

# Clonidine Use in Psychiatry: Panacea or Panache?

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## Key Words

Clonidine · Psychiatric uses

## Abstract

Clonidine, an alpha agonist, formally prescribed in clinical medicine as antihypertensive medication, is currently being used more frequently to address a multitude of psychiatric entities. The long-acting formulation is approved by the Food and Drug Administration for use in treating the attention-deficit/hyperactivity disorder. In addition to this only legitimate indication, it has long been used successfully for opiate detoxification, post-traumatic stress disorder and de la Tourette syndrome. Moreover, clonidine helps in the treatment of neuroleptic-induced akathisia, stimulant-induced insomnia and clozapine-induced sialorrhea. It has been tried in treating menopausal syndrome and psychogenic polydipsia. Although the strength of evidence supporting the use of clonidine in such clinical scenarios is highly variable and oscillating, from strong to only flimsy, this overview is intended to shed some light on the clonidine portfolio as a potential and attractive addition to the psychopharmacologic armamentarium.

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## Introduction

Clonidine is a non-selective alpha-2 adrenergic agonist that has been used in psychiatric practice in panoply of clinical indications. According to recent trends, its utilization is on the increase. In this study, we are reviewing the pharmacology of clonidine followed by its use in such diverse indications and the extant evidence. Searching PubMed database was pursued using key words of 'clonidine' 'psychiatric uses'.

## Pharmacology of Clonidine

Clonidine is an alpha-2 adrenergic agonist. It is non-selective in the sense that it binds to alpha-2A, B and C subtypes [1] (cf. guanfacine, which is more selective to alpha-2A). It acts presynaptically to reduce sympathetic outflow and hence, decreasing cardiac output, peripheral vascular resistance and blood pressure. It specifically targets alpha-2 receptors in the brainstem vasomotor centre, decreasing presynaptic Ca levels and release of NE. It may also reduce plasma renin activity and catecholamine ex-

cretion. It possesses imidazoline I1 agonistic activity that contributes to its antihypertensive action [2].

Clonidine comes in a variety of drug formulations, namely, oral tablets, transdermal patches and concentrates for injection as epidural infusion. Also, topical gel is increasingly being used in diabetic neuropathy. This would translate into clinically user-friendly administration [1].

Posology (dosage) differs according to indication and formulation employed but generally between 100 and 800 µg/day (divided) [1].

Half-life is 12 h in most. Peak effect is at 2–4 h. Bioavailability is 75–95% with 1/2 of drug metabolized into inactive metabolites and the other half excreted unchanged in urine [1].

Most common adverse drug reactions are dose-related, time-limited and mostly affect CNS (dizziness, somnolence, depression), CVS (orthostasis, bradycardia) and GIT (dry mouth, constipation). Rebound hypertension with abrupt discontinuation is a definite risk [1]. It is pregnancy category C. It has been used even in preschool children reflecting high safety and tolerability issues.

### Clonidine in ADHD

Alpha-2 adrenergic receptors are present in high concentrations in the prefrontal cortex (PFC) but only in low concentrations in the nucleus accumbens. The most prevalent subtype in PFC is the alpha-2A apparently mediating inattentiveness, hyperactivity and impulsivity. Alpha-2B receptors are located mainly in thalamus associated with sedation. Alpha-2C is located in locus coeruleus associated with hypotensive and also sedative actions [3].

All these pharmacologic properties would explain the utility of clonidine in attention-deficit/hyperactivity disorder (ADHD). And hence, the long-acting formulation was approved by the Food and Drug Administration as monotherapy or adjunctive to stimulants in treatment of ADHD above the age of 6 [4].

Two randomized, double-blind, placebo-controlled, 8 weeks efficacy studies in paediatric patients aged 6–17, demonstrated significant improvement over placebo in ADHD rating scale total score at the end of week 5 [4].

A multi-centre, open-label, flexible-dose, chronic exposure evaluation of safety study including 301 cases in the age group 6–17, reported only one case of suicidal behaviour [4].

A meta-analysis of 11 small double-blind and open-label studies (less than 50 subjects) reviewing the effect of immediate-release clonidine on symptoms of ADHD

alone or with comorbidities determined a moderate overall effect size of  $0.58 \pm 1.6$  [5].

A systematic review and meta-analysis of 12 placebo-controlled trials – 9 as monotherapy and 3 as augmentation – was recently conducted to evaluate safety and efficacy of alpha-2 agonists (clonidine but also guanfacine) in paediatric ADHD and demonstrated superiority to placebo as monotherapy and to a lesser extent as a co-treatment. However, somnolence, bradycardia and hypotension were greater in the active arm [6].

This clearly obviates previous earlier concerns about cardiovascular fatalities reported with clonidine-stimulant combinations [7].

It seems that clonidine may work in a synergistic fashion with stimulants through the regulation of PFC [8].

This enhanced efficacy has been ensured without compromising safety [9].

Moreover, clonidine seems to be an attractive option targeting insomnia in ADHD [10] and remain a good remedy for paediatric insomnia in general [10], and a case series has also reported that clonidine seems to be beneficial and fairly well tolerated in intractable sleep disorders in children and young adults with neurodevelopmental disorders [11].

To extrapolate, clonidine has been tried in 8 kids with hyperkinetic autism spectrum disorder (ASD), with statistically and clinically relevant decrease in irritability subscale of aberrant behaviour checklist [12].

Clonidine was also effective in reducing sleep initiation latency and night awakening, to a lesser degree in improving ADHD symptoms, mood instability and aggressiveness in a cohort of 19 children with ASD [13].

A double-blind, placebo-controlled trial of clonidine in hyperactive children with mental retardation found it both safe and effective with drowsiness as a common side effect that typically wore off by 2–4 weeks [14].

### Clonidine in Opiate Detoxification

Clonidine has long been used successfully to rapidly suppress opiate withdrawal signs and symptoms [15] and a review on the topic suggested utility especially when methadone substitution is inappropriate.

It helps opiates detoxification by reducing sympathetic overactivity, for example, tachycardia, hypertension, sweating, flashes and restlessness [16].

Moreover, it eases accompanying insomnia.

Clonidine has also been used for enabling alcohol withdrawal [17], as its superiority to placebo was demonstrated in several double-blind studies.

Clonidine was more effective than placebo for long-term smoking cessation [18] in a Cochrane database review of 6 trials with dry mouth and sedation reported as most troublesome side effects.

### Clonidine in PTSD

A burgeoning body of evidence exists as regards the role of clonidine in post-traumatic stress disorder (PTSD).

This is achieved putatively through the reduction of CNS noradrenergic activity.

Clonidine was reported in an open-label case series to reduce PTSD trauma nightmares and improve sleep in Cambodian refugees and improve PTSD symptoms in veterans [19].

Improved sleep in one open-label study was accompanied by improved sleep physiology objectively demonstrated with polysomnography [20].

Clonidine has been shown to block traumatic memories in an animal model of PTSD [21, 22].

Clonidine has helped with nightmares in 2 case reports of PTSD comorbid with TBI [23].

Clonidine, as add-on, has been demonstrated in a randomized, double-blind, placebo-controlled cross-over study of 18 patients, to improve hyperarousal in borderline personality disorder (BPD) particularly with comorbid PTSD, although this did not achieve significance possibly due to small sample size [24].

Also, a study of 14 female patients with BPD showed efficacy of clonidine in acute states of aversive inner tension, dissociative symptoms, and urge to commit self-injurious behaviours [25].

Conceivably, due to sedative effects, clonidine would address sleep disturbance in PTSD.

### Clonidine in dTS

Studies supporting utility of clonidine in ameliorating tics abound demonstrating efficacy of circa 45% with few, if any, side effects [26, 27]. Antipsychotics were more efficacious in an open trial [28]. Some have found clonidine to be as efficacious as haloperidol [29] and another pilot study has demonstrated equal efficacy with risperidone in children with de la Tourette syndrome (dTS) [30].

In patients who have been shown to respond to clonidine, positive effects have been reported on a range of behavioural symptoms in addition to tics. These include compulsions [31], hyperactivity and impulsivity [27].

Some authors have demonstrated that 70% of patients showed a reduction in tics and that additional improvement in frustration, aggression, obsessive-compulsive and oppositional behaviours were noticed [32].

A small (including 12 subjects) double-blind cross-over study compared clonidine and the anti-epileptic levetiracetam. Subjects were aged 8–27. There was a small but significant benefit from clonidine with an effect size of 0.57 [33].

As ADHD is the most common comorbid condition in dTS up to 60–80% [34], clonidine seems a reasonable option targeting both symptomatology without concern about using stimulants that are still considered a relative contraindication in dTS for unjustifiable fears of inducing or exacerbating tics.

In a meta-analysis to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette's syndrome and ADHD, Alpha-2 agonists demonstrated ESs of 0.76 and 0.75 in treating inattention and hyperactivity/impulsive symptoms of ADHD, whereas the ESs for methylphenidate were 0.41 and 0.82, respectively. Alpha-2 agonists seem like a better choice of medication when targeting comorbid tic symptoms, and methylphenidate derivatives as a better choice when targeting tics is not a priority. A combination treatment of both agents may be most effective in targeting both disorders together [35].

Given the complexity of dTS exemplified by the heterogeneity of clinical presentation, numerous neurotransmitters have been proposed as potential pathophysiologic mechanisms including dopamine, glutamate, GABA, serotonin, acetylcholine, norepinephrine and opiates [36].

Although, this could explain in part the role of clonidine in treatment of dTS, the definite mechanism is far from clear.

Recent work pointed to sensorimotor gating abnormalities in dTS and that clonidine could normalize these deficits [37].

### Clonidine in Neuroleptic-Induced Akathisia

Although, there are several effective lines of treatment tackling neuroleptic-induced akathisia (i.e. beta-blockers, BDZs, anticholinergics, 5HT<sub>2a</sub> antagonists), clonidine remains a potential option [38–40].

Six patients with akathisia were treated with clonidine in an open on-drug/off-drug trial, all demonstrated substantial improvement of which 4 achieved complete remission [38].

**Table 1.** Clonidine uses in psychiatry

| Indication             | Level of evidence* |
|------------------------|--------------------|
| ADHD**                 | Level I            |
| PTSD                   | Level II-1         |
| Opiate detox           | Level II-3         |
| TS                     | Level II-3         |
| Neuroleptic akathisia  | Level II-1         |
| Insomnia               | Level II-3         |
| Sialorrhea             | Level I            |
| Menopausal syndrome    | Level III          |
| Psychogenic polydipsia | Level III          |

\* USPSTF rankings (1998).

Level I: evidence obtained from at least one properly designed randomized controlled trial.

Level II-1: evidence obtained from well-designed controlled trials without randomization.

Level II-2: evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

\*\* Only FDA indication.

Another 6 hospitalized patients with neuroleptic-induced akathisia were treated with clonidine under single-blind conditions. Akathisia and anxiety at maximum clonidine dose were significantly lower than at baseline, although it was difficult to differentiate specific therapeutic effects from sedation [39].

### Clonidine in Clozapine-Sialorrhea

Despite demonstrated superiority of clozapine in treatment-resistant schizophrenia, its use is usually plagued with a myriad of troublesome side effects, including sialorrhea.

One postulated mechanism of this sialorrhea is alpha-2 adrenergic action.

This can in theory be opposed by clonidine and in practice has been shown to be useful [41, 42].

Oral clonidine was tried on 12 stable outpatients of schizophrenia maintained on clozapine. Wet area over the pillow as reported by the patients was recorded at baseline and at 4 weeks of treatment along with the subjective response after the treatment. Most of the patients reported a decrease in sialorrhea without any adverse events [41].

A 0.1 mg/day once-a-week clonidine patch was administered to 4 patients with clozapine-induced hyper-

salivation. The author reports a sustained improvement in 2 patients, a limited and short-lived improvement in another and no improvement in the fourth [42].

Similarly, clonidine has been used with success to address sialorrhea in Parkinson's disease [43] in a prospective double-blind placebo compared study following Parkinson's disease patients for 3 months.

### Clonidine in Psychogenic Polydipsia

Psychogenic polydipsia is characterized by compulsive water drinking typically in excess of 3 liters, often in circa 6–20% of the mentally ill or developmentally disabled with cerebral oedema and potentially fatal outcome [44].

This is commonly seen in people with schizophrenia, developmental disability and middle-aged women with anxiety disorders [45].

Treatment options include managing hyponatremia, restriction of fluids and medications, for example, clozapine [46], demeclocycline [47], enalapril and clonidine [48].

Animal studies have suggested the involvement of adrenergic system in drinking behaviour [49] and this was demonstrated in a pilot study of 4 patients with chronic schizophrenia presenting with intermittent hyponatremia and polydipsia, where mianserin, unlike clonidine, was helpful.

A pilot study included 3 patients with chronic schizophrenia and primary polydipsia questioned overall effectiveness of clonidine, which was unsuccessful [50].

### Clonidine in Menopausal Syndrome

Vasomotor changes including hot flashes and night sweats occurred in up to 70% of women at the time of menopause with significant impact on quality of life [51].

Management included lifestyle modifications, some herbal and vitamin supplement, HRT, clonidine, SNRIs and gabapentin [52].

CNS sympathetic overactivity, mediated through  $\alpha$ -2 adrenergic receptors, is an important factor responsible for the narrowing of the thermoneutral zone underlying hot flashes [52].

### Other Uses

Clonidine has also been tried in a multitude of neuropsychiatric disorders [53].

This includes, inter alia, migraine, tardive dyskinesia [54], essential tremor [55], neurogenic bladder [56], idiopathic orthostatic hypotension, paroxysmal localized hyperhidrosis [57], diabetic neuropathy [58] and stiff-man syndrome [59].

### Conclusion

This overview has cast some light on the clonidine portfolio as a pluripotent, reasonably safe and appealing contribution to the psychopharmacologic armamentarium. Nevertheless, the level of evidence supporting the use of clonidine in all these off-label indications is highly variable (table 1), and hence, sound clinical judgment, manipulating all other viable treatment options at hand, would dictate its judicious and proper use and placement in real-life psychiatric practice.

### Disclosure Statement

Author declares no conflicts of interest or financial affiliations with pharmaceutical companies or industry-sponsored research.

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