# the medicine cabinet: clonidine...

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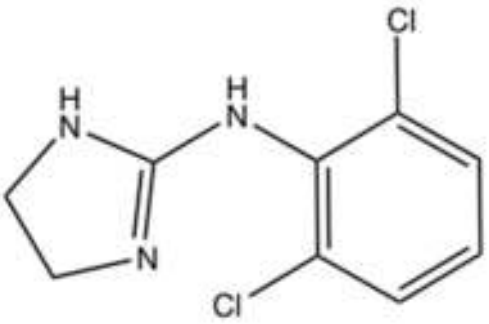
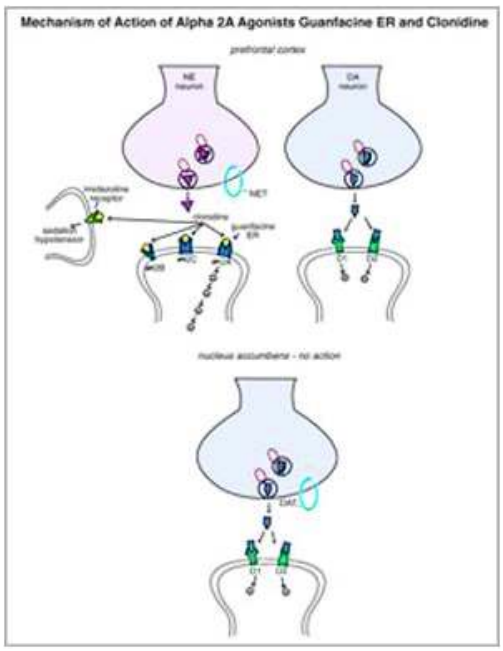



**Background**
Clonidine is an older medication that has been used in medicine, especially paediatrics, for many years. As a result, many doctors have become accustomed to using it safely and it has been used in many different ways. Clonidine has always been used to lower blood pressure and is used in emergencies to do this, such as when a child is very ill in the Intensive Care Unit. It does this by working on parts of the nervous system that respond to adrenaline, and cousins of adrenaline, to dampen their activity. It acts like a break on the adrenaline-type system in the brain. It has been used in general medicine for everything from hot flushes around menopause to migraine, chronic pain in cancer to painful periods.

**Why is it used in Child Psychiatry?**
Dampening down adrenaline-type activities in the body helps reduce the stress response as well as our blood pressure. It can make a child less "wired" or over activated. It can make a child sleepy and less twitchy in the muscles. When people are withdrawing from drugs like morphine, and alcohol, they can become very overactive, sleepless, "wired" and twitchy. Clonidine can make them less stressed and less worried and help them through the withdrawal. Children and young people who have been through severe physical and emotional trauma benefit from reducing the volume on their reactions to stress. The indications for clonidine, then, are:- Attention Deficit hyperactivity Disorder, Sleep disorders, Tourette syndrome, Withdrawal syndromes in those with established addictions such as opiates (eg heroin) and alcohol, Severe anxiety disorders and Post Traumatic Stress Disorder




A more general statement of indications would be to help children to be less overactive, less stressed, less impulsive and distractible, less worried and more sleepy, when they have trouble doing so.

Clonidine when taken regularly can take up to 4 weeks to have a full effect at the required therapeutic dose. But clonidine is also found to have a short lived effect, lasting for only 4 hours and help to control impulses.

**Adverse effects**
The main adverse effects of clonidine are dry mouth, dizziness, low blood pressure and drowsiness. Some of the side effects are also the reasons we use the medication. For example drowsiness may be wanted. The "dry mouth" effect is used in patients for whom drooling is a problem. Most adverse effects relates to the action of clonidine on the body so it has the potential to cause dizziness due to dropping blood pressure, but also drowsiness, sleep disturbance and sedation. This can be helped by not standing up too quickly and not taking hot showers. Also if a child is going pale and might faint, then lying down will help. Other side effects include reports of nausea and vomiting as well as constipation and dry mouth. Dry mouth can be helped by sucking on sugar free lollies, or gum. Mood disturbance and nightmares have been reported infrequently as well. Most children don't notice these side effects, while adults do. With prolonged use, it is important to remain aware of an additional unusual side effect of depression or misery, which is reversible on ceasing the medication.

**Adverse effects by incidence**
**Very common (greater than 1 in ten patients) adverse effects include:** Dizziness, Orthostatic hypotension (a drop in blood pressure that occurs upon standing up), Drowsiness (dose-dependent), Dry mouth, Headache (dose-dependent) and Fatigue
**Common (between 1 in 10 and 1 in a hundred) adverse effects include:** Anxiety, Depression, Constipation, Sedation (dose-dependent), Nausea/vomiting, Malaise (generally feeling unwell), Abnormal liver function tests, Rash and Weight gain/loss
**Uncommon (1 in a hundred to 1 in a 1000 ) adverse effects include:** Delusions, Hallucinations, Nightmares, Pins and needles, Slow normal heart rate, Raynaud's phenomenon (tips fingers become white or red or blue because of blood flow changes), Itchiness and Hives
**Rare (1 in thousand and 1 in 10,0000) adverse effects include:** Swelling of breast tissue in males, Impaired ability to form tears, Heart block leading to a slow and sometimes irregular pulse, Nasal dryness, Bowel slowdown or stoppage, Hair loss and High blood glucose

**Withdrawal – rebound high blood pressure and the need to taper slowly (incidence unknown)**
If a child has been on clonidine for sometime, sudden ceasing of clonidine can cause a rapid rise in blood pressure. This is called rebound hypertension. If we imagine that taking clonidine is pushing blood pressure down like someone pushing down the end of a diving board, then stopping clonidine is like letting go of a diving board that has been held down. The blood pressure will go up – sometimes dangerously so. For this reason most clinicians recommend that clonidine should generally be gradually tapered off when discontinuing. It is important not to stop and start it without advice from the prescribing physician. It is also important not to skip or avoid doses.

**How is it used?**
Some medicines used to treat ADHD, like Ritalin, Concerta and dexamphetamine, make it difficult for children to sleep, even though they help with concentration and school work. Clonidine is sometimes added to ADHD therapy to help with sleep. The doses used are smaller than the doses used to lower blood pressure in very unwell children. Doses such as 100 micrograms (100 millionths of a gram) are used. Even though this can still lower blood pressure, the child normally rapidly adjusts and the blood pressure moves back to normal over a week. At these lower doses clonidine is anxiety relieving and helps reduce impulsive behaviour. At higher doses it becomes sedating. It can therefore be used for different purposes at different doses.

At the beginning of treatment, a child can

be dizzy, light headed, or even faint. Medical advice should be sought and the dose adjusted accordingly. If feeling tired all the time, especially early in treatment, the dose might need to be adjusted, then increased to the desired dose when the body adjusts to the clonidine

When used for impulse control, clonidine is sometimes used on 'a when needed basis' and then a dose is given at the first sign of 'losing it' to get the full effect of the medication, as it still takes 40 minutes before it is absorbed by mouth into the body. If given too late then the episode may have escalated too much for the medication to be effective and the episode will need to 'run its course'. The child may take a longer time de-escalate and recover themselves. Most clinicians avoid this approach because the use of the medication can inadvertently reinforce the behaviour in the longer term. We can end up prescribing impulsively.

Other adverse effects include constipation which can be managed with making sure there are enough fibre as well as cereals and fruit in the diet as well as drinking enough fluids. Mild laxative might also help if dietary measures are ineffective.

Clonidine is also quite toxic in overdose so it should be handled with care and kept out of the reach of children. Further information about clonidine can be found www.choiceandmedication.org/queenslandhealth

**FOR PRESCRIBERS**

The licensed indication under the Therapeutic Goods Administration Clonidine is marketed in Australia by Boehinger Ingelheim, under the trade name of *Catapres®*. Clonidine XR has been approved by the FDA in the United States for the treatment of ADHD. In Australia, while ADHD is an accepted use for clonidine (which in Australia is only available in immediate release formulations) it has not been approved by the TGA for this indication.

It is the only alpha partial agonist on the Australian market and is available in tablet form as well as an injectable. Overseas, another alpha partial agonist, guanfacine, which is more selective for $a_{2A}$ receptors, is available and designed for use in ADHD.

Clonidine is available as a long acting preparation and as skin patches. It is also an Imidazoline 1 receptor ($I_1$) which mediates the sympatho-inhibitory actions of imidazolines to lower blood pressure and sympathetic arousal more generally.

Five P450 enzymes-CYP2D6, 1A2, 3A4, 1A1, and 3A5-catalyzed measurable formation of 4-hydroxyclonidine. CYP2D6 accounts for approximately two-thirds of the activity.

> "It acts like a break on the adrenaline-type system in the brain..."

**How to give**

Clonidine begins to work within an hour. Plasma level of clonidine peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. Following oral administration about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Two thirds of this metabolism is achieved via the CYP 2D6 pathway.

Doses are usually given in portions of whole tablets, which are 100 or 150 micrograms. Clonidine is also readily dissolvable in water so a crushed tablet can be dissolved in freshly boiled and cooled water and then a portion of the final solution given as a dose if needed, for example, in a syringe by mouth. This is useful for some children who find swallowing tablets difficult.

***A general guide is:-***

A) *Start at 1-2 micrograms / kg / day per day in three divided doses* (for example 100 micrograms /day might be 25 micrograms before school, 25 micrograms after school and 50 micrograms at night, two hours before bedtime).

B) *Four times a day requires a lot of cooperation* - Where parents are not too stressed, and therefore forgetful, children are compliant at school, and teachers are willing, a four times a day regimen to start with 25 micrograms at 7am, 11am and 3pm and 100 micrograms at night, can be implemented. This achieves a smoother introduction and more continuous effect, but requires very tight administration.

*Maximum initial dose* - Limit the total dose to 350 micrograms in 24 hours within the first 4 weeks of using clonidine and allow two weeks for each increment. Pharmacokinetic steady state is achieved after five half lives (ie around three days) but pharmacodynamic steady state may take closer to a month.

D) *Adjust to individual need* - The dose then needs to be adjusted according to effect. Intermediate doses can be achieved by such as 37.5 microgram doses can be achieved from a quarter tablet of the 150 microgram tablet.

**How does it work?**

Clonidine's primary role is as an antihypertensive agent. It stimulates the brakes (alpha adrenergic (a) auto-receptors) of the sympathetic nervous system. Clonidine is a non-selective agonist of $a_2$ auto-receptors, with actions on $a_{2A}$, $a_{2B}$, and $a_{2C}$ receptors. Although the actions of clonidine at $a_{2A}$ receptors exhibit therapeutic potential for ADHD, it is the actions at the other receptors that increase the potential for adverse effects.

$a_2$ receptors are found in high concentrations in the prefrontal cortex of the brain (the brakes for the rest of the brain and behaviour) but low concentrations in the nucleus accumbens (where addictions are enabled). The most prevalent of the three subtypes of alpha-adrenergic receptors in the prefrontal cortex is $a_{2A}$ and these mediate the hyperactivity, inattention and impulsivity of ADHD. Alpha $_{2B}$ receptors in the thalamus are associated with sedative effect. Alpha $_{2C}$ receptors are located in the locus coeruleus with a few in the prefrontal cortex that are associated with hypotensive and sedative effects. Clonidine blockade of the post-synaptic receptors can increase noradrenaline signalling to normal levels.

Clonidine also has action on imidazoline receptors, which are thought to be responsible for some of the sedating and hypotensive actions. The stimulatory effect of clonidine on imidazoline receptors in a particular part of the locus coeruleus neurons (nucleus paragigantocellularis) means that there is a stimulus of quite particular cells reaching right forward to the frontal lobes. We therefore have reduced adrenergic activity in some areas and increased in others. This means that there are both stimulating and inhibitory effects of the adrenergic system. "Increased behavioural brakes and decreased behavioural accelerators" is a summary of clonidine's role.

**Managing withdrawal rebound hypertension**

There are two main strategies for managing clonidine withdrawal:- 1. Reintroduce of clonidine for mild cases and 2. Alpha and beta-blockers, for more urgent situations. NB: Beta-blockers should NOT be used alone to treat clonidine withdrawal

as alpha vasoconstriction can still continue.

**Overdose**
Clonidine overdose is characterised by a classic triad of CNS clinical signs, and a biphasic haemodynamic response: *Triad of Signs of Clonidine Overdose*. CNS depression (stupor or coma), Respiratory depression (breathing reduced or stopped), Miosis (pin-point pupils), *Biphasic Haemodynamic Response Post- Overdose* a) Hypertensive phase b) Hypotensive and bradycardic phase.

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Have you been to a conference, read a book or visited a website that you loved? Send us an overview to: schoollink@chw.edu.au

The beautiful artworks in this newsletter are taken from the participants of the **Operation Art project** at the Children's Hospital at Westmead. You can find out more at http://www.pau.nsw.edu.au/Visual_arts/Operation_Art/index.htm

A sincere thankyou to all children and adults involved in the production of these artworks and this newsletter. Remember; **Think Kids**

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