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

Emma Macías-Cortés[1]

[1] Outpatient Homeopathy Service, Hospital Juárez de México, Secretaría de Salud, Mexico City, Mexico

Homeopathy 2024;113:54–66.

Address for correspondence Emma Macías-Cortés, MD, PhD, Outpatient Homeopathy Service, Hospital Juárez de México, Secretaría de Salud, Ave. Instituto Politécnico Nacional 5160, Col. Magdalena de las Salinas, CP 7760, Mexico City, Mexico (e-mail: ecmc2008@hotmail.es).

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*

received
January 10, 2023
accepted after revision
March 24, 2023
article published online
July 3, 2023

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0043-1769734.
ISSN 1475-4916.

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 IMBIOMED. 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

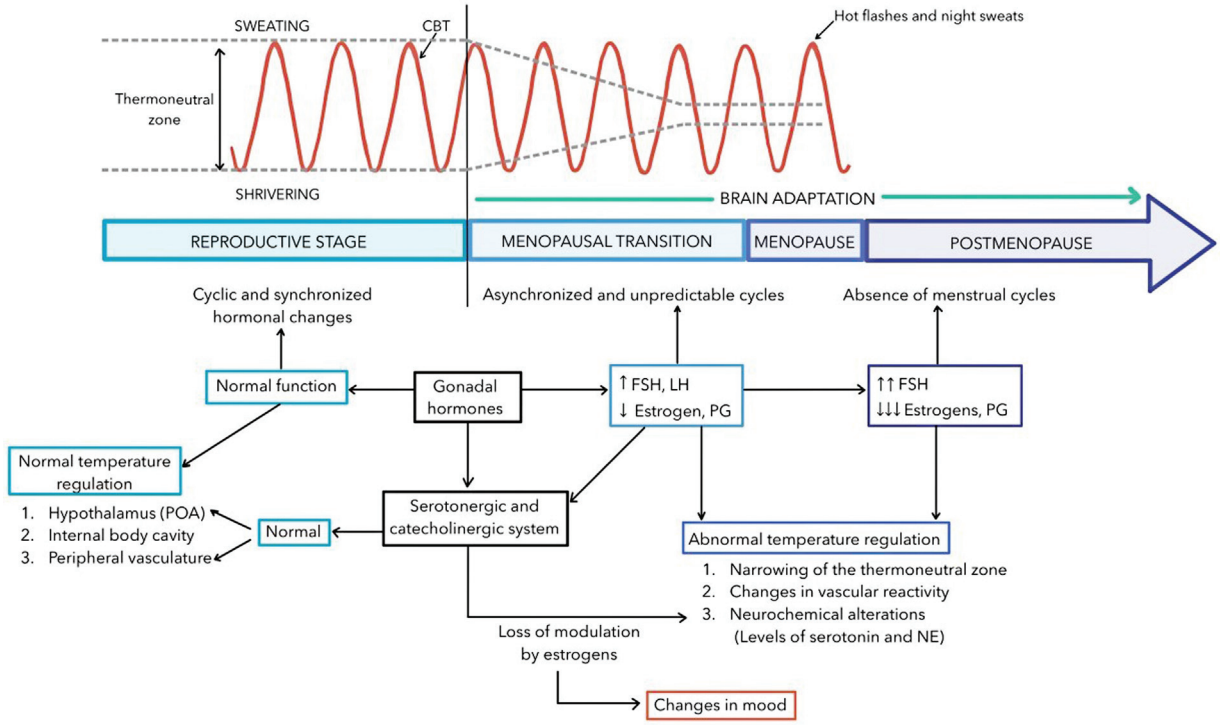

Fig. 1 Pathophysiology of vasomotor symptoms and changes in mood during menopause. Abbreviations: CBT, corporal body temperature; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NE, norepinephrine; PG, progesterone; POA, pre-optic area.

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 asynchronized 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 bi-directional 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 level[64] 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, maniac 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 ultradiluted preparations, usually beyond Avogadro's limit, some researchers using DNA microarray-based transcriptomic 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 fibrinogeneses), 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 muscle[91]; 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 fibrinopeptides[93]; 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 $1{,}136 \pm 57$ 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*

Lachesis mutus		*Sepia officinalis*	
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.

References

1 Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. Arch Women Ment Health 2007;10:247–257
2 Santoro N, Roeca C, Peters BA, Neal-Perry G. The menopause transition: signs, symptoms, and management options. J Clin Endocrinol Metab 2021;106:1–15
3 Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. Ann Intern Med 2003;138:393–399
4 Macías-Cortés E. Menopause: questions and answers for improving homeopathic clinical practice. Homeopathy (article published online: 22 November 2022).
5 Bordet MF, Colas A, Marijnen P, Masson J, Trichard M. Treating hot flushes in menopausal women with homeopathic treatment—results of an observational study. Homeopathy 2008;97:10–15
6 Nayak C, Singh V, Singh K, et al. Management of distress during climacteric years by homeopathic therapy. J Altern Complement Med 2011;17:1037–1042
7 Ruiz-Mandujano ME, García-Vivas J, Luna-Reséndiz R, Ochoa-Bernal F, Sánchez-Monroy V. Evaluación del tratamiento homeopático de mujeres en climaterio entre los 45 y 60 años con la Menopause Rating Scale (MRS). La Homeopatía de México 2019;88:28–35
8 Thompson EA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. J Altern Complement Med 2005;11:13–20
9 Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: a preliminary

randomized controlled trial. J Altern Complement Med 2005; 11:21–27
10 Heudel PE, Van Praagh-Doreau I, Duvert B, et al. Does a homeopathic medicine reduce hot flushes induced by adjuvant endocrine therapy in localized breast cancer patients? A multicenter randomized placebo-controlled phase III trial. Support Care Cancer 2019;27:1879–1889
11 Macías-Cortés E. Menopause is more than hot flashes: what is missing in homeopathic research? A narrative review. Homeopathy 2022;111:79–96
12 Deecher D, Andree TH, Sloan D, Schechter LE. From menarche to menopause: exploring the underlying biology of depression in women experiencing hormonal changes. Psychoneuroendocrinology 2008;33:3–17
13 Tournier A, Würtenberger S, Klein SD, Baumgartner S. Physicochemical investigations of homeopathic preparations: a systematic review and bibliometric analysis – Part 3. J Altern Complement Med 2021;27:45–57
14 Deecher DC. Physiology of thermoregulatory dysfunction and current approaches to the treatment of vasomotor symptoms. Expert Opin Investig Drugs 2005;14:435–448
15 Cabanac M, Massonnet B. Thermoregulatory responses as a function of core temperature in humans. J Physiol 1977;265:587–596
16 Hensel H. Neural processes in thermoregulation. Physiol Rev 1973;53:948–1017
17 Martin GR. Vascular receptors for 5-hydroxytryptamine: distribution, function and classification. Pharmacol Ther 1994;62:283–324
18 Tataryn IV, Lomax P, Bajorek JG, Chesarek W, Meldrum DR, Judd HL. Postmenopausal hot flushes: a disorder of thermoregulation. Maturitas 1980;2:101–107
19 Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. Mayo Clin Proc 2003;78:603–612
20 Brooks EM, Morgan AL, Pierzga JM, et al. Chronic hormone replacement therapy alters thermoregulatory and vasomotor function in postmenopausal women. J Appl Physiol 1997; 83:477–484
21 Joswig M, Hach-Wunderle V, Ziegler R, Nawroth PP. Postmenopausal hormone replacement therapy and the vascular wall: mechanisms of 17 beta-estradiol's effects on vascular biology. Exp Clin Endocrinol Diabetes 1999;107:477–487
22 Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. Mayo Clin Proc 2002;77:1207–1218
23 Gould E, Woolley CS, Frankfurt M, McEwen BS. Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. J Neurosci 1990;10:1286–1291
24 Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 1996;81:1495–1501
25 Birge SJ. Estrogen and the brain: implications for menopause management. In: Schneider HPG, ed. Menopause: The State of the Art—in Research and Practice. Parthenon, New York, 2003: 191–195
26 McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999;20:279–307
27 McEwen B. Estrogen actions throughout the brain. Recent Prog Horm Res 2002;57:357–384
28 Woolley CS, McEwen BS. Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. J Comp Neurol 1993;336:293–306
29 McEwen BS. Invited review: estrogens effects on the brain: multiple sites and molecular mechanisms. J Appl Physiol 2001;91:2785–2801
30 Bachmann GA. Menopausal vasomotor symptoms: a review of causes, effects and evidence-based treatment options. J Reprod Med 2005;50:155–165
31 Pecins-Thompson M, Bethea CL. Ovarian steroid regulation of serotonin-1A autoreceptor messenger RNA expression in the dorsal raphe of rhesus macaques. Neuroscience 1999;89: 267–277
32 Gundlah C, Lu NZ, Bethea CL. Ovarian steroid regulation of monoamine oxidase-A and -B mRNAs in the macaque dorsal raphe and hypothalamic nuclei. Psychopharmacology (Berl) 2002; 160:271–282
33 Bethea CL, Gundlah C, Mirkes SJ. Ovarian steroid action in the serotonin neural system of macaques. Novartis Found Symp 2000;230:112–130, discussion 130–133
34 Lu NZ, Bethea CL. Ovarian steroid regulation of 5-HT1A receptor binding and G protein activation in female monkeys. Neuropsychopharmacology 2002;27:12–24
35 Le Saux M, Di Paolo T. Changes in 5-HT1A receptor binding and G-protein activation in the rat brain after estrogen treatment: comparison with tamoxifen and raloxifene. J Psychiatry Neurosci 2005;30:110–117
36 Blier P. Crosstalk between the norepinephrine and serotonin systems and its role in the antidepressant response. J Psychiatry Neurosci 2001;26(Suppl):S3–S10
37 Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet 2000;356:2059–2063
38 Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002; 20:1578–1583
39 Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. J Clin Oncol 2005;23:6919–6930. Erratum in: J Clin Oncol 2005; 23:8549
40 Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA 2003;289:2827–2834
41 Avis NE, Crawford S, Stellato R, Longcope C. Longitudinal study of hormone levels and depression among women transitioning through menopause. Climacteric 2001;4:243–249
42 Joffe H, Hall JE, Soares CN, et al. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. Menopause 2002;9:392–398
43 Blümel JE, Castelo-Branco C, Cancelo MJ, et al. Relationship between psychological complaints and vasomotor symptoms during climacteric. Maturitas 2004;49:205–210
44 Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression. Results from the Massachusetts Women's Health Study. Ann Epidemiol 1994;4:214–220
45 Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry 2006; 63:385–390
46 Harlow BL, Cohen LS, Otto MW, Spiegelman D, Cramer DW. Early life menstrual characteristics and pregnancy experiences among women with and without major depression: the Harvard study of moods and cycles. J Affect Disord 2004;79:167–176
47 Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. Arch Gen Psychiatry 2007; 64:327–337
48 Mansour A, Meador-Woodruff JH, Lopez JF, Watson SJ. Biochemical anatomy: insights into the cell biology and pharmacology of the dopamine and serotonin systems in the brain. In: Schatzberg AF, Nemeroff CB, eds. American Psychiatric Press Textbook of Psychopharmacology. 2nd ed. Washington, DC: American Psychiatric Press; 1998:55–74
49 Treadway MT. The neurobiology of motivational deficits in depression—an update on candidate pathomechanisms. Curr Top Behav Neurosci 2016;27:337–355
50 American Psychiatric Association. Practice Guideline for the Treatment of Patients with Major Depression, 2nd ed. Washington, DC: American Psychiatric Association; 2000

51 Fernández-Ruiz JJ, Amor JC, Ramos JA. Time-dependent effects of estradiol and progesterone on the number of striatal dopaminergic D2-receptors. Brain Res 1989;476:388–395
52 Kolatorova L, Vitku J, Suchopar J, Hill M, Parizek A. Progesterone: a steroid with wide range of effects in physiology as well as human medicine. Int J Mol Sci 2022;23:7989
53 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009;71:171–186
54 Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;65:732–741
55 Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13:467–475
56 Reynolds JN, Hyland BI, Wickens JR. A cellular mechanism of reward-related learning. Nature 2001;413:67–70
57 Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004;306:1940–1943
58 Wieland S, Schindler S, Huber C, Köhr G, Oswald MJ, Kelsch W. Phasic dopamine modifies sensory-driven output of striatal neurons through synaptic plasticity. J Neurosci 2015;35:9946–9956
59 Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 1999;19:5034–5043
60 Hahnemann S. Organon de la medicina, 6° ed. , Instituto Politécnico Nacional, México; 2001:306
61 Eizayaga JE. ¿En qué consiste la homeopatía? 3a. ed,. Universidad de Maimónides, Argentina, 2018. Accessed April 4, 2023 at: http://homeos.org/wp-content/uploads/2018/09/En-qu%C3%A9-consiste-la-homeopat%C3%ADa.-Sept2018-1.pdf
62 American Psychiatric Association. Manual Diagnóstico y Estadístico de los Trastornos Mentales DSM-5. México. Editorial Médica Panamericana; 2018
63 Lathoud. Materia médica homeopática. Buenos aires: Editorial Albatros; 1998
64 Bellavite P, Magnani P, Marzotto M, Conforti A. Assays of homeopathic remedies in rodent behavioural and psychopathological models. Homeopathy 2009;98:208–227
65 Gupta P, Sundaram EN, Sharma M, et al. Pre-clinical pharmacology: an important aspect in homoeopathic research. Indian J Res Homoeopathy 2018;12:164–179
66 Czéh B, Simon M. Benefits of animal models to understand the pathophysiology of depressive disorders. Prog Neuropsychopharmacol Biol Psychiatry 2021;106:110049
67 Magnani P, Conforti A, Zanolin E, Marzotto M, Bellavite P. Dose-effect study of Gelsemium sempervirens in high dilutions on anxiety-related responses in mice. Psychopharmacology (Berl) 2010;210:533–545
68 Bellavite P, Bonafini C, Marzotto M. Experimental neuropharmacology of Gelsemium sempervirens: recent advances and debated issues. J Ayurveda Integr Med 2018;9:69–74
69 Marzotto M, Olioso D, Brizzi M, Tononi P, Cristofoletti M, Bellavite P. Extreme sensitivity of gene expression in human SH-SY5Y neurocytes to ultra-low doses of Gelsemium sempervirens. BMC Complement Altern Med 2014;14:104
70 Olioso D, Marzotto M, Moratti E, Brizzi M, Bellavite P. Effects of Gelsemium sempervirens L. on pathway-focused gene expression profiling in neuronal cells. J Ethnopharmacol 2014;153:535–539
71 Marzotto M, Conforti A, Magnani P, Zanolin ME, Bellavite P. Effects of Ignatia amara in mouse behavioural models. Homeopathy 2012;101:57–67
72 Pinto SA, Bohland E, Coelho CdeP, Morgulis MS, Bonamin LV. An animal model for the study of Chamomilla in stress and depression: pilot study. Homeopathy 2008;97:141–144
73 Khuda-Bukhsh AR. Potentized homeopathic drugs act through regulation of gene expression: a hypothesis to explain their mechanism and pathways of action in vivo. Comp Ther Med 1997;5:43–46
74 Khuda-Bukhsh AR. Towards understanding molecular mechanisms of action of homeopathic drugs: an overview. Mol Cell Biochem 2003;253:339–345
75 Jyoti S, Tandon S. Impact of homeopathic remedies on the expression of lineage differentiation genes: an in vitro approach using embryonic stem cells. Homeopathy 2016;105:148–159
76 Demarque D, Jouanny J, Poitevin B, Saint-Jean Y. Farmacología y materia médica homeopática. España. CEDH Edición Francesa; 1997
77 Vijnovsky B. Tratado de Materia Médica Homeopática I, II, III. Buenos Aires. Talleres Gráficos Didot; 1980
78 Draiman M. Las Personalidades Homeopáticas, Vol 1. Buenos Aires: Libros de Edición Argentina; 1991
79 Silva Haad J. Accidentes humanos por las serpientes de los géneros *Bothrops* y *Lachesis*. Mem Inst Butantan 1982;44: 403–423
80 Warrell D. Snakebites in Central and South America epidemiology, clinical features and clinical management. In: Campbell J, Lamar W, eds. The Venomous Reptiles of the Western Hemisphere. Ithaca and London: Comstock Publishing; 709–761
81 Hardy DL, Silva Haad JJ. A review of venom toxicology and epidemiology of envenoming of the bushmaster (*Lachesis*) with report of a fatal bite. Bull Chic Herp Soc 1998;33:113–123
82 Pardal PPO, Souza SM, Monteiro MRCC, et al. Clinical trial of two antivenoms for the treatment of Bothrops and Lachesis bites in the north eastern Amazon region of Brazil. Trans R Soc Trop Med Hyg 2004;98(01):28–42
83 Madrigal M, Sanz L, Flores-Díaz M, et al. Snake venomics across genus Lachesis. Ontogenetic changes in the venom composition of Lachesis stenophrys and comparative proteomics of the venoms of adult Lachesis melanocephala and Lachesis acrochorda. J Proteomics 2012;77:280–297
84 Pla D, Sanz L, Molina-Sánchez P, et al. Snake venomics of Lachesis muta rhombeata and genus-wide antivenomics assessment of the paraspecific immunoreactivity of two antivenoms evidence the high compositional and immunological conservation across Lachesis. J Proteomics 2013;89:112–123
85 Junqueira-de-Azevedo IL, Ching AT, Carvalho E, et al. Lachesis muta (Viperidae) cDNAs reveal diverging pit viper molecules and scaffolds typical of cobra (Elapidae) venoms: implications for snake toxin repertoire evolution. Genetics 2006;173:877–889
86 Soares MR, Oliveira-Carvalho AL, Wermelinger LS, et al. Identification of novel bradykinin-potentiating peptides and C-type natriuretic peptide from Lachesis muta venom. Toxicon 2005; 46:31–38
87 Sanz L, Escolano J, Ferretti M, et al. Snake venomics of the South and Central American Bushmasters. Comparison of the toxin composition of Lachesis muta gathered from proteomic versus transcriptomic analysis. J Proteomics 2008;71:46–60
88 Graham RL, Graham C, McClean S, et al. Identification and functional analysis of a novel bradykinin inhibitory peptide in the venoms of New World Crotalinae pit vipers. Biochem Biophys Res Commun 2005;338:1587–1592
89 Diniz MR, Oliveira EB. Purification and properties of a kininogenin from the venom of Lachesis muta (bushmaster). Toxicon 1992;30:247–258
90 Felicori LF, Souza CT, Velarde DT, et al. Kallikrein-like proteinase from bushmaster snake venom. Protein Expr Purif 2003;30; 32–42
91 Weinberg ML, Felicori LF, Bello CA, et al. Biochemical properties of a bushmaster snake venom serine proteinase (LV-Ka), and its kinin releasing activity evaluated in rat mesenteric arterial rings. J Pharmacol Sci 2004;96:333–342
92 Dias L, Rodrigues MA, Rennó AL, et al. Hemodynamic responses to Lachesis muta (South American bushmaster) snake venom in anesthetized rats. Toxicon 2016;123:1–14

93 Aird SD. Ophidian envenomation strategies and the role of purines. Toxicon 2002;40:335–393
94 Giovanni-De-Simone S, Aguiar AS, Gimenez AR, Novellino K, de Moura RS. Purification, properties, and N-terminal amino acid sequence of a kallikrein-like enzyme from the venom of Lachesis muta rhombeata (Bushmaster). J Protein Chem 1997;16: 809–818
95 Sánchez-Reséndiz, J. Temas de Investigación en Homeopatía. México: Edición conmemorativa 50 aniversario de Propulsora de Homeopatía. 1991
96 Carlsson A, Waldeck B. A fluorimetric method for the determination of dopamine (3-hydroxytyramine). Acta Physiol Scand 1958;44:293–298
97 Sourkes TL, Murphy GF. Determination of catecholamino acids by differential spectrophotofluorimetry. In: Quastel JH, ed. Methods in Medical Research. Chicago: Year Book Med Publ; 1961:197
98 Seo D, Patrick CJ, Kennealy PJ. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggress Violent Behav 2008;13:383–395
99 Linnoila VM, Virkkunen M. Aggression, suicidality, and serotonin. J Clin Psychiatry 1992;53(Suppl):46–51
100 Daw ND, Kakade S, Dayan P. Opponent interactions between serotonin and dopamine. Neural Netw 2002;15:603–616
101 Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996;153:466–476
102 Wong PT, Feng H, Teo WL. Interaction of the dopaminergic and serotonergic systems in the rat striatum: effects of selective antagonists and uptake inhibitors. Neurosci Res 1995; 23:115–119
103 De Simoni MG, Dal Toso G, Fodritto F, Sokola A, Algeri S. Modulation of striatal dopamine metabolism by the activity of dorsal raphe serotonergic afferences. Brain Res 1987;411:81–88
104 Fiore G, Poli A, Di Cosmo A, d'Ischia M, Palumbo A. Dopamine in the ink defence system of Sepia officinalis: biosynthesis, vesicular compartmentation in mature ink gland cells, nitric oxide (NO)/cGMP-induced depletion and fate in secreted ink. Biochem J 2004;378(Pt 3):785–791
105 Lucero MT, Farrington H, Gilly WF. Quantification of L-dopa and dopamine in squid ink: implications for chemoreception. Biol Bull 1994;187:55–63
106 Russo GL, De Nisco E, Fiore G, Di Donato P, d'Ischia M, Palumbo A. Toxicity of melanin-free ink of Sepia officinalis to transformed cell lines: identification of the active factor as tyrosinase. Biochem Biophys Res Commun 2003;308:293–299
107 Prota G, Ortonne JP, Voulot C, Khatchadourian C, Nardi G, Palumbo A. Occurrence and properties of tyrosinase in the ejected ink of Cephalopods. Comp Biochem Physiol 1981;68:415–419
108 Artigas F. Future directions for serotonin and antidepressants. ACS Chem Neurosci 2013;4:5–8
109 Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry 2015;14:158–160
110 Harmer CJ, Goodwin GM, Cowen PJ. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. Br J Psychiatry 2009;195:102–108
111 Duman RS. Pathophysiology of depression: the concept of synaptic plasticity. Eur Psychiatry 2002;17(Suppl 3):306–310
112 Mendiola-Quezada R. Bases científicas de la medicina homeopática. Tomo II. México: Instituto Politécnico Naciona; 1996
113 Vickers AJ. Independent replication of pre-clinical research in homeopathy: a systematic review. Forsch Komplementarmed 1999;6:311–320
114 Petković A, Chaudhury D. Encore: behavioural animal models of stress, depression and mood disorders. Front Behav Neurosci 2022;16:931964
115 Rutten AL, Stolper CF, Lugten RF, Barthels RW. Statistical analysis of six repertory rubrics after prospective assessment applying Bayes' theorem. Homeopathy 2009;98:26–34
116 Rutten AL, Stolper CF, Lugten RF, Barthels RW. New repertory, new considerations. Homeopathy 2008;97:16–21
117 Rutten AL, Stolper CF, Lugten RF, Barthels RW. Repertory and the symptom loquacity: some results from a pilot study on likelihood ratio. Homeopathy 2004;93:190–192
118 Rutten AL, Stolper CF, Lugten RF, Barthels RW. Is assessment of likelihood ratio of homeopathic symptoms possible? A pilot study. Homeopathy 2003;92:213–216
119 Rutten AL, Stolper CF, Lugten RF, Barthels RW. Assessing likelihood ratio of clinical symptoms: handling vagueness. Homeopathy 2003;92:182–186
120 Bagot RC, Labonté B, Peña CJ, Nestler EJ. Epigenetic signaling in psychiatric disorders: stress and depression. Dialogues Clin Neurosci 2014;16:281–295