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PEER REVIEWED FEATURE
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Biological aspects of treating women with severe mental illness

Key points

- Fluctuations in oestrogen and progesterone can influence the onset and relapse of mental illnesses in some women.
- For women with premenstrual symptom exacerbations, our clinical practice is to trial the oral contraceptive pill with continuous hormone delivery.
- Contraception, sexual health and pregnancy planning are often overlooked in settings that focus on mental health care.
- Lifestyle advice plus metformin can help weight loss in women with antipsychotic-induced weight gain.
- Oestrogen augmentation and selective oestrogen receptor modulators (SERMS) such as raloxifene are being trialled as adjuncts to antipsychotic medication in women with severe mental illness.
- Choice of antipsychotic medication in pregnancy is not clear; the National Register of Antipsychotic Medication in Pregnancy study may help resolve this question.

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Management of women with severe mental illness needs to take into account the influence of oestrogen and progesterone fluctuations on the illness, as well as sex-specific issues such as contraception, fertility, pregnancy and breastfeeding.

Severe mental illnesses such as schizophrenia, schizoaffective disorder and bipolar disorder affect 1% of women around the world.[1] Managing women with severe mental illnesses requires a holistic approach that combines biological, psychological and social strategies and focuses clearly on issues specific to women. Although some of these issues are psychosocial, here we will discuss biological factors that impact on the management of women with severe mental illness.

Some of these biological factors are outlined in the box on page 45. They include the hormonal fluctuations associated with the menstrual cycle and menopause, the need for contraception, fertility issues and management of psychotropic medications during pregnancy and breastfeeding. In addition, oestrogen has been shown to have a positive impact on psychotic symptoms, providing an additional therapeutic strategy in some women.[2] As the primary healthcare providers, GPs are ideally placed to use their expertise in both physical and mental health care to provide an integrated approach for women with mental disorders.

REPRODUCTIVE HORMONES AND PSYCHOSIS

Fluctuations in reproductive hormones such as oestrogen and progesterone can be important factors influencing the onset and relapse of mental illnesses in some women.

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Oestrogen

Clinical research studies have shown oestrogen to be neuroprotective, to have antidepressant actions and, when used as an adjunct to antipsychotic therapy, to reduce the positive symptoms of psychosis.[2] Essentially, oestrogen is postulated to modulate the action of serotonin and to downregulate dopamine receptors.[3]

Progesterone

Progesterone can have a calming effect, but a significant number of women experience depressive symptoms in response to progestogens.[4,5] These include the progestogens in the oral contraceptive pill, hormone therapy, contraceptive implants and depot injections, and the levonorgestrel-secreting intrauterine device.

In our experience, for some women with severe mental illness, hormonal treatments that avoid older style progesterones such as medroxyprogesterone and levonorgestrel are better tolerated. We favour nomegestrol, dydrogesterone and cyproterone (bearing in mind that cyproterone potentially increases the risk of type 2 diabetes). However, individual responses to hormone therapies vary widely.

The menstrual cycle

Many women with severe mental illness report premenstrual exacerbations of their symptoms, such as lowered mood, lethargy or even worsening of psychotic symptoms.[6] Although there have been no clinical trials, it is our clinical practice for these women to trial the use of the oral contraceptive pill with continuous exogenous hormone delivery – the nonactive pills are taken only once every three months (that is, one set of nonactive tablets per box of tablets). This strategy is successful for some women. Others find they feel worse while taking the nonactive pills, so further reducing the frequency of withdrawal bleeds can be helpful.

For many women, understanding the cyclical variation in their mood and planning to reduce any stressful activities at this time is empowering. Other treatment strategies for women with psychosis include increasing the dose of antipsychotics premenstrually and for those with persistent symptoms, considering oestrogen or raloxifene augmentation, as described in the box on page 46.[6-9]

BIOLOGICAL ASPECTS OF TREATING WOMEN WITH MENTAL ILLNESS

- **Reproductive hormones** – oestrogen and progesterone fluctuations can influence the onset and relapse of mental disorders in some women
- **Contraception** – reliable contraception is an important long-term management issue for many women
- **Sexual health** – women may have an increased risk of sexually transmitted infections, and many experience poor-quality sex lives because of drug side effects
- **Menstrual dysfunction** – antipsychotic therapy may cause amenorrhoea or weight gain that can trigger polycystic ovary syndrome (PCOS)
- **Fertility and pre-pregnancy care** – many women require assisted reproductive technology to become pregnant; physical and mental health and antipsychotic therapy should be optimised before pregnancy
- **Pregnancy and postpartum** – clinicians need to be vigilant for metabolic complications during pregnancy and worsening psychotic symptoms, particularly postpartum
- **Menopause** – women may develop depression or psychosis or experience a relapse at menopause
- **Metabolic health** – antipsychotic-induced weight gain may increase cardiovascular risk
- **Preventive care** – regular screening tests such as mammograms and Pap smears are easily overlooked

CONTRACEPTION

Pregnancy rates for women with severe mental illness have been increasing in recent decades, possibly because modern antipsychotic drugs are less likely to cause hyperprolactinaemia and because assisted reproductive technologies have improved.[10,11] Furthermore, although the overall rate of pregnancy in women of child-bearing age with schizophrenia is lower than in the general population, the percentage of unwanted pregnancies is higher.[12] This may be related to more risky behaviours and less use of contraception.

Reliable contraception is an important long-term management issue for women with mental illness. Clinicians treating women in facilities that provide only psychiatric treatment may not ask about contraception or may not feel skilled enough to provide this information. GPs are ideally trained to discuss contraception with women with severe mental disorders, even

POTENTIAL NEW TREATMENTS FOR WOMEN WITH MENTAL ILLNESS

Treatments for schizophrenia

Oestrogen augmentation

Our clinical trials have demonstrated that oestradiol 100 µg added to conventional antipsychotic treatment reduces positive symptoms such as hallucinations, delusions and disorganised thinking in women with treatment-resistant schizophrenia.[2] However, there is a high risk of endometrial cancer with oestrogen-only therapy, and the progesterone in combined hormone therapies can cause depressive symptoms.

Selective oestrogen receptor modulators

Because of the potential risks of oestrogen-only adjunctive therapy, we have now progressed to studies of adjunctive raloxifene 120 mg with promising results. The advantage of raloxifene is that it has an oestrogenic action on the central nervous system and bone but not on the breast or uterus.

In the future, raloxifene and other selective oestrogen receptor modulators (SERMs) may be useful adjunctive therapies for women and men with schizophrenia.[7,8] However, currently their use remains under investigation in randomised controlled trials. Our practice is to use these drugs as adjunctive therapy in women whose symptoms are refractory to all other available therapies, but we do not recommend their routine use outside research settings and highly specialised clinics.

Treatments for bipolar disorder

In a study of tamoxifen and progesterone adjuncts to mood stabilisers in women with mania, we found that both adjuncts reduced mania symptoms more than a placebo adjunct.[9]

if women do not raise the subject themselves.

Most women are able to take responsibility for contraception with advice from their treating doctor. Barrier contraception and the oral contraceptive pill may be suitable, but adherence to these forms of contraception may be difficult for some severely unwell women. Long-acting contraceptives and intrauterine contraceptive devices are highly effective and should be discussed with women.[12]

However, even the very low systemic exposure to progestogen seen with the levonorgestrel-secreting intrauterine device can worsen mood symptoms in a small minority of women. If depressive symptoms appear soon after insertion of the device then its removal needs to be part of the management plan, and other contraceptive methods should be discussed. The newer intrauterine devices can be offered to nulliparous women, as long as insertion is careful and expert.

SEXUAL HEALTH

Sexually transmitted infections (STIs) are common in people with severe and persistent mental illness.[13] Women with severe mental disorders experience high rates of sexual abuse. They may feel pressured to have sex, may exchange sex for money, drugs or other favours, and often experience poor social circumstances that also put them at high risk of STIs.[14]

In addition, common symptoms during a manic episode of bipolar disorder include increased libido and disinhibited behaviour, which can have major social ramifications, disrupt family relationships and lead to significant personal and physical harm. The potential for pregnancy and STIs are especially serious issues for these women and require a 'prophylactic' approach. A detailed sexual history should be obtained, with regular follow up and screening for STIs.

Further, many women with mental disorders experience poor-quality sex lives, with medication-related anorgasmia, low libido or painful intercourse. These problems can have a significant negative impact on a woman's quality of life and relationships and need to be addressed.

MENSTRUAL DYSFUNCTION

Amenorrhoea

Menstrual dysfunction is more common in women with severe mental illness than in the general population, and can also be associated with worsening of psychiatric symptoms and reduced quality of life.[15] It can affect fertility and cause women concern even if not immediately desiring a pregnancy.

Amenorrhoea is often induced by hyperprolactinaemia secondary to antipsychotic drug treatment.[16] In some women there is the option of changing to antipsychotics that are less likely to cause hyperprolactinaemia, such as quetiapine, olanzapine and aripiprazole.[17,18] Metformin has shown efficacy in reversing antipsychotic-induced amenorrhoea as well as antipsychotic-induced weight gain.[19] Medications specifically aimed at reducing prolactin levels, such as bromocriptine and cabergoline, should be avoided as their dopaminergic activity may induce psychosis.[20] In women not desiring fertility, the oral contraceptive pill can be used to provide regular withdrawal bleeds as well as bone protection.

If amenorrhoea persists, referral to a psychiatrist may be needed for specific advice about altering a woman's antipsychotic medication. Changing from medications such as risperidone, amisulpride or the older first-generation antipsychotic drugs may require inpatient treatment.

Gynaecologist or endocrinologist referral will be required for advice on fertility and ongoing fertility treatments.

Polycystic ovary syndrome

Antipsychotic-induced weight gain may precipitate polycystic ovary syndrome (PCOS), although there may also be pathogenic links between PCOS and psychiatric illness. Sodium valproate,

a commonly used antiepileptic and mood-stabilising drug, increases the risk of PCOS developing, and cessation of sodium valproate will lead to PCOS remission in some women.[21,22] We try to avoid prescribing sodium valproate for women when possible because of the association with PCOS, as well as the drug's known teratogenic effect in pregnancy.

FERTILITY AND PRE-PREGNANCY CARE

Fertility is reduced in women with mental illness. We are currently conducting a large study of pregnancy in women with severe mental disorders, the National Register of Antipsychotic Medication in Pregnancy (NRAMP). We have found that utilisation of assisted reproductive technologies by women in our NRAMP database is approximately double that of the general population. This is likely due to an increased incidence of reproductive disorders, lifestyle factors and the subfertility found in large studies of women with schizophrenia. Early referral to a fertility specialist should be considered for women having difficulty becoming pregnant.

Pregnancy planning seems to be rarely discussed by women with mental illness and their doctors, as the control of psychosis symptoms tends to dominate the clinical interaction. Enabling women with mental illness to mother their children well is a crucial role for clinicians to optimise the outcome for both mother and baby.

Pre-pregnancy care is important, with the key goal of optimising the woman's mental and physical health. Education about nutrition, smoking cessation, ceasing illicit drug use, taking folate and minimising alcohol intake before and during pregnancy are important. In addition, we suggest considering early referral to a psychiatrist with an interest in women's mental health or perinatal psychiatry to optimise psychotropic medications and link the woman with relevant services.

PREGNANCY AND POSTPARTUM

Despite the reduction in fertility in women with severe mental illness, most become mothers.[23-25] Many will require ongoing antipsychotic treatment during pregnancy and the postpartum period to avoid catastrophic consequences, such as severe psychosis and loss of custody of the infant. Our preliminary results from the NRAMP study show that clinicians need to be particularly vigilant for metabolic complications during pregnancy, such as excess weight gain and gestational diabetes, and for worsening psychotic symptoms, particularly in the postpartum period.[26] Of the first 147 pregnancies in the NRAMP register to April 2012, 40% of women required psychiatric admission during pregnancy or, more commonly, in the first year postpartum. The infants had high rates of withdrawal symptoms and respiratory distress after delivery (often mild), with around 40% requiring admission to a special care nursery or neonatal intensive care unit.

There is no concrete advice on which antipsychotic is the best choice during pregnancy, nor is there an evidence base on antipsychotics and breastfeeding. Our NRAMP database shows that babies who were breastfed had half the rate of withdrawal symptoms as those who were bottle fed, suggesting that enough drug passes into breast milk to affect the infant brain.[27]

An emerging resource on the use of psychotropic medications in pregnancy is the Perinatal Psychotropic Medication Information Service. This collation of case reports of adverse events related to psychotropic medication in pregnancy is hosted at the Royal Women's Hospital, Melbourne (http://www.ppmis.org.au).[26]

Postnatal management of women with mental illness requires a holistic approach, with a special focus on keeping the mother and baby together. Referral to a perinatal psychiatrist or specialist clinic is desirable. It is important that the mother be booked for the birth into a hospital with access to adequate psychiatric facilities (such as a mother–baby psychiatric unit).

MENOPAUSE

Women may develop depression or psychosis for the first time at menopause or may experience a relapse of a pre-existing mental disorder. Perimenopause begins at around age 47 years with variations in menstrual cycle length. Women experience symptoms to varying degrees, including hot flushes, mood changes or low mood, anxiety or panic symptoms, difficulty concentrating, poor memory, night sweats and poor sleep, aching muscles and joints, vaginal dryness and weight gain. Many women with bipolar disorder suffer with depressive symptoms during the perimenopause. A study suggests that women with bipolar disorder who take hormone therapy are less likely to have depressive symptoms than women with bipolar disorder who do not take hormone therapy.[26]

Hormone therapy and antidepressants can be helpful in treating the mood symptoms associated with menopause, and the combination of both may be needed. Before hormone therapy is prescribed the potential risks such as stroke and thromboembolic disease should be carefully considered, particularly in women with other risk factors. Ensuring women have regular mammograms and Pap smears is also particularly important for those using hormone therapy.

METABOLIC HEALTH

The leading cause of death for women with severe mental illness is cardiovascular disease. People with schizophrenia die on average 11 years earlier than the general population.[28] The increased rates of cardiovascular disease are partly related to antipsychotic-induced obesity but were also seen before the development of antipsychotics.[29]

Weight gain associated with antipsychotics is an important factor to consider in the care of women with

mental illness, particularly those who also have features of polycystic ovary syndrome. Women should be screened regularly for diabetes and hypercholesterolaemia. Thyroid function is known to be adversely affected by drugs such as lithium, which is commonly used to treat bipolar disorder and severe depression. Women taking lithium should have their thyroid function monitored every six to 12 months.

Attention to lifestyle factors such as diet, exercise, alcohol use and smoking cessation is important, and GPs are ideally placed to have an impact in this area. Some health professionals feel that efforts to modify lifestyle factors are unlikely to be successful in those with severe mental illness, but there is good evidence that realistic goals are achievable for many.[30]

It is also worth considering an adjuvant medication such as metformin to help weight loss in women with antipsychotic-induced weight gain, but this use may be limited as metformin is not currently PBS-listed for those without diabetes. The combination of lifestyle advice and metformin is the most successful strategy to aid weight loss.[31] Topiramate has also shown some efficacy for weight loss in the research setting and is worth considering if a mood stabiliser is also required (although it should be noted that topiramate is not currently approved for use as a mood stabiliser in Australia).[32]

PREVENTIVE CARE

Women with mental illness often miss out on preventive screening tests such as mammograms and Pap smears. Many women with severe mental illness have experienced sexual abuse and may find Pap smears and vaginal examinations traumatic. A sensitive approach is required and referral to a female doctor may be beneficial. Focused supportive psychotherapy with a mental health practitioner before the Pap smear may also help a woman work through potential issues related to the vaginal examination.

In general, women with severe psychoses are not well engaged in the primary health sector and as a result experience poor physical health. It is imperative that mental health clinicians work together with GPs to improve the overall health of their female patients with severe mental disorders.

CONCLUSION

The care of women with severe mental illness is complex, requiring a team effort. GPs are central to successful outcomes for women with severe mental illness. Through better-integrated research and advances in biotechnology, we are gaining a better understanding of the biological, psychological and social factors that impact on women's mental health. Tailoring treatments for women remains an important goal. In particular, taking into account hitherto overlooked biological factors is a key part of managing the many special issues for women with mental illness. MT

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