The Role of Guanfacine for Adult ADHD

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Conflicts of Interest

We have no financial conflicts of interest.

Objectives

- **Understand the diagnostic criteria, epidemiology, and treatment options for attention deficit/hyperactivity disorder (ADHD)**
- Review the literature regarding the use of guanfacine extended release in the treatment of adult ADHD
- Appraise the pharmacological implications of the pharmacokinetic, pharmacodynamic, and pharmacogenomic properties of guanfacine
- Appreciate the osteopathic considerations in the care of adult patients with ADHD using guanfacine

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Diagnosis

DSM-V-TR Criteria for ADHD (APA 2022)

- A persistent pattern of inattention and/or hyperactivity and impulsivity that interferes with functioning or development.
- Several inattentive or hyperactive-impulsive symptoms were present when the child was < 12 years old.
- Several inattentive or hyperactive-impulsive symptoms are present in ≥ 2 settings (eg, at home, school, or work; with friends or relatives; in other activities.
- There is clear evidence that the symptoms interfere with or reduce the quality of social, academic, or occupational functioning.
- The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder.

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Diagnosis: Primarily Inattentive Type (APA 2022)

Must meet at least six of the following criteria

- Fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities.
- Has difficulty sustaining attention in tasks or play activities.
- Does not seem to listen when spoken to directly.
- Does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.
- Has difficulty organizing tasks and activities.
- Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
- Loses things necessary for tasks or activities.
- Is easily distracted by extraneous stimuli (for older adolescents and adults, may include unrelated thoughts).
- Is forgetful in daily activities.

Diagnosis: Primarily Hyperactive - Impulsive Type (APA 2022)

Must meet at least six of the following criteria

- Fidgets with or taps hands or feet or squirms in seat.
- Leaves seat and situations when remaining seated is expected.
- Runs about or clients in situations where it is inappropriate (in adolescents or adults, may be limited to feeling restless).
- Is unable to play or engage in leisure activities quietly.
- Is “on the go“, acting as if “driven by a motor.”
- Talks excessively.
- Blurts out an answer before a question has been completed.
- Has difficulty waiting his or her turn.
- Interrupts or intrudes on others.

When should I suspect that an adult may have ADHD?

Common presenting concerns (chadd.org)

- Inconsistent performance In jobs or careers; Losing or quitting jobs frequently.
- History of academic and/or career underachievement.
- Poor ability to manage day-to-day responsibilities, such as completing household chores, maintenance tasks, paying bills or organizing things.
- Relationship problems due to not completing tasks.
- Forgetting important things or getting upset easily over minor things.
- Chronic stress and worry due to failure to accomplish goals and meet responsibilities.
- Chronic and intense feelings of frustration, guilt or blame.

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Assessing ADHD

- Self-rated behavior scales (Taylor, 2011)(Ganzenmüller, 2024)
- Clinical Interview (Haavik, 2010)
- ADHD is highly comorbid (Kessler, 2006)
- Family or friends present (Bukstein, 2025)
- Appropriate medical examination (Sadek, 2023)

Additional considerations

- Majority of childhood ADHD cases persist into adulthood (Barkley 2002)
- Gifted in school or career (Webb, 2006)
- 2 additional DSM ADHD categories (APA, 2022)
- Possible adult-onset subtype
    - 90% of adults who met criteria for ADHD, did not meet it as children. (Moffitt, 2015)
    - Most adults with ADHD did not show symptoms as young adults or children. (Caye, 2016)
    - Those diagnosed with adult-onset ADHD has higher IQ and less problems with externalization as children. (Agnew-Blais, 2016)
    - 95% adult-onset diagnoses were false positives. (Sibley, 2018)
- Reduced Lifespan (Stott, 2025)

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Basic ADHD Pharmacotherapy

- Stimulants (FDA-approved): Amphetamine-based and Methylphenidate-based.
- Non-stimulants (FDA-approved): Atomoxetine, Viloxazine, Clonidine, and Guanfacine. (Clonidine and Guanfacine FDA-approved in children only).
- Off-label treatments (Not FDA-approved): Bupropion, Tricyclic antidepressants, Modafinil, and Memantine (Fava, 2024)

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Guanfacine XR (Intuniv®)

- Alpha 2A agonist (Fava, 2024)
- Approved for pediatric ADHD (Fava, 2024)
- 1-7mg daily (Fava, 2024)
- Initial improvement within days (NAMI)(Bello, 2015)
- Lasts 24 hours (Kaiser Permanente, 2024)
- Side effects of dizziness and drowsiness (Fava, 2024)

Advantages of Guanfacine XR

- Stimulants aren't right for every patient (Fava, 2024)
- No abuse potential (Fava, 2024)
- Lowers blood pressure (Pliszka, 2025)
- Synergistic effect with stimulants (McCracken, 2016)
- Inexpensive (Pharmacy Checker, 2025)
- Tolerable (Martinez-Raga, 2015)

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Literature review

- Systematically reviewed PubMed, APA PsychNet, and Cochrane
    - 4 relevant articles. 3 from same study series.
- The other article compared Methylphenidate/Guanfacine combination to Methylphenidate
    - No greater symptomatic reduction to either intervention, but combination intervention reduced drop out due to adverse effects.
- Lancet meta-analysis

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Best Study to Date of Guanfacine

- Guanfacine Extended Release mono-therapy trialed on 101 patients
- 100 in placebo group
- Dose optimized to 4-6 mg based on efficacy and tolerability
- Result: Guanfacine extended release superior to placebo without any serious adverse effects

Table 2. Key Efficacy Endpoints

Endpoint	Baseline, Mean (SD)	Change From Baseline, LS Mean (SE)	Difference vs Placebo	
			LS Mean (95% CI)	*P* Value
Primary Endpoint				
ADHD-RS-IV total scores[a]				
GXR	31.45 (5.92)	−11.55 (1.10)	−4.28 (−6.67 to −1.88)	.0005
Placebo	31.70 (6.83)	−7.27 (1.07)		

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Extension Trial and Post-hoc Analysis

- 124 patients completed guanfacine extended release intervention through 50 weeks
- Efficacy continued improving at 50 week mark
- No emergent treatment-related serious adverse effects
- Post-hoc analysis showed efficaciousness regardless of age, sex or ADHD subtype

Pharmacological Properties of Guanfacine and Implications for Treatment of Adult ADHD

Andrea Belovich PhD

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Dysregulation of the Prefrontal Cortex (PFC) is associated with ADHD symptoms

- The PFC mediates working memory, behavioral inhibition, and attention
  - **Top-down attention:** stimulus gating, reduced distractibility, sustained attention
- Deficits in the PFC may manifest as:
  - Distractibility
  - Hyperactivity
  - Forgetfulness
  - Reduced impulse control
  - Poor organization/planning

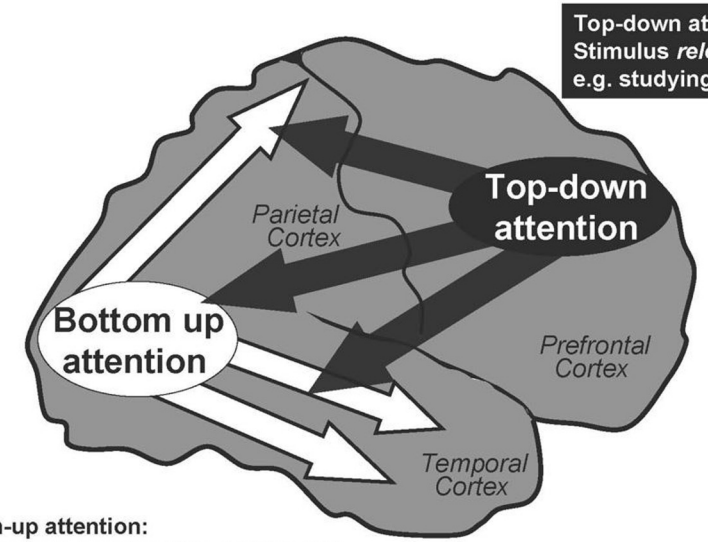


Image from Arnsten, 2009; Bidwell, 2010; Galgani, 2023

Balanced Catecholamine Signaling is Necessary for Optimal PFC Function

- Balanced norepinephrine (NE) and dopamine (DA) signaling is essential for optimal function of the PFC
    - Excess NE/DA results in mental inflexibility
    - Insufficient NE/DA results in impaired attention
- Goal of ADHD pharmacotherapy is to **restore** optimal NE/DA balance

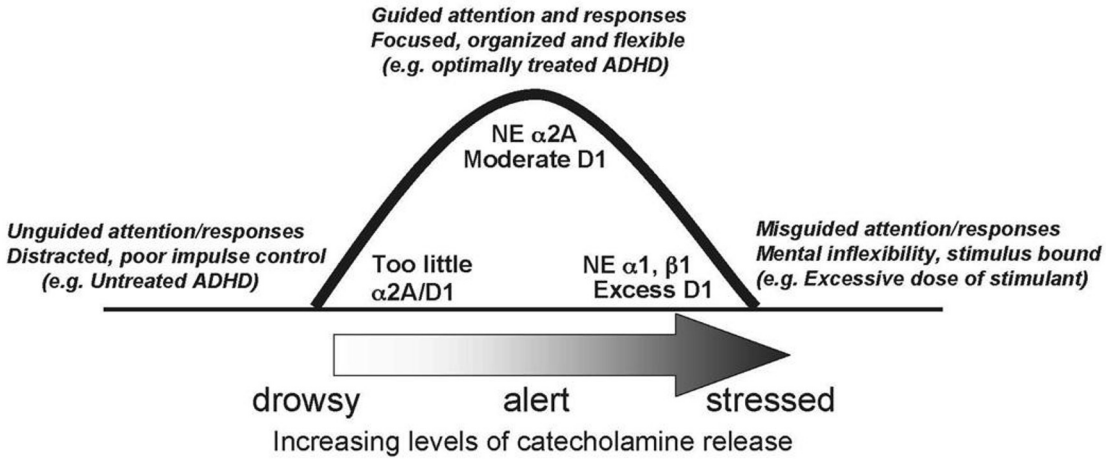


Image modified from Arnsten, 2009; Bidwell, 2010; Galgani, 2023

Noradrenergic Pathways in the Brain

- Noradrenergic cell bodies originate in the Locus Coeruleus (LC)
    - Projections extend throughout the brain, **including the PFC**, and release NE
- NE signaling mediates:
    - Attention focusing and shifting
    - Memory formation (encoding and retrieval)
    - Stress response and mood regulation
    - Sleep/wake cycle and circadian rhythm
- Deficits in NE signaling are associated with ADHD symptoms
- *Note*: *Animal studies are useful, but have inherent limitations in mapping neurophysiology to human behaviors*

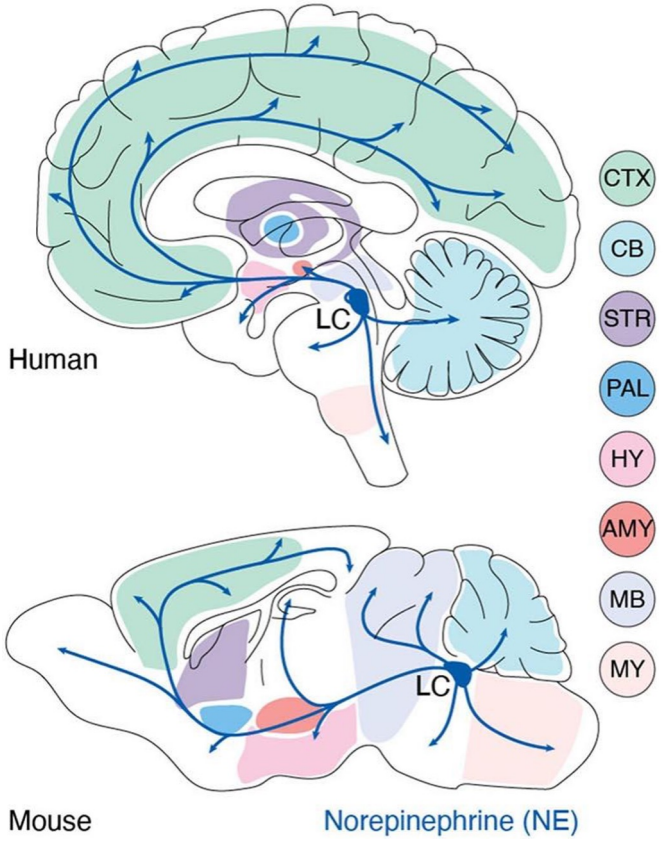


Image from Breton-Provencher, 2021; Galgani 2023

The Noradrenergic Synapse: Pharmacological Targets in ADHD Treatment

- Central adrenergic neurons synthesize and release norepinephrine (NE)
- Adrenergic receptors (AR) are GPCRs

  α_1-ARs are **excitatory**, coupled to $G_{\alpha q/11}$

  α_2-ARs are **inhibitory**, coupled to $G_{\alpha i/o}$

  $ß_1$, $ß_2$, and $ß_3$, are **excitatory**, coupled to $G_{\alpha s}$
- The Norepinephrine Transporter (NET) clears NE from the synapse after firing, terminating signal

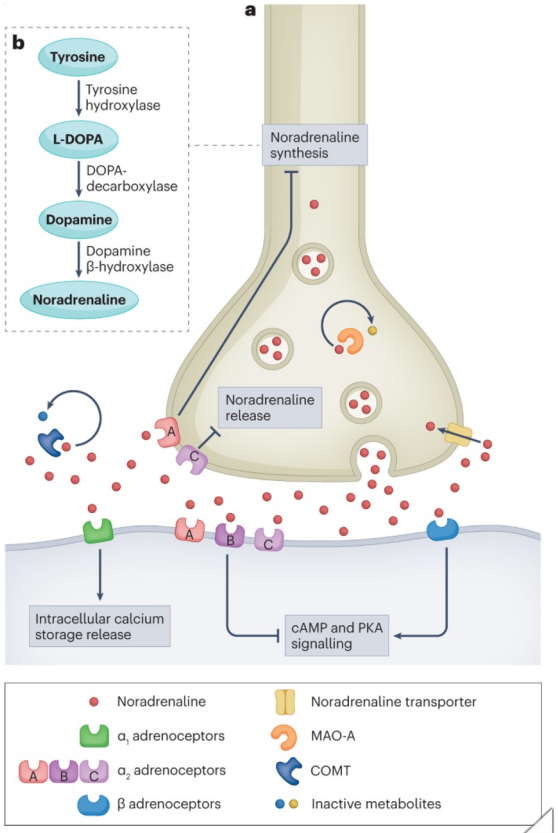


Image from Chaudhuri, 2023

Many Medications Used to Treat ADHD Modulate NE Signaling

- Stimulants (amphetamines, methylphenidate) inhibit both the Dopamine Transporter (DAT) and the NET

  Prevent reuptake of NE and DA, increasing levels of both neurotransmitters in multiple brain regions

- Nonstimulants (atomoxetine, guanfacine, clonidine) are more selective for NE

  Atomoxetine selectively inhibits NET

  Clonidine and guanfacine are α_2-AR agonists

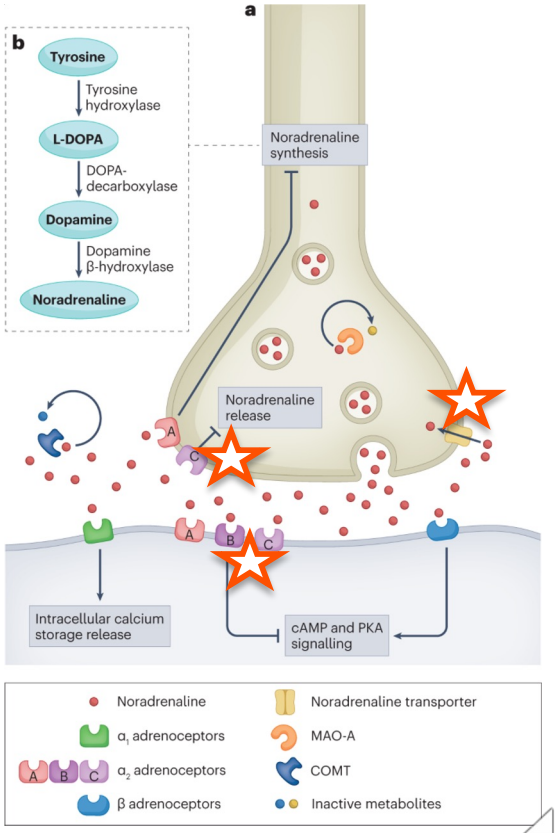


Image from Chaudhuri, 2023

Guanfacine Targets α_2-Adrenergic Receptors

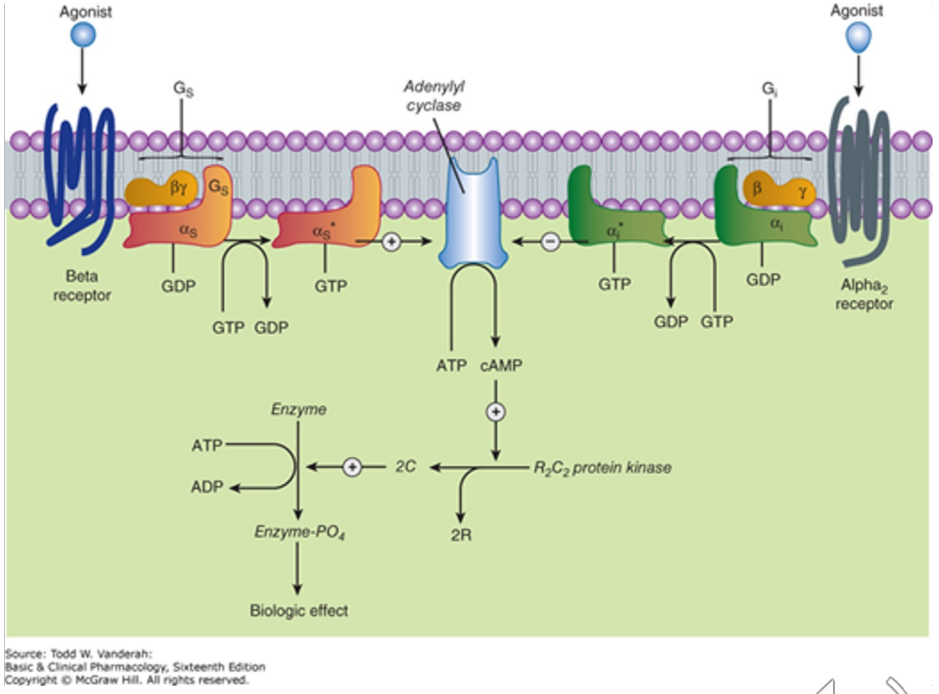
- Agonism of α_2-ARs reduces neuronal activity:

  $G_{\alpha i/o}$ activity decreases cAMP-mediated signaling

  $G_{\beta\gamma}$ activity activates inhibitory K^+ channels, and deactivates excitatory Ca^{2+} channels

- α_2-ARs may be expressed on both postsynaptic and presynaptic neurons (autoreceptors) and increase action potential threshold
- 3 subtypes with different expression profiles in the CNS (α_{2A}, α_{2B}, and α_{2C})

  In the PFC, α_2-ARs are preferentially expressed on **postsynaptic** neurons, with the α_{2A}-subtype most important for beneficial effects of NE



Source: Todd W. Vanderah:
Basic & Clinical Pharmacology, Sixteenth Edition

How does agonism of an inhibitory receptor enhance NE signaling in the PFC?

Arnsten, 2009

Mechanism: α_{2A}-AR agonism, HCN Channels, and Working Memory Networks in the PFC

- Post-synaptic dendrites of pyramidal cells in the neuronal networks mediating working memory express Hyperpolarization-activated Cyclic Nucleotide-gated (**HCN**) channels:

  HCN channels open in the presence of cAMP and “leak” membrane potential, reducing signal strength

  Closure of HCN channels increases signal strength

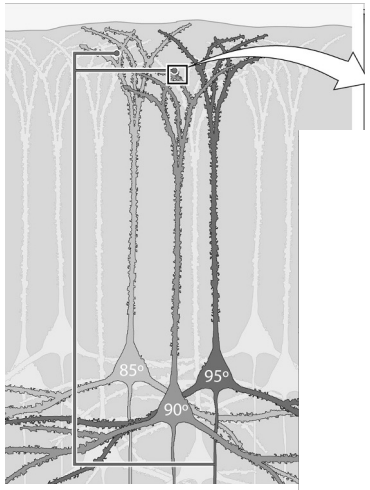


Image modified from Wang, 2007

“Signal vs. Noise” Model of Working Memory

- Working Memory requires both the reduction of undesired “noise” and preservation of desired “signal”
- **Normal NE release in the PFC supports transmission of desired “signal” in Working Memory circuits**

  Activation of α_{2A}-ARs preserves desired “**signal**”
- Normal DA release in the PFC supports “leakage” from extraneous input in Working Memory circuits

  Activation of excitatory DA receptors (D1Rs) results in signal leakage from extraneous input (“**noise**”)

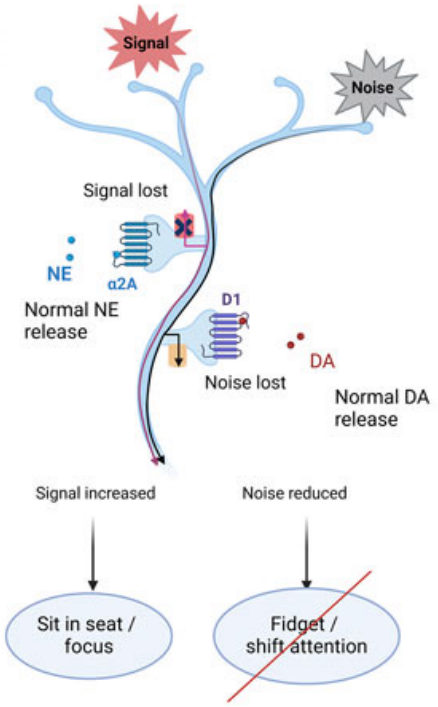


Image modified from Guo, 2024; Arnsten, 2009; Bidwell, 2010, Wang, 2007

The “Signal vs. Noise” Model Applied to ADHD Treatment

- In ADHD, both NE and DA in the PFC are decreased
  - Working memory circuit’s abilities to enhance signal and decrease noise are impaired
- Stimulants increase both NE and DA levels in the PFC, restoring the signal-enhancing effects of NE and the noise-blocking effects of DA
- **Guanfacine, as a selective α_{2A}-AR agonist, may improve working memory by reducing signal loss**
  - Supports use of guanfacine as treatment for cognitive deficits in ADHD

In general, stimulants are considered most effective at treating core symptoms of ADHD, although nonstimulants tend to have better safety profiles

ADHD

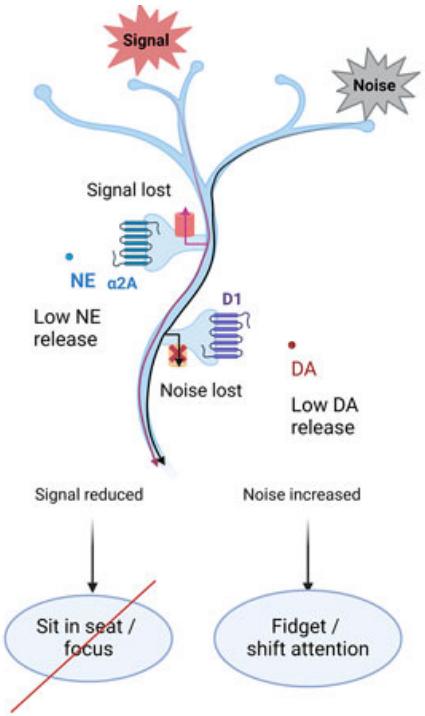


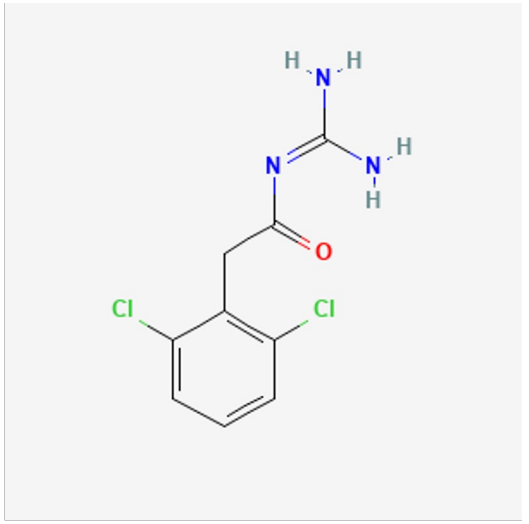
Image modified from Guo, 2024; Arnsten, 2009; Bidwell, 2010, Wang, 2007

Compound Overview - Guanfacine

α_2-selective adrenergic receptor **agonist**

10X more selective for α_2-ARs than clonidine

Greater affinity for α_{2A}-AR subtype than either α_{2B}-AR or α_{2C}-AR



National Center for Biotechnology Information, 2025; Uhlen, 1995

Guanfacine – Pharmacokinetics

- Guanfacine is available in immediate release (**GIR**) and extended release (**GXR**) oral preparations

  Daily dosage: 1 – 7 mg

  $t_{1/2}$ = 17 h (range: 10-30 hours)

- GXR and GIR formulations are **not** mass-equivalent and should not be interchanged without changing dosage

  If switching from GXR to GIR, dosage should be reduced due to increased C_{max} and AUC

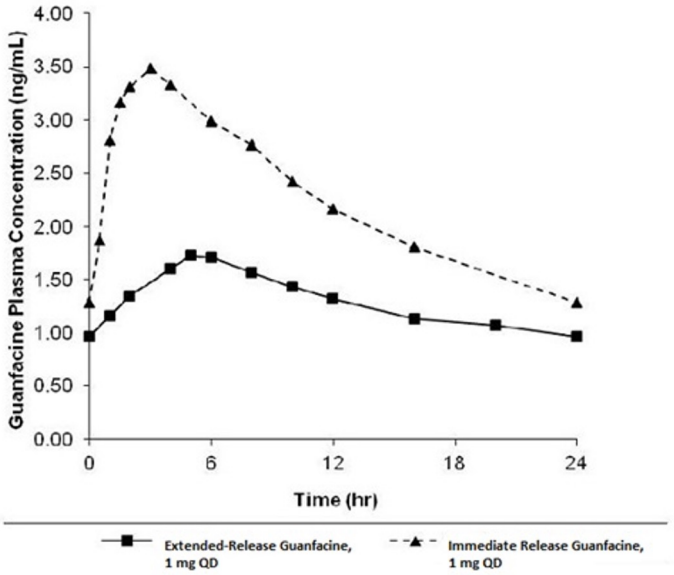


Figure 1: Comparison of Pharmacokinetics: Guanfacine Extended-Release vs. Immediate-Release in Adults

Image from Apotex, 2022; Martinez-Raga, 2015

Guanfacine – Pharmacokinetics

- **Metabolism & Elimination**

  Hepatically metabolized by CYP3A4 to 3-hydroxyguanfacine

  3-hydroxyguanfacine is then glucuronidated or sulphated and renally eliminated

  Not a **P-gp** substrate

  Not a **CYP2D6** substrate

    Limited pharmacogenomic variation in metabolism rate

National Center for Biotechnology Information, 2025; Martinez-Raga, 2015

Guanfacine – Adverse Drug Responses (ADRs)

- α_2 -ARs are expressed throughout the periphery and the central nervous system (CNS)

  CNS: cortex, cerebellum, hypothalamus, **brain stem (pons-medulla)**

  Locus coeruleus (sympathetic output), dorsal motor nucleus of the vagus (parasympathetic output)

- Agonism of α_2 -ARs in the pons medulla reduces sympathetic output

  Reduces cardiovascular tone and heart rate (hypertension)

- Monitoring parameters:

  Heart rate, blood pressure, mental alertness

Coghill, 2021; Tavares, 1996; Punnen, 1987

Guanfacine - Adverse Drug Responses (ADRs)

- GXR treatment in adults with ADHD not associated with elevated safety risks
- Fewer cardiac adverse events than treatment with stimulants
- No hepatoxicity reported, possibly due to low daily dosage (1-7mg)
- Significant ADRs:

  Sedation, orthostatic hypotension, bradycardia/syncope, decreased cardiac contractility

  Patients with preexisting conditions may be at risk for A/V block with XR formulation

Other Common Side Effects
Weight gain
Headache
Irritability
Dry mouth
Constipation

Coghill, 2021; Tropiceanu, 2022; Neuchat, 2023

Select Guanfacine Drug Interactions

- Pharmacodynamic:
  - Hypotension, CNS Depression
- Pharmacokinetic considerations:
  - CYP3A4 inducing agents
  - CYP3A4 inhibiting agents or substrates (including grapefruit juice)
- Monitoring parameters:
  - HR, BP, mental alertness

Selected Drug	Adverse Effect	Risk Rating
SSRIs (sertraline)	N/A	Considered safe
SNRIs (duloxetine)	Increased hypotension	Monitor therapy
Levetiracetam	Increased CNS depression	Monitor therapy
Valproic Acid and derivatives	CYP3A4 inhibition, may increase VA concentration	Monitor therapy
Benzodiazepines	Increased CNS Depression	Monitor Therapy
First generation antipsychotics (haloperidol)	Increased CNS Depression	Monitor therapy
Second generation antipsychotics (aripiprazole)	Increased risk of hypotension	Monitor therapy
Tricyclic Antidepressants (nortriptyline)	Increased risk of hypertension	Consider therapy modification
Carbamapezine	CYP3A4 inhibition	Consider therapy modification
Antimicrobial agents (-azole antimycotics, antiretroviral agents, etc.)	CYP3A4 inhibition	Consider therapy modification; may need to decrease guanfacine XR dose by 50%
Grapefruit juice	CYP3A4 inhibition	Consider therapy modification
Alpha2 Agonists (tizanidine)	Increased hypotension	Avoid combinatio

UpToDate, LexiDrug (2025)

Potential Withdrawal Symptoms

- Abrupt discontinuation may precipitate a withdrawal syndrome
    - Anxiety, rebound hypertension, and elevated heart rate
    - Plasma concentrations of catecholamines may be increased due to sudden lack of α_2 -AR agonism
    - Hypertension, elevated heart rate, and changes to QTc interval (in patients with underlying cardiac conditions)
- Dose should be tapered when discontinuing (up to 1 mg reduction every 3-7 days)
    - Guanfacine treatment should continue through perioperative periods
- Symptoms are generally less severe than that of clonidine due to guanfacine's longer half-life
- Higher doses and longer duration of therapy may contribute to risk of withdrawal

UpToDate, LexiDrug (2025); Martinez-Raga 2015; Reid, 1984

Guanfacine - Pharmacogenomic considerations

- Guanfacine is metabolized by CYP3A4/3A5, which is not typically recognized as a polymorphic CYP isoform
- The gene encoding α_{2A}-ARs (***ADRA2A***) is polymorphic
    - Heterogeneity in association between *ADRA2A* and ADHD
    - Potential link between *ADRA2A* and ADHD endophenotypes
- ***ADRA2A*-1291 C>G polymorphism**
    - Associated with inattentive symptoms
    - Associated with increased response to methylphenidate
    - Link between response to guanfacine and *ADRA2A*-1291 C>G polymorphism being explored
- Note: Genomind's Genecept® Assay and the GeneSight® Psychotropic Test both include the *ADRA2A* polymorphism, AmpliChip does not

Polancyzk, 2007; Bidwell, 2010; Hoang, 2018; Maruf, 2020

Summary

- **Balanced NE/DA signaling in the PFC is necessary for optimal function**
  - Insufficient DA and NE signaling in the PFC contribute to core ADHD symptoms
  - Restoration of DA and NE signaling is therapeutic mechanism to alleviate common ADHD symptoms
- **Adrenergic receptors play a significant role in mediating attention and working memory in the PFC**
  - α_{2A}-ARs are the predominant receptor subtype expressed on postsynaptic neurons in the PFC
  - Agonism thought to reduce "signal leak" in working memory networks in the PFC and facilitate attention
- **ADHD medications enhance NE signaling in the PFC**
  - Stimulants (amphetamine, methylphenidate) block reuptake of both DA and NE in the PFC
  - Nonstimulants (atomoxetine, clonidine, guanfacine) are more selective for NE
    - Atomotexine is selective NET inhibitor
    - Clonidine is an α_2-AR agonist
    - Guanfacine is a selective α_{2A}-AR agonist
- **Compared to stimulants, α_2-AR agonists**
  - May not be as effective at controlling core symptoms (esp. hyperactivity)
  - Have a generally safer ADR-profile than stimulants (lower arrhythmia risk)
- **Compared to clonidine, guanfacine:**
  - Is much more selective for α_{2A}-ARs
    - Less effective against inattentive subtypes
    - Less impact on heart rate, blood pressure, and sedation
    - Increased risk of long-term weight gain
  - Is metabolized by CYP3A4, not polymorphic CYP2D6
    - Risk of drug-drug interactions
    - Lower risk of overdose/failure due to absence of slow/rapid metabolizing allele
  - Has a longer half-life ($t_{1/2}$)
    - Lower risk of withdrawal symptoms

Osteopathic Considerations in the Care of Adult Patients with ADHD

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Psychotherapy for Adults with ADHD

- Adults with ADHD have higher rates of emotional dysregulation
- 3 RCT found significant benefit of Med+CBT>Med alone, 1 RCT no benefit
    - CBT targeting executive dysfunction (CBT-EF)
        - organization, prioritizing tasks, and planning not challenging irrational cognitions
- Little to no evidence
    - Dialectical behavior therapy
    - Mindfulness Based Cognitive Therapy
- Evidence of no effect
    - Neurofeedback

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Psychotherapy for Adults with ADHD

- Stimulants
  - Amphetamines
    - Amphetamine, Dextroamphetamine/Amphetamine
  - Methylphenidate
    - Methylphenidate, Dexmethylphenidate, Lisdexamphetamine, Serdexmethylphenidate/dexmethylphenidate
- Non-stimulants
  - Atomoxetine (SNRI)
  - Viloxazine (SSNRI)

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Osteopathic Considerations Adult ADHD

- ADHD is a Body Unit disorder effecting Body, Mind and Spirit
  - Treatment should target all elements- avoid biological reductionism
    - Body- Exercise, nutrition, medications, OMT
    - Mind- CBT-EF, Comorbidity focused psychotherapy
    - Spirit- Value system utilization

Osteopathic Considerations Adult ADHD

- Medication Considerations
  - ADHD Associated Areas: DLPFC, ACG, Frontal, Corpus Striatum, Corpus Callosum, Cerebellar Vermis
  - Not a precise understanding of condition or medication mechanisms
    - Dopamine and NE effects
- Stimulants best evidence
- Augmenting with non-stimulants for additional symptom management (McCracken) or primary option for those with substance use risk
- Guanfacine
  - No adult FDA approval, Studies reviewed show benefit, low risk mechanism/side effect profile
  - Consider taking at bedtime while stimulant is taken in morning

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Summary

- ADHD occurs into adulthood
- Novel pharmacologic mechanism
- Pharmacodynamic, pharmacokinetics and pharmacogenetics
- Stimulants have FDA approval and best evidence for ADHD child and adult
- Non-stimulant options can be clinically indicated or augmentation option
- Guanfacine XR has efficacy evidence in adults with ADHD
- Reasonable option for mono therapy or as an adjunct to a stimulant

Thank you
Questions?

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