

Understanding Why Homeopathic Medicines are Used for Menopause: Searching for Insights into Neuroendocrine Features

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Abstract

Background Menopause is a physiological event that marks the end of a woman's reproductive stage in life. Vasomotor symptoms and changes in mood are among its most important effects. Homeopathy has been used for many years in treating menopausal complaints, though clinical and pre-clinical research in this field is limited. Homeopathy often bases its prescription on neuropsychiatric symptoms, but it is unknown if homeopathic medicines (HMs) exert a neuroendocrine effect that causes an improvement in vasomotor symptoms and mood during menopause.

Objectives The study's objectives were to address the pathophysiological changes of menopause that could help in the understanding of the possible effect of HMs at a neuroendocrine level, to review the current evidence for two of the most frequently prescribed HMs for menopause (*Lachesis mutus* and *Sepia officinalis*), and to discuss the future directions of research in this field.

Methods An extensive literature search for the pathophysiologic events of menopause and depression, as well as for the current evidence for HMs in menopause and depression, was performed.

Results Neuroendocrine changes are involved in the pathophysiology of vasomotor symptoms and changes in mood during menopause. Gonadal hormones modulate neurotransmitter systems. Both play a role in mood disorders and temperature regulation. It has been demonstrated that *Gelsemium sempervirens*, *Ignatia amara* and *Chamomilla matricaria* exert anxiolytic effects in rodent models. *Lachesis mutus* and *Sepia officinalis* are frequently prescribed for important neuropsychiatric and vasomotor symptoms. Dopamine, a neurotransmitter involved in mood, is among the constituents of the ink of the common cuttlefish, *Sepia officinalis*.

Conclusion Based on all the pathophysiologic events of menopause and the improvement in menopausal complaints that certain HMs show in daily practice, these medicines might have a direct or indirect neuroendocrine effect in the body, possibly triggered via an as-yet unidentified biological mechanism. Many unanswered questions in this field require further pre-clinical and clinical research.

Keywords

- ▶ homeopathy
- ▶ menopause
- ▶ depression
- ▶ vasomotor symptoms
- ▶ pre-clinical research
- ▶ *Lachesis mutus*
- ▶ *Sepia officinalis*

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Introduction

Menopause is a physiological event that marks the end of the reproductive stage of a woman's life. In general, women above 40 years of age start with hormonal changes some years before menopause, which is considered the last menstrual period after 12 months of amenorrhea. All these hormonal changes cause a wide range of symptoms that may vary among women. Vasomotor symptoms (VMS; hot flashes and night sweats) are the most common (as many as 70 to 80% of menopausal women may experience them).¹ Changes in mood (depression and anxiety), insomnia, headaches, arthralgias, cognitive impairment, decreased sexual desire, vaginal dryness, and urinary symptoms are some of the most important disorders during this period of time. Cardiovascular disease (i.e., hypertension) and metabolic dysfunction (i.e., obesity, dyslipidemia, insulin resistance, or diabetes), as well as osteoporosis, are also frequent.²

Homeopathy is "a therapeutic method that uses small doses of various substances to stimulate autoregulatory and self-healing processes. Homeopathy selects substances by matching a patient's symptoms with symptoms produced by these substances in healthy individuals. Medicines are prepared by serial dilution and shaking, which proponents claim imprints information into water."³ The importance of a comprehensive and individualized homeopathic evaluation for improving homeopathic prescription in daily clinical practice has been described.⁴ *Sepia officinalis*, *Lachesis mutus*, *Sanguinaria canadensis*, *Sulphur* and *Cimicifuga racemosa* are among the well-known homeopathic medicines (HMs) prescribed for menopause. Both observational studies and case reports have reported encouraging results when prescribing these HMs for menopause,⁵⁻⁷ but few randomized controlled trials in this area have shown positive results.⁸⁻¹¹ The *Homeopathic Materia Medica* (HMM) provides a full description of the mental, general and physical symptoms of all the HMs that can be prescribed for menopausal complaints. Nevertheless, the physiologic mechanism by which menopausal symptoms improve when these HMs are prescribed is unknown.

Currently, there are *in-vitro* and *in-vivo* studies with specific animal models for studying the biology of the neuroendocrine changes of menopause.¹² A body of evidence explains the therapeutic effects of conventional medicines for menopause and depression,^{1,12} but in the case of HMs there is scarce information. Hence, the scientific evidence underlying the biology of the neuroendocrine changes of menopause and depression is worth exploring for a possible explanation of the effect of HMs. Research teams in homeopathy have contributed toward elucidating the mechanism of action of HMs; however, the subject remains unclear.¹³

Therefore the aims of this review are: (1) to understand the key points underlying the biology of the neuroendocrine changes of menopause and depression; (2) to investigate the current evidence of the effect of HMs in animal models that evaluate depression, anxiety and menopause; (3) to address the scientific evidence of two of the most important HMs prescribed for menopausal women in daily clinical practice,

Lachesis mutus and *Sepia officinalis*; and (4) to discuss future directions in homeopathy research.

Literature Search Methods

Extensive literature research was conducted in the following electronic databases: Medline (Ovid), the Cochrane Library, Google Scholar, PubMed, Science Direct, Scopus and IMBIOEM. The search terms were: (pathophysiology of menopause AND depression); (homeopathy AND menopause OR climacteric OR depression); (menopause OR depression and *Lachesis mutus* OR *Sepia officinalis*) and (animal models AND homeopathy).

Pathophysiology of Vasomotor Symptoms during Menopause

Temperature regulation is a complex process integrated by a network of neuroendocrine, autonomic and somatomotor responses.¹⁴ The thermoregulatory circuitry is made up of three main components: (1) the brain (hypothalamus, specifically the pre-optic area [POA]); (2) the internal body cavity; and (3) the peripheral vasculature.¹⁴ There is a thermoneutral zone with two thresholds: the upper one triggers heat loss (sweating) and the lower one triggers heat conservation (shivering).¹⁵ The limits are defined according to the circadian cycle.¹⁶ Within the thermoneutral zone, major thermoregulatory responses do not occur. The body's various thermoregulatory zones send temperature signals to the hypothalamus to maintain optimal core body temperature (CBT) by provoking increased blood flow (vasodilatation to diminish heat) or reduced blood flow (vasoconstriction to conserve heat) to peripheral blood vessels (–Fig. 1).¹

Multiple levels of thermoregulatory neural circuitry—central and peripheral—are under catecholaminergic and/or serotonergic control. The POA is the target for norepinephrine (NE; or noradrenaline) pathways and has serotonin (5-hydroxytryptamine; 5-HT) receptors. Peripheral vasodilatation and vasoconstriction are modulated by noradrenergic and serotonergic input.¹⁷ VMS are a consequence of a malfunction of one or more of the thermoregulatory control mechanisms.¹⁴ There are three proposed hypotheses to explain the pathophysiology of VMS (–Fig. 1):

1. A change or miscommunication in the pre-defined acceptable temperature set-points. A narrowing of the thermoneutral zone therefore triggers an exaggerated reaction (hot flash) to normally insignificant elevations in CBT (threshold changes).¹⁸
2. Changes in vascular reactivity that interfere with the ability of blood vessels to respond rapidly and to the appropriate degree, resulting in an exaggerated response.¹⁹ Estrogen and progesterone (PG) influence skin blood flow control.²⁰ The low levels of estradiol during post-menopause reduce the elasticity of blood vessels, causing delayed responses to changes in internal body temperature (dysregulation).²¹
3. Neurochemical alterations as an underlying cause of thermoregulatory dysfunction. The levels of 5-HT

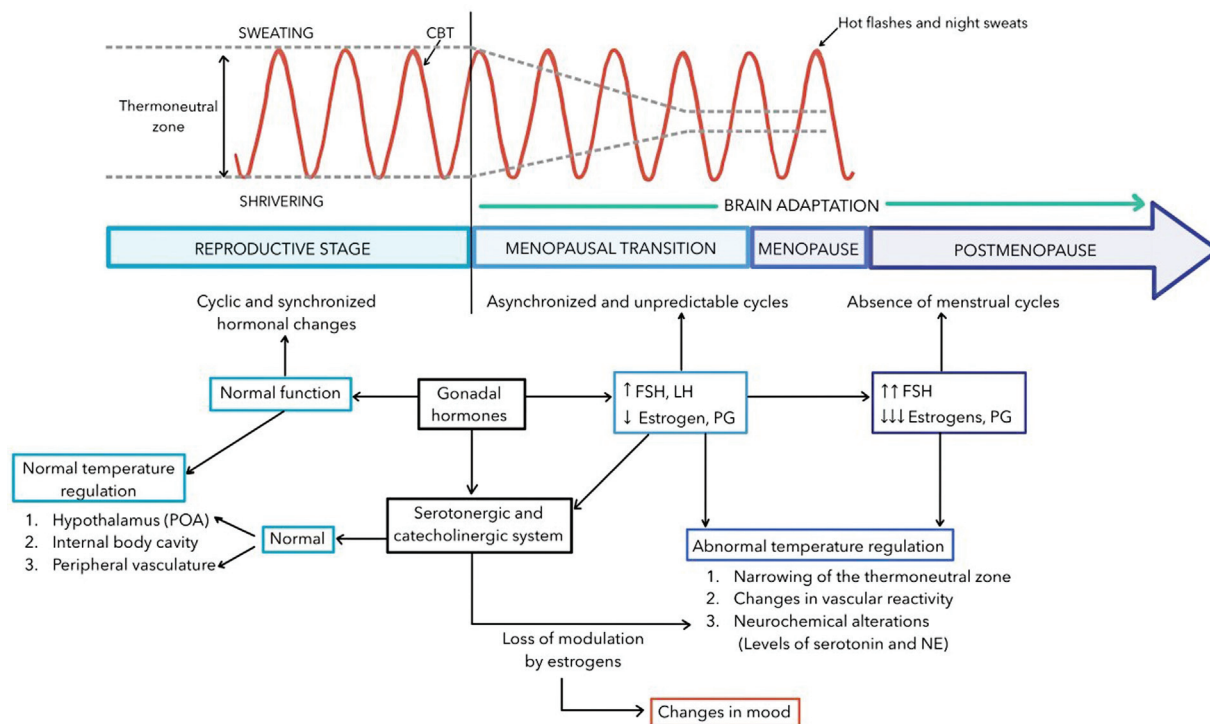


Fig. 1 Pathophysiology of vasomotor symptoms and changes in mood during menopause. Abbreviations: CBT, corporal body temperature; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NE, norepinephrine; PG, progesterone; POA, pre-optic area.

and/or NE are thought to be affected due to loss of modulation by estrogens.^{1,22}

The Role of Gonadal Hormones and Neurotransmitters in Menopause

The post-menopausal stage is characterized by elevated luteinizing hormone and follicle-stimulating hormone (FSH). The production of estradiol and PG decreases along with the decline of ovarian follicles. Both estradiol and PG have the ability to modulate neurotransmitter systems (serotonergic, cholinergic and dopaminergic).^{1,22} They are involved in the regulation of the structure and function of neuronal circuits throughout the central nervous system.²³ During the reproductive stage, women experience cyclic and synchronized hormonal changes due to neuroendocrine input and it is thought that the brain must be flexible to respond to these changes. However, during the transition to menopause, the cycles become asynchronous and unpredictable due to exaggeration in ovarian hormone levels.²⁴ Hence, greater flexibility in neuronal responsiveness is necessary. Moreover, during the post-menopausal stage, the brain must adapt or “reset” to the absence of ovarian hormones and should establish a new baseline homeostasis to maintain normal brain function.²⁵ But if this adaptation does not occur, there is a great susceptibility to brain-related dysfunctions, that is, impaired temperature regulation (–Fig. 1).

Estrogens are involved in the synthesis or degradation of neurotransmitters, in the expression of receptors, as well as

in neuron membrane function.^{23,26–30} Decreasing hormone levels may cause a diminution in neuronal function due to an imbalance of key neurotransmitters (5-HT and NE). Estrogens increase the availability of 5-HT by boosting the capacity to synthesize the transmitter and by slowing its degradation.^{31–33} They also regulate 5-HT receptor density and binding and slow the transmitter removal from the synapse.^{34,35} Similarly, the estrogens modulate the noradrenergic system.

There is a dynamic and inter-dependent relationship between the serotonergic and noradrenergic systems. Serotonergic neurons have an inhibitory effect on noradrenergic excitation and thus a decrease in noradrenergic transmission. By contrast, noradrenergic firing has a stimulatory effect on serotonergic neurons, causing a net increase in 5-HT transmission.³⁶ It is important to notice that the neurobiology of the 5-HT and NE systems is complex and the role of estrogen is not fully understood. However, further research in this field would provide relevant information for therapeutic decision-making for menopausal women with depression. For example, there is a hypothesis that the neurotransmitters are involved in the regulation of temperature because the selective serotonin re-uptake inhibitors (SSRIs) and serotonin and NE re-uptake inhibitors (SNRIs) can reduce hot-flash scores by 65%.^{37–40}

Biology of Depression during Menopause

Though genetic, psychological and social factors are related to an increased risk of depression, it is now known that

changes in ovarian hormone regulation are associated with more vulnerability to depression during the transition to menopause.¹² Estrogen is also known to alter neurotransmitter systems involved in depression.¹² Moreover, the presence of VMS may also be associated with an increased risk for depression.^{41–46} Women who experience VMS are four times more likely to have depression compared with women without VMS during the transition to menopause, but not during the post-menopausal stage.⁴³ It is also noticeable that the longer a woman experiences the erratic hormonal period, the greater the risk of depression.⁴⁶ Hence, there is a bidirectional relationship between hormones and mood changes. It is suggested that the association between depression and VMS involves shared pathophysiologic events in which hormonal changes play an important role. The ability of the brain to rapidly “adapt” to hormonal changes may be an important factor for the increased susceptibility to depression associated with reproductive events.¹²

Role of Dopamine in the Pathophysiology of Depression

Evidence supports a role for decreased dopaminergic neurotransmission in depression.⁴⁷ The dopamine (DA) system regulates motivation, learning, reward, decision-making, concentration, psychomotor speed, and the ability to experience a pleasure. DA is synthesized in pre-synaptic neurons and exerts its effects on the post-synaptic neuron through interaction with specific receptors.^{48,49} Impaired DA release may be due to changes in receptor number or function (decreased receptor binding) and/or altered intracellular signal processing. Furthermore, there is an interaction between the 5-HT and DA systems. Activation of certain 5-HT receptors may stimulate DA release or inhibit the DA system in specific brain regions. Treatment with antidepressants frequently fails to achieve remission of depression.⁴⁷ The American Psychiatric Association suggests that this partial response results from a failure of increased serotonergic or noradrenergic neurotransmission to induce similar alterations in the DA system.⁵⁰

Estrogens and PG can also affect dopaminergic neurotransmission via multiple mechanisms (number of dopaminergic receptors).^{51,52} Interestingly, solid evidence has shown that inflammation may play a role in motivation-related impairments in major depression.⁴⁹ A sub-set of depressed patients may have increased inflammatory signaling that depletes DA availability, reduces DA-moderated regulation of inflammation, and produces motivational impairments, as observed in animal models.^{49,53,54}

In addition, many patients with depression and anhedonia do not exhibit immune signaling impairment.⁵⁵ It has been stated that another mechanism underlying motivational alterations is impaired synaptic plasticity. DA signaling helps strengthen synaptic connections that link reward-related cues to rewarding outcomes.^{56–58} Therefore, the alterations of post-synaptic plasticity mechanisms may manifest as blunting of DA-related reinforcement signals, contributing to dysfunction in the DA system without reflecting a deficit

in DA-releasing neurons.⁴⁹ Neuroimaging and post-mortem studies support the view that neuroplasticity is altered in major depression.^{49,59}

Pre-clinical Evidence of Homeopathy for Mood Disorders and Menopause

Classical homeopathy is the “gold standard” in homeopathic prescription. In this type of prescription, one remedy is prescribed at a time using only a minimal dose—specifically, the lowest dose and fewest number of repetitions required in each particular case.^{60,61} This approach should be a great opportunity for the health care system due to the utilization of individualization when evaluating and treating depressed women during menopause.⁶⁰ Though the mental symptoms described in some HMs correspond to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),⁶² for depressive and anxiety disorders, each HM has its own “picture”, meaning a cluster of individual symptoms associated with menopause that includes both emotional and physical complaints. However, it is noticeable how many mental symptoms are exhibited by some HMs such as *Sepia officinalis*, *Natrum muriaticum* or *Lachesis mutus*: sadness, weeping, anxiety, loss of pleasure, irritability, poor concentration, and fatigue, among many others.⁶³ It is also important that these HMs are specifically useful during certain reproductive events: menarche, menses, pregnancy, or menopause. Taking into consideration all these points, there are two possibilities: (1) the HMs might have a direct neuroendocrine effect, though exactly how is as yet unknown; or (2) the HMs trigger an (as yet unidentified) biological mechanism in the body that then stimulates a neuroendocrine effect. Thus, research in this field is mandatory. Data from pre-clinical studies could explain why depression, anhedonia, the inability to feel pleasure from daily activities, and VMS are improved when *Sepia officinalis* is prescribed in homeopathic practice, for example.⁶³

Nowadays, with the advancement in scientific knowledge, including animal models and molecular biology techniques, some homeopathy research teams are actively involved in conducting both *in-vitro* and *in-vivo* pre-clinical research to elucidate the therapeutic mechanism by which the HMs produce their biological effects.^{64,65} However, efforts in neuroendocrine biology are still insufficient. In 2009, Bellavite and co-workers published a review of HMs in rodent behavioral and psychopathological models.⁶⁴ They reported 15 exploratory studies with this research, often published in non-indexed and non-peer-reviewed journals, studying anxiolytic activity only. In 2017, Gupta and colleagues compiled pre-clinical findings from both *in-vitro* and animal studies of the effect of HMs in some common pathophysiologic conditions (anti-microbial, anti-inflammatory, analgesic, and anti-cancer effects, among others). They also reported animal studies that showed an anxiolytic effect of certain HMs but they did not include pre-clinical research related to menopause or depression.⁶⁵

Animal models are valuable for their contribution to the understanding of the development of disease at the tissue,

cell, and molecular level⁶⁴ or, in the case of menopause, they can help to elucidate the mechanisms of absorption, distribution, transformation, and excretion of different medicines for menopausal complaints. Important information about conventional antidepressants has been obtained using animal models. A large number of animal models of depression have been developed over the years, but all of them have imperfections. However, these models provide invaluable help in the development of drugs.⁶⁶

Currently, information derived from the effect of HMs in mouse behavioral models is useful but scarce. Bellavite and colleagues have been working on the experimental neuropharmacology of *Gelsemium sempervirens*, at low doses and high dilutions, for anxiety and fear in validated behavioral models in mice. An anxiolytic-like effect in mice was observed in two of these experimental models: the open-field (OF) and light-dark (LD) tests. Results indicated that lower dilutions (4C) were less effective than higher dilutions (9C and 30C) for anxiety.^{64,67} Controversial commentaries on these investigations were then published.⁶⁸ However, other independent laboratories have shown evidence that *Gelsemium* exerts anxiolytic, analgesic and anti-depressive effects in a wide range of doses and dilutions. It was also found that low doses and high dilutions of *Gelsemium* modulate the expression of genes involved in neuronal function (G-protein coupled receptor signaling, calcium homeostasis, inflammatory pathways, and neuropeptide receptors).^{69,70} It is important to notice that in high-dilution research there seems to be no linear or proportional relation between the molecular concentration of the active substance and the therapeutic effect.⁶⁵ The same Italian laboratory, using appropriate test models such as the above, has found that *Ignatia amara* dilutions (peaking at 9C potency)—an HM also used for anxiety and depression symptoms, manic episodes, and hypersensitivity to emotions in homeopathic daily practice—modify some emotion-related symptoms in mice without affecting locomotion.⁷¹

A Brazilian pilot study by Pinto and co-workers tested the effect of *Chamomilla* in stress and depression. They combined several models (stress, depression, and anxiety) with methods to evaluate the effect on the immune system. It is known that stress causes several psychopathological disturbances that affect the immune and nervous system. There is a mouse model to assess the behavioral and immune effects after cohabitation with a sick cage-mate, which causes stress shown by leucopenia and disturbances in exploratory activity. The forced swimming test, an animal model that evaluates depression in mice, was used. The results showed that mice subjected to stress conditions and treated with *Chamomilla* 6C recovered their basal behavioral condition.⁷² As previously stated, inflammation may play a role in depression by increasing inflammatory acute-phase proteins and affecting DA neurotransmission.⁴⁹ Though the results from this study are interesting, research on the neurotransmitter systems was not pursued.

To date, the mechanism of action of HMs in menopause and depression at a molecular level is unknown. More generally, research teams have tested homeopathic preparations at different potencies, hypothesizing mechanisms of

action based on different techniques and phenomena (nanoparticles, quantum coherence domain, dynamic water clusters, and weak quantum theory).¹³ Tournier and colleagues concluded that these hypotheses need to be further assessed experimentally. Taking into account that HMs are ultra-diluted preparations, usually beyond Avogadro's limit, some researchers using DNA microarray-based transcriptional analysis have revealed alterations in the gene expression of key signaling pathways.^{73,74} Regarding *Sepia*, Jyoti & Tandon studied its safety associated with taking 30C potency during pregnancy, using mouse embryonic stem cells as the model. They found that *Sepia*, and also *Nux vomica*, led to modulations in the expression of certain lineage-specific genes, but these differences were not significant with respect to their solvent controls.⁷⁵

Several randomized controlled trials, clinical observational studies and case reports have indicated the most important HMs that seem to improve menopausal complaints. The HMM fully describes their most characteristic symptoms. Some of these HMs, called “polychrests”, may be used to cure a broad range of diseases; they may alleviate both emotional and physical complaints. This is the case for *Sepia officinalis* and *Lachesis mutus*, each of which can be used for depression, anxiety, and also for VMS, headaches, insomnia or fatigue in menopausal women.^{76–78} However, there are other “organotropic” HMs with specific actions in the body: for example, *Sabina*, *Erigeron*, *Trillium pendulum* or *Millefolium* for menorrhagia in menopausal women. In addition to *Sepia officinalis*, *Lachesis mutus* or *Sulphur*, the less-known HMs *Manganum*, *Melilotus* or *Pilocarpus jaborandi* may also be used for VMS.^{76–78} To elucidate why HMs are used for treating VMS and mood disorders, it is important to analyze the current scientific information about two of the most frequently prescribed HMs for menopause: *Lachesis mutus* and *Sepia officinalis*.

Lachesis mutus

Lachesis muta, the largest venomous snake in the Americas, lives long and has nocturnal habits, remaining throughout the day in a state of torpor. Several studies have been published regarding the toxicologic effects of the snake's venom.⁷⁹ Homeopathic *Lachesis mutus* is prepared using the venom; hence, the toxicologic information is useful for homeopathy and allows us to understand the symptoms described in the HMM. However, pre-clinical studies using *Lachesis mutus*, prepared according to the homeopathic method (serial dilution and succussion), are still lacking in explaining why it improves menopausal complaints in daily practice.

The envenomation caused by *Lachesis* causes both local effects (pain and edema a few minutes after the bite, hemorrhage, and necrosis) and systemic alterations (coagulopathy, systemic hemorrhage, marked hypotension, bradycardia, renal damage, uncoordinated walking, and lapses of consciousness), as well as manifestations suggestive of autonomic cholinergic signaling via parasympathetic pathways (profuse sweating, salivation, abdominal pain, and vomiting).^{79–82}

A range of enzymatic and non-enzymatic proteins has been isolated and characterized from the snake venom,

primarily metalloproteases, phospholipase A2 (PLA2), serine proteases (including thrombin-like enzymes, kallikrein-like enzymes, and fibrinogenes), C-type lectins, and L-amino acid oxidase.^{83–85} The venom also contains bradykinin-potentiating peptides (BPPs)^{84,86,87} and bradykinin receptor antagonists.⁸⁸ *Lachesis mutus* venom contains kallikrein-like enzymes that release bradykinin to cause hypotension^{89,90} and relax vascular and non-vascular smooth muscle⁹¹; this hypotension may be potentiated by BPPs.^{86,92} BPPs act directly on the renin-angiotensin-aldosterone system through the inhibition of angiotensin-converting enzyme (ACE).

The mechanisms responsible for the venom-induced hypotension are probably multifactorial and may involve: (1) parasympathetic (cholinergic) pathways; (2) the release of nitric oxide by venom components acting directly on the vasculature, or indirectly through the release of fibrinopeptides⁹³; and (3) the release of autacoids such as histamine and/or prostaglandins by venom PLA2 and bradykinin by kallikrein-like enzymes.^{89,90,94} Proteases and metalloproteases can affect hemostatic mechanisms in different ways: for example, by interfering with clotting factors and/or platelets, by activating or inhibiting their functions; and they can also damage the integrity of blood vessel walls due to the action of hemorrhagic factors.

The HMM states that the action of homeopathic *Lachesis mutus* is characterized by a circulatory disruption—which might explain why it is prescribed for VMS, throbbing headaches and hypertension during menopause.^{63,76} However, there is a lack of basic research in this field. Regarding temperature regulation, it is unknown if the venom's biologic effect might be a consequence of a malfunction in the peripheral vasculature, specifically changes in vascular reactivity that interfere with the ability of blood vessels to respond rapidly to changes in external temperature. The venom's components might act directly or indirectly on the vasculature due to a range of enzymatic and non-enzymatic proteins. When *Lachesis mutus*, manufactured according to the homeopathic procedure of dilutions and succussion, is administered to a patient, there is often an improvement in VMS and in the symptoms derived from circulatory disruption (headaches, for example). It is also unknown if homeopathic *Lachesis mutus* plays a role in improving neurochemical alterations or if it contributes to the adaptation that the brain experiences when all the asynchronized and unpredictable hormonal changes appear in the menopausal transition. Based on the description of *Lachesis mutus* symptoms in the HMM, it can be inferred that it exerts a direct neuroendocrine effect or perhaps it acts indirectly by triggering an unknown biological action; however, these considerations remain unresolved. Both basic and clinical research works in this field are necessary to clarify the point.

An explanation for the possible neuroendocrine effect and mechanism of action of homeopathic *Lachesis mutus* in menopause is likely to be profound and complex. Draiman describes the “personality profile” and the “reactive conduct” of both *Lachesis* and *Sepia*,⁷⁸ enabling a structured summary of the most important symptoms of the two

medicines (→ **Table 1**). The *Lachesis* “personality” or “picture” includes the descriptions loquacious, jealous, suspicious, aggressive, and prone to hatred, seeking revenge.⁷⁸ The aggressive impulses are described as a menopausal woman who is sarcastic, cruel, teasing, disdainful and quarreling. The *Lachesis* personality also has sexual energy, with great excitement of sexual desire, being passionate and lascivious, but if this high sexuality is not satisfied deep depression may set in. Its depressive mood is present mainly during the mornings.^{63,76–78}

A study by Sánchez-Reséndiz and colleagues in Mexico measured brain DA levels in 72 Wistar rats.⁹⁵ Thirty-nine rats were administered *Lachesis trigonocephalus* 12C (10⁻²⁴ in 22.5% ethanol) via a catheter at a dose of 0.25 mL every 8 hours for 10 days. The control group (33 rats) received the same dose of ethanol but without *Lachesis*. At the end of the study, catecholamine levels were determined—dopamine by the Carlsson & Waldeck procedure,⁹⁶ and adrenaline and noradrenaline using the Sourkes & Murphy technique.⁹⁷ The *Lachesis* 12C group was found to have a mean of 1,136 ± 57 ng/g of DA compared with 998 ± 43 in the control group ($p < 0.05$).⁹⁵ Noradrenaline levels were 528 ± 29 ng/g in the control group and 452 ± 16 ng/g in the *Lachesis* 12C group ($p < 0.025$). In contrast, adrenaline levels did not show statistically significant differences.

The authors then studied the effect of *Lachesis trigonocephalus* in different dilutions (3C, 6C, 12C, and 30C) compared with placebo (ethanol only) on the concentration of catecholamines (DA, noradrenaline, and adrenaline). They found no statistically significant inter-group differences in DA levels with 3C and 6C. Statistically significant differences between groups were found only with *Lachesis* 12C and 30C. Regarding noradrenaline concentration, only the rats treated with *Lachesis* 12C had a statistically significant concentration difference from the control group (452 ± 99 vs. 528 ± 166 ng/g respectively, $p < 0.025$). In the case of adrenaline, the group treated with *Lachesis* 30C had higher levels compared with placebo (102 ± 28 vs. 85 ± 34 ng/g respectively, $p < 0.025$).⁹⁵

That study was not peer-reviewed, and an independent research team has not yet reproduced it. Hence, its results should be considered with the utmost caution. In any event, the hypothesis that an effect in the neurotransmitter systems might explain the wide range of mental symptoms of *Lachesis* has not been tested. The aggressive behavior, as well as the other mood changes, described in *Lachesis* could be related to an impairment in neurotransmitter function that might improve when it is administered according to the homeopathic procedure of dilutions and succussion. Its specific action during menopause could also be related to hormonal changes during the menopausal transition.

It is well known that aggressive behavior is characterized by an inability to regulate affective as well as aggressive impulses and is notably co-morbid with other mental disorders, including depression, suicidal behavior and substance abuse.⁹⁸ Low levels of the neurotransmitter 5-HT have been associated with impulsive aggression in both human and animal studies.^{98,99} As previously described, evidence suggests that the 5-HT and DA systems interact

Table 1 Personality profile and main mental symptoms of *Lachesis mutus* and *Sepia officinalis*

<i>Lachesis mutus</i>		<i>Sepia officinalis</i>	
Suspicious and affective possessiveness (jealousy)		Affective indifference and self-antagonism	
Personality profile	Reactive conduct	Personality profile	Reactive conduct
1. Emotional excitement - Loquacious - Rambling - Eccentricity	1. Defending her possessions: "attacks" - Arrogant - Boastful - Dictatorial - Aggressive - Seeks revenge	1. Incapacity to love (with unsuccessful intellectual intentions to) - Affective "anesthesia" - Indifference to loved ones (family, husband, children), to pleasure, business - Aversion to company - Avoid seeing people	1. Looks for alternative motivations (to fill her affective emptiness) - Better when occupied - Industrious - Makes plans - Conscientious - Busy
2. Alternating mood - Depression, bad mood and anxiety during the morning - Happiness, excitement, and industrious at night	2. Possessive defense - Violent jealousy - Unbearable - Reproaches	2. Emotiveness - Involuntary weeping - Laughs and cries - Worse by consolation - Feels abandoned - Happy when thunder	2. Competitiveness - Hypercritical - Disposition to defame - Hypocritical - Mocking - Envious
3. Fear - Of being poisoned - Of death - Of evil - Of snakes	3. Harassment - Hatred - Sarcastic - Disdainful - Quarreling - Cruel - Teasing	3. Fear - Of poverty - Of her social position - Of being alone - Of death - Of madness - Thinks she will die soon	3. Aggressiveness - Anger due to contradiction, before menses, after intercourse - Quarrelsome
4. Anxiety - Conscience anxiety: - About the salvation of her soul - About her health - Faintness in closed rooms - When suffering hot flashes	4. Escape attitude - Looks for activity - Hard-working - Impatient - Ambitious	4. Anxiety - About the future - About her health - Hypochondriac - Worse with sexual relations - Desperate for her recovery, for her existence	4. Social distance - Aversion to company - Avoids seeing people - Aversion to her husband and family
5. Oversensitive - One is under powerful influence - Delusions of being afloat - Worse when touching the neck		5. Sexual aversion - Frigidity - Aggravation by intercourse - Dyspareunia	
6. Bad mood - During the menopause - Improves during menses - Nymphomania - Lascivious		6. Bad mood - After intercourse - When contradicted - Before menses	
7. Insecurity - Lack of self-confidence - Hesitant		7. Insecurity - Shy - Cowardly - Irresolute	
Main modalities ^{76,77}		Main modalities ^{76,77}	
Aggravation: heat, sun, hot drinks, after sleeping, in the morning, constriction	Amelioration: appearance of discharges, during menses, during the night	Aggravation: resting, before storms, with cold, consolation.	Amelioration: exercise, lying on the right side.
Menopausal symptoms ^{76,77}		Menopausal symptoms ^{76,77}	
Hot flashes with congestion in head	Hypertension	Hot flashes and night sweats	Violent pressing headache with rush of blood to head
Migraine	Sensation of constriction in chest	Genital prolapse and pelvic congestion	Violent stitches upwards in vagina
Sensitive to touch or constriction (in the neck)	Sensation of beating	Sensation of emptiness, of a ball in inner parts, relaxation and bearing down in abdomen	She must sit with her limbs crossed to ameliorate the sensation of a ball in inner parts.

Source: Based on the concepts "personality profile" and "reactive conduct" described by Draiman.⁷⁸

closely at a basic neurophysiological level^{100–102} and that impairment of serotonin system function can lead to dysregulation of the dopamine system.¹⁰³ Specifically, serotonin hypofunction may represent a biochemical trait that predisposes individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive fashion to the serotonergic deficit.

It is also important to study if there is an effect of *Lachesis* in any part of the hypothalamic-hypophysial-ovarian axis that can explain its action during the reproductive stages in women. If the results of the Mexican study by Sánchez-Reséndiz are confirmed, DA could somehow be involved in the aggressive behavior of *Lachesis*. Interestingly, the same Mexican research team investigated the estrogenic effect of *Pulsatilla nigricans* 3D in Wistar rats. They found cytological alterations that might indicate that this HM affects the menstrual cycle; however, they concluded that it does not act in the same way as estrogen. Its effect is more likely to be in the hypothalamus or hypophysis.⁹⁵ Unfortunately, this study was also not peer-reviewed and has not been reproduced by independent researchers.

Sepia officinalis

Sepia officinalis is another important polychrest that is frequently prescribed for women's ailments in daily practice, especially for menopausal symptoms. A gland of the common cuttlefish *Sepia officinalis* produces an inky juice that can be used for homeopathic preparation. Mental symptoms are one of the most important features of this HM. A brunette woman who has lost the ability to feel natural love or to be affectionate characterizes the "picture" of *Sepia officinalis* (→ Table 1). She becomes depressed and indifferent toward anything; only wants to be alone, losing enthusiasm toward life; is irritable and easily offended; expresses great sadness with much weeping, especially when telling her symptoms; feels sluggish and dull, both physically and mentally; has lack of vital heat during chronic diseases; experiences hot flashes, with weakness and perspiration, during menopause; has sensitivity to cold air; faints easily from extremes of temperature or getting wet; and has a bearing-down sensation and constipation.^{75–78} Besides the mental symptoms previously described, it is noticeable that the HMM also describes skin features in *Sepia officinalis* such as yellowness of face and conjunctiva, yellow spots on the chest, brown saddle over upper parts of cheeks and nose, herpetic eruptions, and lentigo.⁶³

The *Sepia officinalis* ink gland is involved in the unique defense mechanism of this cephalopod. Nevertheless, it has traditionally been considered as a convenient model system for the study of melanogenesis. The ink gland of *Sepia officinalis* is a highly specialized organ that promotes the conversion of tyrosine into melanin, which is secreted into the lumen of the gland, accumulated into the ink sac, and ejected on demand.¹⁰⁴ In addition to melanin, both dopa and DA have been detected in squid ink,^{105,106} which suggests a broader significance for tyrosine metabolism in cephalopods than the simple production of melanin.

Furthermore, Fiore and colleagues, searching for catecholamines in a biochemical analysis of crude extracts from pools

of freshly collected *Sepia* ink glands, indicated the presence of dopa and DA (2.18 ± 0.82 and 0.06 ± 0.02 nmol/mg of protein), but no detectable noradrenaline or adrenaline.¹⁰⁴ They also found that in the mature ink gland cells of *Sepia officinalis*, part of the tyrosine pool is converted into DA. It also seems that DA might play a role in the mechanisms of cell maturation in addition to functioning as neurotransmitter and hormone in the ink gland.¹⁰⁴ The occurrence of large amounts of tyrosinase in the ejected ink would ensure the efficient conversion of catecholamines into toxic quinones, acting as a preventive measure against predators.¹⁰⁷

In summary, homeopathic *Sepia officinalis* is prepared from the ink produced by the gland of this cuttlefish. Biochemical analysis shows that tyrosinase, melanin and DA are among its constituents. The HMM states that *Sepia officinalis* is associated with an important loss of pleasure in previously enjoyable activities or loss of interest or motivation in pursuing them. According to the DSM-5, this feature is called "anhedonia", which is one of the two symptoms required for the diagnosis of a depressive episode.⁶² It is worth highlighting that animal models (effort-based decision-making tasks) have shown robust evidence linking DA to motivated behavior, as previously stated.⁴⁹ Consequently, it is possible that the effect of *Sepia officinalis* might be related to DA or other neurotransmitters. All this information may result in new interesting clues to start understanding the mechanism of action of homeopathic *Sepia officinalis* for improving menopausal symptoms. Pre-clinical research in this field is thus important and compelling.

Discussion

The information about the underlying biology of depression and menopause might help to guide homeopathy research. Nevertheless, the path of such research in this field might be as challenging as it is ambitious and complex. Though many advances in the development of new treatments have been made during the last decades, current antidepressants have three main limitations: low efficacy, delayed onset of therapeutic action, and side effects.¹⁰⁸ Conventional antidepressant medications such as SSRIs or SNRIs block 5-HT and/or NE transporters. Thus, it has been hypothesized that conventional antidepressant medications have beneficial effects on depressive symptoms by increasing serotonergic function. Nonetheless, this is a complex field, due to the existence of many different 5-HT receptors, with different locations in brain networks and sometimes opposing actions on neuronal activity. Moreover, it remains undetermined which of the different 5-HT receptors plays a role in the therapeutic effects of SSRIs and SNRIs.¹⁰⁸ In the case of HMs, researchers might face the same difficulties due to the complexity of the neurotransmitter systems and the role of gonadal hormones during menopause. The description of the neuropsychiatric symptoms of the HMs, such as *Lachesis* or *Sepia officinalis*, could allow the formulation of a hypothesis to investigate whether there is a direct or indirect neuroendocrine effect. However, several points should be considered in research due to the involvement of hormonal and mood changes, co-

morbidities, social and psychological factors, as well as other aspects inherent to homeopathy: for example, type of prescription, individualization, or the effect of the HMs at different potencies.

Nowadays, the simplest hypothesis that diminished activity of serotonin pathways has a causal role in the pathophysiology of depression is insufficient.¹⁰⁹ Therefore, homeopathy research could face more difficulties. It has been suggested that low serotonin function may affect some mechanisms related to the recovery from depression rather than having a primary effect to lower mood in vulnerable people. Thus, improving serotonin activity may effect a positive shift in automatic emotional responses, not altering mood directly. This leads to changes in the processing associated with emotional experiences, a “relearning” process involved in the alleviation of depression.¹¹⁰ This fact is supported by the promotion of synaptic plasticity caused by SSRIs.¹¹¹ In consequence, many questions arise. How do HMs improve mood and VMS during menopause? Do they act directly on neurotransmitter systems? Do they have an effect within this “relearning” process associated with emotional experiences? Do they promote synaptic plasticity like SSRIs? What is their effect on depression associated with inflammation in specific vulnerable individuals? What is their role in the hormonal changes related to menopause? How do they affect the process of thermoregulation during menopause? Do they have a mechanism of action similar to SSRIs? Do they act as estrogen?

It is valuable to discuss some points of note regarding the two well-known HMs for menopause that have been reviewed above. For both *Lachesis* and *Sepia officinalis*, there is available information about the snake’s venom and the gland’s ink, respectively, that can give clues in the understanding of their biological effect. In the case of *Sepia*, the presence of DA has been determined among the ink’s constituents. In the case of *Lachesis*, a wide range of enzymatic and non-enzymatic proteins are known to act directly or indirectly on the vasculature; DA may also be involved in its effects. Hypotheses about why they improve menopausal symptoms when they are administered according to the homeopathic method can be proposed. However, other HMs—some of them originating as an inert substance that nevertheless exerts a biological effect when it is administered according to homeopathic procedures—can also improve the mental state if the symptoms match with those of the patient. *Natrum muriaticum* (sodium chloride), for example, reveals a wide range of mental symptoms corresponding to major depression disorder.^{63,77} It is unknown how homeopathically prepared *Natrum muriaticum* acts to improve mood.

The lack of standardization in the criteria for selecting potencies among homeopathic physicians in daily practice is another key point. Some homeopathic practitioners claim that higher potencies (above 30C) are preferable when the patient expresses clear mental or emotional symptoms, which also describe the whole person.¹¹² This is the case for menopausal women. Nevertheless, as previously stated, animal models have shown that *Gelsemium sempervirens* exerts anxiolytic effects even in lower potencies (4C and 9C).

It has been noticed that there is no linear or proportional relation between the molecular concentration of the active substance and the therapeutic effect.⁶⁴ Therefore, the effect of the different potencies (lower and higher dilutions) is an important field to investigate in conjunction with pre-clinical and clinical homeopathy research.

In addition, there has been a lack of independent replication in both homeopathic pre-clinical and clinical research for many medical conditions.¹¹³ The methods used in the studies should have a detailed published description to guarantee the opportunity for replication. As many HMs are diluted to such an extent that they may not contain any molecule of the original substance, independent replication is key to verifying their biological effects. Pre-clinical research is the great opportunity to demonstrate that HMs can have an effect different from placebo.¹¹³

Future Directions

Bringing basic and clinical homeopathic research together in this field is a real challenge. Hence, future directions in both clinical and pre-clinical research in homeopathy for menopause and depression should be encouraged. Besides the epidemiological and clinical studies, homeopathy can use animal models for examining if there is a direct or an indirect biological effect of HMs on ovarian hormones and brain function. Molecular studies might also be useful. However, taking into account the multifactorial complexity of depression and the hormonal changes, animal models may only mimic part of the pathophysiology involved. Animal models can be useful for: (1) studying how HMs might affect the behavioral impact of ovarian hormonal changes; (2) evaluating antidepressant effects of HMs; (3) elucidating the specific interplay of gonadal hormones and HMs that might clarify their effect on VMS; and (4) elucidating the function of neurotransmitters and receptors that may play a role in mood disorders when HMs are used.¹²

Frequently, animal models are focused on a particular symptom related to depression—for example, stress—but they do not take into account co-morbidity aspects associated with depression.¹¹⁴ Translating into the homeopathy research scenario, this limitation might also complicate the extrapolation of experimental results. The homeopathic clinical approach considers the patient as a whole, not only a single symptom. It is necessary to select the most characteristic symptoms of the patient using a comprehensive, individualized, approach for a correct prescription.⁶⁰ An animal model will study one particular symptom out of all the complex processes of depression and menopause. Thus, the extension of the results to humans may be compromised by the obvious inter-species differences, multifactorial aspects of mood disorders, and the absence of the individualization that is required in homeopathy.

Accuracy in the homeopathic prescription is essential to enable a patient’s recovery: the better the “match” between a patient’s symptoms and the HM, the better the success in the treatment.⁶⁰ It has been stated that homeopathic signs and symptoms have a diagnostic value. Rutten et al have shown

that they are diagnostic indicators: they are used for the selection of an individualized HM, being in fact “prognostic factors” for predicting treatment success with that specific HM.^{115–119}

There is considerable difficulty in translating the findings from basic research into tangible clinical treatments.¹¹⁴ Some neuropsychiatric symptoms can be mimicked in animal models, but it is uncertain how these add up to a particular human disorder. There are different rodent models for depression and menopause that could be used in future homeopathy research. Each has its different strengths and weaknesses, as well as its different degrees of validity.¹¹⁴ It is thought that severe stress interacts with and exacerbates pre-existing genetic and epigenetic vulnerability.¹²⁰ Interestingly, there are animal models that study, for example, chronic stress corresponding to a human being’s daily unpleasant situations at work or an abusive job or prolonged disturbances in daily life.¹¹⁴ It is important to highlight that there are HMs used in clinical practice for the consequences of different daily life stressors, some of them suffered for long periods of time (*Natrum muriaticum* for example).⁶³ The Homeopathic Repertory includes a specific rubric named “ailments from...” (admonition; violence; accusations; lack of affection; deceived friendship; disappointed love; anxiety; not being appreciated; anticipation; punishment; anger; indignation; overwork; and so on). People sicken when they have a stressor in their lives. Homeopathic prescribing pays special consideration to these stressors and their consequences.⁶⁰ It is thus necessary to facilitate further homeopathy research in human participants that would complement ongoing work on behavioral models.

Regarding menopause, homeopathy research can use rodents because they share multiple physiological features, including endocrine changes, that are found in humans. Ovariectomized rat models, with or without supplementation of hormones, are widely used to study the impact of hormones on physiologic changes that occur during menopause.¹² A hypoestrogenic state can be recreated using models to simulate surgically or chemically induced menopause; however, it might be difficult to study the erratic hormonal state that occurs in the peri-menopause. Nevertheless, it is important to mention that researchers state that pre-clinical translational animal models of human menopause need to keep step with changes in clinical practice. Thus, homeopathy has an open field because innovative animal models of human menopause have the opportunity to indicate new routes for menopausal clinical care with homeopathy for women worldwide.

Conclusions

Some HMs, specifically *Sepia* and *Lachesis*, have been prescribed for improving important neuropsychiatric symptoms that correspond to mood disorders. They are also frequently prescribed for menopausal complaints in daily practice. Scarce pre-clinical research has demonstrated that some HMs exert anxiolytic effects. Taking into consideration current evidence regarding the pathophysiologic features of

menopause and depression, it is feasible that HMs have a direct neuroendocrine effect—though the exact mechanism is unknown. Another possibility is that HMs trigger an as-yet unidentified biological mechanism in the body that then stimulates a neuroendocrine effect. It is still undetermined if HMs play a role in the neurotransmitter systems or in the hormonal changes that characterize the menopausal transition. Animal models may contribute to finding answers to the mechanism of action of certain HMs during menopause. Simultaneously, clinical research in humans is mandatory. Independent replication is necessary to corroborate findings in both pre-clinical and clinical research.

Highlights

- Gonadal hormones and neurotransmitter systems are involved in the pathophysiology of VMS and changes in mood during menopause.
- *Lachesis mutus* and *Sepia officinalis* reveal a wide range of mental symptoms that correspond to neuropsychiatric symptoms that appear to be caused by neuroendocrine effects.
- Both pre-clinical and clinical research in homeopathy for menopause and mood disorders are mandatory and challenging.
- Animal models can help to investigate the possibility of a direct or indirect neuroendocrine effect that may explain the improvement of VMS and depression when HMs are used for treating menopausal complaints.

Conflict of Interest

None declared.

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