ADHD PHARMACOLOGIC TREATMENTS IN CHILDREN & ADOLESCENTS

(Non Stimulant Medications)

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ADHD TREATMENT:

- Pharmacological treatment of ADHD is the best studied intervention in child and adolescent psychiatry.
- In the treatment of ADHD there are both **stimulant** and **non-stimulant** medications to consider.
- ***Stimulant Medications***:
  - Meyhylphenidate preparations
  - Amphetamines preparations
- ***Non Stimulant Medications:***
  - Atomoxetine
  - Clonidine
  - Guanfacine

GENERAL PRINCIPLES

- The **principal treatment** for ADHD is **pharmacological**, involving **Stimulants**, **Atomoxetine**, and **α agonists**.

- **Stimulants**, **Atomoxetine**, or **α agonist** can be used as **first-line treatment**, although stimulants are typically preferred as the initial choice because of **larger effect size** and **rapid onset of action.**

- The **α agonists** and **Atomoxetine** may be used as **monotherapy** or may be **added to a stimulant for partial responders**.

GENERAL PRINCIPLES

- Psychosocial interventions (primarily **behavior therapy**) for ADHD should be added when:

1-comorbid disorders are present or

2-response to pharmacological intervention does not result in remission of symptoms.

- behavioral treatment showed stronger effects for a range of parenting behaviors and behavioral problems than for core ADHD symptoms.
- Behavior management can be used as a stand-alone treatment (particularly in milder cases) or in combination with medication treatment in cases of partial response.

GENERAL PRINCIPLES

- approximately **41%** of subjects with ADHD responded equally to MPH and amphetamine, while **44%** responded preferentially to one of the classes of stimulants.
- the initial response rate to stimulants There for may be as high as **85%** if both stimulants are tried (in contrast to the finding of a **65%–75%** response rate when only one stimulant is tried).
- At present, there is no method to predict which stimulant will produce the best response in a given patient.
- If one class of stimulant (methylphenidate or amphetamine) does not yield satisfactory results, **the other class of stimulant** should be used.

GENERAL PRINCIPLES

- **Dose for behavior may not be optimal for attention.**

- With any of the drugs, it is important to **start low** and **titrate, preferably weekly**, to **individual optimal effect**. Because of **wide individual variability in sensitivity**, the size of the patient is only a rough guide to dose:

  One 30-kg child may require and tolerate 30 mg/day of amphetamine while another 30-kg child has an optimal response to 5 mg/day, with severe side effects above 10 mg.

GENERAL PRINCIPLES

- ADHD is associated with **comorbid disorders**, including **anxiety** (~33%), **depression** (~11%),**oppositional defiant/conduct disorders** (up to 50%), **learning disorders** (~20%), and,
  bipolar disorder (4%–16%) and… .

- Comorbid disorders **complicate treatment** and Comorbidity **influences the order of agents** used for the treatment of ADHD.

GENERAL PRINCIPLES

- ***When anxiety is present:***

1-Atomoxetine may be more likely to treat symptoms of both disorders.

2-Alternatively, treatment may be initiated with a **Stimulant for ADHD symptoms**, and a **SSRI** may be added in order to address remaining anxiety.

GENERAL PRINCIPLES

- ***comorbidity of ADHD and MDD:***

1-the clinician should determine which of the two disorders is most severe; the **MDD Medication** should be initiated if the **depressive disorder** is causing the **most impairment**.

2-In contrast, if the **ADHD** is clearly more problematic, pharmacological intervention for it should take precedence.

3- Whichever disorder is treated first**, treatment for the comorbid disorder should be added if monotherapy does not lead to remission of both ADHD and depressive symptoms**.

GENERAL PRINCIPLES

- ***comorbidity of ADHD and TIC:***

1-the presence of tics is not a contraindication to the use of Stimulants for treatment of ADHD .

2-The clinician should step through the various agents until one is found that reduces ADHD symptoms without worsening tics.

3- Atomoxetine may reduce tics .

4-In some cases, the ADHD can be controlled only by a stimulant that worsens the child's tics; an **α agonist** can be **added to the stimulant** to remedy this situation.

GENERAL PRINCIPLES

- ***Comorbidity of ADHD and BMD***:

1-response to both *ADHD treatments* and *mood-stabilizing treatments* is often less robust than in the uncomplicated versions of either condition.

2- Atypical anti-psychotics alone appear to be more effective than mood stabilizers alone.

3-In the case of clear acute mania, consensus documents recommend stabilizing the mood disorder symptoms **first** and **then** treating the comorbid disorder.

ADHD TREATMENT

- **Non Stimulant Medications:**

- **Atomoxetine**
- **Clonidine**
- **Guanfacine**

ATOMOXETINE(STRATTERA)

- a **Selective Norepinephrine Reuptake Inhibitors**
- selectively inhibits the presynaptic norepinephrine transporter and has some indirect agonism on dopamine.

- US FDA-approved for monotherapy of ADHD in children from the **age of 6 years** and **adolescents** and **adult**.

- In contrast to methylphenidate and amphetamine, *full therapeutic effect and clinical efficacy* was not evident immediately after the first dose, but developed gradually after repeated administration (between **3** and **7** weeks).

- However, *some benefits* may be noticed *after the first dose*.

ATOMOXETINE

- Available in **10**, **18**, **25**, **40**, **60**, 80, 100 mg **cap**

- Capsules can be taken with or without food .

- Absorption is minimally affected by food, but taking it with meals does result in a 9% lower maximum plasma concentration in children and adolescents.

- Capsules should not be opened because the contents of the capsule may be an skin and ocular irritant.

- Duration of action :at least **10 to 12 hrs**

ATOMOXETINE

- Can be taken once or twice per day
- it can be taken at any time of the day
- once daily: efficacy is better with **morning** than evening dosing
- **Evening dosing** is associated with fewer overall adverse effects than morning dosing and may be **better tolerated when initiating therapy**

ATOMOXETINE *indication*

- often used as either a **second-line agent** or as an **augmentation strategy:**

1-patients who have **failed one or more stimulants**, a trial of atomoxetine is often considere(indadequate response to stimulants).

2-can be used as an **augmenting agent for those patients whose stimulant dose has been maximized**. the stimulant dose can be reduced and Atomoxetine can be added to the regimen.

3- patient with **unpleasant medication side effect with a stimulant** and can not tolerate stimulant medication.

ATOMOXETINE *indication*

- Atomoxetine is usually use as second-line therapy for ADHD

- Atomoxetine may be considered **a first-line agent** In the case of patients with history of:

1-comorbid substance abuse

2- **Family member with a substance abuse problem**

3-comorbid anxiety

4-Comorbid tics

- some patients who take it for ADHD have noticed improvements in their symptoms of ***depression***, ***anxiety***, and/or ***tics***.

ATOMOXETINE *Pharmacokinetics*

- Metabolism is hepatic via **CYP2D6**. (Atomoxetine itself neither inhibits nor induces the CYP2D6pathway)

- rapidly resorbed in adults and children; the maximal plasma concentration (c max) is reached after **1–2 h**.

- In poor metabolizers with lower CYP2D6 activity, this can be considerably longer, leading to a **fivefold increase** in c max .
- Poor metabolizers have **higher plasma concentrations** of atomoxetine compared with people with normal activity.

ATOMOXETINE *Dosages*

- dosage for children and adolescents is **weight-dependent**.

- **usually** administered as a **single morning dose**, but can, if necessary, also be given in the evening or divided into two doses.

- ***starting dosage*** : 0.5 mg/kg per day during the first week.
- The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to ***clinical response*** and ***tolerability***.
- ***target dosage*** :**1.2 mg/kg per day** can be administered.
- ***Maximum daily dose:*** **should not exceed 1.4 mg/kg or 100 mg/day, whichever is less.**

ATOMOXETIN*E* ***Dosages***

- A slow increase in dosage from the first to the third week (e.g., 10, 18, 25 mg) probably decreases the number of treatment-emergent adverse events.

- Where tolerability to Atomoxetine is a problem:

1- slower increase in dosage is recommended.

2-Administration of the capsule with food .

- daytime sleepiness as a side effect can be addressed by administering the drug in the evening or bedtime.

ATOMOXETIN*E* ***Dosages***

- *Dose adjustment in moderate* ***hepatic problems***: 50% reducing dose
- patient with ***renal insufficiency***:No dosage adjusment

  (but may exacerbate hypertension in end-stage renal disease)

- *coadministration of MPH and atomoxetine* did not increase cardiovascular effects beyond those seen with MPH alone.
- ***Poor Metabolizers:***
- • Oral: Initial: 0.5 mg/kg/day
- • If initial dose well tolerated therapy but inadequate response, may increase **after a minimum of 4 weeks to target dose**

ATOMOXETIN*E* ***Dosages***

- Dose adjustments may be necessary for patients receiving **drugs that are strong inhibitors of CYP2D6** :Fluoxetine Paroxetine**…**

- Atomoxetine may be discontinued without a taper, although a taper may be recommended.

- **switching from a stimulant to Atomoxetine:**

1-**Stimulan**t medication should be **continued for the first few weeks**

2- If switching from Atomoxetine to stimulants for lack of response, **Atomoxetine can be stopped abruptly**

ATOMOXETIN*E* ***Adverse Drug Reactions***

- generally **well tolerated** in the long-term treatment of children and adolescents with ADHD and **ADRs** are **mostly temporary**.

- It appears better tolerated among extensive(normal) metabolizers than poor metabolizers.

- In **poor metabolizers**, ADRs such as reduced appetite, problems with falling and staying asleep, urinary incontinence, depressive mood, and tremor are considerably more frequent than in normal metabolizers.

ATOMOXETIN*E* ***Adverse Drug Reactions***

- In children and adolescents, sedation,Fatigue,headache, abdominal pain, reduced appetite, nausea, and vomiting are the **most frequent ADRs (≥ 5 %**) and can lead to discontinuation of medication.

- Loss of appetite and the associated weight reduction appear to be dose-dependent.

- Following mild initial weight loss(average of **0.5Kg**), patients treated with atomoxetine tend, however, to increase in weight 6–9 weeks later.

ATOMOXETIN*E* ***Adverse Drug Reactions***

- Increased cardiac rate(pulse) of up to 5 beats/min often occurs, as does a mild increase in blood pressure, but orthostatic hypotention may also be experienced.

- Probable mild growth slowing:

1-In general, gains in both height and weight for patients taking Atomoxetine are less than expected for the **first 9 to 12 months** of medication use.

2-**After approximately 12 months**, gains in height and weight stabilize with them approaching expected norms.

ATOMOXETIN*E* ***Adverse Drug Reactions***

- Dryness of mouth, insomnia, constipation,and mood swings, aggression,irritability and dysphoria, diarrhea,constipation, dizziness i**nfrequently** can also be experienced.

- **Bipolar Disorder :**

-Monitor patients to avoid possible induction of a hypomania or mixed/manic episode.

- **Aggressive behavior/Agitation:**

- Monitor for New or worsening symptoms of hostility or aggressive behaviors particularly with the **initiation of therapy.**

- Attention should be given to the possible development of depression.

ATOMOXETIN*E* ***Adverse Drug Reactions***

- meta-analysis studies in children with ADHD and comorbid tics, Atomoxetine significantly improves comorbid tics, some case reports have described an exacerbation of tics during Atomoxetine treatment.

- **some adults** have developed urinary hesitancy and retention, priapism, and/or sexual side effects with this medication

ATOMOXETIN*E* ***Adverse Drug Reactions***

HEPATOTOXICITY: Rare but important

- attention should be paid to clinical symptoms of hepatic disease: pruritus, jaundice, dark urine, upper right-side abdominal tenderness, or unexplained "flu-like" symptoms.
- at the first sign of such symptoms, **treatment should be discontinued** and **not resumed.**
- Monitor liver enzymes upon any sign or symptom of liver dysfunction
- The majority of reported cases occurred within **4 months of initiation of therapy.**
- **do not restart** in patients with **jaundice** or **laboratory evidence of liver injury**

ATOMOXETIN*E* ***Adverse Drug Reactions***

- **FDA black box warning** regarding **suicidal ideation** in children and adolescents: the frequency of suicidal ideation was greater among Atomoxetine(0.4 %) than placebo (0 %).
- no suicides occurred in the trials included in the meta- analysis.
- no difference was found between Atomoxetine and methylphenidate-treated patients.

- **Comorbidities occurring with ADHD may be** associated with an increase in the risk of suicidal ideation and/or behavior.

- Closely monitor patients particularly:

1-during the **first 4-5 months of therapy**

2- when the **dose** is **increased** **or** **decreased**

ATOMOXETINE ***TOXICITY***

- **Symptoms of overdosage :**
- somnolence, agitation, hyperactivity, gastrointestinal symptoms, and indications of sympatheticactivation(mydriasis,tachycardia).
- QT interval prolongation is very rarely observed.
- Cases of fatal overdose with :have been reported, but this has only occurred where patients had been treated with at least one other medication

❑ **Treatment of overdosage :**

respiratory support, activated charcoal during the first few hours, and symptomatic measures with regard to cardiac and vital functions.

ATOMOXETINE ***Monitoring Parameters***

- **cardiac history** at baseline
- **pulse** and **BP** at baseline and priodically during treatment
- **LFT** at first sign and symptoms of liver dysfunction
- **Growth** (weight and height) and **appetite** in children
- **Sleep** and **behavioral changes**.
- Monitor for increased **irritability**,**anger**,**aggressive behavior**, **depression**,possible **mania/hypomania**,**suicidal thought**
- Periodically re-evaluate the long-term usefulness of atomoxetine

ATOMOXETIN*E* ***Drug Interactions***

- Caution is required where Atomoxetine is combined with other medications.

- Concurrent administration of **CYP2D6 inhibitors,**including **paroxetine, fluoxetine**, **thioridazine**, **metoprolol**, or **propanolol**,can require:

1-downward adjustment of the atomoxetine dosage, as levels of atomoxetine and its major metabolites may be increased three- to fourfold.

2-Slower titration and final lower dosage of atomoxetine may be necessary in patients who are already taking CYP2D6 inhibitor drugs.

ATOMOXETIN*E* ***Drug Interactions***

- Coadministration of atomoxetine and **beta-2 agonists** (e.g., **salbutamo**l) can result in clinically significant increases in blood pressure and heart rate.
- Atomoxetine should be administered with caution to patients treated with high-dose nebulized or systemically administered salbutamol .

- **Drugs that affect noradrenaline should be used cautiously when coadministered with** Atomoxetine because of the potential for additive or synergistic pharmacological effects.

Examples include antidepressants such as imipramine, venlafaxine, and mirtazapine, or the decongestants pseudoephedrine or phenylephrine.

ATOMOXETIN*E* ***Drug Interactions***

- There is a potential for an increased risk of QT interval prolongation when atomoxetine is administered with other QT prolonging drugs such as:
- **antipsychotics**
- **class IA and III antiarrhythmics**
- **Erythromycin**
- **methadone**
- **tricyclic antidepressants**
- **lithium**
- **drugs that cause electrolyte imbalance (such as**
- **thiazide diuretics**),
- **drugs that inhibit CYP2D6(fluoxetine,paroxetine)**

ATOMOXETIN*E* ***Drug Interactions***

- Caution is advised with concomitant use of **medicinal drugs which are known to lower the seizure threshold such as tricyclic antidepressants or SSRIs, antipsychotics(**phenothiazines or butyrophenone), **mefloquine**, **chloroquine**, **bupropion**, or **tramadol**.

- In addition, caution is advised **when stopping concomitant treatment with benzodiazepines** due to potential withdrawal seizures.

- Changes in gastric pH **do not affect the bioavailability of Atomoxetine**, so no dosing adjustments need to be made if a patient is also being treated for gastroesophageal reflux.

ATOMOXETIN*E* ***Contraindication***

1-Known Hypersensitivity to drug

2-congenital or acquired long QT syndrome and Family history of prolonged QT interval

3-Current or past history of pheochromocytoma

4-increases in **diastolic blood pressure** ≥ 15mmHg, **systolic blood pressure** ≥ 20 mmHg and/or heart rate (≥20 beats per minute).

5-Severecar diovasculardisorders

6- It cannot, be combined with nonselective MAO inhibitors (discontinuation of the one agent must have been completed at least 2 weeks prior to initiating therapy with the other).

7- severe hepatic dysfunction

8-narrow-angle glaucoma(increased Risk of mydriasis)

ATOMOXETIN*E* ***Advantages*** *versus* ***Disadvantages***

- ***Advantages :***

1-treats ADHD core symptoms:inattention,hyperactivity,impulsivity

2- Nearly as effective as stimulants

3- lack of euphoria and lack of abuse potential

4- long pharmacodynamic half-life,Continuous duration of effect (provide 24-hour treatment of ADHD symptoms and Lower risk of rebound)

5- Little or no insomniac side effect (generally does not worsen sleep)

6- generally does not worsen Tic(good choice with comorbid tics)

7- Some benefit for comorbid oppositional defiant symptoms

8- May help comorbid depression and anxiety

ATOMOXETIN*E* ***Advantages*** *versus* ***Disadvantages***

- ***Disadvantages:***

1- Slower attainment of full effect than stimulants(slower onset)

2-Possibly longer time than stimulants to flush out if adverse effect

3-Probable mild growth slowing and other probable side effects

4-Irritating to skin or eye if capsules opened(The capsule should be swallowed intact)

5- in rare instances tics and anxiety have been worsened by the initiation of atomoxetine.

6- Allergic reactions(rash)

Atomoxetine Versus Stimulants in the Treatment of ADHD in Children and Adolescents

- Atomoxetine and IR MPH have comparable efficacy in the treatment of ADHD and there was no significant difference between MPH and Atomoxetine.

- OROS MPH was considered to be more effective than Atomoxetine.

Atomoxetine in the Treatment of ADHD in Children and Adolescents

- With Atomoxetine:
- 47% of patients were much improved
- 13% had a minimal response
- 40% did not respond.

- most of the responders had at least some improvement in symptoms **by week 4 of treatment**.

- perhaps any patient who is a **nonresponder at week 4** should either have another agent added to the Atomoxetine regimen or should be switched from Atomoxetine to another medication

Atomoxetine in the Treatment of ADHD with Comorbid ODD

- ADHD and ODD are frequent comorbidities
- Atomoxetine resulted in statistically and clinically significant improvements.
- **higher doses** and **divided doses twice a day** are required when ODD is comorbid with ADHD.

Atomoxetine in the Treatment of Children and Adolescents Diagnosed with Comorbid Anxiety Disorder

- **25% to 35%** of children with ADHD have comorbid anxiety disorders.

- double-blind study of patients (age 8 to 17 years old) with ADHD and comorbid generalized anxiety disorder, separation anxiety disorder, and/or social phobia showed that **Atomoxetine was efficacious in reducing both ADHD symptoms and anxiety symptoms**.

Atomoxetine in the Treatment of Children and Adolescents Diagnosed with ASD

- a 8-week double-blind study which included 97 patients between the ages of 6 and 17 with an **ASD and ADHD-like symptoms** showed that **hyperactivity improved significantly** with Atomoxetine compared with placebo.

- Atomoxetine **moderately improved ADHD symptoms** and was generally well tolerated in this group.

- the effects of medications on the treatment of ADHD-like symptoms associated with an ASD are **less robust than the effects of medications on patients with ADHD-only**.

Atomoxetine in the Treatment of Children and Adolescents Diagnosed with ADHD and Lower IQ

- patients with **ID and ADHD-like symptoms** show clinically significant improvements in their ADHD-like symptoms with the use of Atomoxetine.

- children and adolescents with **IQs <85** were less likely to respond to Atomoxetine than children and were adolescents with IQs ≥85.

ALPHA2-ADRENERGIC AGONISTS

- **Clonidine IR(Catapres)**
- **Clonidine Hydrochloride Extended Release (Kapvay)**
- **Clonidine (Catapres-Transdermal Therapeutic System)**
- **Guanfacine IR(Tenex)**
- **Guanfacine Extended Release(GXR) (Intuniv)**

overview

- Immediate-release clonidine and I.R.Guanfacine does not have an FDA-approved indication for the treatment of ADHD.

- However, immediate-release clonidine and Guanfacine has been widely used in children with ADHD.

- Clonidine Extended Release(**CLONXR**/ **Kapvay**)and Guanfacine Extended Release (**GXR**/ **Intuniv**) FDA approval in patients **ages 6–17 years** with ADHD.

- compared with methylphenidate clonidine worked as well as methylphenidate on ADHD symptoms, but clonidine was most helpful for impulsivity and hyperactivity and not as helpful for inattention.

overview

- Clonidine is an **alpha-2-adrenergic receptor agonist**
- There are 3 different subtypes of alpha-2 adrenoceptors: the 2A, 2B, and 2C.
- **2A** and **2C**: wide distributions in the brain,specially in the prefrontal cortex (PFC) (**A subtype** being more prevalent)
- **2B** :thalamus
- these varying brain areas may account for their effects on cognitive as well as emotional functioning.
- alpha-2 agonists exhibit their therapeutic effects by strengthening (PFC) regulation of attention and behavior through direct stimulation of postsynaptic **alpha-2A adrenoceptors**

overview

- Alpha-2 agonists bind to the alpha-2B and alpha-2C receptors as well.

- ***All three alpha-2-adrenoceptors subtypes*** are associated with **sedative effects.**

- **hypotensive effects :**associated with **subtype 2C**.

- Clonidine bind to all three alpha-2-receptor subtypes fairly equally, whereas **guanfacine** appears to be 15× to 20× more selective for the **alpha-2A-receptor subtype**.(Less sedation and Hypotension *than Clonidine*)

CLONIDINE and Guanfacine *indication*

- The most common past use of clonidine in pediatric psychiatry was treatment of: **Tourette's disorder /other tic disorders**, **ADHD**, and **ADHD-associated sleep disturbances**.

- The only formulation that has a pediatric indication for ADHD are clonidine and Guanfacine extended release (CXR), which are indicated for the treatment of ADHD as **monotherapy** and as **adjunctive therapy to stimulant** medications.

- However Clonidine IR Frequently prescribed off-label for the treatment of ADHD,and comorbid conditions anxiety, insomnia, tics, and aggression.

CLONIDINE *Dosages*

- **Clonidine IR(Catapres):**Tablets 0.1 or 0.2 mg
- Clonidine should be titrated gradually
- **Daily dose :0.003–0.01mg/kg** tid or qid
- **Initial dose :0.05 mg at bedtime**
- **increase every 3 to 7 days in 0.05 mg/day**
- **maximum daily dose(≤45 kg): 0.2- 0.3 mg/day**
- **maximum daily dose (>45 kg): 0.4 mg/day**
- When **discontinuing** therapy, taper **over 1 to 2 weeks** (gradual tapering)

CLONIDINE *Dosages*

- **Extended release (Kapvay):**tablets 0.1 or 0.2 mg(must be swallowed whole and never crushed, cut, or chewed) **Recommended dosage** is from **0.1 mg once a day** up to **0.2 mg bid**.
- (**Daily dose:0.003 - 0.01 mg/kg)**
- **starting dose:0.1 mg at bedtime**
- titrated to response in increments of **0.1 mg at weekly intervals**
- **maximum daily dose:0.4 mg/day**
- should be administered **twice per day**
- **Divided equally** or with the **higher dose administered at bedtime**
- When **discontinuing** therapy**, taper daily dose by no more than 0.1 mg every 3 to 7 days.**

CLONIDINE *Dosages Adjusments*

- **Dosing adjustments: Renal Impairment:**
  - consider using doses **at the lower end of the dosage range**
  - monitor patients closely

- **Dosing adjustment: Hepatic Impairment:**
  - There are **no dosage adjustments provided** in the manufacturer's labeling.

- Clonidine does not significantly affect exposures of methylphenidate and lisdexamfetaminewhen coadministered: no dose adjustments in methylphenidate or lisdexamfetamine are necessary.

Guanfacine Dosages

- **Guanfacine IR (Tenex):):**Tablets 1 or 2 mg
- **Daily dose :0.003–0.01 mg/kg/day bid or tid**

- ***Children up to 11 years of age:***
- **starting dose:**0.5 mg/day and, on the basis of clinical response, individually titrated guanfacine in **0.5-mg increments every 3 days** to a **maximum** of **4 mg/day**

- ***Adolescents ≥12 years of age and adults****:*
- ***Initial* dose** of **1 mg at bedtime** is recommended to minimize the impact of any initial sedation
- If clinically indicated, higher doses may be administered.

Guanfacine Dosages

- **Guanfacine extendedrelease(Intuniv):** *tablets:1,2, 3, and 4 mg*
- **Daily dose 1–4 mg Once daily (morning** or **evening)**

- **Begin** at a dose of 1 mg/day and adjust in increments of **no more than 1 mg/week.(**Maintain dose range of 1–4 mg once daily, depending on **clinical response** and **tolerability.**

- **Starting doses range** as **monotherapy** or **adjunctive therapy** with stimulant :**0.05 to 0.08 mg/kg** once daily.

- Efficacy increased with increasing weight-adjusted dose (mg/kg).
- If well tolerated, doses **up to 0.12 mg/kg** once daily may provide additional benefit.

Guanfacine *Dosages Adjusments*

- Clonidine does not significantly affect exposures of methylphenidate and lisdexamfetaminewhen coadministered: no dose adjustments in methylphenidate or lisdexamfetamine are necessary .

- **Dosing adjustments: Renal Impairment:**
- Guanfacine and its metabolites are excreted in the urine:clearance of guanfacine in patients with varying degrees of renal insufficiency reduced,but plasma levels of drug only slighty increased compared to patients with NL renal function.

CLONIDINE *Adverse Drug Reactions*

- Clonidine is not known to be associated with long-term adverse effects.
- Guanfacine ADRs:Same as clonidine but:Less sedation and hypotension

- The most common short-term adverse effect :**Sedation**(**28%**)
- Sedation is most severe during the **first 2 to 4 weeks**, after which tolerance usually develops
- ***In some cases***:
- hypotension and low heart rate (rare)(hypotension not usually clinically significant)
- fatigue
- dry mouth
- depression

CLONIDINE *Adverse Drug Reactions*

- confusion (with high dose)
- Irritability
- Sore throat
- Trouble sleeping(insomnia)
- Nightmares
- Change in mood:Clonidine worsened or induced depressive symptomatology in approximately 5% of children
- Constipation
- Stuffy nose
- Increased body temperature

Effects of CXR and Clonidine IR on the ECG of Children and Adolescents

- In the CXR studies, there were no changes on ECGs to suggest a medication related effect.

- clonidine **alone** or **in combination with stimulants** has no significant effect on ECG parameters. (PR, QRS, and QTc intervals)

- clonidine alone or in combination with stimulants had no systematic cardiac effects on these behaviorally disturbed children, but that
- **"rare idiosyncratic responses"** could occur.

CLONIDINE /Guanfacine *Withdrawal Symptoms*

- Suddenly stopping clonidine may cause **withdrawal symptoms**:
- increased blood pressure
- headache
- increased heart rate
- lightheadedness
- tightness in the chest
- nevousness and Anxiety.

- Because of its short serum half-life,clonidine is sometimes administered three to four times daily and at bedtime.

some children have shown a loss of therapeutic effect or withdrawal symptoms when it is **administered less frequently**

CLONIDINE /Guanfacine *Withdrawal Symptoms*

- Because of possible rebound phenomena, including nervousness and anxiety (from relative increases in catecholamines) and increases in blood pressure to over baseline, ***GIR*** **should be tapered gradually** when discontinued.
- discontinuing **GXR formulations** recommended to taper the dose in decrements of no more than 1 mg every 3 to 7 days.
- Owing to guanfacine's relatively long half-life, if rebound is to occur, it usually does so **2 to 4 days after abrupt withdrawal**.
- Although rebound hypertension can occur, it is infrequent and blood pressure usually returns to pretreatment levels

Clonidine and Guanfacine TOXICITY

- Sign and symptoms overdose occure within 60 minutes of ingestion and may pesist for up to 48h
- **Symptoms**:Hyotension,bradycardia,weakness,pallor,sedation,vomiting,hypothermia
- **Can progress to**: CNS depression, diminished or absent reflexes, apnea, repiratory depression ,cardiac conduction defects, seizures and coma

Treatment: supportive and symptomatic

Clonidine Monitoring Parameters

- **Pulse rate** and **blood pressure** :baseline, weekly during titration,and repeated every 4 to 6 weeks on maintenance dosage.

- ***ECG:*** should also be assessed if clinically appropriate.
- *Baseline bradycardia or impaired AV conduction indicating firstdegree,*second-degree, or complete heart block or QRS interval >120 ms necessitates cardiac consultation .

❑ monitor for depressive reactions secondary to clonidine

CLONIDINE *Drug Interactions*

- Clonidine **enhanced The CNS depressive effects** of **alcohol**, **barbiturates**, **Hypnotics** and **Antihistamines** and **illicit** drugs.

- potential for additive effects such as **bradycardia** and AV block, in patients receiving clonidine concomitantly with **agents affect sinus node function or AV nodal conduction** e.g **digitalis**, **calcium channel blockers**, and **betablockers**

- Report of Sudden death (MPH and Clonidine combination):

combination clonidine–MPH treatment of ADHD is usually safe and the available evidence did not support discontinuation of such therapy in patients experiencing significant clinical benefit.

Guanfacine Drug Interactions

- Guanfacine primarily metabolized by CYP3A4:its plasma concentrations can be affected significantly by CYP3A4 inhibitors or inducers.
- **Strong CYP3A4 inhibitors:** use caution when guanfacine is administered with ketoconazole and other strong CYP3A4 inhibitors, because **elevation of plasma guanfacine concentrations** increases the risk of AEs such as hypotension, bradycardia, and sedation.
  - dose should be limited to no more than 2 mg/day.
  - *When discontinuing CYP3A4 inhibitors*, the guanfacine dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day
- **Strong CYP3A4 inducers (e.g., rifampin):** coadministration **decreases guanfacine** plasma guanfacine concentrations and The dose may be **titrated up to 8 mg/day**.
  - *When discontinuing CYP3A4 inducers*, the guanfacine dose should be decreased by half in 1–2 weeks based on patient tolerability.
- The maximum dose should not exceed 4 mg/day

Guanfacine Drug Interactions

- Coadministration of guanfacine and valproic acid can result in increased concentrations of valproic acid.

- Both drugs are metabolized by glucuronidation, possibly resulting in competitive inhibition.

- patients should be monitored for potential additive CNS effects and consideration given to monitoring serum valproic acid concentrations.

- Adjustments in the dose of valproic acid may be indicated when coadministered with guanfacine.

CLONIDINE *contraindication*

1-Known hypersensitivity to clonidine

2-Significant cardiovascular disease(Sinus node and AV node disease): relative contraindication(careful and frequent monitoring is Required)

3-renal disease: relative contraindications.

4-A careful risk/benefit analysis should be considered in the administration of clonidine to children and adolescents with depressive symptomatology, a past history of depression, or family history of mood disorder.

- clonidine worsened or induced depressive symptomatology in **5%** of children.

❑ should not be administered concomitantly with **beta-blockers** eg **propranolol** (Additive bradycardia and hypotension)

CLONIDINE /Guanfacine Advantages versus Disadvantages

- ***Advantages :***

1-Can boost effect of stimulants

2- No appetite effect

3- Effective for kids

4- Good for those overaroused, possibly with comorbid anxiety

5- Helps with sleep difficulties

6- Not addictive

7- treat comorbid tic disorders

8-Treat both hyperactivity impulsiveness

9-Treat comorbid aggression

10- May be especially good with comorbid autism

CLONIDINE /Guanfacine Advantages versus Disadvantages

- ***Disadvantages***

1-Doesn't help all ADHD presentations(Not as helpful for attention as stimulants)

2- Little research on adults

3- Less effective than stimulants

4-May cause drowsiness(sedation)

5-Response delayed (May take up to 2 weeks for initial response)

6-Hypertensive rebound if dose missed

7-other probabable side effects:Hypotensive dizziness,Dry mouth

Rare hallucinations …..

THANK YOU FOR YOUR ATTENTION