*Serious, lifetime disorder*

*Unique needs*

*Unique safety benefits*

*Core symptom efficacy*

# ADHD realities

Lilly

# ADHD is a serious, lifetime disorder

*Persistent, heritable, continuous*

## *Persistent*

- 60% of children with ADHD carry its symptoms into adulthood[1]

## *Heritable*

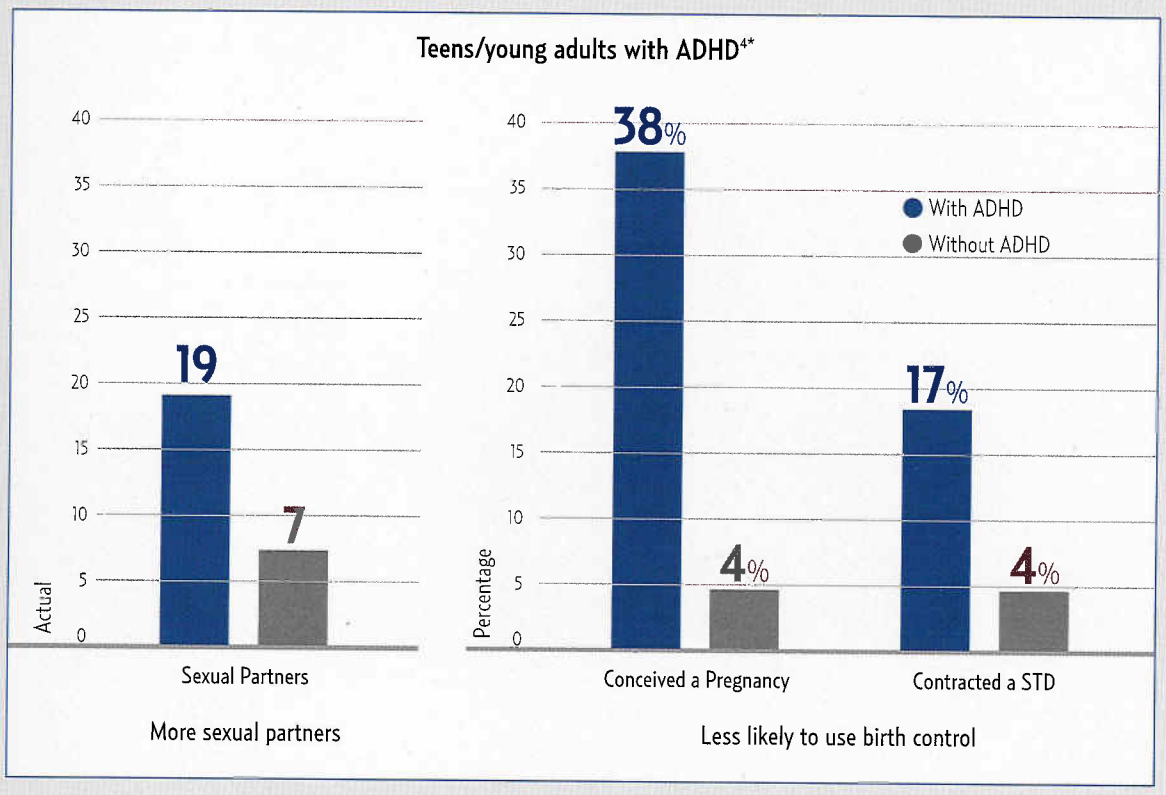
- Approximately 35% of parents of children with ADHD have adult ADHD themselves[2]

## *Continuous*

- Symptoms of ADHD can cause impairments at any time of the day or evening
- ADHD is a continuous disorder that can benefit from uninterrupted treatment

## *Important to treat*

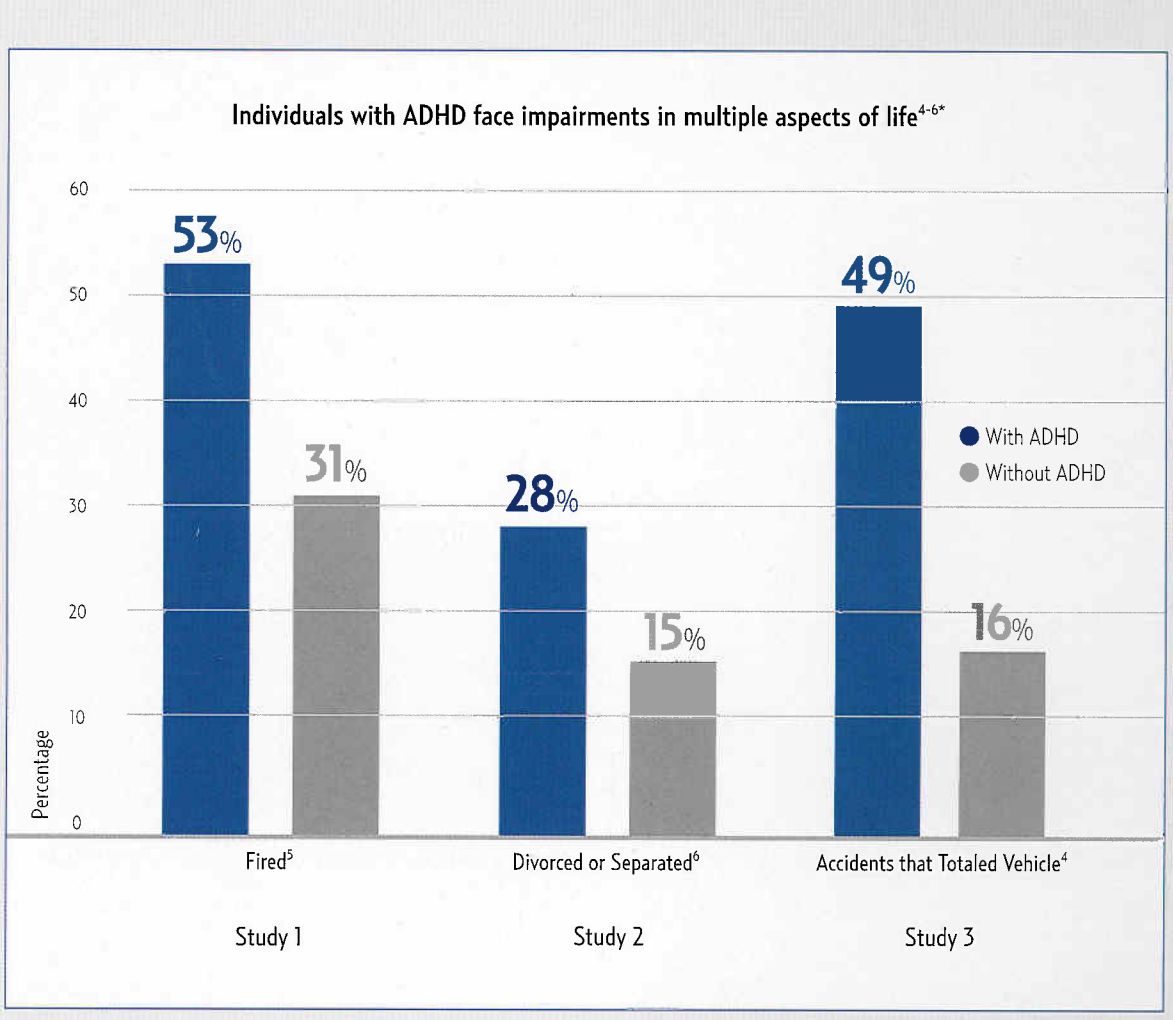
- Untreated children may be inattentive and hyperactive—facing academic, social, and family problems[3]
- Untreated teens and adults may be unfocused/restless and act impulsively at work, in relationships, and while driving[3]




* Data is from a 13-year follow-up study, taken at the "young adult" stage when subjects ranged in age from 19 to 25 years (with a mean age of 21 years).

# ADHD is a serious, lifetime disorder

*Important to treat*




* These data were not derived from a Lilly clinical study.

# ADHD impairments can be costly

## Symptoms may lead to negative health outcomes

- Distractibility may lead to car accidents and injuries[4]
- Impulsive sexual behavior may lead to teen pregnancy, STDs[4]

## ADHD increases health service usage

- Children and adolescents with ADHD were more likely to have had[7†]:
  - An inpatient hospitalization (26% vs 18%, $P<.001$)
  - An outpatient hospitalization (41% vs 33%, $P=.006$)
  - An emergency department visit (81% vs 74%, $P=.005$)

## Median costs for all medical care more than double[7‡¶]

- $4,306 annually for an individual with ADHD
- $1,944 annually for an individual without ADHD

† As compared to a control group without ADHD.

‡ A 9-year retrospective study of more than 4,000 children and adolescents with ADHD.

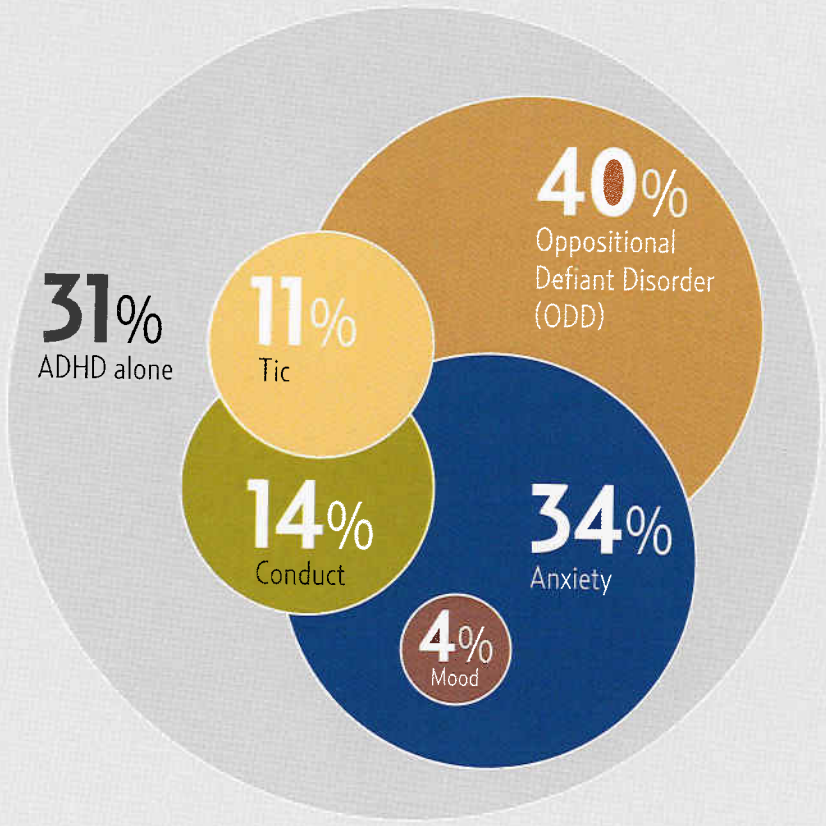
¶ Excludes drug costs.

Serious, lifetime disorder

# ADHD patients have unique needs

## *Coexisting disorders are common*

### Children and adolescents[8]




### MTA Study[8]

The Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA Study) conducted by the National Institute of Mental Health was a 14-month, multi-site, randomized clinical trial designed to address questions about children with ADHD.[8]

### *Drug abuse or dependence*

- 75% of adolescents with ADHD have a substance abuse disorder[9*]

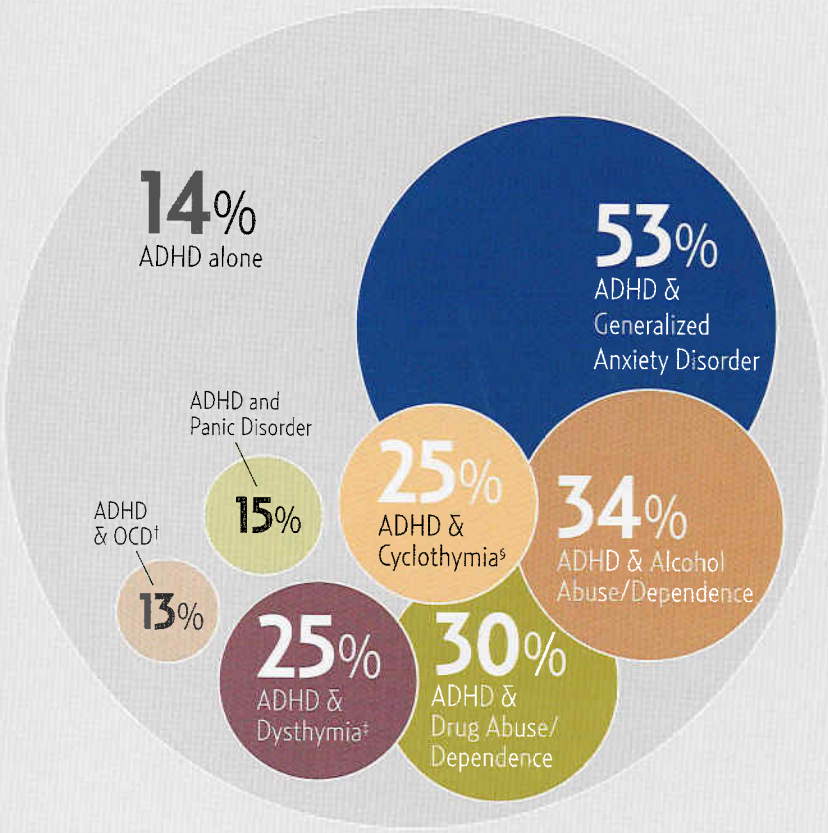
### Biederman Study[9]

Joseph Biederman and other noted ADHD experts studied the cumulative incidence of substance use disorders throughout adolescence in patients with ADHD compared to non-ADHD control subjects. The analysis included both baseline assessments and a 4-year follow-up assessment conducted by trained personnel using DSM-III-R criteria for substance dependence disorder.

*The American Academy of Pediatrics' clinical practice guidelines indicate that assessment for coexisting conditions should be an integral part of an evaluation for ADHD and may impact treatment planning.*[10]

* 75% for non-medicated ADHD patients and 25% for medicated ADHD patients, 18% for patients without ADHD.

## Adults[1]




### Shekim Study[1]

The purpose of this study was to report on the demographic and clinical profile of 56 adults who presented with Adult ADHD and met DSM-III-R criteria for the disorder.

† OCD is Obsessive-Compulsive Disorder.

‡ Dysthymia is chronically depressed mood.

§ Cyclothymia is chronic, fluctuating mood disturbance involving numerous periods of hypomanic symptoms and numerous periods of depressive symptoms.

# ADHD patients have unique needs

*Treatment challenges may exist for some patients with ADHD and coexisting disorders*

## Anxiety

*"The bulk of [stimulant] data would suggest that ADHD individuals with anxiety manifest a poorer response[12-16] and more side effects[14,17] than their ADHD peers without anxiety."*

– Wilens and Spencer[18]

### Excerpts from FDA labeling for various ADHD medications*

Adderall XR®/Dexedrine®: "Contraindication: Agitated states" for Adderall XR and Dexedrine.[19,20]

Concerta®: "Agitation: Concerta is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms."[21]

Focalin™ XR: "Agitation: Focalin XR extended-release capsules is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms."[22]

Metadate CD®: "Metadate CD is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms."[23]

Ritalin®:" Marked anxiety, tension, and agitation are contraindications to Ritalin."[24]

* Products are registered trademarks of their respective companies.

## Drug Abuse

### Excerpts from FDA labeling for various ADHD medications*

Adderall XR: "Contraindication: Patients with a history of drug abuse" for Adderall XR.[19]

Dexedrine: "Contraindication: Patients with a history of drug abuse" for Dexedrine.[20]

## Tics

### Excerpts from FDA labeling for various ADHD medications*

Concerta: "Concerta is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome."[21]

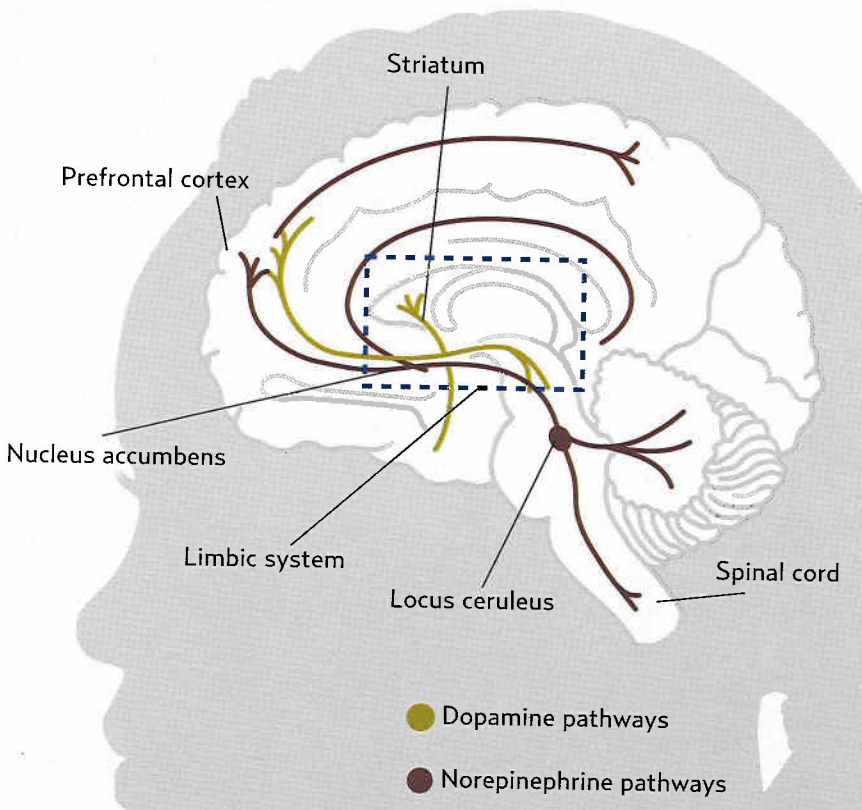
Focalin XR: "Focalin XR is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome."[22]

Metadate CD: "Metadate CD is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome."[23]

Ritalin: "Ritalin is contraindicated ... in patients with motor tics or with a family history or diagnosis of Tourette's syndrome."[24]

# ADHD patients have unique needs

*Unique patient needs warrant tailored treatment mechanisms*




***Dopamine modulates*[25-33]:**

- Motor activity
- Stress and fear
- Reward and reinforcement
- Executive function

***Norepinephrine modulates*[25-29,32,33]:**

- Cognition
- Selective attention
- Arousal/adaptation
- Executive function

*A formulary needs a range of ADHD medications with different mechanisms to address individual ADHD needs and maximize patient outcomes.*

# Strattera offers unique safety benefits

*Based on preclinical data*:*

*Strattera is a targeted noradrenergic agent for ADHD*[34]

*Strattera selectively modulates norepinephrine*[34]

*Strattera does not increase dopamine in the striatum and nucleus accumbens*[34]

---

*Clinical data has shown that Strattera improves ADHD without causing unwanted problems such as substance abuse, tics, and anxiety, which are believed to be related to these areas of the brain.*

Strattera is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 and older, adolescents, and adults.

*The precise mechanism by which atomoxetine produces its therapeutic effect in ADHD is not known.*

* ***Effects of atomoxetine in rat brain neurotransmission***
In rat studies, the extracellular concentrations of norepinephrine in the prefrontal cortex (PFC) were increased by atomoxetine. Atomoxetine increased dopamine to about the same magnitude in the PFC. However, atomoxetine did not increase dopamine (DA) in the DA & DA transporter rich subcortical areas (nucleus accumbens and striatum).

**Important Safety Information**

- Strattera increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD).
- Patients started on therapy should be monitored closely for suicidal thinking and behavior.

- Is not contraindicated in patients with anxiety
- Lacks potential for abuse
- Is not contraindicated in patients with substance abuse history
- Study data show no pattern for drug diversion
- Is not contraindicated in patients with tics or Tourette's disorder



See Important Safety Information and boxed warning on page 25 and full Prescribing Information for Strattera provided by your Lilly Account Executive.

# Strattera offers unique safety benefits

*Not contraindicated in patients with anxiety*




Trial in child and adolescent patients, 8-17 years of age, with ADHD and an anxiety disorder†

Strattera is not indicated to treat anxiety disorders.

* PARS is Pediatric Anxiety Rating Scale.

† Please see #1, page 39, for study explanation.

‡ Excludes patients with 25% reduction of anxiety symptoms during 2-week placebo lead-in as *a priori* in the study protocol.

§ Baseline scores: Strattera 17.5, placebo 17.0.

¶ Included all randomized patients.

\# Baseline scores: Strattera 51.8, placebo 48.3.

†† Categorical change based on worsening of 1 point or more on the PARS Total from baseline to endpoint.

## Adverse events

**Adverse events[35ff‡‡] for Strattera patients incidence ≥5%**

| | Strattera (n=77) | Placebo (n=80) | *P*-value |
|---|---|---|---|
| Decreased appetite | 11 (14.3%) | 3 (3.8%) | .025 |
| Headache | 11 (14.3%) | 7 (8.8%) | NS |
| Abdominal pain upper | 9 (11.7%) | 4 (5.0%) | NS |
| Vomiting | 8 (10.4%) | 4 (5.0%) | NS |
| Irritability | 5 (6.5%) | 3 (3.8%) | NS |
| Nasopharyngitis | 5 (6.5%) | 5 (6.3%) | NS |
| Nausea | 5 (6.5%) | 2 (2.5%) | NS |
| Cough | 4 (5.2%) | 5 (6.3%) | NS |
| Influenza | 4 (5.2%) | 1 (1.3%) | NS |
| Sinusitis | 4 (5.2%) | 3 (3.8%) | NS |

Trial in child and adolescent patients, 8-17 years of age, with ADHD and an anxiety disorder.[§§]

Treatment-emergent adverse events indicated no worsening of anxiety in either treatment group.

‡‡ Adverse events reported for all patients who took at least 1 dose of study drug.

§§ Please see #1, page 39, for study explanation.

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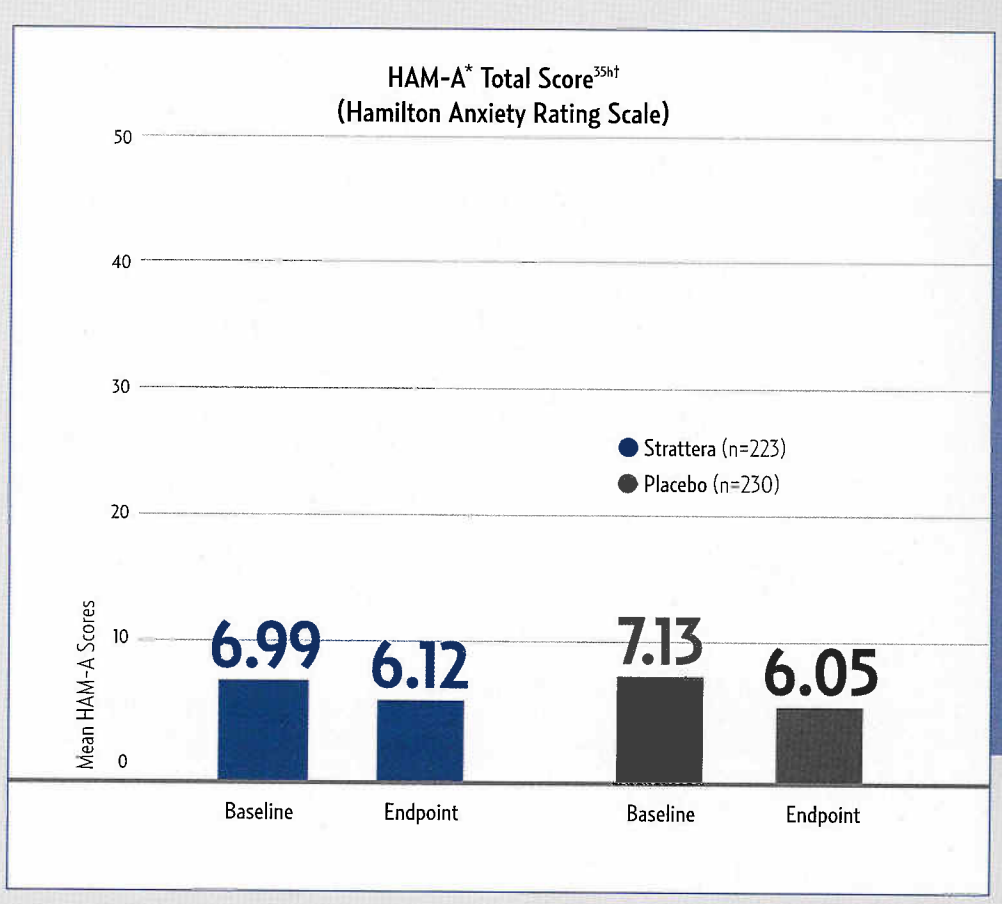
# Strattera offers unique safety benefits

*Not contraindicated in patients with anxiety*




Trials in adult patients with ADHD†

Patients who met DSM-IV diagnostic criteria for a current anxiety disorder (including generalized anxiety disorder, panic disorder, social phobia) were excluded from the study.

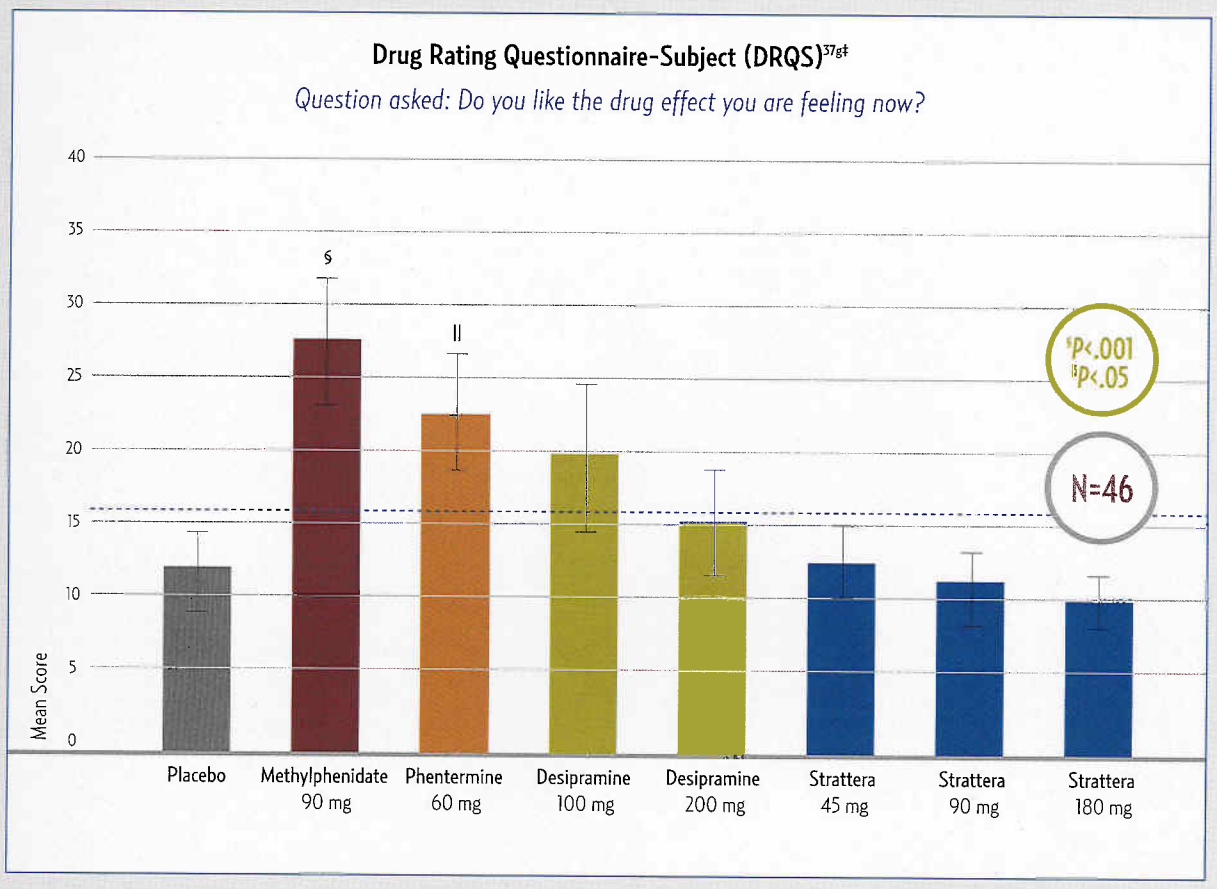
Baseline severity scores (HAM-A) were very low, indicating that patients at study entry did not have marked anxiety.

Strattera is not indicated to treat anxiety disorders.

* The Hamilton Anxiety Rating Scale assesses severity of anxiety. Total scores range from 0 to 56, with higher scores representing greater symptom severity. Some items measured by the HAM-A include: anxiety, tension, fears, and insomnia.

† Please see #3 and #4, page 39, for study explanation.

## *Lacks potential for abuse*




Note: The scale was administered to stimulant-preferring drug abusers (aged 21-55), including cocaine and/or amphetamines (within the past 30 days), and measures the reinforcing potential of a medication that correlates with abuse potential.

‡ Please see #2, page 39, for study explanation.

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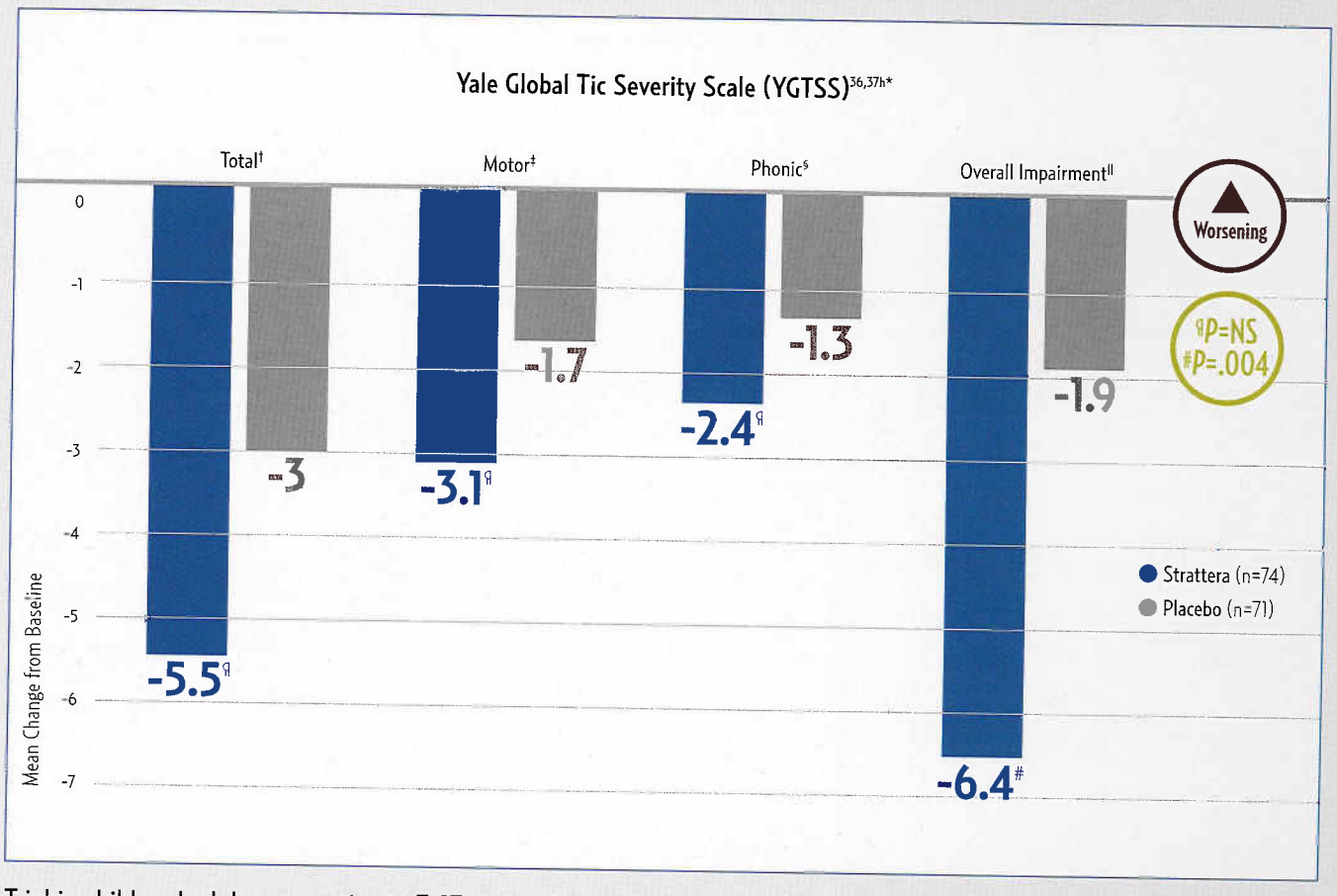
# Strattera offers unique safety benefits

*Not contraindicated in patients with tics or Tourette's disorder*




Trial in child and adolescent patients, 7-17 years of age, with ADHD and tics or Tourette's disorder

Strattera is not indicated to treat tics or Tourette's disorder.

* Please see #5, page 39, for study explanation.

† Baseline scores: Strattera 21.7, placebo 22.2.

‡ Baseline scores: Strattera 13.2, placebo 12.8.

§ Baseline scores: Strattera 8.5, placebo 9.4.

|| Baseline scores: Strattera 21.6, placebo 19.9.

# Adverse events

**Adverse events[37]** incidence ≥5%**

| | Strattera (n=76) | Placebo (n=72) | *P*-value |
|---|---|---|---|
| Headache | 16 (21.1%) | 14 (19.4%) | NS |
| Vomiting | 12 (15.8%) | 6 (8.3%) | NS |
| Decreased appetite | 12 (15.8%) | 2 (2.8%) | .010 |
| Nausea | 12 (15.8%) | 1 (1.4%) | .002 |
| Fatigue | 9 (11.8%) | 3 (4.2%) | NS |
| Abdominal pain upper | 7 (9.2%) | 9 (12.5%) | NS |
| Nasopharyngitis | 6 (7.9%) | 6 (8.3%) | NS |
| Pyrexia | 6 (7.9%) | 6 (8.3%) | NS |
| Somnolence | 5 (6.6%) | 3 (4.2%) | NS |
| Cough | 4 (5.3%) | 9 (12.5%) | NS |
| Irritability | 4 (5.3%) | 2 (2.8%) | NS |
| Tic | 4 (5.3%) | 2 (2.8%) | NS |
| Pharyngitis | 3 (3.9%) | 9 (12.5%) | NS |
| Diarrhea | 3 (3.9%) | 8 (11.1%) | NS |
| Initial insomnia | 3 (3.9%) | 4 (5.6%) | NS |
| Rhinorrhea | 2 (2.6%) | 4 (5.6%) | NS |

Trial in child and adolescent patients, 7-17 years of age, with ADHD and tics or Tourette's disorder.

** Adverse events reported for all patients who took at least 1 dose of study drug.

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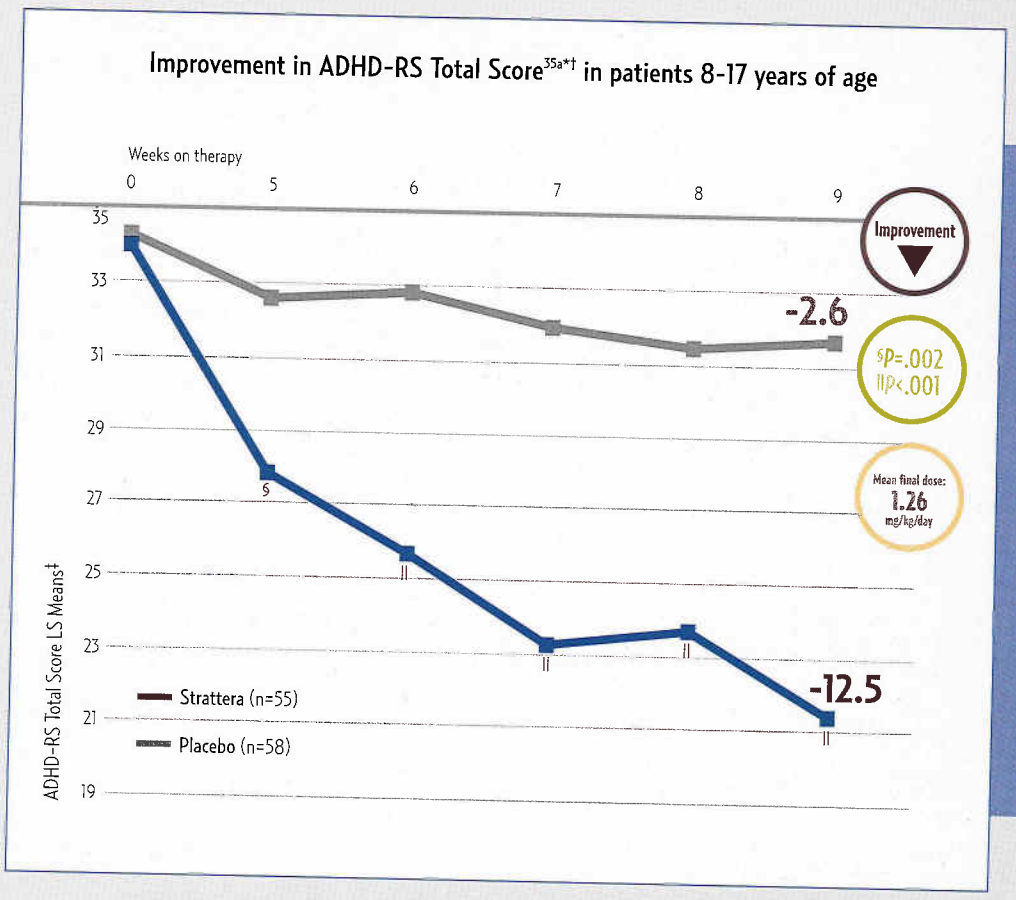
# Strattera provides core symptom efficacy

*Effectively treats ADHD in patients with ADHD and coexisting anxiety*

**Improvement in ADHD-RS Total Score[35a*†] in patients 8-17 years of age**




**Representative ADHD-RS measures[9¶]:**

- Fidgets
- Difficulty sustaining attention
- Does not seem to listen when spoken to directly
- Fails to finish work
- Difficulty organizing tasks and activities
- Avoids tasks that require sustained mental effort
- Easily distracted
- Forgetful

Strattera is not indicated to treat anxiety disorders.

*Percent of Strattera patients with the following anxiety diagnosis[37i]:*

- 69%–Generalized anxiety
- 24%–Social phobia
- 30%–Separation anxiety disorder

Percentages above do not equal 100% due to presence of more than one diagnosis.

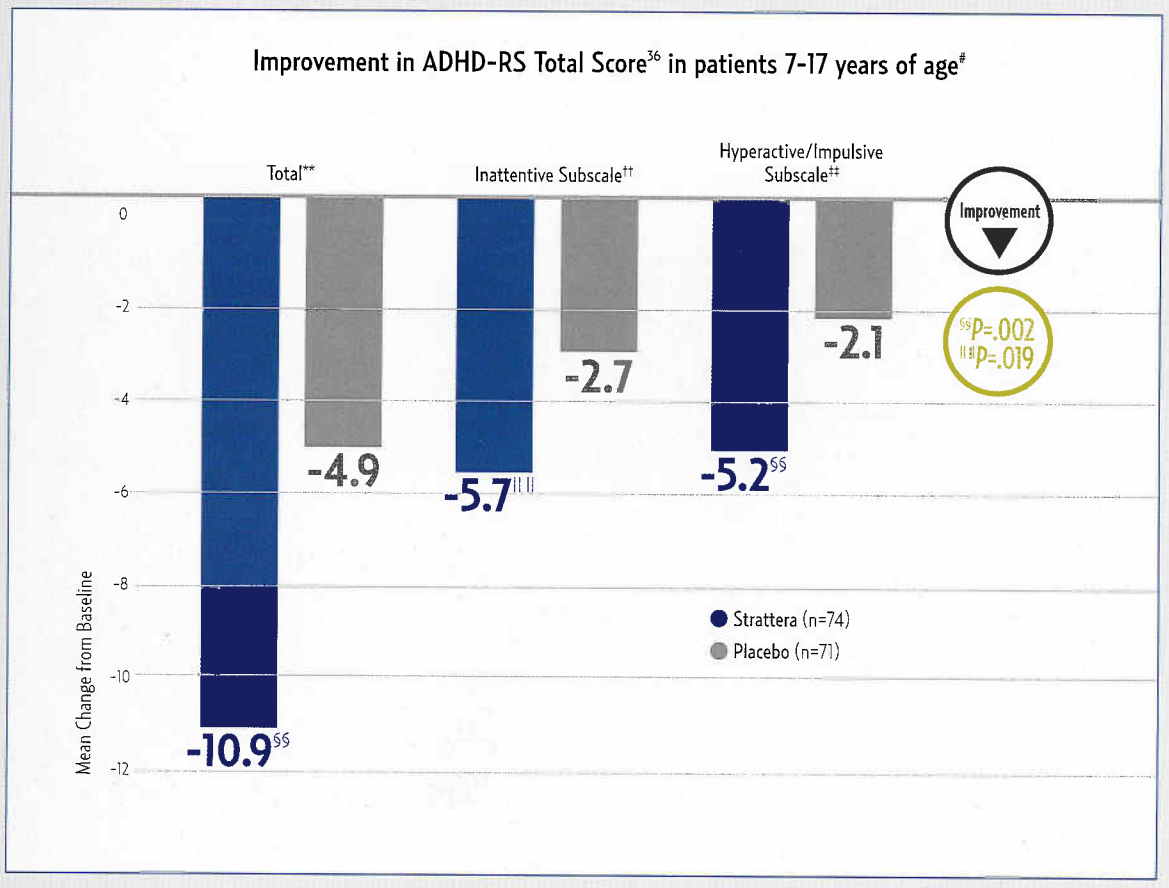
* Please see #1, page 39, for study explanation. Active treatment period: 10 weeks.

† Excludes patients with 25% reduction of anxiety symptoms during 2-week placebo lead-in as *a priori* in the study protocol.

‡ Baseline scores: Strattera 33.9, placebo 34.2.

¶ Adapted from the ADHD Rating Scale-IV.

*Effectively treats ADHD in patients with ADHD and tics or Tourette's disorder*




Strattera is not indicated to treat tics or Tourette's disorder.

*Percent of Strattera patients with the following diagnosis[36]:*

- 80%-Tourette's disorder
- 30%-Chronic motor tics
- 18%- Chronic vocal tics

\# Please see #5, page 39, for study explanation.

** Baseline scores: Strattera 38.9, placebo 35.0.

†† Baseline scores: Strattera 21.6, placebo 20.5.

‡‡ Baseline scores: Strattera 17.2, placebo 14.6.

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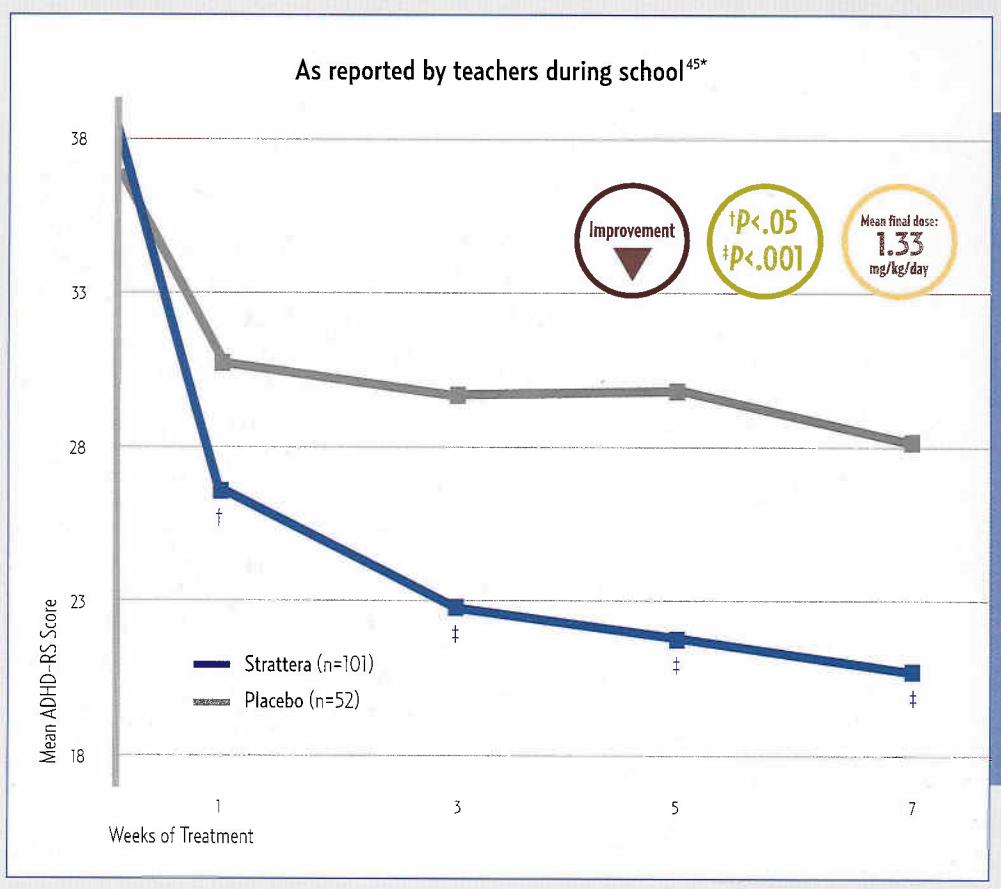
# Strattera provides core symptom efficacy

*Efficacy builds over time for children*




**Representative ADHD-RS measures[5]:**

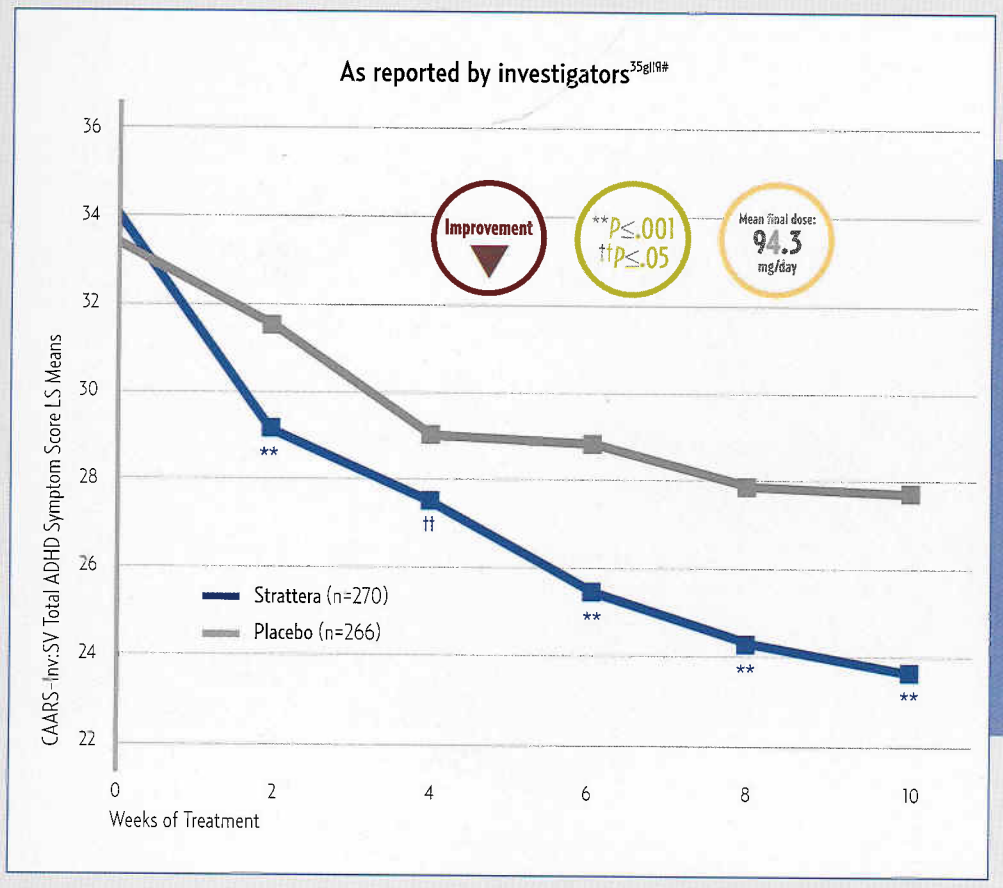
- Fidgets
- Difficulty sustaining attention
- Does not seem to listen when spoken to directly
- Fails to finish work
- Difficulty organizing tasks and activities
- Avoids tasks that require sustained mental effort
- Easily distracted
- Forgetful

* Please see #6, page 39, for study explanation.

§ Adapted from the ADHD Rating Scale-IV.

Patients in this trial were 8-12 years of age.

## *Efficacy builds over time for adults*




**Representative CAARS-Inv measures:**

- Difficulty sustaining attention in activity
- Easily distractible
- Cannot organize
- "Driven by a motor"
- Intrudes/interrupts others
- Squirms/fidgets

|| Results from Studies #3 and #4 combined.

9 Measures are based on Conners' Rating Scale investigator administered and rated. Two randomized, double-blinded, placebo-controlled studies of adult patients aged 18 and older who met DSM-IV criteria for ADHD.

# Please see #3 and #4, page 39, for study explanation.

See Important Safety Information and boxed warning on page 25 and full Prescribing Information for Strattera provided by your Lilly Account Executive.

# Using Strattera

| | Child and teen [up to 70 kg (154 lbs)] | Adult [and children and adolescents over 70 kg (154 lbs)] |
|---|---|---|
| Initiation dose<br>Use 7-day sample pack | 0.5 mg/kg/day | 40 mg/day |
| Increase to target dose | 1.2 mg/kg/day | 80 mg/day |
| Maximum dose | 1.4 mg/kg/day or 100 mg, whichever is less | 100 mg/day |

- Once- or twice-daily dosing
- Can be taken with or without food
- Dosage adjustment is recommended for patients on concomitant strong CYP2D6 inhibitors and/or those with hepatic impairment. Please see full Prescribing Information for specific adjustment recommendations
- Strattera is an ocular irritant. Strattera capsules are not intended to be opened.

**Child**
- Parents may notice benefits in the first week
- Full efficacy may take up to 4-6 weeks
- GI upset and somnolence are commonly transient upon starting treatment
  - To possibly minimize stomach upset, Strattera can be taken with food
  - To possibly minimize tiredness, you can adjust the time of day Strattera is taken

**Adult**
- Benefits may be noticed in the first 2 weeks
- Full efficacy may take up to 4-6 weeks
- GI upset and insomnia are commonly transient upon starting treatment
  - To possibly minimize stomach upset, Strattera can be taken with food
  - To possibly minimize sleep problems, you can adjust the time of day Strattera is taken

See Important Safety Information and boxed warning on page 25 and full Prescribing Information for Strattera provided by your Lilly Account Executive.

# *Important Safety Information on Strattera for children aged 6 and older, adolescents, and adults*

**Suicidal Ideation in Children and Adolescents**

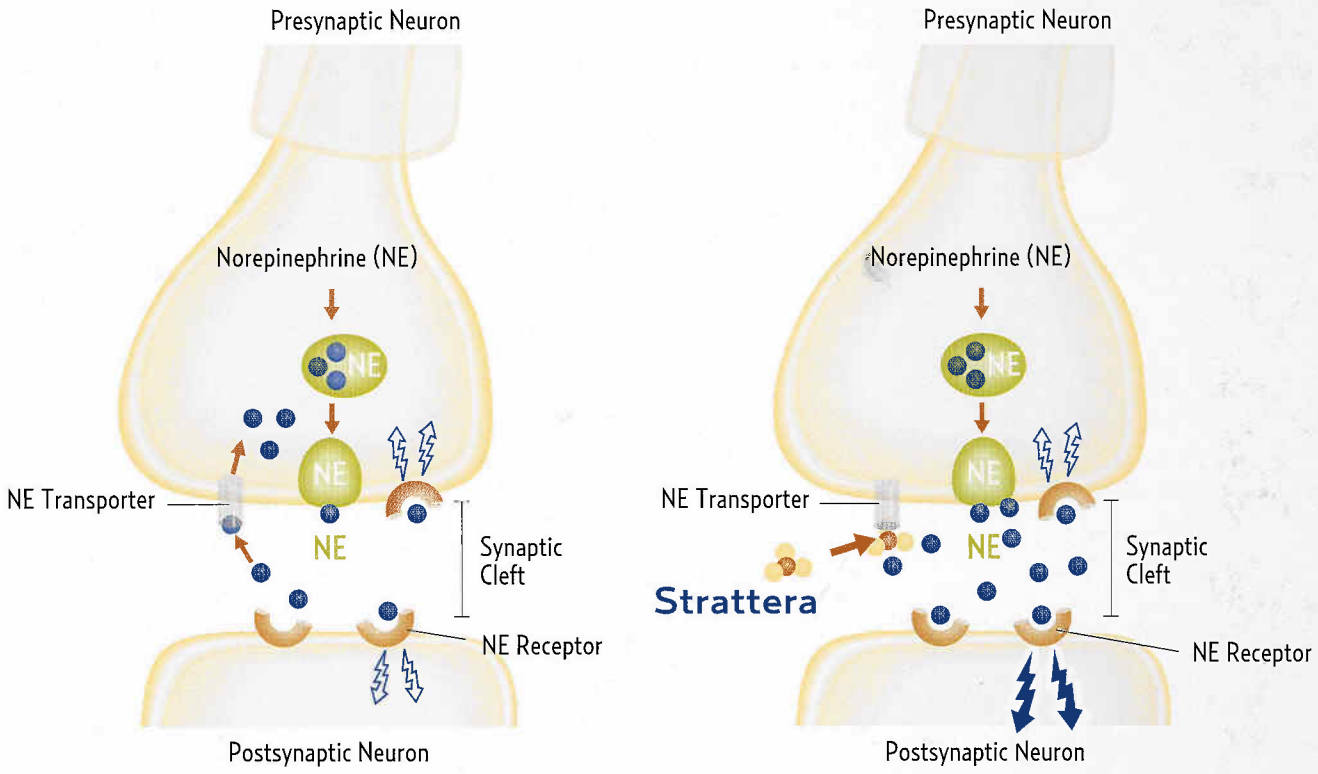
**Strattera (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of Strattera in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Strattera is approved for ADHD in pediatric and adult patients. Strattera is not approved for major depressive disorder.**

**Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving Strattera compared to placebo. The average risk of suicidal ideation in patients receiving Strattera was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.**

- Strattera should not be taken within 2 weeks of taking an MAOI and is contraindicated in patients with narrow-angle glaucoma.
- **All pediatric patients being treated with Strattera should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients who are experiencing emergent suicidality or symptoms that might be precursors to emerging suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patient's presenting symptoms.
- A similar analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of Strattera.
- **Postmarketing reports indicate that Strattera can cause severe liver injury in rare cases; although no evidence of liver injury was detected in clinical trials of about 6000 patients. Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (eg, pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms).**
- Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported with Strattera.
- Strattera should be used with caution in patients with hypertension, hypotension, tachycardia, or cardiovascular or cerebrovascular disease. A complaint of urinary retention or urinary hesitancy should be considered potentially related to Strattera.
- As with all ADHD medications, growth should be monitored during treatment, although height and weight data measured up to 3 years indicates minimal, if any, long-term effects.
- In children and adolescents, the most common adverse events reported in clinical trials were decreased appetite, nausea, vomiting, fatigue, dyspepsia, dizziness, and mood swings.* In adults, the most common adverse events reported in clinical trials were dry mouth, insomnia, nausea, appetite decrease, constipation, erectile disturbance, dysmenorrhea, dizziness, and libido decreased.*
- Anyone considering the use of Strattera in a child or adolescent must balance the potential risks with the clinical need. Safety and effectiveness have not been established in pediatric patients less than 6 years of age or in geriatric patients.

* In clinical trials, adverse events reported in at least 5% of patients and twice the rate of placebo.

# Mechanism of action




The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown.

*Strattera is a Norepinephrine Reuptake Inhibitor (NRI) that works by:*

1. Selectively blocking the norepinephrine (NE) reuptake transporter located on the presynaptic neuron
2. Increasing the concentration of the NE in the synaptic cleft
3. Enhancing the forward transmission of NE

# Drug classification

## Drug Categorization[38-40]

- Independent, third-party organizations classify Strattera differently than stimulants

### American Hospital Formulary Service (AHFS) Drug Information 2005

| *Drug* | *Category* |
|---|---|
| Atomoxetine (Strattera) | Miscellaneous Central Nervous System Agents |
| Amphetamines | Anorexigenic Agents and Respiratory and Cerebral Stimulants |
| Methylphenidate | Anorexigenic Agents and Respiratory and Cerebral Stimulants |

### US Pharmacopeia (USP) Drug Information 2005

| *Drug* | *Category* |
|---|---|
| Atomoxetine (Strattera) | ADHD Therapy Agent |
| Amphetamines | Central Nervous System Stimulant |
| Methylphenidate | Central Nervous System Stimulant |

## Drug Classification[41]

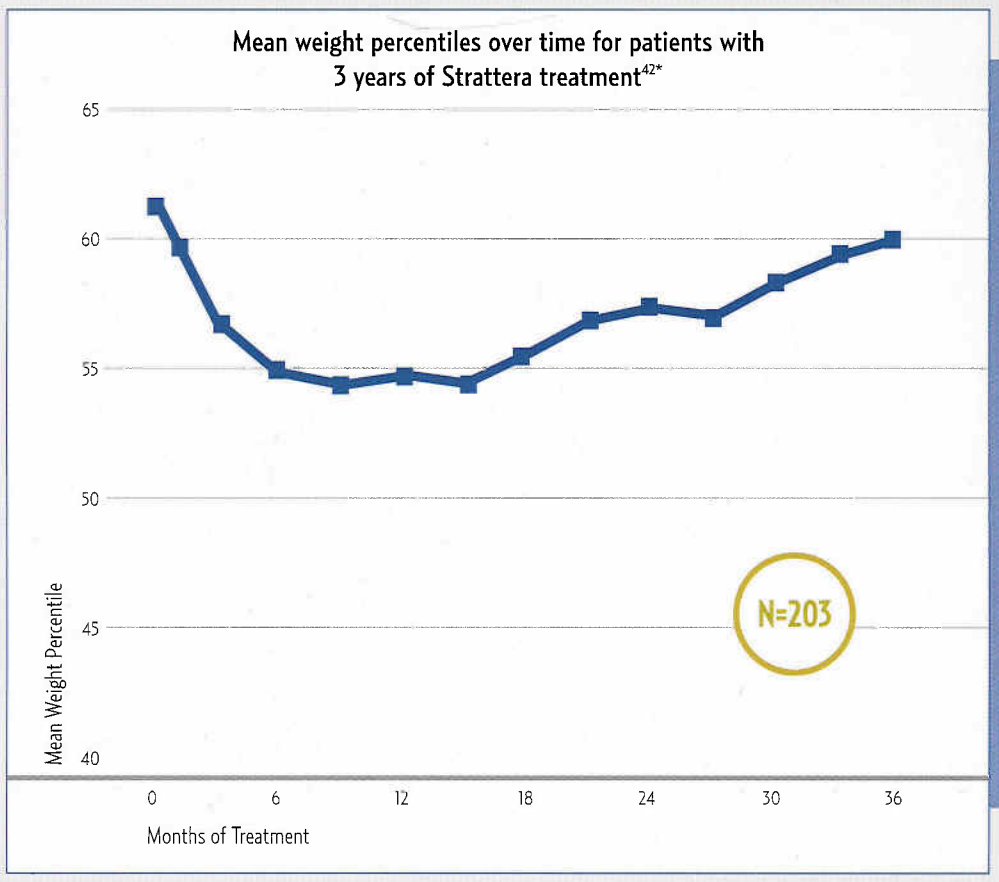
- Strattera is a non-stimulant and is not classified as a controlled substance

### US Drug Enforcement Agency (DEA) Classification

| *Drug* | *Class* |
|---|---|
| Atomoxetine (Strattera) | Not Scheduled, Non-controlled |
| Amphetamines | Schedule II controlled substance |
| Methylphenidate | Schedule II controlled substance |

See Important Safety Information and boxed warning on page 25 and full Prescribing Information for Strattera provided by your Lilly Account Executive.

# Effect of Strattera on a child's weight over time

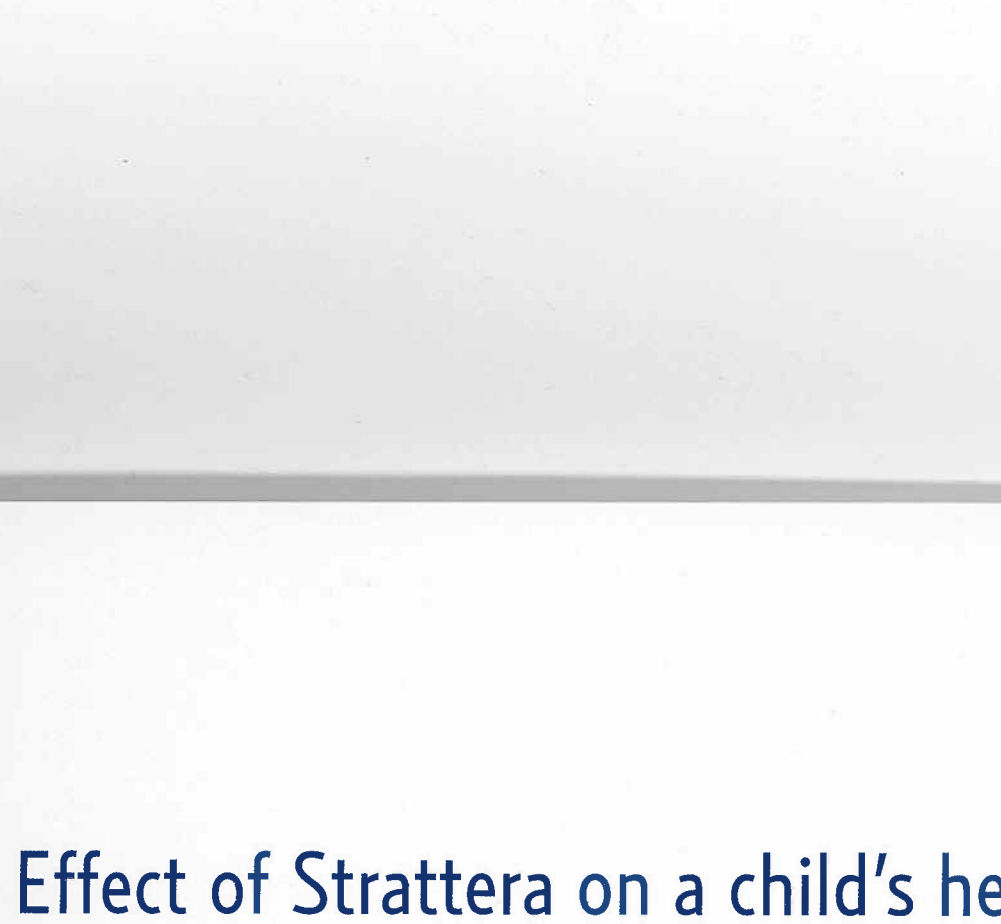



Growth should be monitored during treatment with Strattera. Data on the long-term effects of Strattera on growth come from open-label studies, and weight and height changes are compared to normative population data for about the first 9-12 months of treatment. Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with Strattera have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data. After about 12 months, gain in height stabilizes, and at 3 years, patients treated with Strattera have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data.

Population: Patients with at least 3 years of Strattera treatment (integrated pediatric database).

* Please see #7, #8, and #9, page 39, for study explanations.

# Effect of Strattera on a child's height over time




Population: Patients with at least 3 years of Strattera treatment (integrated pediatric database).

Growth should be monitored during treatment with Strattera. Data on the long-term effects of Strattera on growth come from open-label studies, and weight and height changes are compared to normative population data for about the first 9-12 months of treatment. Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with Strattera have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data. After about 12 months, gain in height stabilizes, and at 3 years, patients treated with Strattera have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data.

† Please see #7, #8, and #9, page 39, for study explanations.

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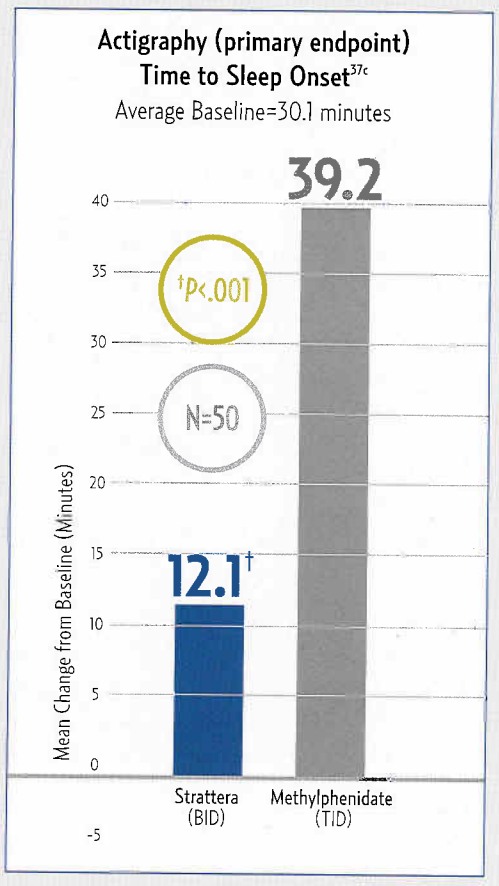
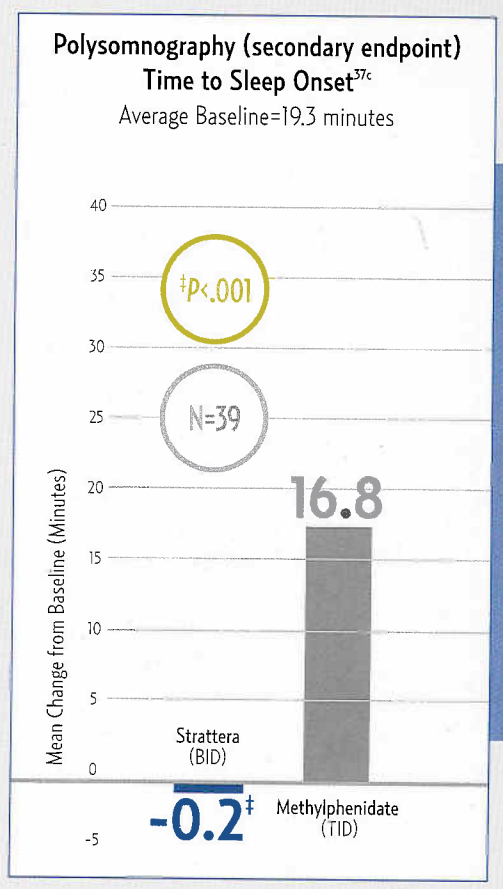
# Time to sleep onset

*Children with ADHD taking Strattera fall asleep faster than children with ADHD taking methylphenidate**

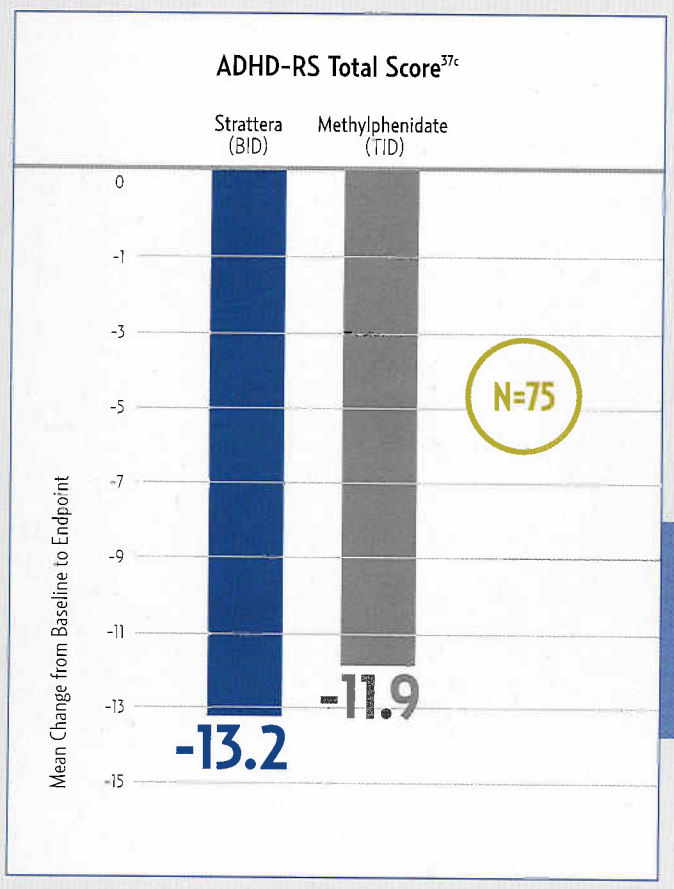



- **Actigraphy**—Patient wears a bracelet device to measure physical movement during sleep (home-based measurement)
- **Polysomnography**—Simultaneous and continuous monitoring of relevant normal and abnormal physiologic activity during sleep through measurement of brain waves (lab-based measurement)

* Please see #10, page 39, for study explanation.

*In the sleep study, there was no difference in efficacy between children on Strattera and children on methylphenidate; there was no correlation between ADHD symptom response and sleep onset*[37c§]




Testing for treatment effect by comparing 2 sequence groups using difference of change scores.

§ Please see #10, page 39, for study explanation.

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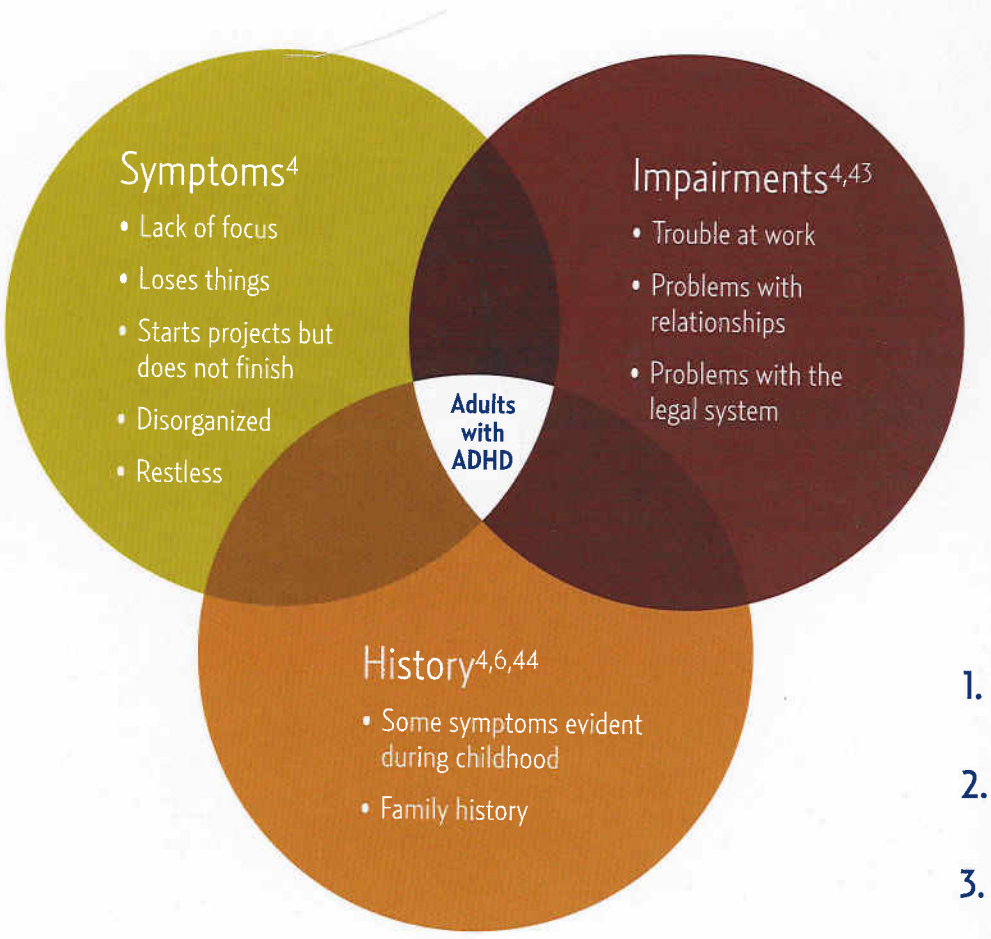
# Diagnosing adult ADHD*




1. Look for symptoms by utilizing the Adult Self Report Scale-V1.1
2. Check for impairments in two or more settings
3. Ask about history consistent with childhood onset of disorder

* Adapted from DSM-IV-TR
For complete diagnostic criteria, see the DSM-IV-TR. Diagnostic criteria include having 6 or more symptoms in either subtype, impairment in multiple settings, and a history of symptoms and impairments evident in childhood.[43]

## Check for symptoms

### ASRS-V1.1 Screener Results

A score of 4 or more

- Indicates that symptoms may be consistent with Adult ADHD
- Further assessment of symptoms, impairment, and history by healthcare professionals for diagnosis
  - 6 of 9 symptoms based on DSM-IV-TR criteria
  - Symptoms must have been persistent for more than 6 months and not explained by another mental disorder

### Sensitivity and Specificity of Screener (predictive factor)

- 7 of 10 with ADHD are correctly identified†
- 9 of 10 without ADHD are correctly screened out‡

### Development of the ASRS-V1.1 Screener

Collaboration between the Workgroup on Adult ADHD and the World Health Organization (WHO)

- Administration of DSM-IV-TR-based 18-item scale to ADHD and non-ADHD controls
- Diagnosis confirmed by trained raters and expert clinicians
- Psychometric analyses revealed the subset of questions (6/18) that would discriminate between true cases and noncases

† Sensitivity

‡ Specificity

# Diagnosing adult ADHD

## *Check for impairments*

### Ask the patient

Do the symptoms just described cause problems in:

- Work settings?
- Social settings?
- Family settings?

To what extent do these symptoms cause problems?

## *Ask about history*

### Ask the patient

How would your grade school teachers describe you?

- Your grades?
- Your behavior?

# *Making a differential diagnosis*


**ADHD** vs **Depression**
**Bipolar Disorder**
**Anxiety**

- ADHD tends to be more continuous in nature

- Depression/Bipolar Disorder/ Anxiety tend to be more episodic or cyclical in nature

# Tolerability of non-stimulant Strattera

*Most common side effects in child and adolescent trials**

| | Strattera (n=425) | Placebo (n=292) | Statistical Significance |
|---|---|---|---|
| Appetite decreased | 14.1% | 5.8% | <.001 |
| Dizziness | 6.1% | 2.4% | .019 |
| Dyspepsia | 4.5% | 1.4% | .029 |
| Dermatitis | 4.5% | 1.7% | NS |
| Constipation | 2.4% | 1.0% | NS |
| Influenza | 2.1% | 1.0% | NS |
| Mood swings | 2.4% | 0.7% | NS |

Events reported in the QD trials but not in the BID trials included: vomiting, nausea, dyspepsia, and fatigue ($P$<.05 vs placebo).

* Events reported by at least 2% of patients treated with Strattera and greater than placebo in QD and BID trials. The following events did not meet this criterion but were reported by more Strattera-treated patients than placebo-treated patients and are possibly related to Strattera treatment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients treated with Strattera and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

## Most common side effects in adult trials†

| | Strattera (n=269) | Placebo (n=263) | *P*-value | Discontinuation |
|---|---|---|---|---|
| Dry mouth | 21% | 6% | <.001 | 0 |
| Insomnia and/or middle insomnia | 16% | 8% | .002 | 3 |
| Nausea | 12% | 5% | .005 | 1 |
| Constipation | 10% | 4% | .009 | 0 |
| Appetite decreased | 10% | 3% | <.001 | 0 |
| Urinary retention, hesitation, and/or difficulty in micturition | 8% | 0% | <.001 | 2 |
| Erectile disturbance‡ | 7% | 1% | .006 | 1 |
| Dysmenorrhea§ | 7% | 3% | NS | 0 |
| Dizziness | 6% | 2% | .015 | 0 |
| Libido decreased | 6% | 2% | .01 | 1 |
| Ejaculation failure and/or ejaculation disorder‡ | 5% | 2% | NS | 1 |

† Events reported by at least 5% of Strattera patients and at least twice the rate of placebo.

‡ Based on total number of males (Strattera, n=174; placebo, n=172).

§ Based on total number of females (Strattera, n=95; placebo, n=91).

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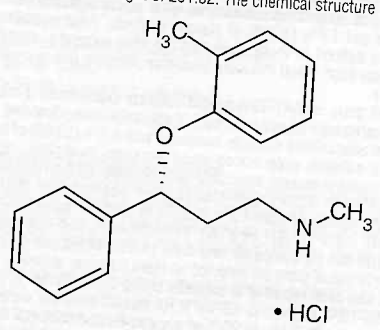
# STRATTERA® (atomoxetine HCl)

**WARNING**

**Suicidal Ideation in Children and Adolescents—STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder.**

**Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use).**

**DESCRIPTION:** STRATTERA® (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO \cdot HCl$, which corresponds to a molecular weight of 291.82. The chemical structure is:




• HCl

Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

STRATTERA capsules are intended for oral administration only.

Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide. The capsules are imprinted with edible black ink.

**CLINICAL PHARMACOLOGY:** *Pharmacodynamics and Mechanism of Action*—The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is

## Summary of clinical trials

#1 Phase 3b, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of Strattera in reducing signs and symptoms of ADHD and anxiety in children and adolescents ages 8-17 with ADHD and a comorbid anxiety disorder.

This trial used a twice-daily dosing of Strattera with a mean final dose of 1.26 mg/kg/day. The active treatment period was 10 weeks with a blinded 2-week placebo lead-in to assess patients for significant placebo response.

Although all patients continued in the study, only patients with no more than a 25% reduction of anxiety symptoms during the placebo lead-in were included in the primary analyses.

#2 Phase I/II, randomized, double-blind, placebo-controlled, crossover phase comparing 3 Strattera doses with MPH, oxycodone, and diazepam in drug-abusing adults ages 21-55 years.

#3 Randomized, double-blind, placebo-controlled study to assess the efficacy in adult outpatients with DSM-IV attention-deficit/hyperactivity disorder. This trial used a twice-daily dosing of Strattera with a mean final prescribed dose of 96 mg/day. The active treatment period was 10 weeks.

#4 Randomized, double-blind, placebo-controlled study to assess the efficacy in adult outpatients with DSM-IV attention-deficit/hyperactivity disorder. This trial used a twice-daily dosing of Strattera with a mean final prescribed dose of 92.6 mg/day. The active treatment period was 10 weeks.

#5 Multicenter, randomized, double-blind investigation of the acute safety and efficacy of Strattera in children and adolescents ages 7-17 with ADHD and comorbid Tourette's Syndrome or chronic motor tics. The trial used a twice-daily dosing of Strattera with a mean final prescribed dose of 1.33 mg/kg/day. The acute treatment period was 18 weeks.

#6 Phase 4, multicenter, double-blind, placebo-controlled study to evaluate efficacy in a school setting in children ages 8-12 with ADHD. This trial used a once-daily dosing of Strattera with a mean final dose of 1.33 mg/kg/day. The active treatment period was 6 weeks.

#7 Investigation of long-term safety and tolerability of Strattera (up to 80 weeks' duration) in patients ages 6 years and older (but less than 18 years of age at the time of entry into their prior study). This trial used a twice-daily dosing of Strattera for an active treatment period of 6 months or longer (up to 80 weeks).

#8 Open-label, nonrandomized investigation of long-term safety and tolerability of Strattera up to a 5-year duration in patients 6 years and older (but less than 18 years of age) at the time of entry in the first Strattera study. This trial used a twice-daily dosing of Strattera for an active treatment period of 6 months or longer (up to 80 weeks).

#9 Phase 3, multicenter, open-label investigation of the long-term safety and efficacy of Strattera in approximately 1000 outpatients who are at least 6 years of age but less than 18 years of age and have met DSM-IV criteria for ADHD. Patients who responded to acute treatment with Strattera (approximately 10 weeks) were eligible to enter a long-term treatment phase of approximately 2 years. This trial included an active treatment period of 10 weeks as well as a longer term of approximately 2 years.

#10 Study objectives were to compare the time to onset of persistent sleep via actigraphy of Strattera (BID) vs MPH (TID) and to evaluate the correlation between ADHD symptom change and sleep in children ages 6-14. Phase 1 included a control arm containing 40 healthy volunteers. These data were used to establish baselines.

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strattera®
atomoxetine HCl

ADHD is a *serious, lifetime disorder*

ADHD patients have *unique needs*

Strattera offers *unique safety benefits*

Strattera provides *core symptom efficacy*
for children, adolescents, and adults

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