of age and older and may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for everyone with ADHD.¹

OVERVIEW OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Etiology

The causes of ADHD are unknown. After years of research and experience, knowledge about its causes remains largely speculative. Most children with the disorder do not show evidence of gross structural damage in the central nervous system. Possible contributory factors include prenatal toxic exposures, prematurity, and prenatal mechanical insult to the fetal nervous system. There is also some evidence for a genetic basis for ADHD. For example, siblings of hyperactive children have about twice the risk of having the disorder compared with the general population. Also, biological parents of children with the disorder have a higher risk for ADHD than do adoptive parents.³

Symptoms

ADHD is characterized by developmentally inappropriate symptoms of inattention, distractibility, hyperactivity, emotional lability, and impulsivity (Table 2).⁴

Table 2. Characteristic ADHD Symptoms⁸

Inattention	Hyperactivity	Impulsivity
Messy work	Fidgetiness or squirming	Impatience
Careless mistakes	Excessive running	Interrupting
Lack of follow-through	Excessive talking	Intrusiveness
Poor listening	Hand tapping	Grabbing objects
Easily distracted	Excessive foot/leg shaking	Clowning around
Forgetful	Restlessness	Accidents

Diagnosis

ADHD is the most commonly diagnosed behavioral disorder of childhood.⁴ The diagnosis of this disorder remains dependent on the reports of observed behaviors from those most closely supervising children, such as parents and teachers.

Interestingly, recorded prevalence rates for ADHD vary substantially, in part, owing to changing diagnostic criteria,⁹ different methods of obtaining data, choice of informant (often there are significant discrepancies between parent and teacher ratings),⁹ the existence of other medical conditions with similar symptoms, and the inherent subjectivity of the diagnostic criteria.¹⁰

To minimize these factors, a clinical practice guideline for the diagnosis and evaluation of children with ADHD was recently developed by the American Academy of Pediatrics. Among the guideline recommendations are 1) evaluation by a physician, 2) use of diagnostic criteria from the *DSM-IV*, 3) obtainment of direct evidence of symptoms from parents and classroom teachers, and 4) assessment for coexisting conditions that may make the diagnosis more difficult or complicate treatment planning.⁹

Diagnostic Criteria. The criteria for what constitutes ADHD have broadened, and it is now clear that ADHD may persist into adolescence and adulthood. As a result, more children—especially girls—adolescents, and adults are being diagnosed and treated, and children are often treated for longer periods of time.¹¹ While the increase in the number of diagnosed children and the concurrent increase in the use of stimulants are cause for concern, experts have concluded that misdiagnosis, overdiagnosis, and overprescription of stimulants for ADHD are not widespread. One report has estimated, based on prescribing rates, that of the 4 million children in the United States with ADHD, only 650,000 (or 1 in 6) are being actively treated, and many of these children may be inadequately or inconsistently treated. A smaller sampling of communities found that only 1 in 8 children with ADHD, within a

given year, was actually being treated with ADHD medications. Thus, contrary to public opinion, the data suggest that the majority of children with ADHD are not recognized, evaluated, or adequately treated. This low rate of treatment may, in part, be due to lingering stigma and parental concerns about the use of psychostimulants.¹²

The *DSM-IV* criteria, which reflect the current consensus among clinicians, are based on clinical experience and have more support in the literature than other available diagnostic criteria. When applied appropriately, use of these specific criteria will help ensure an accurate diagnosis and decrease the variation in how the diagnosis is made.⁹

To meet the *DSM-IV* diagnostic criteria for ADHD, the disorder must demonstrate the following:

- Presence for at least 6 months;
- Significant impairment in social, academic, or occupational functioning;
- Evidence in at least 2 settings (eg, home, school, or work);
- Occurrence before the age of 7 years.⁸

There are 3 subtypes of ADHD: 1) predominantly inattentive type; 2) predominantly hyperactive type; and 3) combined type (Table 3).

Table 3. Subtypes of ADHD

Inattentive Type At least 6 of the following symptoms must have persisted for at least 6 months.	
Lack of attention to details/careless mistakes	Avoidance of tasks requiring sustained mental effort
Lack of sustained attention	Frequent loss of things
Poor listening	Easily distractible
Failure to follow through on tasks	Forgetful
Poor organization	
Hyperactive Type At least 6 of the following symptoms must have persisted for at least 6 months.	
Fidgeting/squirming; inappropriately leaving seat	Excessive talking
Inappropriately running/climbing	Blurting answers
Difficulty with quiet activities	Unable to wait turn
Excessively “on the go”	Intrusive
Combined Type Requires both inattentive and hyperactive criteria be met.	

Incidence and Prevalence

ADHD affects approximately 4%-12% of school-aged children in the United States,⁹ appears 3-5 times more often in boys than in girls, and is most common in first-born boys.³ Reports on the incidence of ADHD in the United States have varied from 2%-20% of grade school-aged children,³ prompting public concern that the disorder is overdiagnosed or misdiagnosed. Prevalence rates also vary greatly between different geographic regions and across countries.⁹ Reports on the prevalence of treatment for ADHD vary by study and by region. One study found that 88% of physician-diagnosed children with ADHD were prescribed methylphenidate, and a survey of Baltimore schools found that 6% of school-aged children received methylphenidate treatment. A Tennessee study, however, found that only 15%-40% of the children diagnosed with ADHD by researchers had been so diagnosed with ADHD by clinicians, and only 21%-32% were receiving drug therapy.¹¹

Treatment Options

It has been determined that the response rate for any single stimulant drug in ADHD is approximately 70%, and that up to 90% of children will respond to at least 1 stimulant without major adverse events if drug titration is done carefully.¹¹ Thus, it appears that this common childhood disorder may be successfully managed in most cases if appropriate stimulant medication is available.

Several studies have demonstrated that children who receive adequate treatment for ADHD have fewer problems with school, peers, and substance abuse and show improved over-all function compared with those who do not receive treatment.¹³ A wide variety of treatments have been used to treat ADHD. These include psychotropic medications, psychosocial treatment, dietary management, herbal and homeopathic treatments, biofeedback, meditation, and perceptual stimulation/training. Of these, stimulant medications and psychosocial interventions have been most studied.⁴

Psychosocial Treatments. Behavioral strategies such as contingency management (eg, point/token reward systems, timeout, response cost), parent training (parent is taught child management skills), and clinical behavior therapy (parent, teacher, or both are taught to use contingency management procedures) have been demonstrated to produce beneficial effects in short-term studies. Cognitive-behavioral treatment (eg, self-monitoring, verbal self-instruction, self-reinforcement), in contrast, has not been found to be beneficial.⁴

Medication Management. Numerous short-term trials have clearly demonstrated that stimulants are superior to placebo in the reduction of hyperactivity.¹⁴ Methylphenidate is the most studied and most often used of the stimulants.⁴

Given public concerns regarding the use of stimulants in children, wide variances in treatment practices, and the paucity of long-term studies, a 14-month clinical trial of 579 children with ADHD was performed to determine how long-term medication treatment compares with behavioral treatment and if combination treatment (medical and behavioral) has additional benefits.¹⁵

All groups (medical treatment, behavioral treatment, and combined) showed reductions in ADHD symptoms over time. Primarily, the study found that medication management was superior to behavioral treatment for treating core ADHD symptoms. This was assessed by parents' and teachers' ratings of inattention and teachers' ratings of hyperactivity-impulsivity. Perhaps, surprisingly, combined treatment did not yield significantly greater benefits than medication alone for core ADHD symptoms, although modest advantages for non-ADHD symptom and positive function outcomes were noted. As expected, combined treatment was superior to behavioral treatment alone for the reduction of numerous ADHD symptoms (Table 4).¹⁵

Table 4. Comparison of Medical Management (MM), Behavioral Management (BM), and Combined Management (CM) for the Treatment of ADHD Symptoms

Measure and Rater	MM vs BM	P	CM vs BM	P
Inattention				
Teacher	MM > BM	.001	CM > BM	.005
Parent	MM > BM	.001	CM > BM	.001
Hyperactive/Impulsive				
Teacher	MM ≈ BM	.004*	CM ≈ BM	.04*
Parent	MM > BM	.001	CM > BM	.001
*P values not significant after Bonferroni correction. Adapted from MTA Cooperative Group. ¹⁵				

Misuse of Stimulants

It is estimated that stimulants are used between 10 and 30 times more frequently in the United States than in the United Kingdom.¹⁴ Given the widespread use of stimulants for the treatment of ADHD, concern has arisen over the potential for abuse in schools. A recent government study reported that actual incidents of stimulant abuse are rare. For the first 7-9 months of the 2000-2001 school year, approximately 8% of public middle and high school principals reported that attention disorder drugs had been diverted or abused at their schools. In most of these cases, principals reported knowledge of only 1 incident. This low prevalence of abuse, in part, may be due to careful practices in schools. Thirty-seven states and the District of Columbia have statutes, regulations, or mandatory policies addressing the administration of medication to students. Such state provisions require schools to