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DERLEME | REVIEW

Guanfacine XR and ADHD: A Brief Review of Efficacy, Safety, and Clinical Applications in Children and Adolescents

Guanfacine XR ve DEHB: Çocuklarda ve Ergenlerde Etkinlik, Güvenlik ve Klinik Uygulamaların Kısa Bir Derlemesi

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Abstract
Guanfacine extended-release (XR) has emerged as an important non-stimulant therapeutic option for the management of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents, particularly in cases characterized by inattention, impulsivity, and sleep-related difficulties. Evidence from randomized controlled trials as well as long-term observational studies consistently demonstrates clinically meaningful improvements with guanfacine XR, both when used as monotherapy and in combination with stimulant medications. Through its selective α2A-adrenergic receptor agonism, guanfacine XR modulates prefrontal cortical networks, thereby enhancing executive functioning and supporting behavioral regulation. Although sedation is frequently reported during the early stages of treatment, this effect generally subsides with continued use, and several studies suggest potential benefits for sleep continuity. Importantly, clinical investigations indicate that guanfacine XR provides effective symptom control without impairing cognitive performance, with additional advantages observed in some cases when used adjunctively with stimulants. In Turkey, guanfacine XR is available under the trade names Arislow® and Guago®. Despite international guideline recommendations highlighting its role as a non-stimulant treatment alternative, evidence from local clinical practice remains scarce. Ongoing research is needed to further elucidate its long-term efficacy and safety profile in diverse populations. Additionally, increased awareness and training among healthcare providers in Turkey could enhance its utilization in clinical settings.
Keywords: Guanfacine XR, ADHD, children, adolescents, pharmacotherapy

Öz
Guanfacin uzatılmış salım (XR), çocuk ve ergenlerde dikkat eksikliği ve hiperaktivite bozukluğunun (DEHB) tedavisinde giderek daha fazla önem kazanan stimülan dışı bir farmakoterapi seçeneği olarak öne çıkmaktadır. Randomize kontrollü araştırmalar ve uzun süreli gözlemsel çalışmalar, ilacın hem tek başına kullanımında hem de psikostimülan tedavilere eklenmesi halinde belirgin klinik iyileşmeler sağladığını ortaya koymaktadır. Seçici α2A-adrenerjik reseptör agonizması yoluyla prefrontal korteksteki sinir ağlarını düzenleyerek yürütücü işlevleri ve davranışsal kontrolü desteklediği düşünülmektedir. Tedavinin erken döneminde sedasyon sık gözlenmekle birlikte, genellikle zaman içinde azalma eğilimi gösterir ve bazı olgularda uyku sürekliliği üzerinde ek yararlar bildirilmiştir. Ayrıca, bilişsel performans üzerinde belirgin olumsuz bir etkisinin bulunmadığı ve semptom kontrolünü bozmadığı gösterilmiştir. Türkiye'de Arislow® ve Guago® ticari isimleriyle ruhsatlı olarak bulunan Guanfacin XR, uluslararası kılavuzlarda stimülan dışı tedavi seçenekleri arasında yer almakla birlikte, yerel klinik veriler hâlen sınırlıdır. Çeşitli popülasyonlarda uzun vadeli etkinliği ve güvenlik profilini daha ayrıntılı olarak aydınlatmak için devam eden araştırmalara ihtiyaç vardır. Ayrıca, Türkiye'deki sağlık hizmetleri sağlayıcıları arasında farkındalığın artırılması ve eğitimlerin yaygınlaştırılması, klinik ortamlarda kullanımını artıracaktır.
Anahtar kelimeler: Guanfacin XR, dikkat eksikliği ve hiperaktivite bozukluğu, çocuk, ergen, farmakoterapi

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that begins in childhood and frequently persists into adulthood, characterized by inattention, hyperactivity, and impulsivity (Rugino 2018). Globally, the prevalence of ADHD among school-aged children is estimated to be approximately 5–7% (Faraone and Glatt 2010; Rugino 2018). The disorder adversely affects multiple domains, including academic achievement, social relationships, and family functioning, leading to substantial reductions in overall quality of life (Arnsten 2009). The etiopathogenesis of ADHD is multifactorial, involving the interaction of genetic predisposition, neurobiological mechanisms, and environmental influences (Arnsten, 2009). Dysfunction in the regulatory role of the prefrontal cortex has been particularly implicated in symptom manifestation, which explains why many therapeutic interventions aim to restore neurotransmitter balance in this region (Newcorn et al., 2013). Pharmacotherapy constitutes a cornerstone in the treatment of ADHD. Stimulant medications, such as methylphenidate and amphetamine derivatives, remain the most commonly preferred first-line therapies (Wolraich et al., 2019).

However, a subset of patients fails to respond adequately, experiences intolerable side effects, or presents with comorbid conditions, thereby requiring alternative pharmacological approaches (U.S. Food and Drug Administration, 2013; Wolraich et al., 2019). Within this context, guanfacine extended-release (XR), a non-stimulant agent, has emerged as both an alternative and adjunctive treatment option to stimulants, particularly in children and adolescents (Biederman et al., 2008; Sallee et al., 2009; Martin et al., 2014). Guanfacine XR received FDA approval in 2009 and has since been widely introduced into clinical practice across many countries (U.S. Food and Drug Administration, 2013). Recent clinical studies have provided robust evidence regarding its efficacy, safety profile, and long-term outcomes, with particular emphasis on its effects on impulsivity, sleep regulation, and comorbid behavioral problems (Faraone et al., 2013; Elbe, 2014; Yu et al., 2023).

Pharmacological Properties

Guanfacine exerts its effects by selectively binding to α2A-adrenergic receptors within the central nervous system. Through this mechanism, it plays a “noise-reducing” role in synaptic transmission of the prefrontal cortex, thereby enhancing the efficiency of signals that regulate attention and executive functioning (Wolraich et al., 2019). As a result, improvements can be observed in domains such as behavioral control, planning, and impulse regulation. The extended-release (XR) formulation reaches peak plasma concentrations approximately five hours following oral administration, with an elimination half-life averaging 17–18 hours (Martin et al., 2014). Owing to this prolonged half-life, once-daily dosing is sufficient, which improves treatment adherence in children and adolescents. Guanfacine is primarily metabolized in the liver via the CYP3A4 enzyme. Consequently, concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin) may alter plasma concentrations, requiring appropriate dose adjustments (U.S. Food and Drug Administration, 2013).

Dosing and Titration

In clinical practice, guanfacine XR is generally initiated at 1 mg/day in a single dose. Depending on clinical response and tolerability, the dose can be increased by up to 1 mg at weekly intervals. In children and adolescents, the recommended dosage range is 1–4 mg/day, with a maximum daily dose of 4 mg (U.S. Food and Drug Administration, 2013; Wolraich et al., 2019). Abrupt discontinuation should be avoided due to the risk of rebound hypertension; therefore, tapering in 3–7 day intervals is recommended when discontinuing treatment (U.S. Food and Drug Administration, 2013).

Adverse Effect Profile

The most frequently reported side effects of guanfacine XR include sedation, dizziness, hypotension, and dry mouth (Biederman et al., 2008; Sallee and McGough, 2009; Cruz, 2010). Sedative effects tend to be most prominent during the early weeks of therapy but are often tolerated over time (Faraone and Glatt, 2010). Because guanfacine does not directly influence dopaminergic pathways, the risk of dependence or abuse potential is considered minimal (U.S. Food and Drug Administration, 2013).

Efficacy

The efficacy of guanfacine XR has been demonstrated in multiple randomized controlled trials. In an 8-week double-blind, placebo-controlled trial, Biederman et al. (2008) reported a significant reduction in ADHD-RS-IV total scores, with clinical improvements that were statistically superior to placebo. Similarly, a large multicenter study by Sallee et al. (2009) confirmed that all examined doses of guanfacine XR were effective in achieving symptom control. In this study, significant ADHD-RS reductions and improvements in the Clinical Global Impressions–Improvement Scale (CGI-I) were reported. Beyond its role as monotherapy, guanfacine XR has also shown benefit when combined with stimulant medications. Wilens et al. (2012) found that adjunctive administration with long-acting stimulants enhanced symptom control, particularly during morning and evening hours. In line with this, Young et al. (2014) demonstrated that guanfacine XR not only improved ADHD symptoms but also contributed to reductions in oppositional defiant behaviors (ODD), leading to observable improvements across different times of the day. Long-term data provide additional support for sustained efficacy. In an open-label study extending over 12 to 24 months, Sallee et al. (2009) reported that symptom improvements were maintained and the overall safety profile remained favorable throughout extended treatment. Similarly, multicenter longitudinal trials conducted in Europe confirmed that guanfacine XR continued to be effective and well-tolerated during prolonged use (Huss et al., 2018). Recent systematic reviews and meta-analyses reinforce these findings. A comprehensive review by Yu et al. (2023) concluded that guanfacine XR significantly reduces ADHD symptoms while maintaining a generally positive safety profile, underscoring its clinical utility as a non-stimulant treatment option. The key clinical findings regarding the efficacy, safety, and cognitive outcomes of guanfacine XR in children and adolescents are summarized in Table 1.

Table 1. Summary of clinical findings on guanfacine XR

Study (Year)	N (Age)	Design	Duration	Key Outcomes
Biederman et al. 2008	345 (6–17)	RCT, GXR vs placebo	8 weeks	Significant reduction in ADHD-RS scores
Sallee et al. 2009	324 (6–17)	RCT	8 weeks	ADHD-RS reduction; CGI-I improvement
Young et al. 2014	333 (6–12)	RCT (morning vs evening comparison)	8 weeks	Sustained efficacy; reduction in ODD symptoms
Huss et al. 2018	1018 (6–17)	Long-term, open-label	1–2 years	Sustained efficacy and safety
Wilens et al. 2012	461 (6–17)	Combination RCT	8 weeks	GXR + stimulant superior
Kollins et al. 2011	182 (6–17)	Cognitive/psychomotor assessments	—	No impairment in cognitive performance
Yu et al. 2023	18 studies, >2500 children/adolescents	Systematic review & meta-analysis	—	Strong evidence for efficacy and predictable safety

Safety and Tolerability

Guanfacine XR is generally regarded as a well-tolerated treatment option in children and adolescents. The most frequently reported adverse effects include somnolence, sedation, dizziness, hypotension, dry mouth, and fatigue (Biederman et al., 2008; Sallee et al., 2009; Cruz, 2010). These events are usually mild to moderate in severity and can often be managed with careful dose titration during treatment. In a long-term open-label study, Sallee et al. (2009) observed that most adverse events were not clinically serious and rarely required treatment discontinuation. Consistent findings were reported in a large European multicenter trial, where safety and tolerability were sustained throughout 1–2 years of follow-up (Huss et al., 2018). Sedative effects tend to be most pronounced during the initial weeks of therapy but diminish over time as patients adapt to the medication (Faraone and Glatt, 2010). Some observational data suggest that guanfacine XR may facilitate sleep initiation and improve sleep quality (Rugino 2018). However, polysomnography-based studies have yielded mixed findings regarding its impact on total sleep duration, highlighting ongoing uncertainty in this area (Faraone and Glatt, 2010). With respect to cognitive functioning, Kollins et al. (2011) reported that guanfacine XR did not significantly impair psychomotor performance or attentional processes. Cardiovascular effects are generally limited to mild bradycardia or hypotension, which are manageable through

titration. Importantly, abrupt discontinuation can increase the risk of rebound hypertension, underscoring the need for gradual tapering when treatment is withdrawn (U.S. Food and Drug Administration 2013).

Use in Turkey and Available Preparations

In Turkey, guanfacine XR has been approved and marketed under the trade names Arislow® (Recordati İlaç) and Guago® (VEM İlaç) (Turkish Medicines and Medical Devices Agency, 2013a; 2013b). Both formulations are extended-release tablets indicated for the treatment of ADHD in children and adolescents aged 6–17 years. In clinical practice, guanfacine XR is considered an important alternative particularly for patients who do not respond adequately to stimulants, cannot tolerate their side effects, or have contraindications to stimulant use (Arnsten, 2009; NICE, 2018). While international clinical trials provide strong evidence for its efficacy as both monotherapy and adjunctive therapy, no prospective or retrospective clinical studies have yet been conducted in Turkey. The current body of knowledge within the country remains largely limited to prescribing information and clinical experience from practitioners (Turkish Medicines and Medical Devices Agency, 2013a; 2013b). Nevertheless, international guidelines consistently recommend guanfacine XR as a robust non-stimulant treatment option for ADHD (NICE, 2018; Wolraich et al., 2019). Therefore, large-scale multicenter and prospective studies are needed to strengthen the evidence base regarding the use of guanfacine XR in Turkish pediatric populations and to better inform clinical practice.

Conclusion

Guanfacine XR has emerged as a particularly valuable option for children and adolescents with ADHD who either do not respond adequately to stimulant treatment or are unable to tolerate these agents due to adverse effects (Arnsten, 2009; Wolraich et al., 2019). Evidence from randomized controlled trials consistently demonstrates that guanfacine XR produces significant improvements in core symptoms such as inattention, impulsivity, and behavioral difficulties that are often more pronounced in the evening hours (Biederman et al., 2008; Sallee et al., 2009; Wilens et al., 2012; Young et al., 2014). The pharmacological mechanism of action, mediated through α2A-adrenergic receptor agonism, allows guanfacine XR to enhance prefrontal cortical regulation, thereby supporting executive functions (Newcorn et al., 2013). This modulation contributes to measurable functional improvements, not only in academic performance but also in broader daily life activities. Sedation remains one of the most frequently reported adverse events, particularly in the early stages of treatment. However, clinical experience suggests that tolerance often develops over time, enabling most patients to continue therapy (Faraone and Glatt, 2010). Although some observational studies indicate improvements in sleep initiation and quality, polysomnographic research has produced inconsistent findings regarding overall sleep duration (Faraone and Glatt, 2010; Rugino, 2018). Long-term data, while limited, indicate that guanfacine XR maintains both efficacy and tolerability for periods of up to one to two years (Sallee et al., 2009; Huss et al., 2018). Despite these encouraging results, there is currently no locally generated clinical evidence from Turkey. Consequently, multicenter prospective studies in Turkish pediatric populations are essential to clarify the drug's effectiveness and safety profile in real-world practice (Turkish Medicines and Medical Devices Agency, 2013a; 2013b).

Guanfacine XR represents a valuable pharmacological option for the treatment of ADHD in children and adolescents, with its efficacy and safety supported by multiple clinical investigations (Biederman et al., 2008; Sallee et al., 2009; Elbe, 2014). Randomized controlled trials have consistently demonstrated significant symptomatic improvement when guanfacine XR is used either as monotherapy (Biederman et al., 2008; Sallee et al., 2009) or in combination with psychostimulants (Wilens et al., 2012; Young et al., 2014). Sedation-related side effects are most prominent during the initial weeks of treatment but generally diminish to a tolerable level over time (Faraone and Glatt ,2010). In some cases, this sedative property may confer clinical advantages, such as improved evening behavior regulation and better sleep quality. Nevertheless, polysomnography-based studies have yielded conflicting results regarding total sleep duration (Faraone and Glatt, 2010; Rugino, 2018). Findings from medium- to long-term investigations indicate that guanfacine XR preserves its therapeutic efficacy for up to one to two years while maintaining a favorable safety profile (Sallee et al., 2009; Huss et al., 2018). Furthermore, longitudinal data suggest no adverse impact on pediatric growth parameters, including height, weight, and body mass index, offering an additional clinical advantage. In Turkey, guanfacine XR is available under the trade names Arislow® and Guago®, providing clinicians with a practical alternative or adjunctive option to stimulant medications (Turkish Medicines and Medical Devices Agency, 2013a; 2013b). However, large-scale multicenter prospective trials conducted in the Turkish context are warranted to strengthen the evidence base and further establish the role of guanfacine XR in national clinical practice.

References

Arnsten, A. F. T. (2009). Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: An important role for prefrontal cortex dysfunction. CNS Drugs, 23(Suppl. 1), 33–41. https://doi.org/10.2165/00023210-200923000-00005

Biederman, J., Melmed, R. D., Patel, A., McBurnett, K., Konow, J., Lyne, A., Scherer, N., & SPD503 Study Group. (2008). A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics, 121(1), e73–e84. https://doi.org/10.1542/peds.2006-3695

Cruz, M. P. (2010). Guanfacine extended-release tablets (Intuniv), a nonstimulant selective alpha(2A)-adrenergic receptor agonist for attention-deficit/hyperactivity disorder. P & T: A Peer-Reviewed Journal for Formulary Management, 35(8), 448–451.

Elbe, D. (2014). Review of the pharmacotherapy of irritability of autism and attention-deficit/hyperactivity disorder in children and adolescents. Journal of the Canadian Academy of Child and Adolescent Psychiatry, 23(3), 195–202.

Faraone, S. V., & Glatt, S. J. (2010). A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. The Journal of Clinical Psychiatry, 71(6), 754–763. https://doi.org/10.4088/JCP.08m04902pur

Faraone, S. V., McBurnett, K., Sallee, F. R., Steeber, J., & López, F. A. (2013). Guanfacine extended release in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. Clinical Therapeutics, 35(11), 1778–1793. https://doi.org/10.1016/j.clinthera.2013.09.013

Huss, M., Chen, W., & Ludolph, A. G. (2018). Guanfacine extended release: A new pharmacological treatment option in Europe. European Child & Adolescent Psychiatry, 27(12), 1571–1581. https://doi.org/10.1007/s00787-018-1186-6

Kollins, S. H., López, F. A., Vince, B. D., Turnbow, J. M., Farrand, K., Lyne, A., Wigal, S. B., & Roth, T. (2011). Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology, 21(3), 245–252. https://doi.org/10.1089/cap.2010.0064

Martin, P., Satin, L., & Vince, B. D. (2014). Pharmacokinetics of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Clinical Drug Investigation, 34(12), 875–883. https://doi.org/10.1007/s40261-014-0240-2

National Institute for Health and Care Excellence. (2018). Attention deficit hyperactivity disorder: Diagnosis and management (NICE Guideline NG87). https://www.nice.org.uk/guidance/ng87

Newcorn, J. H., Stein, M. A., & Cooper, K. M. (2013). Dose-response characteristics in adolescents with attention-deficit/hyperactivity disorder treated with guanfacine extended release. Journal of Child and Adolescent Psychopharmacology, 23(6), 434–439. https://doi.org/10.1089/cap.2012.0103

Rugino, T. A. (2018). A review of the use of guanfacine ER in children and adolescents with attention-deficit/hyperactivity disorder. Pediatric Drugs, 20(5), 417–428. https://doi.org/10.1007/s40272-018-0302-7

Sallee, F. R., & McGough, J. J. (2009). Guanfacine extended release in the treatment of attention-deficit/hyperactivity disorder. Expert Review of Neurotherapeutics, 9(7), 917–925. https://doi.org/10.1586/ern.09.51

Sallee, F. R., McGough, J., Wigal, T., Donahue, J., Lyne, A., & Biederman, J. (2009). Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: A placebo-controlled trial. Journal of the American Academy of Child & Adolescent Psychiatry, 48(2), 155–165. https://doi.org/10.1097/CHI.0b013e318191769e

Turkish Medicines and Medical Devices Agency. (2013a). Arislow® prescribing information. Recordati İlaç.

Turkish Medicines and Medical Devices Agency. (2013b). Guago® prescribing information. VEM İlaç.

U.S. Food and Drug Administration. (2013). Intuniv (guanfacine) extended-release tablets: Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022037s009lbl.pdf

Wilens, T. E., Bukstein, O., Cutler, A. J., McBurnett, K., Rugino, T., Sallee, F. R., & Youcha, S. (2012). Efficacy and safety of guanfacine extended release as adjunctive therapy to psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. Journal of Child and Adolescent Psychopharmacology, 22(6), 402–411. https://doi.org/10.1089/cap.2012.0022

Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., Evans, S. W., Flinn, S. K., Froehlich, T., Frost, J., Holbrook, J. R., Lehmann, C. U., Lessin, H. R., Okechukwu, K., Pierce, K. L., Winner, J. D., & Zurhellen, W. (2019). Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics, 144(4), e20192528. https://doi.org/10.1542/peds.2019-2528

Young, J. L., Sarkis, E., Qiao, M., & Wietecha, L. (2014). Once-daily treatment with guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder and oppositional symptoms. Journal of Child and Adolescent Psychopharmacology, 24(8), 424–433. https://doi.org/10.1089/cap.2014.0021

Yu, G., Li, G., & Markowitz, J. S. (2023). A systematic review of guanfacine extended release in the treatment of attention-deficit/hyperactivity disorder. Clinical Therapeutics, 45(1), 4–17. https://doi.org/10.1016/j.clinthera.2022.11.006

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