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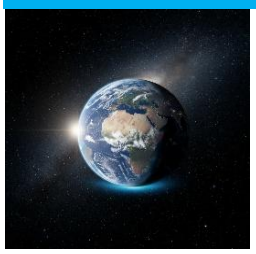

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Guanfacine Extended Release in the Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: A Narrative Review

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neurodevelopmental disorder in children and adolescents and is associated with substantial functional impairment. Although psychostimulants are considered first-line pharmacotherapy, a significant proportion of patients experience inadequate response, poor tolerability, or contraindications to stimulant use. Consequently, non-stimulant medications remain an important component of ADHD management. Guanfacine extended release (GXR), a selective α2A-adrenergic receptor agonist, is approved for the treatment of pediatric ADHD and represents a well-established non-stimulant option.

Evidence derived from randomized controlled trials, meta-analyses, and systematic reviews indicates that GXR is effective as monotherapy and as adjunctive therapy to psychostimulants in children and adolescents aged 6–17 years. Across studies, GXR demonstrates clinically meaningful reductions in core ADHD symptoms compared with placebo, with reported effect sizes generally ranging from 0.5 to 0.8. The most commonly reported adverse events are sedation-related symptoms, including somnolence and fatigue, which are typically mild to moderate and tend to decrease with ongoing treatment. Cardiovascular effects are usually modest and consist mainly of small reductions in blood pressure and heart rate, with clinically significant events occurring infrequently.

Overall, available data indicate that guanfacine extended release is an effective and generally well-tolerated non-stimulant treatment for ADHD in pediatric and adolescent populations. Its clinical utility is particularly relevant in patients with insufficient response or intolerance to stimulants, as well as in those requiring adjunctive pharmacotherapy. Further studies are warranted to evaluate long-term outcomes and to better define its comparative effectiveness in specific clinical subgroups.

Key words: Attention-deficit/hyperactivity disorder; guanfacine extended release; non-stimulant pharmacotherapy; pediatric psychopharmacology; alpha-2 adrenergic agonist

1. Introduction and Purpose

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in children and adolescents, with a global prevalence estimated at 5–7% [1]. The disorder is characterized by persistent patterns of inattention, hyperactivity, and impulsivity that interfere with functioning across academic, social, and family domains. Although psychostimulant medications, including methylphenidate and amphetamine derivatives, are well established as first-line pharmacological treatments with robust efficacy, approximately 30% of patients experience inadequate response, poor tolerability, or contraindications to stimulant therapy [2,3].

These limitations have driven the development of non-stimulant treatment options targeting alternative neurobiological mechanisms. Guanfacine, initially developed as an antihypertensive agent, has emerged as a clinically relevant non-stimulant therapy for ADHD. Unlike stimulants, guanfacine acts as a selective α2A-adrenergic receptor agonist with preferential postsynaptic activity in the prefrontal cortex, a brain region critical for executive functions including attention regulation, working memory, and behavioral control [4–7]. By enhancing the signal-to-noise ratio within prefrontal cortical networks, guanfacine is thought to improve cognitive control and emotional regulation.

The extended-release formulation of guanfacine (GXR) was developed to optimize pharmacokinetic properties for ADHD treatment, enabling once-daily dosing with sustained therapeutic plasma concentrations [8]. Compared with immediate-release guanfacine, GXR is associated with reduced peak-to-trough fluctuations, improved tolerability, and enhanced treatment adherence [9]. GXR received approval from the U.S. Food and Drug Administration in 2009 for the treatment of ADHD in children and adolescents aged 6–17 years, both as monotherapy and as adjunctive therapy to stimulants [10]. This was followed by approval from the European Medicines Agency in 2015 for patients in whom stimulants are unsuitable, not tolerated, or ineffective [11].

The purpose of this review is to provide a critical synthesis of current evidence regarding the efficacy, safety, and clinical utility of guanfacine extended release in pediatric and adolescent ADHD. Specifically, this review examines therapeutic efficacy, tolerability, comparative

effectiveness relative to other pharmacological treatments, patient populations most likely to benefit from GXR, and key gaps in the existing evidence base to inform future research.

2. Background and Theoretical Foundations

To fully appreciate the clinical role of GXR in ADHD management, it is essential to understand the broader context of ADHD as a neurodevelopmental disorder and the evolving landscape of available treatments.

2.1. Epidemiology and Clinical Burden of ADHD

Attention-deficit/hyperactivity disorder affects approximately 5–7% of children and adolescents worldwide, although prevalence estimates vary across geographic regions and depend on diagnostic criteria and assessment methods [1]. In childhood, ADHD is diagnosed more frequently in males, with an approximate male-to-female ratio of 2:1; however, this sex difference diminishes during adolescence and adulthood as combined and predominantly inattentive presentations become more prevalent.

The clinical burden of ADHD extends well beyond core symptoms of inattention, hyperactivity, and impulsivity. Affected children and adolescents commonly experience significant academic difficulties, including poorer academic performance, increased rates of grade retention, and higher risk of school dropout. Social functioning is frequently impaired, with higher rates of peer rejection, difficulties in social skills development, and reduced social support. ADHD also places substantial strain on family functioning, contributing to increased parent–child conflict and overall family stress.

Comorbidity is common and contributes substantially to functional impairment. Oppositional defiant disorder is observed in approximately 50–60% of pediatric patients, reflecting the close association between ADHD and behavioral regulation difficulties [23]. Anxiety disorders affect an estimated 25–35% of patients, learning disabilities 30–50%, and mood disorders approximately 15–20%. In the long term, individuals with ADHD are at increased risk of adverse outcomes, including substance use disorders, accidental injuries, unemployment, and involvement with the criminal justice system.

2.2. Neurobiology of ADHD

Neurobiological Rationale for α2A-Adrenergic Modulation. Contemporary neurobiological models of attention-deficit/hyperactivity disorder implicate dysfunction of fronto–striatal–cerebellar circuits and dysregulation of catecholaminergic neurotransmission. Neuroimaging studies consistently demonstrate structural and functional abnormalities in the prefrontal cortex, particularly within the dorsolateral prefrontal cortex, along with alterations in the anterior cingulate cortex, striatum, and large-scale executive control networks.

The prefrontal cortex is critical for executive functions such as working memory, inhibitory control, and attention regulation, which are core domains impaired in ADHD. Noradrenergic signaling via α2A-adrenergic receptors, densely expressed in the prefrontal cortex, enhances signal-to-noise ratio and stabilizes neuronal firing within prefrontal networks. This mechanism provides a strong neurobiological rationale for the therapeutic use of guanfacine extended release in ADHD [12,13].

2.3. Current Treatment Landscape

Role of Stimulant and Non-Stimulant Pharmacotherapy. Psychostimulants remain the first-line pharmacological treatment for attention-deficit/hyperactivity disorder, with methylphenidate and amphetamine formulations demonstrating robust efficacy in reducing core ADHD symptoms. Effect sizes in well-controlled trials typically range from 0.8 to 1.0, reflecting strong therapeutic effects [2,3]. Despite their effectiveness, stimulant medications are associated with several important limitations. Approximately 30% of patients show an inadequate or incomplete response, and common adverse effects include appetite suppression, insomnia, and emotional lability. Additional concerns relate to potential effects on growth, cardiovascular safety, abuse liability, and the need for multiple daily doses with immediate-release formulations. Stimulants may also be contraindicated in certain comorbid medical or psychiatric conditions.

Non-stimulant medications therefore represent important alternatives within ADHD pharmacotherapy. Atomoxetine, a selective norepinephrine reuptake inhibitor, demonstrates moderate efficacy with effect sizes of approximately 0.6. Alpha-2 adrenergic agonists, including guanfacine and clonidine, exert their effects through modulation of prefrontal cortex function and are similarly associated with moderate efficacy. Other agents, such as bupropion

or tricyclic antidepressants, have been explored but are used less frequently due to safety considerations and a more limited evidence base.

2.4. Rationale for Non-Stimulant Therapies

Clinical Role of Non-Stimulant Therapy. Non-stimulant medications such as guanfacine extended release play a particularly important role in several clinical scenarios. They are especially valuable in patients who demonstrate inadequate or partial response to stimulant therapy, as well as in those who experience clinically significant stimulant-related adverse effects, including severe appetite suppression, insomnia, or emotional side effects.

The presence of comorbid conditions, such as anxiety disorders, tic disorders, or a history of substance misuse, further supports consideration of non-stimulant treatment. Guanfacine extended release may also be preferred in patients with pre-existing cardiovascular concerns or in families seeking alternatives to controlled substances due to concerns about diversion or abuse. In addition, its extended duration of action allows for effective symptom control during early morning and evening periods. Finally, guanfacine extended release may be used as adjunctive therapy to enhance treatment response in patients with partial benefit from stimulant medications.

3. Pharmacology and Mechanism of Action

Understanding the pharmacological properties of GXR provides important insights into its clinical effects, appropriate dosing strategies, and potential drug interactions.

3.1. Molecular Pharmacology

Guanfacine is a selective α2A-adrenergic receptor agonist, exhibiting approximately 15–20-fold greater affinity for α2A receptors compared with α2B and α2C receptor subtypes, a property that contributes to its favorable clinical profile [13]. This selectivity is clinically relevant because α2A receptors are densely expressed in the prefrontal cortex, a brain region central to executive functions and attention regulation.

α2A receptors are located both presynaptically, where they modulate norepinephrine release, and postsynaptically, where they influence neuronal excitability. Activation of postsynaptic

α2A receptors in the prefrontal cortex enhances neuronal firing patterns associated with working memory and attentional control and strengthens functional connectivity within prefrontal networks. Through these mechanisms, guanfacine supports more efficient executive functioning and cognitive regulation.

3.2. Pharmacokinetics and Pharmacodynamics

Guanfacine extended release is formulated to provide gradual drug release over approximately 24 hours, allowing stable plasma concentrations with once-daily dosing. Peak plasma concentrations are reached within 5–7 hours after administration, and oral bioavailability is approximately 80% [8]. Steady-state levels are typically achieved within 3–4 days of regular dosing.

Guanfacine is primarily metabolized via hepatic CYP3A4/5 pathways, with an elimination half-life of approximately 14–18 hours in pediatric populations, supporting once-daily administration [8]. Pharmacokinetics are linear across the therapeutic dose range, with renal excretion of metabolites.

Clinically relevant drug interactions include increased guanfacine exposure with strong CYP3A4 inhibitors and reduced exposure with CYP3A4 inducers. Additive sedative effects may occur with concomitant central nervous system depressants, and enhanced hypotensive effects may be observed when combined with antihypertensive agents.

3.3. Neurobiological Effects on Prefrontal Cortex Function

Preclinical and neuroimaging studies indicate that guanfacine enhances prefrontal cortex function through modulation of α2A-adrenergic signaling. Guanfacine strengthens delay-related neuronal firing in the dorsolateral prefrontal cortex during working memory tasks, a mechanism demonstrated in both animal models and human neuroimaging studies [5,14]. This effect is associated with improved working memory performance, enhanced top-down control of impulsive responses, and improved attentional regulation.

Additionally, guanfacine reduces spontaneous neuronal firing, thereby improving the signal-to-noise ratio within prefrontal networks. Functional MRI studies in patients with ADHD further demonstrate that guanfacine normalizes prefrontal activation patterns during executive function tasks and enhances functional connectivity within attention-related networks [14].

3.4. Extended-Release Formulation Advantages

The extended-release formulation of guanfacine provides several clinically meaningful advantages over immediate-release preparations. Once-daily dosing simplifies treatment regimens, improves adherence, and supports consistent symptom control. By reducing peak-to-trough plasma concentration fluctuations, the extended-release formulation minimizes adverse effects associated with peak exposure, particularly somnolence. In addition, sustained drug delivery allows for continuous symptom coverage throughout the day, including morning, school-time, and evening periods, thereby addressing functional impairments across multiple daily contexts.

4. Clinical Efficacy of Guanfacine Extended Release

The efficacy of GXR has been evaluated extensively through rigorous clinical trials conducted across diverse pediatric and adolescent populations.

4.1. Monotherapy in Pediatric Populations

Several large, randomized, double-blind, placebo-controlled trials have established the efficacy of guanfacine extended release (GXR) as monotherapy in pediatric ADHD. In a pivotal 9-week trial, Biederman et al. evaluated once-daily GXR (2–4 mg) in 345 children and adolescents aged 6–17 years, using change in the ADHD Rating Scale IV (ADHD-RS-IV) total score as the primary outcome measure.

GXR treatment resulted in significant, dose-dependent reductions in ADHD-RS-IV scores compared with placebo, with mean differences ranging from −6.5 to −8.6 points and effect sizes of 0.5–0.8, indicating moderate to large clinical efficacy. Response rates (≥30% symptom reduction) ranged from 45% to 62% in GXR-treated patients, compared with 34% in the placebo group. Improvements were observed across both inattentive and hyperactive–impulsive symptom domains, with statistically significant effects emerging within the first 1–2 weeks of treatment [9].

Long-term efficacy and tolerability were further supported by an open-label extension study by Sallee et al., which demonstrated sustained symptom improvement over up to 24 months of continuous treatment without evidence of tolerance development and with an acceptable safety profile [15].

4.2. Monotherapy in Adolescent Populations

Attention-deficit/hyperactivity disorder in adolescents is often associated with increased comorbidity, greater academic demands, and challenges related to treatment adherence. Clinical studies evaluating guanfacine extended release in adolescent populations demonstrate efficacy comparable to that observed in younger children.

Adolescents treated with GXR show similar response rates and effect sizes to pediatric patients, with improvements observed across core ADHD symptom domains. Notably, particular benefits have been reported for emotional dysregulation and oppositional behaviors, as well as for symptom control during morning and evening periods. The tolerability profile of GXR in adolescents is comparable to that observed in younger pediatric populations, with no new safety concerns identified [16].

4.3. Adjunctive Therapy with Psychostimulants

Guanfacine extended release (GXR) represents a valuable adjunctive treatment option for patients with an inadequate response to stimulant monotherapy. Combination therapy has been shown to enhance overall symptom reduction, improve control of oppositional and emotional symptoms, extend symptom coverage into morning and evening periods, and, in some cases, allow for lower stimulant doses.

In a randomized, double-blind, placebo-controlled trial, Wilens et al. evaluated GXR as adjunctive therapy in children and adolescents with ADHD who exhibited suboptimal response to stimulants. Participants received GXR at optimized doses of 1–4 mg added to a stable stimulant regimen or placebo plus stimulant. Adjunctive GXR resulted in significantly greater reductions in ADHD symptoms compared with placebo plus stimulant, with a mean difference of −6.8 points on the ADHD Rating Scale IV. Notably, improvements were observed in oppositional behaviors, emotional regulation, and functional outcomes during morning and

evening periods. The combination was generally well tolerated, with a manageable adverse event profile [17].

4.4. Efficacy in Specific ADHD Symptom Domains

Guanfacine extended release demonstrates efficacy across multiple ADHD symptom domains. Clinical trials show moderate to large improvements in inattention and hyperactivity–impulsivity, with effect sizes typically ranging from 0.5 to 0.8 and benefits maintained throughout the school day and into the evening. In addition to core symptoms, GXR is associated with improvements in executive functions, including working memory, planning, and cognitive flexibility. Notably, guanfacine shows particular benefit in emotional regulation, reducing irritability, emotional lability, and frustration intolerance, which may contribute to improved behavioral control and functional outcomes.

4.5. Comparative Effectiveness with Other ADHD Treatments

Network Meta-Analyses and Comparative Effectiveness. Network meta-analyses and comparative effectiveness studies provide important context for understanding the relative efficacy of guanfacine extended release compared with other pharmacological treatments for ADHD. In a meta-analysis of alpha-2 adrenergic agonists, Hirota et al. evaluated data from 13 randomized controlled trials involving guanfacine and clonidine. Guanfacine extended release monotherapy demonstrated a moderate effect size of 0.63, indicating clinically meaningful efficacy among available ADHD treatments. When used as adjunctive therapy, guanfacine extended release showed a smaller but still relevant additional benefit, with an effect size of 0.31. Overall efficacy was comparable to atomoxetine but lower than that observed for stimulant medications, while tolerability was more favorable than stimulants in certain domains [18].

Further comparative evidence was provided by a large network meta-analysis conducted by Cortese et al., which included 133 randomized controlled trials across multiple ADHD pharmacotherapies. In this analysis, guanfacine extended release ranked in the middle tier for efficacy outcomes but demonstrated a favorable tolerability profile compared with stimulant medications. The authors highlighted particular advantages of guanfacine extended release in specific clinical scenarios, including the presence of comorbid conditions and intolerance or contraindications to stimulant therapy [19].

Clinical Interpretation**:** While GXR demonstrates lower overall efficacy than psychostimulants, it offers unique advantages in patient selection, tolerability, and management of comorbid symptoms. Clinical utility extends beyond simple efficacy comparisons to encompass individualized treatment considerations.

5. Safety, Tolerability, and Adverse Event Profile

A clear understanding of the safety profile of guanfacine extended release (GXR) is essential for informed clinical decision-making and patient counseling.

5.1. Common Adverse Events

Pooled data from randomized controlled trials indicate that GXR is generally well tolerated, with most adverse events being mild to moderate in severity and occurring early in treatment, often diminishing with continued therapy or dose adjustment. Somnolence and sedation are the most frequently reported adverse effects, affecting approximately 30–40% of patients compared with 10–15% in placebo groups, and are dose-related and typically transient [20]. Fatigue occurs in 15–25% of patients, while headache (15–20%), abdominal pain (10–15%), and decreased appetite are generally mild and self-limiting. Appetite suppression is less pronounced than with stimulant medications and has shown minimal impact on growth parameters in long-term studies.

Discontinuation due to adverse events occurs in approximately 5–10% of patients, most commonly because of somnolence or fatigue. Overall discontinuation rates for GXR appear lower than those reported for many stimulant formulations, supporting a favorable tolerability profile [20].

5.2. Cardiovascular Effects

As a selective α2A-adrenergic receptor agonist, GXR produces predictable cardiovascular effects that are typically mild and clinically manageable. Treatment is associated with mean reductions of approximately 3–6 mmHg in systolic and diastolic blood pressure and decreases in heart rate of 5–10 beats per minute, most often occurring during early treatment and stabilizing with continued use [21]. Clinically significant hypotension (<2%) and bradycardia

(<3%) are uncommon. Thorough QT studies have not demonstrated clinically meaningful QTc prolongation, indicating a low risk of cardiac arrhythmias.

Baseline assessment of blood pressure and heart rate is recommended prior to treatment initiation, with regular monitoring during dose titration and follow-up. Electrocardiography should be performed when indicated by clinical history, and caution is advised in patients with known cardiac conduction disorders or significant hypotension [21].

5.3. Sedation and Somnolence Management

Sedation represents the primary tolerability-limiting adverse effect of GXR. Mitigation strategies include gradual dose titration starting at 1 mg with weekly increments, evening dosing to reduce daytime somnolence, and use of the lowest effective dose. Sedative effects are often transient and may improve within 2–4 weeks of continued treatment. Patient and family education regarding the expected course of sedation is essential to support adherence.

Dose reduction or discontinuation should be considered if persistent or severe somnolence results in clinically significant impairment in daily functioning, academic performance, or social activities despite dose and timing adjustments.

5.4. Long-Term Safety and Special Populations

Long-term studies with follow-up of up to 24 months indicate that guanfacine extended release (GXR) is well tolerated without clinically meaningful effects on growth or development. Mean changes in height and weight percentiles are minimal, and available data suggest less growth suppression compared with stimulant medications, representing a potential advantage in long-term pediatric treatment [22]. GXR has not been associated with clinically significant effects on glucose or lipid metabolism, and weight changes are generally minimal.

Gradual dose tapering is recommended when discontinuing GXR to reduce the risk of rebound symptoms. Dose reductions of approximately 1 mg every 3–7 days are advised, as abrupt discontinuation may result in transient rebound hypertension, tachycardia, or anxiety, although withdrawal symptoms are uncommon with appropriate tapering.

Guanfacine extended release has no known abuse potential and is not classified as a controlled substance, which may be advantageous in pediatric and adolescent populations at risk for substance misuse.

In special populations, dose adjustment is recommended in patients with moderate to severe hepatic impairment and may be necessary in cases of severe renal dysfunction, with close clinical monitoring. Caution is also advised in patients with cardiac conduction abnormalities or significant cardiovascular disease, for whom baseline electrocardiography and ongoing cardiovascular monitoring should be considered.

6. Clinical Applications and Practical Considerations

Translating clinical trial evidence into routine practice requires careful patient selection, individualized dosing, and systematic monitoring.

6.1. Patient Selection Criteria

Guanfacine extended release (GXR) is particularly well suited for children and adolescents with inadequate or partial response to stimulant monotherapy, especially when residual symptoms include emotional dysregulation or oppositional behaviors. It represents an important alternative for patients who do not tolerate stimulants because of adverse effects such as appetite suppression, weight loss, insomnia, emotional lability, or cardiovascular concerns.

GXR may be especially beneficial in patients with comorbid anxiety disorders, tic disorders, oppositional defiant disorder, or autism spectrum disorder with co-occurring ADHD symptoms. The absence of abuse potential further supports its use in individuals with a personal or family history of substance misuse. In addition, sustained 24-hour symptom coverage and once-daily dosing make GXR advantageous for patients with prominent morning or evening impairments and for families preferring non-stimulant therapies.

Relative contraindications include severe bradycardia, advanced atrioventricular conduction disturbances, clinically significant hypotension, known hypersensitivity to guanfacine, and severe hepatic impairment. In patients with hepatic dysfunction, dose adjustment and careful monitoring are recommended rather than absolute avoidance.

6.2. Dosing Strategies and Titration

Guanfacine extended release should be initiated at 1 mg once daily and titrated gradually based on clinical response and tolerability. In children aged 6–12 years, the usual maintenance dose ranges from 1 to 4 mg once daily, while adolescents aged 13–17 years may require doses up to 7 mg once daily. Dose increases of 1 mg at weekly intervals are generally recommended.

GXR is administered once daily, with or without food, and tablets should be swallowed whole. Evening dosing may reduce daytime sedation, although dosing time can be individualized. Optimal treatment involves using the lowest effective dose and allowing sufficient time at each dose level (typically 1–2 weeks) to assess efficacy and adverse effects.

When discontinuing GXR, gradual tapering is advised to minimize rebound symptoms. Dose reductions of approximately 1 mg every 3–7 days are recommended, with monitoring of blood pressure and heart rate during discontinuation. Patient and family education regarding tapering is essential.

6.3. Combination Therapy and Management Considerations

Guanfacine extended release (GXR) is commonly used in combination with psychostimulants in patients who show a partial response to stimulant monotherapy. Adjunctive GXR may enhance overall symptom control, particularly for early morning and evening symptoms, oppositional behaviors, and emotional dysregulation, and may allow for lower effective stimulant doses, thereby improving tolerability. This approach is especially useful in patients with comorbid anxiety or tic disorders.

When initiating combination therapy, GXR should be started at 1 mg once daily while maintaining a stable stimulant dose. Dose optimization of GXR should generally precede any stimulant dose adjustments, and cautious stimulant dose reduction may be considered in patients demonstrating a robust clinical response. Evidence for combination therapy with atomoxetine remains limited; however, integration of GXR within a multimodal treatment framework that includes behavioral interventions and educational accommodations is strongly recommended.

6.4. Management of Treatment-Emergent Adverse Events

Somnolence and sedation are the most common treatment-emergent adverse effects of GXR and are typically managed through slower dose titration, evening dosing, and use of the lowest effective dose. Sedative effects are often transient and may improve within 2–4 weeks of continued treatment. Persistent or functionally impairing sedation may warrant dose reduction or discontinuation.

Hypotension and dizziness may occur, particularly during early treatment or dose escalation, and can usually be mitigated by ensuring adequate hydration, gradual positional changes, and regular blood pressure monitoring. Headache and abdominal discomfort are generally mild and self-limiting; supportive measures are typically sufficient, with further evaluation reserved for persistent or severe symptoms.

6.5. Treatment Monitoring and Follow-Up

Prior to initiating GXR, a comprehensive baseline assessment should include confirmation of the ADHD diagnosis, evaluation of comorbidities, and documentation of baseline blood pressure, heart rate, height, and weight. Cardiac history and physical examination are recommended, with electrocardiography performed when clinically indicated.

Follow-up during the initial treatment phase should focus on tolerability and early response, with more frequent visits during dose titration. After dose stabilization, periodic monitoring every 3–6 months is generally sufficient. Ongoing assessments should include evaluation of ADHD symptoms using standardized rating scales, monitoring for adverse events, cardiovascular measurements, and review of functional outcomes across academic, social, and family domains. Commonly used instruments include the ADHD Rating Scale–IV, Conners 3 scales, Clinical Global Impression scales, and the Weiss Functional Impairment Rating Scale.

7. Efficacy in Comorbid Conditions

Comorbid psychiatric and neurodevelopmental conditions are common in children and adolescents with ADHD and significantly influence treatment selection and outcomes.

Guanfacine extended release (GXR) demonstrates particular utility in several clinically relevant comorbidities.

7.1. Oppositional Defiant Disorder

Oppositional defiant disorder (ODD) co-occurs with ADHD in approximately 50–60% of pediatric patients. Multiple studies have demonstrated that GXR significantly reduces oppositional and defiant behaviors, with effect sizes comparable to improvements in core ADHD symptoms. Benefits have been observed in both monotherapy and adjunctive therapy settings and extend to improvements in parent–child conflict and overall family functioning [24]. These findings support consideration of GXR as a preferred pharmacological option in patients with ADHD and prominent oppositional symptoms.

7.2. Autism Spectrum Disorder

ADHD symptoms are present in approximately 30–50% of children with autism spectrum disorder (ASD), where pharmacological management is often limited by poor tolerability. Emerging evidence suggests that GXR may reduce hyperactivity, impulsivity, and irritability in children with ASD and comorbid ADHD, with potentially better tolerability than stimulants in some patients [23,24]. Careful dosing, slower titration, and close monitoring are recommended in this population.

7.3. Anxiety Disorders

Comorbid anxiety disorders affect approximately 25–35% of children with ADHD and may complicate stimulant treatment. GXR does not typically exacerbate anxiety symptoms and may provide modest anxiolytic benefits, making it a useful alternative in patients whose anxiety worsens with stimulant therapy. While GXR is not indicated for primary anxiety disorders, it may be considered a first-line ADHD treatment option when anxiety symptoms are prominent.

7.4. Tic Disorders

Tic disorders, including Tourette syndrome, occur in up to 20% of children with ADHD. GXR does not exacerbate tics and may be associated with modest reductions in tic severity, supporting its use as a preferred option in patients with comorbid tics [25]. In some cases, GXR may reduce the need for additional tic-specific pharmacotherapy.

8. Comparative Analysis and Network Meta-Analyses

Network meta-analyses provide an important framework for comparing ADHD pharmacotherapies in the absence of direct head-to-head trials. In a landmark network meta-analysis published in *The Lancet Psychiatry*, Cortese et al. evaluated 133 randomized controlled trials involving 10,068 children and adolescents, comparing both efficacy and tolerability across commonly used ADHD medications. In this analysis, amphetamine and methylphenidate preparations ranked highest for efficacy, whereas atomoxetine and guanfacine extended release (GXR) occupied a middle efficacy tier. Notably, GXR demonstrated a more favorable tolerability profile compared with stimulant medications, highlighting its clinical relevance in patients where safety and tolerability are key considerations [19].

Additional evidence was provided by a meta-analysis by Hirota et al. focusing on alpha-2 adrenergic agonists. Guanfacine extended release monotherapy showed a moderate effect size (0.63), while adjunctive use with stimulants provided a smaller but clinically meaningful additional benefit (effect size 0.31). Efficacy was comparable between guanfacine and clonidine, with guanfacine exhibiting a slightly more favorable tolerability profile [18].

While network meta-analyses offer valuable comparative insights, treatment selection in ADHD must remain individualized, taking into account patient characteristics, comorbidities, prior treatment response, adverse effect sensitivity, and practical considerations. Within this context, GXR occupies a distinct therapeutic niche, offering meaningful benefits in selected clinical scenarios despite lower overall efficacy compared with stimulant medications.

9. Limitations of Current Evidence and Research Gaps

Limitations and Knowledge Gaps. Despite a substantial body of evidence supporting the efficacy and safety of guanfacine extended release, several limitations and gaps in the current literature warrant consideration. Most randomized controlled trials have relatively short durations, typically 8–12 weeks, which limits conclusions regarding long-term effectiveness. Although open-label extension studies provide follow-up data of up to 24 months, the lack of placebo control and potential selection bias restrict definitive interpretation of sustained benefits. In addition, the predominance of industry-sponsored trials raises the possibility of publication and reporting bias, while restrictive inclusion criteria—often excluding patients

with complex psychiatric or medical comorbidities—limit generalizability to real-world clinical populations.

Important clinical knowledge gaps remain. Individual predictors of treatment response are poorly defined, and optimal dosing varies considerably between patients, with limited guidance on personalization. While adjunctive use with psychostimulants has been relatively well studied, controlled data on combinations with other non-stimulant agents, such as atomoxetine, are sparse. Comparative effectiveness evidence is also limited, as few head-to-head trials have directly compared guanfacine extended release with other non-stimulant therapies. Moreover, a persistent gap exists between efficacy observed in controlled trials and effectiveness in routine clinical practice.

Evidence is particularly limited in specific populations, including preschool-aged children, adults with ADHD, and individuals with intellectual disability or severe psychiatric comorbidities. In addition, the underrepresentation of diverse racial, ethnic, and socioeconomic groups in many studies constrains conclusions regarding cross-cultural efficacy and tolerability.

Finally, mechanistic understanding remains incomplete. No validated biomarkers are available to predict treatment response, and data linking clinical outcomes to neuroimaging or genetic markers are limited. Although guanfacine extended release is generally well tolerated, existing studies lack sufficient power to detect rare adverse events, and long-term data addressing developmental and cardiovascular safety remain needed, particularly in pediatric populations.

10. Discussion

This review synthesizes current evidence on guanfacine extended release (GXR) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in pediatric and adolescent populations. The available data support GXR as a clinically relevant non-stimulant option with moderate efficacy, acceptable tolerability, and distinct advantages in selected patient groups.

Across randomized controlled trials and meta-analyses, GXR demonstrates effect sizes in the moderate range (approximately 0.5–0.8), which are lower than those typically reported for psychostimulants but remain clinically meaningful. Importantly, efficacy should not be interpreted solely through effect size comparisons. Clinical utility is strongly influenced by

individual patient characteristics, including comorbidities, tolerability, cardiovascular risk, and concerns regarding abuse potential. Within this context, GXR occupies a valuable therapeutic niche, particularly in patients with comorbid anxiety disorders, tic disorders, and oppositional defiant disorder, where stimulant treatment may be less suitable.

Evidence supporting adjunctive use of GXR with psychostimulants further expands its clinical relevance. In patients with partial stimulant response, combination therapy provides additional symptom reduction, particularly in emotional dysregulation, oppositional behaviors, and early morning or evening symptom control. Although the incremental effect size of adjunctive therapy is modest, these improvements often translate into meaningful functional benefits for patients and families.

The extended-release formulation represents an important practical advantage, providing sustained 24-hour symptom coverage with once-daily dosing. This extended coverage addresses symptom domains that are frequently underrepresented in clinical trials but highly relevant to daily functioning, including morning routines, homework completion, and family interactions.

From a safety perspective, GXR is generally well tolerated. Sedation and somnolence are the most common adverse effects but are typically dose-related, transient, and manageable with gradual titration and appropriate dosing strategies. Cardiovascular effects are modest and predictable, consisting primarily of small reductions in blood pressure and heart rate. The absence of abuse potential and lack of clinically significant growth suppression further distinguish GXR from stimulant medications and support its use in selected clinical scenarios.

Several limitations of the current evidence base warrant consideration. Most controlled trials are of relatively short duration, and long-term data beyond two years remain limited. The predominance of industry-sponsored studies raises the possibility of publication bias, and restrictive inclusion criteria limit generalizability to complex real-world populations. In addition, reliance on symptom rating scales provides limited insight into long-term functional outcomes, highlighting the need for pragmatic and comparative effectiveness studies.

Substantial interindividual variability in response to GXR remains incompletely understood. The selective α2A-adrenergic mechanism targeting prefrontal cortex function provides a strong neurobiological rationale, yet validated predictors of treatment response are lacking. Future

research integrating clinical phenotyping, neuroimaging, and pharmacogenomic approaches may enable more personalized treatment selection.

In clinical practice, GXR should not be viewed solely as a second-line option after stimulant failure. Rather, it may be appropriately considered as a first-line or adjunctive treatment in patients with specific clinical profiles, including comorbid anxiety, tic disorders, oppositional behaviors, cardiovascular concerns, or elevated risk of substance misuse. Optimal outcomes require individualized dosing, careful monitoring, and integration within a multimodal treatment framework that includes behavioral and educational interventions.

In summary, guanfacine extended release represents an important component of the contemporary ADHD pharmacotherapy armamentarium. While it does not replace stimulants as first-line therapy for most patients, it addresses critical unmet needs and expands clinicians' ability to tailor treatment to the diverse presentations of ADHD in children and adolescents.

Author Contribution

Conceptualization, S.C. and J.B.; methodology, G.Ł., E.D. and J.D.; formal analysis, A.D., K.B. and O.B.; investigation, K.B. and H.B.; resources, A.W., S.C. and E.D.; data curation, H.B., G.Ł. and J.D.; writing, S.C., J.B. and E.D.; review and editing, A.D. and O.B.; supervision, S.C.; project administration, S.C. and A.W.;

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Conflicts of Interest

The authors declare no conflicts of interest.

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