

The association between hormones and antipsychotic use: a focus on postpartum and menopausal women

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Ther Adv Psychopharmacol

2019, Vol. 9: 1–20

DOI: 10.1177/
2045125319859973

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Abstract: During the postpartum and menopausal periods of women's lives, there is a well-established and significant drop of circulating estrogens. This may be the reason why both these periods are associated with an increased risk for onset or exacerbation of psychiatric disorders. Whether symptoms are mainly affective or mainly psychotic, these disorders are frequently treated with antipsychotic medications, which calls for an examination of the relationship between hormone replacement and antipsychotic agents at these time periods. The aim of this narrative review is to summarize what is known about the association of hormones and antipsychotics in the postnatal period and at menopause. In the review, we focus on estrogen and oxytocin hormones and include, for the most part, only papers published within the last 10 years. Both estradiol and oxytocin have at various times been implicated in the etiology of postpartum disorders, and estrogens, sometimes combined with progesterone, have been tested as potential treatments for these conditions. The role of estradiol as an adjunct to antipsychotics in the prevention of postpartum relapses is currently controversial. With respect to oxytocin, studies are lacking. Psychosis in menopausal and postmenopausal women has been successfully treated with estrogens and selective estrogen-receptor modulators, mainly raloxifene, in addition to antipsychotics. Some symptoms appear to respond better than others. No oxytocin study has specifically targeted postmenopausal women. Because of feedback mechanisms, there is a theoretical danger of therapy with exogenous hormones interfering with endogenous secretion and disturbing the balance among inter-related hormones. When used with antipsychotics, hormones may also affect the metabolism and, hence, the brain level of specific antipsychotics. This makes treatment with antipsychotics plus hormones complicated. Dose, timing and route of intervention may all prove critical to efficacy. While much remains unknown, this literature review indicates that, within standard dose ranges, the combination of hormones and antipsychotics for postnatal and menopausal women suffering severe mental distress can be beneficial, and is safe.

Keywords: antipsychotics, hormones, menopause, postpartum

Received: 17 November 2018; revised manuscript accepted: 1 April 2019.

Introduction

Following expulsion of the placenta after childbirth, estradiol and progesterone levels in women drop precipitously from their peaks at the end of pregnancy. The sharpness of the drop is in contrast to the more gradual and fluctuating decline of estrogens at perimenopause. It is also time limited, in contrast to the permanent withdrawal of gonadal hormones in menopausal women. Both

these periods in a woman's life, postnatal and perimenopausal, are times of special vulnerability. Psychiatric morbidity characteristic of these periods can sometimes manifest as psychotic symptoms (delusions, hallucinations, and cognitive distortions), which are generally treated with antipsychotic medications. Nonpsychotic affective symptoms during these periods also, at times, respond to antipsychotics. Several questions arise

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from this conjunction of hormone deficiency, mental distress, and antipsychotic agents:

1. Does hormone replacement work and, if so, for which symptoms?
2. Is hormone replacement able to reduce the dose of antipsychotics?
3. Are some antipsychotics more compatible with adjunctive hormones than others?
4. Are hormone/antipsychotic combinations safe and well tolerated and, if so, within what dose range?

The aim of this narrative, nonsystematic review was to synthesize what is known about the association of hormones (estrogens and oxytocin for the most part) and antipsychotics in the puerperal period and at menopause.

Method

We reviewed the clinical literature on estrogens and oxytocin use in the postpartum and at menopause, with an emphasis on studies published within the last 10 years. We also reviewed the efficacy of hormonal treatments as adjuncts to antipsychotics in these same time periods, and address issues of therapeutic safety and tolerability.

Postpartum psychotic disorders

Hormonal involvement in the causation of postpartum psychiatric disorders has long been suspected but never precisely understood.^{1,2} This much is known: over the course of pregnancy, levels of estrogen and progesterone significantly rise. After birth, they fall steeply and do not normalize until approximately 3 weeks after delivery.³ The potential for psychosis at this time is attributable to an increased sensitivity of dopamine receptors due to the abrupt change in estrogen levels at this time.^{4,5} Recent reports point to the induction of psychosis by dopamine agonists such as bromocriptine, used to suppress lactation in women who decide against breastfeeding.⁶ Studies on postpartum experimental animals have also shown alterations in dopamine function.^{7,8} Women already vulnerable as a result of genetic makeup or stressful environmental exposure are thus susceptible to mental distress at times of low estrogen. This has led to the exploration of estrogen-receptor polymorphisms as a potential source of genetic vulnerability⁹ and an association with postpartum psychosis and one variant of the estrogen-receptor alpha (ESR1) has

been reported. Other studies, however, found no polymorphisms of either ESR1 or ESR2 that were associated with postpartum psychosis.¹⁰

Postpartum psychoses fall into three categories: mania or mixed episodes with psychotic features, depressive episodes with psychotic features, and nonaffective psychotic episodes.³ These can occur after one birth (usually the first) and never again or they can recur with every birth (25–50% of the time). They can represent exacerbations of chronic depressive, bipolar, or schizophrenic illness. The incidence of first-time postpartum psychosis varies from 0.25 to 0.6 per 1000 births, 23 times higher within the first 4 weeks of delivery than at any other time of a woman's life. The clinical picture is characterized by cognitive dysfunction: disorientation, confusion, derealization, and depersonalization, with mood-incongruent delusions centered on the theme of childbirth.³

The literature suggests both estradiol¹¹ and oxytocin¹² may be implicated in postpartum psychosis.

Estrogen and postpartum psychosis

Estrogen modulates dopaminergic, serotonergic, glutaminergic, noradrenergic, and cholinergic systems believed to be relevant to psychosis.¹³ The estrogen-protection hypothesis suggests that estradiol exerts antipsychotic effects through its many varied actions in the central nervous system.¹⁴ Judging by these actions and by the results of clinical and epidemiological studies, estradiol appears to play a protective role against the manifestations of both schizophrenia and bipolar psychosis.^{15,16}

Because of the abrupt decline of estrogen temporally associated with the emergence of postpartum psychosis, and because of the known central nervous system actions of estrogens, different forms of estrogen therapy have been used for this condition, sometimes as pretreatment, administered immediately after delivery to prevent relapse in women who have experienced a previous episode or who have a history of psychotic illness.¹⁷ Different formulations of hormones used for the treatment of postpartum disorders are presented in Figure 1.^{18–25}

A team from Finland^{20–22} treated 14 women suffering from postpartum psychosis with sublingual estradiol and measured estradiol concentrations in the serum. The participants in this trial had failed to respond to antipsychotic treatment

	Postpartum depression	Postpartum Non-affective Psychosis
Gonadal hormones (Estradiol +/- Progesterone)		- Conjugated estrogen + medroxyprogesterone ¹⁹
	- Transdermal estradiol [E2] ¹⁸	- 17-beta-estradiol ²⁰
		- 17-beta-estradiol ²¹
		- Sublingual 17-beta-estradiol ²²
Oxytocin	- Intrapartum synthetic oxytocin ²³	
	- Peripartum synthetic oxytocin ²⁴	No evidence to date
	- Intranasal oxytocin ²⁵	

Figure 1. Different formulations for gonadal hormones and oxytocin for the treatment of postpartum affective disorders and nonaffective postpartum psychosis.

alone. The investigators used the Brief Psychiatric Rating scale (BPRS) to evaluate improvement and reported that symptoms decreased within 2 weeks for all women who complied with treatment. In at least one woman, symptoms recurred when estrogen treatment was discontinued.

In 2008, Huang and colleagues¹⁹ reported a case from Taiwan of a woman with postpartum psychosis who improved after 2 weeks of combined estrogen and progesterone treatment. The patient had a long history of episodic psychotic mania and was maintained on lithium plus an antipsychotic. When she became pregnant, she stopped her medications to avoid the risk of teratogenesis. She breastfed her infant. At 1 month after delivery she developed an episode of mania and was prescribed mood stabilizers and haloperidol. Serum levels were adequate but her symptoms did not respond. Conjugated estrogen 0.625 mg/day and medroxyprogesterone 2.5 mg/day were added and the patient responded within 3 weeks. She remained stable when the hormones were stopped 2 months later.

Selective estrogen-receptor modulators (SERMs) have not been tested in postpartum disorders.

When reading the reports of treatment with estrogens in postpartum psychosis, it is difficult to be confident of their specific therapeutic effectiveness, since antipsychotics or mood stabilizers were also being administered to the patients simultaneously. It is, however, possible to interpret the results as supportive of an adjunctive therapeutic role of estrogens in treating

postpartum psychosis. Table 1 shows the main characteristics of recent studies focusing on the use of gonadal hormones for the treatment of psychotic illness during the puerperium.

Prevention. In an effort at prevention of recurrent postpartum psychosis, Hamilton and Sichel²⁶ gave 50 patients injections of 10 mg of estrone immediately after delivery, followed by conjugated estrogen for 12 days. No patients relapsed, although the usual expected rate of recurrence is 25–50%. Sichel and colleagues²⁷ gave 11 women with a history of postpartum depression or postpartum psychosis oral estrogen 5 mg twice daily starting at delivery and reducing the dose every 14 days. Two women received additional intravenous estrogen 25 mg three times daily for the first 2 days. Ten women complied with treatment and none of them relapsed postpartum.

A more recent study was carried out by Kumar and coworkers in 2003.²⁸ This was an open-label study of 29 postpartum women with a previous Research Diagnostic Criteria (RDC) diagnosis of bipolar I disorder, bipolar II disorder or schizoaffective disorder. All patients had been in remission and had received no medication throughout their pregnancies. None of the women breastfed their infants for fear of exogenous hormones entering the breast milk. Transdermal estradiol was administered within 48 h of delivery at three dose levels. Thirteen women received starting doses of 200 µg/day; three received 400 µg/day, and thirteen received 800 µg/day. All doses were reduced by half every 4 days for a total of 12 days. The results of this study were not encouraging.

Table 1. Recent studies focused on the use of gonadal hormones and oxytocin for the treatment of nonpsychotic and psychotic illness in the puerperium.

Authors and year of publication	Study design	Sample (n)	Comparison groups	Assessment	Results
Non-psychotic illness					
Gonadal hormones					
Wisner <i>et al.</i> ¹⁸	8-week, randomized, placebo-controlled trial	n = 85 (postpartum depression)	Transdermal E2 (n = 26) Sertraline (n = 30) Placebo (n = 29)	SIGH-ADS29 Asberg Side-Effects Scale	Efficacy of E2 compared to placebo could not be explored due to non-significant E2 concentration difference between groups
Oxytocin					
Takács <i>et al.</i> ²³	Prospective observational study	n = 260 (data collection available; postpartum maternal mood)	Oxytocin exposure	EPDS	Synthetic oxytocin administration at intrapartum did not have an immediate impact on maternal mood
Kroll-Desrosiers <i>et al.</i> ²⁴	Retrospective population-based study	n = 46,732 (depressive and anxiety disorders)	Oxytocin exposed (n = 9684) Oxytocin nonexposed (n = 37,048)	MiCARD	Peripartum synthetic oxytocin exposure was associated with higher depressive or anxiety symptoms
Mah <i>et al.</i> ²⁵	Within-subject double-blind randomized, placebo-controlled trial	n = 25 (postnatal depression)	Oxytocin Placebo	EPDS Conflict Tactic Scale: Parent Child version Maternal Sensitivity and Non-Intrusiveness Scale	Severe physical abuse during childhood did not moderate OT effect
Psychotic illness					
Gonadal hormones					
Ahokas and Aito ²²	Case reports	n = 2 (postpartum psychosis)	Sublingual 17-beta estradiol (n = 2)	BPRS	Higher estradiol levels were associated with a decline of psychotic symptoms
Ahokas <i>et al.</i> ²¹	Case series (6-week follow up)	n = 10 (postpartum psychosis)	17-beta estradiol (n = 10)	BPRS	Higher estradiol levels were associated with an improvement of psychiatric symptoms
Ahokas <i>et al.</i> ²⁰	Case reports	n = 2 (postpartum psychosis)	17-beta estradiol (n = 2)	BPRS	Elevation of serum estradiol levels was associated with decline in psychotic symptoms
Huang <i>et al.</i> ¹⁹	Case report	n = 1 (postpartum mania)	Conjugated estrogen + medroxyprogesterone (n = 1)	Clinical assessment	Conjugated estrogen combined with medroxyprogesterone improved manic symptoms
Oxytocin					
No evidence is available					
BPRS, Brief Psychiatric Rating Scale; E2, Estradiol; EPDS, Edinburgh Postnatal Depression Scale; MiCARD, Massachusetts Integrated Clinical Academic Research Database; OT, oxytocin; SIGH-ADS20, Structured Interview Guide for the Hamilton Depression Rating Scale—Atypical Depression Symptoms Version.					

Fourteen (50%) of the women relapsed within 90 days of delivery, as evaluated by scores on the Schedule for Affective Disorders and Schizophrenia (SADS); 12 of the women relapsed between 7 and 12 days of delivery while still on their estrogen regimen. One woman committed suicide 4 months after hospital discharge. The women who relapsed were placed on antipsychotic medication and it was discovered that those on 800 µg/day of estradiol recovered on lower doses of antipsychotics (chlorpromazine equivalents) than those on the lower doses of estrogen. Also, the 800 µg/day group was discharged from hospital sooner than the lower-estrogen group. This suggests that although estradiol alone may not prevent postpartum relapse of serious mental illness in vulnerable women, an effective dose of estradiol used as an adjunct to antipsychotic medication can be therapeutic.

Gonadal hormones for nonpsychotic illness in the postpartum period. Most postpartum conditions fall into the category of nonpsychotic affective disorders but these, too, are sometimes treated with antipsychotics²⁹ to which replacement hormones can be added. The idea of treating affective illness with gonadal hormones comes from the finding that a gonadotropin-releasing-hormone agonist, leuprolide acetate, when given to healthy women, and especially to women with a history of postpartum depression, can induce depression.³⁰ The resulting conclusion that the drop in either estrogen or progesterone, or both, is responsible for postpartum depression is controversial, however, as an association between hormone withdrawal and mood symptoms is not always found.³¹ This suggests that estrogen/progesterone levels, though they probably play a part, do not totally explain postpartum mood disorders. Maternal stress plays an important role as well,³² as, probably, do many related, interactive hormones.^{33,34}

An 8-week randomized controlled trial that set out to compare the efficacy of transdermal estradiol (E2), sertraline and placebo in women with postpartum major depressive disorder¹⁸ was stopped because E2 serum concentrations in the E2 arm of the study were found to be lower than expected. The authors hypothesized that the induction of liver enzyme CYP3A4 during pregnancy had led to an increased E2 rate of elimination that continued after delivery. The other possibility they entertained was that endogenous

E2 secretion could be suppressed by exogenous dosing. In other words, they wondered about the wisdom of (a) administering estrogen that would be eliminated before it could work and (b) that could suppress the secretion of a woman's own estrogen.

Several problems have thus been identified in the preventive or therapeutic use of gonadal hormones for puerperal psychiatric disturbance. The timing of administration matters because of elimination rates. The dose is also relevant because suppression of endogenous hormones needs to be avoided. If women are breastfeeding, an added concern is that of infants absorbing maternal hormones in breast milk. Table 1 summarizes recent studies focusing on the use of gonadal hormones for the treatment of nonpsychotic postpartum illness.

Oxytocin and postpartum mood disorders

Mood disorders have been widely considered capable of negatively influencing the adjustment of new mothers and interfering with the establishment of mother–infant bonding. Recent research has implicated oxytocin in mediating this relationship.^{35,36} For instance, recent genetic studies suggest that differential methylation of the oxytocin receptor gene can modulate the risk for postpartum depression and positively influence maternal behavior.³⁷ A number of studies have suggested that oxytocin plays an important role in mood regulation and that oxytocin plasma levels are associated with the development of postpartum mood disorders.

Oxytocin effect in postpartum depression. At 8 weeks postpartum, Cox and colleagues¹² assessed mood symptoms in 39 women who then underwent a standard stress test immediately after breastfeeding. The surge of oxytocin that accompanies breastfeeding buffered the subsequent stress induced by the test, but only in the women who were asymptomatic. The authors concluded that this was putative evidence that oxytocin plays a role in the genesis of postpartum depression. Niwayama and coworkers,³⁸ in partial confirmation, demonstrated a calming effect on mood disturbance of relatively high salivary oxytocin levels in 24 primiparous breastfeeding mothers. Another study found a correlation between relatively low levels of oxytocin and depressive symptoms at 8 weeks postpartum in women who had stopped breastfeeding.³⁹ The

same group also found that oxytocin levels significantly decreased from the prenatal to the postpartum period in their whole sample of women, but women who were depressed or anxious at 6 weeks postpartum exhibited persistently higher mean oxytocin levels over time.⁴⁰

With respect to exogenous oxytocin, in a prospective observational design,²³ the administration of intrapartum synthetic oxytocin was found to not correlate with mood symptoms at 6 weeks, nor at 9 months postpartum. Another recent study found that women exposed to peripartum oxytocin administration were more likely than control women to receive depression and anxiety diagnoses and to be prescribed antidepressants or anxiolytics.²⁴ Finally, in a randomized, double-blind, placebo-controlled trial of intranasal oxytocin in women with postnatal depression,²⁵ the results showed that women receiving oxytocin were more likely than controls to choose a harsh caregiving strategy in response to prerecorded infant crying. On the evidence of these results, the authors recommended that oxytocin not be given to depressed mothers. Oxytocin study results are presented in Table 1.

Oxytocin effect in postpartum mania. The relationship between oxytocin levels and bipolar disorder has been extensively examined for several decades.⁴¹ Relatively recent research has shown high oxytocin levels to be specifically associated with manic episodes in male and female patients diagnosed with bipolar I disorder, when compared to those with other mood disorders and also when compared to healthy subjects.⁴² Oxytocin levels decreased once symptoms had responded to treatment.⁴² These researchers suggested that oxytocin level could even be used as a trait marker for bipolar disorder. Lien and colleagues⁴³ confirmed these results, but a previous study⁴⁴ had found no statistically significant difference in oxytocin levels between depressed and bipolar patients.

A population-based birth cohort study found a disturbing 2.4-fold increased odds of later bipolar disorder in children of women who had been given oxytocin to induce labor.⁴⁵ A study of 161 children born to mothers in whom oxytocin had been used for this purpose found that mothers reported their children as showing a relative lack of interest at 3 months of age, crying or turning away when picked up at 6 months of age, and showing withdrawal behavior at 1.5 years of age.⁴⁶

These studies await replication. There are no studies that assessed the efficacy of oxytocin in the treatment of bipolar disorder with onset in the postpartum period.

Oxytocin effect in nonaffective psychosis. Both social cognition and neurocognition in schizophrenia have been examined in relationship to plasma oxytocin levels.⁴⁷ Low levels of oxytocin were associated with cognitive deficits.⁴⁸ Asociality in schizophrenia has also been associated with low levels of oxytocin.⁴⁹

The administration of intranasal oxytocin has been suggested as a potential treatment for social cognition and neurocognition in patients with schizophrenia⁵⁰ on the basis of study results obtained by Woolley and colleagues,⁵¹ and Davis and colleagues.⁵² A meta-analysis by Bürkner and coworkers⁵³ found intranasal oxytocin to be more effective for high-level social cognition (mentalizing and theory of mind) than for low-level social cognition, highlighting the need for research focused on specific cognitive targets. Two meta-analyses,^{54,55} however, found no significant effect of adjunctive oxytocin either on symptoms or on cognition in schizophrenia. Sasayama and colleagues⁵⁶ investigated oxytocin levels in relation to antipsychotic doses in schizophrenia. Cerebrospinal fluid oxytocin levels were significantly and negatively correlated with doses of second-generation antipsychotics, but not with doses for first-generation antipsychotics, a finding that is difficult to interpret.

No studies have explored the use of oxytocin as an adjunct to antipsychotic medication in postpartum psychosis, which is surprising given the tie of oxytocin to parturition, lactation and mother-child interaction and well-being.^{57,58} It has been suggested that the timing of oxytocin intervention may be critical to its effect, but, thus far, the oxytocin story in relation to psychosis remains confusing.

Antipsychotics in the postpartum period

Antipsychotic treatment has been shown to be highly effective in preventing postpartum relapse of women with a prior history of postpartum disorder or ongoing psychotic illness.^{29,59,60}

Because postpartum mothers may also be breastfeeding mothers, several authors have systematically reviewed the topic of safety of antipsychotic

use during lactation,^{61–64} but criticism has been leveled at some aspects of the reviewed studies.⁶⁵ The issues are the short- and long-term effects of antipsychotics in breastfeeding mothers on children's physical, cognitive, and psychosocial health, and also the antipsychotic side effects on mothers' abilities to care for their neonates.

The most recent systematic review in this field recommends that quetiapine and olanzapine be considered first-line treatments in breastfeeding women.⁶³ The review considers risperidone to be acceptable under conditions of medical monitoring, and both clozapine and amisulpride to be contraindicated. Klinger and coworkers⁶¹ had also found olanzapine and quetiapine to be acceptable for breastfeeding, and chlorpromazine, haloperidol, zuclopenthixol, and risperidone as possible under medical supervision. They could make no recommendations with respect to aripiprazole, clozapine or paliperidone, as adequate information was lacking. Uguz⁶⁴ addressed issues of relative infant dose, milk-to-plasma ratio, infant drug plasma levels, and adverse events, and found antipsychotic plasma levels to be undetectable in most exposed neonates. With respect to clozapine in breast milk, the potential risks for infants are largely unknown. Imaz and coworkers⁶⁶ did not find any acute toxicological effect in newborns exposed to clozapine in pregnancy. The alternative in women who are unresponsive to other antipsychotic drugs is stopping antipsychotic treatment altogether and this, of course, confers risks of its own.⁶⁷ With respect to aripiprazole, Cuomo and colleagues⁶⁸ have suggested that its potential benefits in lactating women suffering from bipolar disorder or schizophrenia may be higher than its potential risks. Case-by-case shared decision making has been recommended when deciding on the use of antipsychotics during the puerperium.⁶⁹ Importantly, the long-term effects of antipsychotic agents on infants of breastfeeding women are not known. There are known short-term sedating effects on mothers, however, and these can interfere with a new mother's ability to look after her infant and can sometimes contribute to a mother losing custody of her child.⁷⁰

With regards to the pairing of hormones and antipsychotics, the success of therapy may depend on the specific antipsychotic agent that is being used. For instance, olanzapine and clozapine are mainly metabolized by liver enzyme CYP1A2, which is inhibited by estrogen, so that adding estrogen will cause the antipsychotic

level to rise. The opposite can be expected when the antipsychotic is mainly metabolized by CYP3A4 (quetiapine is an example), in which case the antipsychotic level will fall.⁷¹ It may be the antipsychotic level rather than the hormone that determines symptom response.

Hormones and menopause

A recent publication reported on a study of over 5000 women who had been diagnosed with an acute psychotic disorder.⁷² The women were divided into two groups: (a) age 18–45; (b) over age 55. The investigators wanted to know whether the advent of menopause (somewhere between age 45 and 55 in most women) induced measurable changes in the characteristics of their psychotic illness. One finding was that the younger group of women, when compared with same-age men with psychosis, was hospitalized half as often. In contrast, women in the older group were 1.5-fold more often hospitalized than their same-age male peers. Another finding was that in a subgroup of the sample ($n=192$) who were on clozapine, the under 45s were maintained on lower clozapine doses than their male controls, while the over 55s were maintained on relatively higher doses. These findings suggest that psychosis gets worse after menopause.

A recent study along the same lines that included patients with schizophrenia and healthy controls investigated the effects of catechol-O-methyltransferase (COMT) haplotypes with ValMet polymorphisms and their potential interplay on cognitive functions in menopause.⁷³ The findings were that functional COMT mutations modulate cognitive functions in schizophrenia according to hormonal status, for example, pre/postmenopause. The authors suggested that genetics, hormonal status and sex interact with each other and need to be taken into account when exploring changes in cognition at menopause.

What is menopause?

The onset of menopause (from the Greek 'meno' meaning month, and 'pauis' meaning cessation), defined as 1 year of amenorrhea, is usually identified retrospectively. It marks the end of fertility and is attributed to the loss of ovarian follicular function (although approximately 1000 oocytes are still present in most women at the time of menopause).⁷⁴ The 2011 STRAW+10 staging system for reproductive aging in women divides

the menopausal period into early and late stages of menopausal transition or perimenopause, followed by four stages of postmenopause, all stages based on progressive changes in follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), and the ovarian protein, inhibin-B.⁷⁵

Throughout a woman's reproductive life, estradiol, progesterone and ovarian regulatory proteins control gonadotropin secretion from the anterior pituitary through a complex mechanism of feedback and feedforward. Pulses of FSH are stimulated by the protein activin and inhibited by estradiol and inhibin B.⁷⁴ As the number of oocytes remaining in the ovaries drop, inhibin B levels decline and FSH levels rise. Low inhibin B and high FSH is the hormonal signature of menopause. More recently, progressively decreasing levels of AMH has become a further marker of approaching menopause. Although the ovary loses its capacity to produce estrogen and progesterone at menopause, androgen (testosterone, dehydroepiandrosterone, and androstenedione) production continues far longer. Androgens produced by the ovary and the adrenal gland are aromatized to estrogen in adipose tissue so that estrogens continue to circulate in postmenopausal women, but at relatively low levels (higher in women with more adipose tissue).⁷⁶

Menopausal symptoms

In general, women's menopausal symptoms vary across different stages of menopause; they are a consequence of estrogen deficiency and also of the aging of estrogen target organs.⁷⁷ Inadequate estrogen and the process of aging work hand in hand and it is often difficult to determine which of the two is responsible for which symptom. Correlations of menopausal symptoms, hormones, and antipsychotic use are presented in Figure 2.⁷⁸⁻⁹¹

Most women experience a variety of symptoms at this time, many of which, such as hot flashes, markedly interfere with quality of life. Hot flashes interfere with sleep and increase in frequency during periods of psychological stress.⁷⁸ Furthermore, changes in the distribution of body fat lead to obesity that, among other health risks, increase the risk for sleep apnea in menopausal women and contribute to sleep disturbance.⁷⁹ In turn, short sleep duration has itself been associated with obesity, especially central obesity.⁸⁰ Muscle and joint aches often start at this time, perhaps as a result of acceleration in the rate of bone loss due to both estrogen loss and to high levels of FSH, which

increase the speed of bone resorption.⁸¹ Moreover, oscillations in estradiol levels during perimenopause contribute to emotional lability during this period, probably because of estrogen effects on the serotonin system.^{82,92,93} In addition, women of menopausal age can become increasingly dependent on alcohol, anxiolytics, and hypnotics. Discontinuation of these substances may produce withdrawal symptoms such as sweating, tremor, dizziness, headache, insomnia, rebound anxiety, tachycardia, and elevated blood pressure, which are often impossible to distinguish from true menopausal symptoms.^{83,84}

Menopausal women can experience subjective cognitive impairment in attention, new learning, and memory.^{85,86} Further, menopausal women experience both pain on intercourse and urinary incontinence. When estrogen levels decline, the tissues lining the vagina, vulva, bladder, and urethra atrophy, leading to vaginal dryness, dyspareunia, vulvar pruritus, and urinary problems.^{87,88}

Metabolic syndrome, defined as insulin resistance plus any two of the following: central obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension, high fasting glucose, or microalbuminuria, has also been associated with menopause.⁸⁹ In addition to increasing the risk for cardiovascular disease and type 2 diabetes mellitus, metabolic syndrome is associated with nonalcoholic fatty liver disease, hyperuricemia, polycystic ovarian syndrome, and obstructive sleep apnea.^{90,91,93,94}

Effect of antipsychotics on menopausal symptoms

In women with psychosis (schizophrenia, delusional disorder, or mood disorder with psychotic features), side effects of the antipsychotic medication such as weight gain and hyperprolactinemia,⁹⁵ intensify naturally occurring menopausal symptoms. For instance, weight gain increases muscle and joint pain and heat intolerance. It also increases the incidence of sleep apnea,⁹⁶ which, in turn, heightens sleep difficulties and leads to daytime sedation.⁹⁷ Most importantly, antipsychotic-induced obesity adds to the risk of metabolic and cardiovascular problems of postmenopausal women.⁹⁸

Furthermore, antipsychotic-induced hyperprolactinemia increases the likelihood of developing osteoporosis⁹⁹ and intensifies urogenital problems and sexual dysfunctions such as diminished libido.

	Symptoms	Main explanation
Vasomotor symptoms	Hot flushes (interfere with sleep) ⁷⁸	Peripheral vasodilation (lack of estrogens)
Fat redistribution and weight gain	Weight gain ⁷⁹ Obesity (mainly central) ⁸⁰	Decrease in energy expenditure (lack of estrogens and antipsychotic use)
Sleep disturbance	Sleep apnea ⁷⁹ Insomnia	Hot flushes (lack of estrogens) Obesity (lack of estrogens and antipsychotic use)
Muscles, joints, bones	Muscle and joints atrophy Accelerated bone loss ⁸¹	Estrogen loss at menopause and hyperprolactinemia (antipsychotic use)
Mood changes and drug dependence	Emotional lability ⁸² Anxiety and insomnia Use of anxiolytics and hypnotics Withdrawal symptoms ^{83,84}	Oscillations in estrogen levels Use of psychotropic medications
Cognitive impairment	Impairment in attention, learning and memory ^{85,86}	Estrogen loss and psychotropic use
Genitourinary	Urinary incontinence Dyspareunia Vaginal dryness Vulvar pruritus Urogenital atrophy ^{87,88}	Estrogen loss effect on estrogen-dependent tissues
Metabolic syndrome	Central obesity ⁸⁹ Hypertriglyceridemia Low high-density lipoprotein (HDL) cholesterol Hypertension High fasting glucose Microalbuminuria	Lack of estrogens Antipsychotic use
Cardiovascular disease	Vasoconstriction - Increased coronary heart disease ^{90,91}	Lack of estrogens Antipsychotic use (endothelial hypothesis)

Figure 2. Correlation of main symptoms of menopause with hormones and antipsychotic use.

Antipsychotics can aggravate other menopausal symptoms, as well. With time, they have been reported to lead, for instance, to a decrease in cognitive abilities.¹⁰⁰ Side effects diminish women's sense of attractiveness,¹⁰¹ further undermining self-esteem and sexual satisfaction, already at a low ebb at menopause.¹⁰²

Changes in psychosis symptoms at menopause

Women with schizophrenia, psychotic affective disorder, and delusional disorder report that their psychotic symptoms worsen at menopause and that their medications no longer work as well as previously. In a study by Sajatovic and colleagues,¹⁰³ over half of 86 women with schizophrenia reported that menopause had a negative effect on their emotional state. The top five

symptoms experienced by these women were feeling depressed, anxious, tired, lacking energy, and experiencing poor memory.¹⁰³

Using magnetic resonance imaging (MRI), Fukuta and coworkers¹⁰⁴ investigated the influences of menopause on brain morphological changes in 20 premenopausal and 20 postmenopausal women with schizophrenia (as well as 50 control women). The gray matter of postmenopausal patients was significantly smaller than that of premenopausal patients in the left middle frontal gyrus, suggesting an impact of estrogen loss on brain structure, which could explain the changes in positive symptoms¹⁰⁵ and cognitive symptoms.¹⁰⁶ Environmental events such as parents dying, social supports dwindling, motherhood becoming permanently impossible, children leaving home, and health

declining⁷⁷ play a partially causative role, but, according to Jacobs and Goldstein,¹⁰⁷ many of the symptom changes experienced at this time are attributable to the decline of sex hormones.

Treatment response to estrogen and SERMs

Following the clinical evidence that psychotic symptoms worsen after menopause and the epidemiological evidence that, in contrast to men, the incidence of psychosis in women increases after age 40,¹⁰⁸ estrogens and selective estrogen-receptor modulators (SERMs, mainly raloxifene) have been used as adjuncts to antipsychotic agents for postmenopausal women with psychosis. Two excellent reviews of these strategies for women (and also men) with schizophrenia^{109,110} summarize the findings thus far. Taking all available randomized controlled trials into account, estrogens, especially estradiol, were found to be superior to placebo for positive, negative and general symptoms. Raloxifene was also found to be superior to placebo for positive, negative, and total symptoms, but not for affective symptoms or cognitive function. In a meta-analysis that included five randomized controlled trials (RCTs) comparing raloxifene augmentation at 60 or 120 mg/day with placebo in 240 postmenopausal women, raloxifene again outperformed placebo.¹¹¹

Included in the meta-analysis was a multicenter negative trial by Weiser and colleagues,¹¹² a 16-week, double-blind, randomized, placebo-controlled study of 200 severely ill, postmenopausal women with schizophrenia that used 120 mg raloxifene/day in addition to antipsychotics. The results showed no differences between groups either in Clinical Global Impression Scale-Severity scores or Composite Brief Assessment of Cognition in Schizophrenia scores. A further meta-analysis that also included the Weiser *et al.* trial¹¹³ concluded that adjunctive raloxifene did have positive effects in postmenopausal women with schizophrenia, but especially in those whose psychotic symptoms were relatively less severe. Severity of symptoms might account for discrepancies among trials. Another possible explanation of discrepant results is raised by Gurvich and colleagues.¹¹⁴ They show that the menopausal raloxifene effect as it relates to cognition depends not only on the specific cognitive parameter studied but also on menopausal stage (perimenopause *versus* postmenopause). The specific antipsychotic drug used can also influence the results, as can concomitant drugs that affect the amount of raloxifene that reaches the brain.

Weickert and colleagues¹¹⁵ had previously shown that the effect of raloxifene on cognition in schizophrenia may depend on a person's estrogen-receptor genotype. Furthermore, Labad and colleagues,¹¹⁶ in a pharmacogenetic analysis of a double-blind, randomized, parallel, placebo-controlled study of 24 weeks' duration of raloxifene in 65 postmenopausal women with schizophrenia, examined four single nucleotide polymorphisms (SNPs): rs9340799, rs2234693 and rs1801132 in the estrogen-receptor 1 (ESR1) gene, and rs1042597 in the UDP-glucuronosyltransferase 1A8 (UGT1A8) gene. They found that the rs1042597 variant was associated with response of negative symptoms, while the rs2234693 variant was associated with response in general psychopathology scores. It appears, therefore, that estrogen agonists may help at least some postmenopausal women with schizophrenia, but that the results depend on several factors such as severity of illness, menopausal stage, genetic profile, and target symptoms, as well as estrogen/antipsychotic interaction.

Table 2 shows the main characteristics of recent studies of the effect of raloxifene on clinical symptoms and cognition in postmenopausal women with schizophrenia.¹¹⁵⁻¹²¹

Antipsychotic/estrogen interaction

It is possible that response to estrogen agonists may partly depend on the specific antipsychotic with which the hormone is paired. With the loss of estrogen postmenopause, olanzapine and clozapine levels decrease and exogenous estrogens or SERMs will raise their level. The levels of most other antipsychotics could, by contrast, rise after menopause; replacement hormones or SERMs could bring these levels down,⁷¹ thus dampening the therapeutic effect. The pharmacokinetics and pharmacodynamics of antipsychotics help to explain why response of psychotic symptoms diminishes with time postmenopausally.¹²²

Pharmacokinetics. Women increasingly accumulate adipose tissue after menopause, which expands the volume of distribution of lipophilic drugs such as antipsychotics, thus decreasing the amount of drug that enters the brain.¹²³ The main liver enzyme that metabolizes olanzapine and clozapine, CYP 1A2, is inhibited by estrogen; when estrogen levels drop at menopause, the enzyme becomes more active so that higher doses of drugs metabolized by this enzyme are required to achieve

Table 2. Recent studies focusing on the effect of adjunctive raloxifene on clinical and cognitive symptoms in postmenopausal women with schizophrenia.

Authors and reference citation	Study design	Sample	Groups	Assessment and outcomes	Conclusions
Psychopathological assessment					
Labad <i>et al.</i> ¹¹⁶	24-week, double-blind, randomized, parallel placebo-controlled trial	<i>n</i> = 65	Raloxifene 60 mg/day Placebo	Psychopathology: PANSS Genetic analyses: ESR1 gene (rs9340799, rs2234693 and rs1801132) and UGT1A8 gene (rs1042597)	Genetic variants in UGT1A8 and ESR1 genes may influence response to raloxifene
Usall <i>et al.</i> ¹¹⁷	24-week, double-blind, randomized parallel placebo-controlled trial	<i>n</i> = 70	Raloxifene 60 mg/day Placebo	Psychopathology: PANSS and SANSS	Raloxifene (60 mg daily) improved negative and general psychopathological symptoms
Kianimehr <i>et al.</i> ¹¹⁸	8-week, parallel-group, placebo-controlled trial	<i>n</i> = 46	Risperidone 6 mg/day + raloxifene 120 mg/day Risperidone 6 mg/day + placebo	Psychopathology: PANSS	Risperidone combined with raloxifene (120 mg daily) was more effective than placebo in positive symptomatology
Usall <i>et al.</i> ¹¹⁹	12-week, double-blind, randomized placebo-controlled, trial	<i>n</i> = 33	Raloxifene 60 mg/day Placebo	Psychopathology: PANSS	Raloxifene (60 mg daily) improved positive, negative, and general psychotic symptoms
Kulkarni <i>et al.</i> ¹²⁰	12-week, double-blind, randomized controlled trial	Current trial: 26 Pilot: 9	Raloxifene 120 mg/day Raloxifene 60 mg/day Placebo	Psychopathology: PANSS and MADRS	Raloxifene (120 mg daily) was associated with better recovery in total and general symptoms compared to 60 mg/day and placebo
Cognitive assessment					
Weiser <i>et al.</i> ¹¹²	16-week, double-blind, randomized placebo-controlled, trial	<i>n</i> = 200	Raloxifene 120 mg/day Placebo	Psychopathology: PANSS, CGI Cognition: Composite Brief Assessment of cognition	No significant improvement in severely ill decompensated patients receiving raloxifene adjunct to antipsychotic medications
Weickert <i>et al.</i> ¹¹⁵	13-week, randomized, double-blind, crossover, placebo-controlled trial	<i>n</i> = 478	Raloxifene 120 mg/day Placebo	Psychopathology: PANSS, DASS Cognition: WAIS-III, WTAR	Adjunctive raloxifene (120 mg daily) may have beneficial effects on attention and processing speed and memory for men and women
Huerta-Ramos <i>et al.</i> ¹²¹	12-week, double-blind, randomized, placebo-controlled trial	<i>n</i> = 33	Raloxifene 60 mg/day Placebo	Psychopathology: PANSS Cognition: neuropsychological battery	Adjunctive raloxifene (60 mg daily) was associated with improvement in memory and executive functioning
CGI, Clinical Global Impression Scale; DASS, Depression and Anxiety and Stress Scale; ESR1, estrogen-receptor 1; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SANSS, Scale for the Assessment of Negative Symptoms; UGT1A8, UDP-glucuronosyltransferase 1A8; WAIS-III, Wechsler Adult Intelligence Scale: third edition; WTAR: Wechsler Test of Adult Reading.					

the prior effect. The opposite is true for drugs metabolized mainly by CYP 3A4, quetiapine for instance, whose activity is enhanced by estrogen. After menopause, this enzyme becomes less active, so that lower doses of the antipsychotics concerned may be sufficient.⁷¹ The use of concurrent drugs is another important issue. Because of sleep problems and pain problems and depression, women at menopause often take more varieties of medication than previously, which affects protein binding of concurrent antipsychotics and may, thus, enhance or inhibit the ability of individual drugs to enter the brain.¹²⁴

Pharmacodynamics. The loss of estrogens at the period of menopause may eventually lead to increased vulnerability for psychotic relapse, poor clinical outcome, and a need for increased antipsychotic dose.^{122,125,126}

Women show more D2 receptor binding sites than men, particularly in the frontal cortex, temporal cortex and thalamus¹²⁵ and estrogens augment the antipsychotic action of antipsychotics at dopamine D2 receptors.¹²⁵ Declining levels of estrogens at menopause thus diminish D2 receptor occupation by antipsychotics, the basis for their effect on psychotic symptoms.^{124,125}

Oxytocin and schizophrenia in menopausal-age women

Oxytocin has been less implicated in menopausal symptoms than in puerperal symptoms in schizophrenia. Both oxytocin and vasopressin have, however, been associated with symptom severity and cognition in middle-aged women with schizophrenia.¹²⁷

Depending on the gender distribution of the study sample, some studies report positive findings when administering oxytocin to schizophrenia patients, whereas other studies report negative results. A potential explanation is that oxytocin affects reproductive-age women differently than it does postmenopausal women or men. The most representative studies are summarized below.

Modabbernia and coworkers¹²⁸ conducted an 8-week, randomized, double-blind, placebo-controlled study in two hospitals in Iran. They recruited 40 male and female patients with schizophrenia aged 18–50. All were on a stable dose of risperidone (5–6 mg/day) for at least 1 month. The patients were randomly assigned to oxytocin nasal

spray or saline nasal spray for 8 weeks. Oxytocin spray was administered as 20 IU (five sprays) twice a day for the first week followed by 40 IU (10 sprays) twice a day for the following 7 weeks. The patients on placebo received the same amount of nasal sprays. By week 8, the patients in the oxytocin group showed significantly greater improvement than the placebo group on positive, negative, and general psychopathology scores of the PANSS. The investigators concluded that, though the improvement was statistically significant, it was unlikely to be clinically significant. Ota and colleagues¹²⁹ administered daily intranasal oxytocin for 3 months to 16 patients with schizophrenia who stayed on their regular medication throughout the trial. MRI was performed on 15 of the study participants. Positive and negative symptoms, but especially negative symptoms, were improved. There was also an improvement in verbal fluency. From the MRI results, the investigators concluded that improvement was related to gray matter volume in the right insula and left cingulate cortex of the brain. In reviewing the studies of oxytocin as an augmenting strategy in schizophrenia, Ettinger and coworkers⁴⁷ concluded that the evidence was inconsistent.

No oxytocin study has specifically targeted postmenopausal women with schizophrenia.

Other hormones potentially relevant to postpartum disorders and menopause

While most of the recent literature about treatment of postpartum and menopausal psychosis concerns estrogens, other hormones have, at times, been considered as potential players. The role of stress hormones has been well summarized elsewhere.¹³⁰ Progesterone is of interest because it exerts effects on the dopaminergic system.¹³¹ Progesterone levels fall dramatically postpartum and this could theoretically contribute to postpartum disorders.¹³² A retrospective study explored the effect of depot medroxyprogesterone acetate given for contraception immediately postpartum; 55 women received the injection and 192 women did not.¹³³ At 6 weeks postpartum, scores on the Edinburgh Postnatal Depression Scale (EPDS) were the same in the two groups. In contrast to these findings, Lawrie and colleagues¹³⁴ had found that long-acting norethisterone enanthate, a progestogen contraceptive, increased the risk of postpartum depression when administered postpartum. The suppression of endogenous secretion of ovarian hormones was hypothesized as the

cause of the increased risk. Misiak and coworkers¹³⁵ have postulated a role for androgens in psychosis. Luteinizing hormone¹³⁶ alone, or in relation to FSH,¹³⁷ has also come under scrutiny, especially in regard to the cognitive symptoms of menopause. Also, the high prolactin levels induced by antipsychotics have been suspected of further impairing cognition at the time of menopause,¹³⁸ perhaps especially so when the antipsychotic used, risperidone for instance, is metabolized by the CYP2D6 enzyme.¹³⁹ Neurosteroids (steroids synthesized in the brain) such as pregnenolone, dehydroepiandrosterone, and allopregnanolone modulate neural plasticity and may have therapeutic potential for psychotic illness.^{140,141} Thyroid hormone is important in the postpartum period because this time period is associated with an increased risk for autoimmune thyroid disorder.¹⁴² Thyroid hormone is also important at menopause in that menopausal symptoms may, at times, mask thyroid disease.¹⁴³ Another hormone, melatonin, may be therapeutically useful during the menopause to counteract sleep disturbance and, also, as has been shown recently, to prevent metabolic side effects induced by antipsychotic drugs.¹⁴⁴⁻¹⁴⁹

Although the evidence for the treatment potential of hormones added to antipsychotics at postpartum or at menopause is only beginning to accumulate, it is worthwhile keeping such options in mind and also appreciating that what may be significant in achieving good response are not levels of individual hormones but the balance of levels of several different hormones.¹³⁷

Summary and Conclusion

In this narrative review, we attempted to summarize evidence bearing on the association of estrogens and oxytocin with antipsychotic use in the postpartum period and menopause. Estradiol and oxytocin have been implicated in postpartum psychosis; however, their use as potential treatments is controversial and critical information is still lacking. Estradiol and SERMs show promise as potential adjuncts to antipsychotics for postmenopausal women with psychosis, whereas oxytocin-augmentation strategies in menopausal women are lacking.

In response to the questions raised at the outset of this review, it should be noted that the jury is still out.¹⁵⁰ We still do not know whether adjunctive hormones are able to reduce the dose of

antipsychotics required to reverse psychotic symptoms during the postpartum and menopause periods. It is also still not clear which psychiatric symptoms may be most responsive to hormones. We do have evidence, however, that combinations of hormones and antipsychotics, when used at standard doses, are generally safe and well tolerated. Research continues so that these and related questions will be answered in the near future.

Key points

1. Hormonal decline at postpartum and at menopause is temporally related with the onset and exacerbation of both psychotic disorders and affective disorders in women.
2. The potential use of estradiol and oxytocin has been tested in postpartum depression. The results have been lackluster. Trials in postpartum psychosis and postpartum mania are sparse.
3. The results of adjunctive use of estrogens and raloxifene in postmenopausal psychosis have been promising. SERMs other than raloxifene have been insufficiently investigated.
4. The use of oxytocin as a potential intervention for schizophrenia at menopause has not yet been investigated.
5. Treatment with a hormone can suppress endogenous secretion of the hormone and affect endogenous synthesis. Dose and timing of intervention are potentially critical to efficacy.
6. Gonadal hormones can inhibit or enhance the action of drug-metabolizing enzymes and thereby affect the level of specific concomitant antipsychotic drugs, depending on the metabolizing pathways involved (e.g. CYP1A2 and CYP3A4).
7. The results of hormones added to antipsychotic medication in the treatment of psychotic and affective symptoms partially depend on their effect on protein binding of antipsychotics drugs, thus modulating their entry into the brain.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

MVS has been a consultant for Clera Inc. Alexandre González-Rodríguez has received

honoraria or travel costs from Pfizer, Janssen, Lundbeck-Otsuka and Ferrer.

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