New Medicine Assessment

Clonidine 25 mcg tablets

For vasomotor symptoms (VMS) associated with menopause

Recommendation: GREEN (restricted)

Hormone replacement therapy (HRT) is the first-line treatment for menopausal VMS.

Where HRT is contraindicated or declined, a trial of Clonidine 25 mcg tablets may be considered for menopausal VMS.

Patients should be reviewed after 4 weeks and if no improvement in symptoms is observed or the patient is experiencing significant adverse events, treatment should be discontinued.

Summary of supporting evidence:

- There is extensive experience in the use of clonidine 25 mcg tablets for the management of vasomotor symptoms in menopause.
- The safety profile of clonidine is well established, and no new or unexpected safety concerns arose when granting a marketing authorisation for a generic formulation in 2008.
- NICE guidance infers that there may be a place in therapy for clonidine after first line therapies have failed: "*Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone….*"
- The International Endocrine Society guidelines suggest clonidine should be reserved for women not responding to, or unable to tolerate SSRI/SNRI antidepressants, gabapentin or pregabalin.
- The efficacy data for clonidine either demonstrates small benefits relative to placebo or no effect on menopausal flushing.
- Clonidine is several times more expensive than the other available nonhormonal comparators.
- Vascular related adverse effects such as hypotension, headache and dizziness may limit the usefulness of clonidine as a treatment option.

Date: January 2022

Details of Review

Name of medicine (generic & brand name)**:**

Clonidine hydrochloride

Strength(s) and form(s):

25 microgram tablets

Dose and administration:

Initially 2 tablets twice daily. If after two weeks there has been no remission, increase to 3 tablets twice daily.

The duration of treatment depends upon the severity of the condition.

If symptoms continue to occur the patient should be informed that it may take 2 - 4 weeks until Clonidine hydrochloride 25 microgram Tablets are fully effective. [1]

BNF therapeutic class / mode of action:

Centrally acting antihypertensives / alpha-2 adrenoceptor agonist

Licensed indication(s):

The prophylactic management of migraine or recurrent vascular headache.

The management of vasomotor conditions commonly associated with the menopause and characterised by flushing. [1]

Proposed use (if different from, or in addition to, licensed indication above):

The management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

Course and cost:

112 x clonidine 25 mcg tablets: £8.12

Dose: 2-3 tablets twice daily

Annual cost: £106 - £158

Costs based on September 2021 NHS Drug Tariff list prices.

Current standard of care/comparator therapies:

- Fluoxetine 20 mg daily / citalopram 20 mg daily / paroxetine 10 mg daily / venlafaxine modified release 75 mg daily
- Gabapentin 300 mg three times daily [2]

Relevant NICE guidance:

- NICE guideline NG23- Menopause: diagnosis and management [3]
- NICE CKS - Scenario: Managing women with menopause, perimenopause, or premature ovarian insufficiency [2]

Background and context

Menopause is when a woman stops having periods as she reaches the end of her natural reproductive life. Oestrogen depletion associated with menopause causes irregular periods and has many other effects on the body. Vasomotor symptoms (VMS; hot flushes and/or night sweats) affect around 80% of women over the menopause transition, are the main reason for seeking medical advice, and are the leading patient priority for treatment. Oestrogen-containing menopausal hormone therapy (MHT) is the most effective treatment for VMS and also improves genitourinary symptoms. However, MHT is unsuitable for some women and avoided by others, and there is a need for safe and effective non-hormonal treatments. [4]

Clonidine hydrochloride is an antihypertensive agent which acts centrally by stimulating alpha 2-adrenergic receptors and producing a reduction in sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate. Treatment with clonidine hydrochloride 25 microgram Tablets diminishes the responsiveness of peripheral vessels to constrictor and dilator stimuli thereby preventing the vascular changes on peripheral vessels associated with menopausal flushing. [5]

Clonidine tablets for VMS associated with menopause was prioritised for review by the LSCMMG following a request from East Lancashire CCG.

Summary of evidence

Summary of efficacy data in proposed use:

MHRA public assessment report (PAR) for clonidine hydrochloride tablets

Data relating to the efficacy of clonidine in VMS associated with menopause is primarily sourced from studies dating back to the 1970s and 1980s. As a result, the PAR published by the MHRA more than 10 years after the original studies states: “Extensive clinical experience with clonidine hydrochloride is considered to have demonstrated the therapeutic value of the active substance”. [5] In addition to the publication of the MHRA PAR, a meta-analysis has been published comparing non-hormonal treatments for menopausal flushes.

Nelson et al meta-analysis (2006) [6]

This meta-analysis assessed the efficacy and safety of nonhormonal therapies for menopausal hot flashes (flushes) based on the published randomised controlled clinical trials. The systematic review included 10 placebo-controlled trials of clonidine of which 4 trials were included in the meta-analysis. Participants included women experiencing menopausal hot flashes who were recruited from health care settings or the general population. Trials enrolling women with breast cancer were included and additional data unique to them, such as concomitant use of tamoxifen or other selective oestrogen receptor modulators (SERMs), were obtained. Trials of women with other major diseases or oestrogen use within 1 month of commencement of the study were excluded.

Of 10 trials comparing clonidine with placebo, all except 3 fair-quality trials met criteria for poor quality due to few patients, lack of clear inclusion and exclusion criteria, high attrition or loss to follow-up, no washout period in crossover trials, lack of data for pre-crossover comparisons, and short treatment duration. Four trials reported reduced frequency of hot flashes with clonidine compared with placebo and 5 did not. Two trials reporting reduced hot flash frequency included women with breast cancer taking tamoxifen; reduced severity and composite score were also reported. Two other trials reported reduced hot flash severity with clonidine compared with placebo, although 3 trials found no differences.

For the meta-analysis, the combined weighted mean difference in the number of daily hot flashes for clonidine compared with placebo in 4 trials was −0.95 (CI95% −1.44 to −0.47) after 4 weeks use and in 2 trials was –1.63 (CI95% −2.76 to −0.50) after 8 weeks use. In the 4-week trials, eliminating the trial with poor methodological quality from the analysis did not influence results (weighted mean difference, −0.95 [CI95% −1.45 to −0.46]). The 2 trials enrolling women with breast cancer and SERM use reported significantly decreased hot flashes (weighted mean difference, −1.00; [CI95% −1.51 to −0.49]), although the 2 trials of women without breast cancer and SERM use did not (−0.53; [CI95% −2.09 to 1.04]).

Other efficacy data:

Additional evidence is available which compares clonidine to other nonhormonal interventions, although patient cohorts within these studies had primary breast cancer or a history of breast cancer. These patient groups may experience VMS due to the menopause or as a consequence of the treatment they receive for their breast cancer and therefore the studies may not be as relevant to the indication under review for this New Medicine Assessment. Due to potential differences in patient characteristics including causes of flushing and severity, details of these studies have been included in this section (other efficacy data) of the review.

Loibl et al RCT (2007) [7]

In a double-blind, randomized phase III study, breast cancer patients suffering from hot flashes (flushes) at least twice a day, who were not taking any medication against hypertension and depression received either clonidine 0.075 mg twice a day or venlafaxine 37.5 mg twice a day for 4 weeks. The primary end point was defined as the frequency of hot flashes after 4 weeks of treatment. A self-reported 1-week hot flash and other symptom questionnaire were kept before the start of treatment until the end of treatment course.

Thirty-three patients received clonidine and 31 venlafaxine. At the end of treatment week 4, the median hot flash frequency dropped by 7.6 hot flashes per day for patients receiving venlafaxine and 4.85 hot flashes per day for those receiving clonidine (P = 0.025).

Cochrane systematic review Rada et al (2010) [8]

The Cochrane review found two studies (252 assessable participants) evaluating a transdermal and an oral formulation of clonidine. One study (Goldberg 1994 [9]), including 89 assessable patients, tested a transdermal patch. At week four, the hot flush frequency in the intervention arm, as a median, had a reduction from baseline of 44% compared to the reduction in the placebo arm of 27% (P = 0.04). The median combined severity score decreased 56% from baseline with the intervention and 30% with placebo (P = 0.04). For the effect after cross-over, the difference at week eight was reported as significant for both frequency (P < 0.0001) and the combined severity score (P = 0.0006).

A second study (Pandya 2000 [10]) that evaluated an oral formulation included 163 assessable patients. At week eight, the hot flush frequency had a mean reduction from baseline of 38% in the treatment arm compared to 24% with placebo (difference in percentage reduction of means of 14%; 95% CI 3% to 27%; P = 0.006). The severity score was reduced by 45% with clonidine and 26% with placebo (P = 0.006).

Summary of safety data:

Most adverse effects for clonidine 25 mcg tablets are mild and tend to diminish with continued therapy. The full list of adverse events listed in the SPC for clonidine 25 mcg tablets is shown below [1]:

	Very common (≥1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (<1/10,000)
Endocrine disorders				Gynaecomastia	
Psychiatric disorders		Depression, sleep disorder	Delusional perception, hallucination, nightmare		
Nervous system disorders	Dizziness, sedation	Headache	Paraesthesia		
Eye disorder				Lacrimation decreased	
Cardiac and vascular disorders	Orthostatic hypotension		Sinus bradycardia, Raynaud's phenomenon	Atrioventricular block	
Respiratory, thoracic and mediastinal disorders				Nasal dryness	
Gastrointestinal disorders	Dry mouth	Constipation, nausea, salivary gland pain, vomiting		Colonic pseudo-obstruction	
Skin and subcutaneous tissue disorders			Pruritis, rash, urticaria	Alopecia	
Reproductive system and breast disorders		Erectile dysfunction			
General disorders		Fatigue	Malaise		
Investigations				Blood glucose increased	

Contraindications

Clonidine is contraindicated in patients with severe bradyarrhythmia resulting from either sick-sinus syndrome or AV block of 2nd or 3rd degree, or in patients with known hypersensitivity to the active substance or to any of the excipients. [1]

Special warnings and precautions

-Hypotension and bradycardia

Provided the recommended Clonidine dosage regimen is followed, no difficulty with hypotension should arise during the routine management of patients with menopausal flushing. Depending on the dose given, Clonidine can cause bradycardia. In patients with pre-existing cardiac conduction abnormalities, arrhythmias have been observed after high doses of Clonidine. Concurrent administration of antihypertensive agents, vasodilators or diuretics may lead to an increased hypotensive effect. Substances with alpha2-receptor blocking properties, such as mirtazapine, may abolish the alpha2- receptor mediated effects of clonidine in a dose-dependent manner.

Concomitant use of beta-blockers and/or cardiac glycosides can cause bradycardia or dysrhythmia (AV-block) in isolated cases. It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders. Orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of Clonidine after prolonged treatment with high doses, agitation, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with Clonidine, the physician should reduce the dose gradually over 2-4 days.

-Other warnings

Patients with renal failure require extreme care. Patients who wear contact lenses should be warned that treatment with clonidine may cause decreased lacrimation. Serious adverse events, including sudden death, have been reported in concomitant use with methylphenidate. The safety of using methylphenidate in combination with clonidine has not been systematically evaluated. [1]

Strengths and limitations of the evidence:

Strengths

- Clonidine is licensed for the management of hot flushes while several nonhormonal comparators (e.g., SSRIs) are not.
- There is extensive experience in the use of clonidine 25 mcg tablets for the management of VMS in menopause.
- The safety profile of clonidine is well established, and no new or unexpected safety concerns arose when granting a marketing authorisation for a generic formulation in 2008.
- NICE guidance infers that there may be a place in therapy for clonidine after first line therapies have failed: "*Do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) or clonidine as first-line treatment for vasomotor symptoms alone*…." [3]
- The International Endocrine Society guidelines suggest clonidine should be reserved for women not responding to, or unable to tolerate SSRI/SNRI antidepressants, gabapentin or pregabalin. [11]

Limitations

- The efficacy data for clonidine either demonstrates small benefits relative to placebo or no effect on menopausal flushing.
- The methodological quality of the RCTs for clonidine in VMS associated with menopause with deemed to be of either poor or fair quality in a meta-analysis. [6]
- There is a lack of head-to-head studies comparing clonidine with nonhormonal treatments, however several international societies conclude that clonidine is less effective than SSRI/SNRI antidepressants, gabapentin or pregabalin. [11] [12] [13]
- Clonidine is several times more expensive than the other available nonhormonal comparators.
- Vascular related adverse effects such as hypotension, headache and dizziness may limit the usefulness of clonidine as a treatment option.

Summary of evidence on cost effectiveness:

N/A

Prescribing and risk management issues:

Patients should be advised that they may experience undesirable effects such as dizziness, sedation, and accommodation disorder during treatment with clonidine. If patients experience the above-mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Clonidine 25 mcg tablets	**2-3 tablets twice daily**	**112 tablets - £8.12**	**£106 - £158**
Fluoxetine 20 mg capsules (Cheapest SSRI option)	1 daily	30 capsules - £1.02	£12.41
Venlafaxine modified release 75 mg tablets	1 daily	30 tablets - £2.60	£31.63
Gabapentin 300 mg capsules	1 three times daily	100 capsules - £3.27	£35.81
Costs based on Drug Tariff list prices September 2021 This table does not imply therapeutic equivalence of drugs or doses.			

Innovation, need and equity implications of the intervention:
Hormone replacement therapy (HRT) is established as the most effective treatment for menopausal VMS and is thus recommended by NICE as the first-line choice for women requiring pharmacological management. However, alternatives may need to be considered for women with contraindications or who do not wish to take HRT. Clonidine provides an additional treatment option for this group of patients.
Financial implications of the intervention:
Defining the potential cost of prescribing of clonidine for VMS is complicated due to the additional licensed use of clonidine in migraine prophylaxis and the lack of data relating to prevalence of clonidine use during the menopause. Current prescribing figures (August 2020 to July 2021) indicate that approximately £150,000 was spent on prescribing clonidine 25 mcg tablets in Lancashire and South Cumbria. The prescribing data also identified approximately 1,600 patients who received a prescription for clonidine 25 mcg tablets over this period of time. It is not possible to define the proportion of these patients prescribed clonidine for VMS in menopause or for migraine prophylaxis. To illustrate the impact of using alternative preparations for VMS in menopause, the difference in annual cost if one patient was treated with the comparator with the lowest acquisition cost

(fluoxetine 20 mg capsules) rather than clonidine 25 mcg tablets (depending on dose) would be:

£106 to £158 - £12.41 = £93.59 - £145.59

In order to reduce annual prescribing costs associated with clonidine 25 mcg tablets by £100,000 in Lancashire and South Cumbria, switching from clonidine to fluoxetine would need to be undertaken in **approximately 689 to 1068 patients** (depending on dose of clonidine 25 mcg tablets).

Service Impact Issues Identified:

No service impact issues are anticipated.

Equality and Inclusion Issues Identified:

Included with the LSCMMG paper.

Cross Border Issues Identified:

GMMMG do not currently hold a commissioning position for the use of clonidine in any indication. The Pan Mersey APC have assigned clonidine an “Amber Recommended” RAG status for all indications. This means that a specialist must recommend the use of clonidine. Following specialist assessment, clonidine is suitable for prescribing in Primary Care.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

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[2] National Institute for Health and Care Excellence, "Clinical Knowledge Summary, Scenario: Managing women with menopause, perimenopause, or premature ovarian insufficiency," November 2020. [Online]. Available: https://cks.nice.org.uk/topics/menopause/management/management-of-menopause-perimenopause-or-premature-ovarian-insufficiency/. [Accessed September 2021].

[3] National Institute for Health and Care Excellence, "Menopause: diagnosis and management," November 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng23. [Accessed September 2021].

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[7] S Loibl et al, "Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients - a double-blind, randomized study," *Annals of Oncology,* vol. 18, pp. 689-693, 2007.

[8] G Rada et al, "Non-hormonal interventions for hot flushes in women with a history of breast cancer (Review)," *Cochrane Database of Systematic Reviews,* no. 9, p. Art. No.: CD004923., 2010.

[9] RM Goldberg et al, "Transdermal clonidine for ameliorating tamoxifen-induced hot flashes," *Journal of Clinical Oncology,* vol. 12, no. 1, pp. 155-158, 1994.

[10] KJ Pandya et al, "Oral clonidine in postmenopausal patients with breast cancer experienceing tamoxifen-induced hot flashes: a University of Rochester Cancer Center," *Annals of Internal Medicine,* vol. 132, no. 10, pp. 788-793, 2000.

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[12] Royal College of Obstetricians and Gynaecologists, "Scientific Advisory Committee Opinion Paper no.6 (2nd Edition). Alternatives to HRT for the management of symptoms of the menopause," September

2010. [Online]. Available: www.rcog.org.uk/en/guidelines-research-services/guidelines/sip6/. [Accessed 2021 September].

[13] The North American Menopause Society, "Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society," *Menopause,* vol. 22, no. 11, pp. pp. 000-000, 2015.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality