**Mental health and the menopause transition**

**Dr Tessa King:** Good evening and welcome to tonight's presentation, Mental Health and the Menopause Transition. My name is Dr. Tessa King, and I'm a women's health GP here at Jean Hailes. I have a strong interest in female hormones and their effect on mood and on cognitive function during the different phases of the menstrual cycle, postpartum, and during perimenopause and menopause. Firstly, I'd like to start by acknowledging the traditional custodians of the land we're presenting on and the lands that we're reaching tonight. I'm in Melbourne on the land of the Wurundjeri and the Bunurong Peoples of the Kulin Nation. I recognise their continuing connections to land, water, and culture, and pay respects to Elders past, present, and future.

Joining us tonight is Professor Rodney Baber. Rod is Clinical Professor of Obstetrics and Gynaecology at the University of Sydney, and is Head of the Menopause and Menstrual Disorders Clinic at Royal North Shore Hospital. Also presenting tonight is Professor Jayashri Kulkarni, who founded and directs two research centres, the HER Centre Australia and the Monash Alfred Psychiatry Research Centre. She's a leader and expert in the field of women's mental health, and in particular works on reproductive hormones and mental illness. You can find the full bios in the Resource tab at the top right of your screen.

We thank you for sending in your questions, and if time, we will answer them at the end of the webinar. You can also submit questions tonight via the Questions tab at the top right of your screen. And at the top right of your screen you'll see a Resource tab. Here you'll find a selection of resources including tonight's presentation slides. Please take a moment to download them now.

So we'll start tonight's presentation with some definitions. Firstly, perimenopause is the time period preceding the menopause until one year after the last menstrual period. And it's defined as a change in cycle length of at least seven days, and it's often accompanied by symptoms such as hot flushes, night sweats, and mood changes. Menopause is the date of the last period, and it can only be diagnosed retrospectively once 12 months has passed since that last period. So a woman is considered postmenopausal once 12 months has passed since their last period. So if we have a look at this slide here with the stages of reproductive aging, it goes through the different stages in a woman's life. And as you can see, the red box highlights the final menstrual period, which is the date of menopause. And the average age for women in Australia is around 51 years for that final menstrual period.

And if we zoom in on this particular slide, we look at the late reproductive phase in a woman's life, so that's just preceding perimenopause. And you can get some subtle changes in menstrual cycle length, but once a woman enters early perimenopause, it's basically defined as a persistent change in their cycle of seven days or more on consecutive cycles. And the FSH is really variable, it can be elevated but it can also be low. So during that perimenopausal period you're not going to be able to diagnose it through blood tests. Once you're hitting the late perimenopause, often you get amenorrhoea of greater than 60 days, and once again, the FSH is not useful in diagnosing perimenopause. Once you've had the final menstrual period, and it's a year post that period, you do get an elevated FSH postmenopausally.

So how do we diagnose perimenopause and menopause? Perimenopause is a clinical diagnosis, so it's that seven-day cycle length variation on consecutive cycles, and it can be accompanied by symptoms. Perimenopause can't be diagnosed with a blood test. FSH/LH oestrogen and progesterone levels will fluctuate between premenopausal and postmenopausal levels during the perimenopause. And menopause, which is the date of the final menstrual period, can only be diagnosed once it's been 12 months since the woman's last period.

The only time that a blood test may be helpful is in someone with a Mirena in, or someone who's had a hysterectomy, or someone who you suspect premature ovarian insufficiency in. So in terms of screening for mental health issues during that menopause transition or the perimenopausal period, we recommend when a woman presents with possible perimenopausal symptoms, it's important not just to screen for vasomotor symptoms like hot flushes and night sweats, but also specifically to ask about mood changes or cognitive changes. Women don't always feel comfortable volunteering this information. They may feel that their concerns around mood changes, or cognitive changes as a result of perimenopause might be dismissed, so it's important to actually ask about them. The other thing is, in a woman who presents with mood changes whose age may indicate that she's perimenopausal, it's also good to ask about cycle length and other perimenopausal symptoms because the mood complaint may be her reason for presenting, but it may be caused from perimenopause.

So asking the question's a great place to start, but you can also use the Meno-D as a screening tool, and Jayashri will talk about that a little bit later. So it's really hard, I think, as a GP to work out, or another healthcare professional, to work out whether a woman presenting with mood changes in perimenopause is a result of hormones or whether it's a result of external factors, or a combination of both. Many women in their late forties and early fifties have multiple things going on in their lives, post-pandemic mental health issues, both in themselves and others, aging parents, teenage kids, relationship issues, career challenges, health issues. But it's really important to think about whether the hormonal fluctuations during perimenopause may be one or the main causal factor for a change in a woman's mood or mental health. And often women at this stage will describe that they just feel different to how they normally would. Their normal coping ability and resilience is just not there, and that's really a clue to think about whether perimenopause is a factor. So I'll hand you over to Rod Baber, and his presentation regarding menopause and brain fog and cognitive changes within menopause. And then we'll come back for Jayashri's presentation.

**Prof Rodney Baber:** Thanks very much Tessa, and hello everybody. I wish I could be with you today in person, but I'll do my best to make this an interesting talk, albeit from Sydney. What I want to talk to you about is the changes we see in menopause and as our brains age normally. These are my disclosures, but this presentation is based entirely on my own clinical experience, my reading and my research.

So when I talk about the aging brain, I think it's important that we understand what is normal and what is abnormal. Normal brain aging happens to all of us and it's generally defined as changes associated with age that don't lead to subsequent dementia. Abnormal brain aging is a spectrum from minimal or mild cognitive impairment, leading on to dementia. And those also are changes associated with age, but usually also associated with underlying pathology, which may eventually lead to dementia.

And dementia itself, importantly, is defined as 'cognitive impairment that interferes with our usual occupational and social activities, or with our independence'. So dementia interferes with our usual occupational and social activities, and with our independence. If we look at the changes that we see with normal aging, some of our skills improve with age and some decline. Those that improve with age are, generally speaking, abilities that draw mainly on skills we've acquired, knowledge we've acquired and experience we've acquired. This is sometimes known as 'crystallised intelligence', and a good example of that is vocabulary. I know more words than my kids.

But other cognitive abilities decline as we get older and they can start quite early in life. It's certainly not in old age that they happen. And these abilities are based on new learning, on abstract reasoning, and on problem solving. And they're sometimes known as 'fluid intelligence'. And I think an example of that is playing a computer game. My kids play computer games much better than I do, and that's typical of fluid intelligence. Those skills are generally better pursued by young people than they are by older people. And if we look at what happens as we age normally you can see some abilities increase, some abilities decrease. There's probably a sweet spot in the middle there where we're just about perfect, but the important take-home message is that normal cognitive aging won't interfere with your normal activities or with your independence.

Let's turn now to brain fog at the menopause. I don't think 'brain fog' is a typical medical term, but it's certainly something that helps us to understand what goes on in a certain situation. It's best described as a constellation of cognitive symptoms, which are experienced around the time of the menopause, sometimes before the last period and certainly after for a while, and they most frequently manifest themselves in memory and attention difficulties. So difficulty in recalling words or names or stories or numbers. Difficulty in maintaining a train of thought, so easily distracted. A situation where you forget intentions, for example, you can't remember why you walked into a room to do something. And also difficulty switching from task to task easily. But it's important also to remember that while these are very typical of the menopause transition, for the very large majority of women, this will not go on to develop into dementia. About three women per 1000 will develop dementia before the age of 64. So the other 997 who experienced some of these symptoms around the menopause transition are experiencing these typically because of changes which occur at that time.

And if we look at that, you can see what a big interaction there is between all of these factors. It's a classic sort of understatement, the few lines on the left of this slide which say 'cognitive changes at the menopause are linked to changes in oestrogen levels, vasomotor symptoms, sleep and mood'. Of course they are. But if you look at the drawing on the right of this slide, they're all listed there. At the top left, 'low and changing levels of oestrogen can affect your memory'. But they can also affect hot flushes, and they can also affect your memory. And hot flushes can cause poor sleep, and that could also affect your memory, but it could also make you quite moody. And if you are moody, then your memory won't be as good as well. But by the way, you also won't sleep as well if you're moody and if you're really depressed, you'll find you're waking up at two or three in the morning quite regularly. And if you have hot flushes, then your mood might change.

So there's this quite dense interaction of symptoms and signs which occur for a lot of reasons, but one important reason is those fluctuating levels of hormones. And if you look at the distribution of oestrogen and progesterone receptors in the brain, you can see, well they're virtually everywhere. But they're certainly very prevalent in key sites, including the frontal cortex, the thalamus and the hypothalamus, the amygdala, the hippocampus and the cerebellum. So it's easy to understand why fluctuating levels of hormones, might have some effection, some impact, on the way our brain works, on how we recall things, on our memory, on our cognition, and of course also on our mood. The burning question really is, if this is what oestrogen does and why oestrogen is so important, and it's because it's a neurotransmitter, of course, and works in conjunction with the catecholamines that also work in the brain. If after the menopause women lose oestrogen, can we give them hormone therapy to correct this problem?

And it's a good question, but it's not an easy question to answer, because what we have learned over time is that the effects of menopausal hormone therapy for any individual woman will depend on her lifestyle factors, her own individual risk factors, the timing of when we use it, the type of hormones that we choose to use, and of course genetic factors which relate to that particular individual. So what I want to summarise for you, really, in this slide is the role of hormone therapy as we understand it at the moment in treating cognitive concerns. And much of this data comes from a very important paper published in Climacteric, the journal of the International Menopause Society, just in October of this year, looking at the issue of brain fog and midlife women's mental health. Published by Pauline Maki and Nicole Jaff, two very distinguished psychologists. And if you see the reference down the bottom-right of this slide, you can download this paper free on the internet if you wish to read more.

But here are the key points. The effect of menopausal hormone therapy on cognitive function in the menopause is, as I just said, influenced by timing of therapy, lifestyle factors and genetic factors. What we do know is that the use of menopausal hormone therapy in the early years after the final menstrual period, and of course in the perimenopause, is safe for cognitive function. That's not saying it's going to make cognitive function better necessarily, but it will alleviate menopausal vasomotor symptoms and improve quality of life, sleep and mood and all of those things may well have an impact on your immediate cognitive health. By 'safe for cognitive function', we mean there is no evidence to show that that would lead to harm in later life. Use of MHT in women with an early or premature menopause may actually be helpful in maintaining cognitive function and lowering their risk of later dementia, because particularly in women with a surgical menopause, we know that cognitive decline moves at a more rapid rate and that giving oestrogen back will make a difference.

Use of oestrogen therapy, even a number of years after the last menstrual period, is also safe for cognitive function. But the areas we need more research in to determine whether or not menopausal hormone therapy will improve cognition in women with bothersome menopausal symptoms. We know it'll relieve their symptoms and we know it'll improve their quality of life and so on, but there have not been enough really thorough studies looking at the effect on cognition as a single standalone factor. And similarly, we need to know more about the effects of hormone therapy, or oral contraceptives, on treatment of cognition in women in the perimenopause. And based on current guidelines, menopausal hormone therapy is not recommended to treat cognition or to prevent cognitive decline or dementia. So I know that seems perhaps a bit difficult to understand. What we're saying is hormone therapy is safe for postmenopausal women, it's good for hot flushes, it's good for bones, it's good for the heart, it's good for moods, and it's safe for cognition, but we don't recommend it as a treatment for cognitive concerns.

What can you do to treat cognitive concerns? This is the really important take-home slide, I think. First of all, if you look at the top on the left, you can see that heart health is brain health. So if your cardiovascular health is good, so will your brain. And so therefore we need to make sure you don't get hypertensive, you don't get high cholesterol, you don't get diabetes, you exercise regularly and of course other things. Give up smoking, stay well connected. Social activity is really important for brain health. Do not put on too much weight. The average weight gain from ages 45 to 55 for women who are careful is half kilo a year. So you need to be careful how much you eat, and you need to make sure you have a healthy diet and a healthy exercise regimen. And lastly, exercise your brain. It doesn't really matter what you do as long as you do something that is stimulating your brain, whether that's reading, whether it's learning a new language, whether it's acting as a volunteer, a new job, or learning a new skill, all of those things will increase your cognitive reserve and therefore reduce the risk of cognitive impairment with age.

So just to summarise the International Menopause Society recommendations on this topic, the normal menopause is not linked to dementia. Menopausal hormone therapy shouldn't be used to enhance cognitive function. Healthy lifestyle measures certainly do help to maintain cognition. Oestrogen therapy may confer cognitive benefit after a surgical menopause, particularly when it's initiated soon after the surgery. MHT initiated during midlife, immediately before or after the last menstrual period may be associated with a reduced risk of Alzheimer's disease and dementia. And finally, and what Jayashri is going to talk about in a little while, MHT may well improve depressive symptoms during the menopause transition. So I hope that set the scene, and what I'd like to do now with you is look at a case study.

This is Jennifer, Jennifer's 51. She has two children, now, aged 22 and 20. Both were born vaginally, and she had no problems during the pregnancies themselves, although she did have a bit of postnatal depression after her first pregnancy. In recent times, she's had four years of heavy, irregular periods. Three years ago she had a progestogen-containing intrauterine device put in. The one that was put into Jennifer was called a Mirena, and that's worked pretty well, so much so that her periods became lighter within a few months, and now they've become less frequent. Her last period was eight months ago, and it's not clear whether that eight months of no periods is due to her perimenopausal status or, of course, to the presence of the Mirena device. One key that she's getting into the perimenopause, however, is that she's having hot flushes more frequently, and she's noticed mood changes as well. Jennifer had no significant medical history or family history, and she's not taking any medications.

Her mood changes have also become more apparent over the last three years. And those symptoms include irritability, poor sleep, poor memory, poor concentration and forgetfulness. Her hot flushes are coming about four or five times a day and she wakes up two or three times at night. Maybe that's due to hot flushes, maybe it's due to poor sleep. She's not quite sure. She has noticed that she's gained weight. She's gained about three kilos in the last three years, which is certainly more than average. And she's also noticed a loss of libido, and she comes because she's worried about this constellation of symptoms and the effects that this is having, not just on her but on her family as a whole. Her blood pressure on examination is 130 on 85, so borderline hypertensive, and she is indeed a bit overweight, her BMI is 27.

So when it comes to diagnosis, what would you say is Jennifer's menopausal stage? Well, as I said a moment ago, she's almost certainly perimenopausal. The presence of the Mirena device makes it a little bit difficult for us to predict, but even if we allow for that, her last period that we know of was eight months ago. And the menopause is not said to have occurred until you have had 12 months without a period. So Jennifer is perimenopausal. Her main complaints are perimenopausal hot flushes, vasomotor symptoms, and a worsening of her mood disorder. But she has other issues. Her libido has worsened and that's bothering her a bit. And she's also overweight and has borderline hypertension. So perimenopausal symptoms, loss of interest in sex, which is distressing and cardiovascular disease. Almost certainly her hot flushes and mood disturbances and her sleep disturbances are due to fluctuating levels of hormones during the menopause.

Her loss of libido is also probably attributable to her perimenopausal symptoms, but it might be just an age-related change and it might be due to her mood disorder. About 30% of midlife women complain of reduced sexual activity, so just age alone could be contributing to Jennifer's complaint of loss of libido. But around 10%, that's one in three of those women, will have a loss of interest in sex which they find distressing. And that is called 'hypoactive sexual desire disorder' or dysfunction. A loss of interest in sexual activity which the individual finds distressing. Not the individual's partner, just the individual. And as I said, Jennifer's mood disorders could be related to the perimenopause and the fluctuating hormone levels, which we see there. Could be related to her sleep, it's hard to be happy when you're not sleeping well. But it could be related to extrinsic factors as well, and it's important that we investigate those as well. It is interesting to note that her mood changes do share some chronological association with the insertion of the progestogen IUD. They've been there for three years, and so is the Mirena.

It's also an important time for us to remember to do all the appropriate checks and screening discussions that we should have with every midlife woman at her midlife consultation. This is the ideal time to make sure we do a full check. So we should discuss her lifestyle, we should ensure that she's exercising regularly, that she has a healthy diet, that she doesn't smoke, and that if she drinks, she drinks in moderation. We should talk about her cardiovascular risk factors. And Jennifer has a couple, doesn't she? She's a bit overweight and she's got borderline hypertension. And we should ensure all of her screening tests are up to date. She certainly should have had a mammogram, should have had a cervical screening test within the last few years and she should have had a faecal occult alcohol blood test. So remember all of those things. And in the pink box at the bottom of this slide, there's a list of other things that we need to look at and talk about in this midlife consultation.

And that brings us then to the management options. So my questions for you are these, would you do blood tests to see if she's menopausal? She's depressed, would you treat her with an antidepressant? She's depressed, would you remove her progestogen intrauterine device? Would you suggest hormone therapy for Jennifer? And if so, what would you choose? And what other advice might you choose to suggest for her?

Well, in answer to the first question, would you do blood tests to see if she was menopausal? I wouldn't. Her last period was eight months ago. So she's a perimenopausal woman of a normal age, and an investigation is just a waste of time and money. Would you treat her with an antidepressant? Well, look, she's depressed, so an antidepressant may well help her depression and some of them might even help some of her hot flushes, but unfortunately most antidepressants commonly reduce libido. So I put to you that that's probably not a very good first choice. Might seem easy, might seem logical, but I don't think it's a good first choice.

Would you remove her progestogen intrauterine device? It's been in for three years. She's been moody for three years, and progestogen intrauterine devices are known to be associated with adverse mood changes in roundabout 10% of women who have them inserted. And they're more likely to be associated with mood changes in women who have a history of PMS or postnatal depression. And Jennifer had postnatal depression after her first pregnancy. The other issue of course, though, in contrast to that, is that if we remove her Mirena device after three years and she is really perimenopausal, then her heavy menstrual bleeding might come back. So then she'll come back to you and say, let's say for example, 'Oh, my moods are a bit better, but now I've got heavy flooding periods every three weeks. What are you going to do about that?' What will you do about that? You'll give her progestogens orally. And it's quite likely that they'll actually make her moods worse than the Mirena device did.

Would you suggest hormone therapy? Jennifer actually is interested in hormone therapy. A friend of hers has been taking Premarin for a while after hysterectomy and she thinks the Premarin are great. Premarin are conjugated oestrogens derived from the urine of pregnant horses. It's a mixture of oestrogens, the exact composition of which we still are not certain of, but it's been used widely in many parts of the world, in fact, in the United States it's still the most commonly prescribed oestrogen. And it's very good for alleviating menopausal symptoms and improving bone density, but it unfortunately doesn't cross the blood-brain barrier, so it has no effect on moods at all. It would not be appropriate for Jennifer.

What other advice would you suggest? Well, you could certainly offer her advice such as regular exercise, and that would be very good for Jennifer. It's a great idea, it would be good for her cardiovascular health, and exercising will also probably help her moods. But it'll do nothing for her hot flushes. In fact, if anything, it could make her hot flushes a bit worse. Would you suggest counselling? Cognitive behavioural therapy is known to work to treat ... [MISSING VIDEO] ... the exact composition of which we still are not certain of, but it's been used widely in many parts of the world, in fact, in the United States it's still the most commonly prescribed oestrogen. And it's very good for alleviating menopausal symptoms and improving bone density, but it unfortunately doesn't cross the blood-brain barrier, so it has no effect on moods at all.

So she did agree that she would try hormone therapy, and then we have to address the issue of what sort of hormone therapy we'd use. My preference would be to use transdermal oestradiol. I would use that because if we prescribe the oestrogen transdermally, it will be delivered in a fairly stable manner, and we won't see the spikes and troughs that we see with oral therapy. In other words, the level of oestrogen in Jennifer's blood is going to be pretty stable from day to day, and that means it's less likely to trigger any changes of an adverse nature with her moods. What dose would you use? I would start low. She hasn't had a period for eight months. She's having vasomotor symptoms. It's likely her oestrogen levels in her blood are quite low, and if we start low, we can titrate upwards until we get satisfactory alleviation of her symptoms.

If we start high, then we could cause her to have breakthrough bleeding despite the Mirena. We could cause her to have breast tenderness. We could cause her to have bloating, and we could cause her to have headaches. All of which will discourage her from continuing with what we have just talked her into as being the best option for treatment. So start low and work up as you need to. I started her on a pump of Estrogel, an oestrogen gel, that you can get available in this country. Just one pump a day, it's a very low dose. And after six weeks, because her symptoms had not completely subsided, we increased that to two pumps a day. The progestogen intrauterine device will provide adequate endometrial protection and no additional progestogen is required. After that second six weeks, so 12 weeks into treatment, her flushes had gone and she had no bleeding. So a pretty good outcome. But her mood changes, although they'd improved, was still bothering her. And it was just a constant, underlying, not quite right low mood. So what would you like to do about that? You could increase her oestrogen dose. You could add an antidepressant to the hormones. Or you could remove the progestogen device and give her oral progesterone.

Well, removing the intrauterine device may well be very effective in terms of reducing some of those mood changes. But once again, remember, we don't know if she's perimenopausal or postmenopausal, in which case we could take it out, her bleeding would come back, and we'd get into trouble. If we added an antidepressant, that would probably help her moods. But unfortunately, once again, it's probably going to make her libido worse. So once again, I would be inclined not to use that. I chose to increase her oestrogen dose further. I switched her to a 75 microgram patch, which would be equivalent to three pumps of the gel, but was a bit more convenient and a bit less expensive. And after a further six weeks, her mood disorder had completely settled. Her BMI had dropped, she was down to 25. She'd initiated a moderate exercise program and she'd taken up tai chi, which is very good for the brain fog, isn't it?

But her libido was still bothering her. So what would you like to do about that? You could conduct a bio-psychosocial assessment to exclude other causes of low libido, and you should. And if you do that, you could then consider introducing transdermal testosterone therapy for what Jennifer has, which is really hypoactive sexual desire disorder, a loss of interest in sex, which bothers her. You could consider changing her from the oestradiol patch and gel to tibolone. Tibolone's an oral form of oestrogen. Well, it's an oral form of a compound which looks like oestrogen and binds to oestrogen, progesterone and testosterone receptors and has a modest effect on libido. You could remove the Mirena. Any of those might be correct. There's no really correct answer, but my preference was to go to options one and two. In other words, conduct a bio-psychosocial assessment and consider introducing testosterone therapy. The 75 microgram patch we've got her on is actually a bit stronger than the effect of oestrogen that you would see with tibolone. So I think switching her to tibolone would not be beneficial.

Once again, I wouldn't remove the Mirena device until its due date, because we still don't know whether she's quite, completely postmenopausal or perimenopausal. And so that would be my last resort. I would measure her baseline testosterone and her sex hormone binding globulin, just to establish a baseline level, not to work out whether it was going to make any difference about treating. Really the critical issue is testosterone levels do not guide our treatment in this regard. The level of testosterone is just to show you where to start. If she had a really high sex hormone binding globulin level that might show us that it was less likely she would respond, but then I would treat her with a testosterone cream using half a mil daily.

In Australia, we are the only country in the world that has a testosterone cream for women, which is approved by and regulated by our government. And that's called AndroFeme 1. Half a mil daily. Tell her to apply it to her thigh or her buttock once a day. Tell her that it will not be an immediate response, it'll probably take three months for it to be a success. And at that stage, you should follow up her by doing a testosterone level again, and you'll demonstrate there's been a biochemical response to therapy. And also by seeing her and assessing her clinical response.

And in Jennifer's case, that turned out to be very successful. Her hypoactive sexual desire disorder had settled. Her moods were good, she had no hot flushes and no bleeding. So after a long and sometimes tiresome battle, we'd actually succeeded. I hope you found that interesting, and I hope it's instructive and informative. You can get lots of information on this from Jean Hailes information sheets, and from the Australasian Menopause Society or the International Menopause Society homepages on the internet. Thanks very much for listening.

**Prof Jayashri Kulkarni:** Hello, I'm Jayashri Kulkarni, and it's my pleasure to speak to you today about menopause and mental health. Let's start with this. Mental health policy in Australia does not consider women's mental health as a separate and important area of need. So this is work from Maria Duggan and others in the Australian Health Policy Collaboration paper. And unfortunately while that was the case in 2016, it still remains the case. And just to reinforce that, in fact, in the recent Victorian Royal Commission into mental health, 62% of the people who submitted any kind of personal story to this commission were women. Now, despite that the interim report remained completely silent about having a specific response about the mental health of women, it just kept it all gender-blind. So after a considerable lobbying by myself and others, we've managed to get a little bit of action, and we are looking forward to seeing whether there will be greater attention paid to women's mental health.

Why do we go on about mental illness in Australian women? It's because mental ill health conditions represent the leading cause of disability, and the highest burden of non-fatal illnesses for women in Australia. About 47% of women have experienced mental ill health at some time. And although we are not through the Covid pandemic, what we noted from all the lockdowns and the impacts of Covid is that women suffered enormously. In particular, their mental health suffered enormously, with rising numbers of women presenting to their family practitioners, to hospital clinics, to private practitioners in psychiatry, to psychologists, and a range of other health practitioners with increasing rates of depression, anxiety, PTSD, eating disorders and alcohol use disorder. There's many, many different studies that show this, but globally and at home, really this has been the impact, that mental ill health in Australian women really suffered as a result of the Covid pandemic.

And of course, this costs our society. The economic impact of depression and anxiety, this is old estimate, pre-Covid, was about, thought to be $32 billion per year in direct loss productivity. So when you add in all the other bits, like the cost of treatments, the lost earnings, the loss of effective parenting of children, the loss of care of elderly parents and others, divorce, the costs go up. So, where to now for women's mental health? I would really like to echo Rod's words, in that a bio-psychosocial approach is really critical. It's critical in mental health, it's critical in physical health. And as you can see here, we need to consider the social impacts of our world and how it's really causing and perpetuating mental ill health in women. Violence against women, poverty, gender inequities in wage, the power imbalance, social roles and so on really do impact on mental ill health and make it worse.

There are biological factors, including hormone impacts, gender differences in drug metabolism systems, gender differences in brain circuitry, and genetic transmission. And the psychology differs as well. Many psychiatric illnesses present very differently in men and women because of gender differences in adaptation to a stress, that is, the psychological responses or defence mechanisms. But one of the things that really bothers me about the field in mental health is the lack of neurobiological research that's translated directly into new and innovative responses, particularly for women with mental ill health. Most of the fields in medicine have really made huge advances through greater understanding of biology, and I always am in awe of oncology, immunology, stroke management. I mean we've just seen vaccines developed very rapidly for Covid. Cardiology, anaesthetics and so on. But unfortunately, really at the moment in psychiatry, we are struggling with the lack of translatable neurobiological knowledge and unfortunately that's meant that in the absence of this understanding psychiatry's focused on psychosocial therapies and support services. Which might be useful, and they are useful, and I'm not descrying the importance of it, but unfortunately it's as if we're skirting around many issues.

And this has led to poor diagnoses, misdiagnoses and lots of euphemisms, such as the 'baby blues', which actually is a terrible term, where what we're talking about is often a major depression post childbirth. That horrible term 'personality disorders' is often applied to women who've actually experienced awful violence against them, and then they're told that their angry responses and so on are because they have a personality disorder, which is just not fair. We also have a lack of biomarkers that makes it difficult for an objective diagnosis of depression and so many other things. So we can all agree that there are many aspects that are yet to be explored, but here is one area that we can look at what's going on in other fields and translate this into the area of women's mental health. And gonadal hormone impact, as Rod and many others have outlined is an important area that really does have a great impact on women's mental health. And this is not news for many women, but unfortunately it might be news for people in the mental health field, and other areas of general medicine.

Hormones are potent neurosteroids. The oestrogens, progesterones and androgens, and notice they're all plural, because there's not just one, are all potent neurosteroids. And they significantly affect modulation of dopamine, noradrenaline, serotonin, glutamate and acetylcholine, because these are the key neurotransmitter systems that we know are actually involved in determining behaviour, mood, and cognition, as well as new learning and memory and so on. So again, these are really critical influences on our mental health and the hormones that are gonadal hormones really do impact these particular neurochemicals. And we get this from longstanding clinical anecdotal evidence for biological hormone impact on mental health, and it's backed up by animal studies.

Perimenopausal depression is a subject that I'm going to speak to you about tonight. And this is unfortunately an under-recognised and a vastly underrated condition. In fact, there isn't even a term that stands up in terms of the DSM, which is the psychiatric diagnostic statistical manual for diagnosing psychiatric illnesses. Perimenopausal depression does not appear. And it's really sad because middle aged women are a high-risk group for developing clinical depression. Yes, there's a lot going on in the middle-aged woman's life, but because this increase in depression is there, we need to look into the neurobiology in a lot, lot more studied way. I recently wrote an article for Nature Outlook, and it's a branch of Nature, and I called it 'the misunderstood female factor' because I actually do worry about the fact that we're underestimating and misunderstanding the toll that menopausal depression takes, and particularly when we look at what happens when there are other factors at play as well. This is one of the things that we may be able to actually assist if we recognise it.

So perimenopausal depression, we know, has a high incidence of first onset in depression in perimenopause. And we also know that people who've had depression before suddenly also relapse. So two groups, those who've never had depression before can suddenly developed significant major depression in the perimenopause time, and people who've had, particularly well-controlled depression, it suddenly all goes pear-shaped at this particular time. So the Harvard study talked about the overall depression rates increasing 16 times in the 42 to 52 year age group of women. And the ABS data, if you look at demographic groups, this is not total across the board suicide, completed suicide, this is a demographic group analysis by demographic groups, women in this age group, midlife women, have the second highest completed suicide, compared to the highest being in men over 84. And that's probably not well known or recognised by women, by our general community or by our health community and health providers.

We really do think that the X-factor here that's tipping women into this dreadful depression with mortality is probably declining, chaotic gonadal hormone function in the CNS, in the brain, occurring first well up to five years before the hot flushes happen, or before periods cease. Once the hot flushes happen and periods cease, then everybody's capable of very quickly making the diagnosis of menopause. But the difficulty is, the brain changes and the mood changes are all happening well before that.

So to help practitioners understand and actually provide some consistency for diagnosis, we've developed the Meno-D. This is a rating scale for perimenopausal depression. The symptoms that we include in this particular questionnaire is plummeting self-esteem, paranoid ideation. This is not paranoia as we see in our people with schizophrenia, this is paranoia of the nature of, for example, the middle-aged woman saying things like, 'You know, I think everybody thinks I'm a dummy at work. I know they're all talking about me. They think I'm past it.' So that level of kind of exclusion, or a sense of others talking about one. There's increased aggressiveness, which can be, aggressiveness and hostility, can be depressive equivalents. So instead of being sad, many times women express feeling aggressive and hostile.

Disconnection, this is where the phenomenon of descriptions from women who say things like, 'Well, you know, the family's sitting around in the lounge room having a great time. I'm there in body, but I just don't feel like I'm actually there. There's sort of this glass disconnecting me from them.' Some of this is about dissociation, which we know is an anxiety symptom, that sense of being out of body, or out of the time. No libido, which again, Rod has spoken about at great detail, and this is a libido that causes the woman herself to feel that there is a problem, not somebody else. The irritability and agitation can be quite different to a depression that we are used to in younger women, or depression in men, where there's often like the moribund sort of tired, going to bed type depression. This can be the opposite. This can be where someone feels agitated and pacing and irritated by everything. Weight gain is common, and there is a menopausal process of usual weight gain between two and eight kilos.

And of course poor sleep, which is part of this depressive syndrome. And then when the hot flushes occur, then the whole sleep story gets much worse. Memory and concentration changes are very, very significant. And this can cause many women to come in to my clinic and say, 'I think I'm dementing because I was okay a couple of weeks ago, and all of a sudden I just can't remember mobile phone numbers. I can't remember where I parked my car. I walk around in a bit of a daze when I go to do things that normally would be really easy.' And anxiety and, in fact, full-on panic attacks are very common in the perimenopausal depressive syndrome. This is what the Meno-D looks like, and I'd be very happy for people to download this from our website and to utilise it, or to get it from the article that I showed you a screenshot of.

So, again, there are many, many treatments for the hormone and other treatment strategies for depression associated with menopause. This is a paper which we recently published to review the hormonal treatments and what is safe. But we need to step back a little bit to think about what do we think are the mechanisms that are behind this type of depression? And I mentioned the neurosteroids, the gonadal hormone neurosteroids that modulate serotonin, but we also need to understand that oestrogen levels that fluctuate during the menopause seem to be the biggest destabilising effects on mood, and that the fluctuations then create fluctuations in serotonergic neurotransmitter systems.

As well as that of course, serotonin is not the only neurotransmitter pathway. We've been very interested in the major neuropeptide pathways that also affect mood in menopause. There are many other mechanisms for menopausal depression, including the DHEAS, and the changes in the GABA neurotransmitter system signalling. GABA in particular, we know, is particularly involved with anxiety symptoms. So here is an explanation for what might be happening in terms of panic disorder and anxiety. The endogenous opioid dysfunction may also be involved in the pathophysiology of major depression, and perhaps the change in neuronal opioid activity could actually explain a lot of the associated depression.

Excuse me. So coming back to it, there are two groups of menopause-related depression. There's the exacerbation in women with a history of mood disorders, and there's the new presentation, first time ever for women with no previous history, who can present with a bang, sudden and severe men menopausal depression. Now the difficulty is we don't have any hormone lab investigations that will tell us what is going on. So many times I see in my clinic women who come along and they say, 'Well, my doctor did hormonal studies, and they said it's all normal.' Well, yes, that's what you would expect. The problem is that the menopausal depression that we're talking about in either group is related to brain oestradiol fluctuations, which we can't pick up in our routine peripheral blood tests of hypothalamic pituitary gonadal axis functioning. We can get a clue later on about when, actually, the menopausal process is done, by the FSH levels, but we can't really get an idea in the perimenopause about what is going on in the brain. That makes it difficult, because which way do we then go?

And many times people say, 'Oh, I've got lots of oestrogen. I've got a high level of oestrogen, and so my doctor doesn't want me to go on any particular hormone strategies.' So here's our crossroads. And we know that there's a high incidence of depression in middle-aged women, which is multifactorial. This is often the time when women are struggling with a relationship that might be a tad stale, with struggles of being quite a senior in the workplace, the struggles of perhaps having adolescent children, the struggles of having to look after elderly and frail parents and others. So there's lots going on, and it becomes, one of the things that might be the last straw is the hormonal fluctuations. And then it becomes the question of what do we do? Do we go with antidepressants or do we go with menopausal hormone therapy? You might end up with both.

I personally think that, if you can, it's easier start with the hormone therapies because they are somewhat easier to titrate, somewhat easier to change or cease. Antidepressants, particularly SSRIs and even more difficult SNRIs are really associated with significant withdrawal syndromes, as well as other side effects. And so the consequences of trying to titrate dose, or even to cease those medications, can be really difficult. Sleep regulation is absolutely critical, because at the beginning of the perimenopausal process there is sleep difficulties, and that continues and can get worse as the other symptoms come on. And of course it's important that we note that many women have tried, and are taking, natural medications, over-the-counter therapies, hormonal preparations in other forms, and it's important to sort of really take a good history and a story of what that's about, so that you understand what's in the cream that she's taking or using, what's in those herbal preparations. Our duty is to understand what's in there, and to see if there's any particular interactions with other medications and so on. Psychotherapy is always a good idea, because it allows the woman to discuss a number of issues that may in fact be quite a significant problem for her.

So our research is to continue to raise the awareness about menopausal depression. Now you note that I'm calling it 'menopausal depression' because it begins in the perimenopause but continues on. And it can be a 10-year process before anyone really understands what's happened for this particular woman. So that's why it's important to recognise this condition as early as possible. We are trying to develop biomarkers for this type of depression. We're also working with safe, shorter-term hormone treatments and with different antidepressants that actually allow an on/off usage rather than having withdrawals from the current SSRI/SNRI group. As Rod has also alluded to, physical health is absolutely crucial to overview and make sure that it's tackled early. We don't want to increase weight gain by using medications that might cause that. Wine consumption really escalated during Covid lockdowns, and we have a number of women who unfortunately now have an addiction problem. And the lack of exercise also. And it's our job to work with natural medications and understand what the interactions are.

So there are many new ways that we are working with, but this is a big problem. And I urge all of us to continue to keep going in thinking about the neurobiology that happens at various times of a woman's life, and in particular to combine that with psychological and social innovations moving forward. Thank you.

I'd now like to raise this issue with you, which is a real-life case study, but the name has been changed. Anne is a 49-year-old intensive care unit nurse. She really had no previous health issues and over two weeks she suddenly presented with panic attacks for the first time ever. Really scary. It happened at work during a handover, and she had actually worked in the same ICU for 10 years at a very senior level, and was a very respected intensive care unit nurse, unit manager. She also described increasing brain fog. She'd been feeling overwhelmed, unable to perform critical tasks in her job, and she also had several panic attacks per week, with a full hyperventilation, jelly legs, a sense that she was going to fall down, and a range of other physiological symptoms of panic. Also at this time she described a rapid onset of sadness, tears, and rage. She had gained five kilos, although she had not changed her food intake, and she had not changed her regular exercise routine. She did not have any particular new issues in her work or in her home. After six weeks of this, Anne saw her GP and said she felt 'not right'. She then burst into tears in her GP surgery and said, 'I just can't live like this.'

So what happened? Well, lifestyle approaches were suggested by her doctor. She was encouraged to take up yoga. She had two weeks' time off work. She was encouraged to eat more healthy food and to walk more. She had been walking about 20 minutes every day and she was asked to encourage that. Three months later, she then appeared feeling worse, in terms of fluctuating sadness, increased rage, on-and-off confusion, she was in bed a lot, arguments with her husband had increased. She'd been very angry and continuing to be angry, out of character, with her 14- and 11-year-old sons, and she'd stopped socialising with her friends and with her family. Her general practitioner prescribed fluoxetine 20 milligrams per day, and then increased that to 40 milligrams per day a week later. Unfortunately, her rage increased. This resulted in a major argument with her ICU consultant, and she stormed out of the ward, leaving her shift.

This is very out of character for this very experienced nurse unit manager. Unfortunately, the hospital then started disciplinary processes, saying that she was unfit to work. She was then referred to a psychiatrist who started a mood stabiliser, lithium carbonate, and had made a diagnosis of bipolar disorder. The psychiatrist's diagnosis of bipolar disorder was because of the rage and the somewhat intermittent agitation that Anne had described. She had a poor response to the fluoxetine 40 milligrams and a poor response to lithium carbonate. Her rage continued. She continued to have all the other symptoms that I've described.

Olanzapine, starting at 5 milligrams, then increasing to 10, and then finally increasing to 20 milligrams per day, was added. Olanzapine, as you know, is a anti-psychotic of a second-generation nature, which has weight gain as one of its major side effects. Poor Anne increased her weight by 20 kilos over five weeks, and was also ruled as to be unfit for work by her hospital and by the nurse's Board. The diagnosis of bipolar disorder was really crucial in the decision by both the hospital and the nurse's Board to suggest that she was unfit to continue as a nurse. Now, this is the first time that Anne had ever had a mental health problem and it came on top of a stable life and a long-term, very satisfying and rewarding career. Her spouse, her husband, who saw the same GP, said in a session with his GP, said, 'We can't go on like this as a family.' So here we are, critical time. We now need to consider what to do in this particular situation. So would you like me to continue to discuss what I did?

**Dr Tessa King:** Definitely.

**Prof Jayashri Kulkarni:** Okay. So I unfortunately, as a psychiatrist with an interest in women's mental health, and particularly an interest in menopause from my research work, but more prominently from my clinical work, I'm often seeing women at this critical stage. Not at the early first lot, and perhaps not even at the second lot when the psychiatrist is involved. So you can see that there's layer upon layer upon layer of issues here, and now it's going to be the job of winding back some of the issues that have taken place. So some of the things that we did for this particular patient was to revisit the diagnosis of bipolar disorder. And I really urge everybody out there to be very, very careful with a diagnosis of bipolar disorder. There is a variant of it called bipolar disorder type 2, and unfortunately it is applied for women all too frequently who are experiencing fluctuations in their mental health due to hormonal fluctuations of the menopause and the perimenopause. So let's be really careful.

A full-on bipolar disorder should have absolutely well observed and well-documented and well consolidated by corroborative story, manic behaviour which includes racing thoughts includes actions of an impulsive nature, poor judgment, hyper spending that doesn't make sense for the person's budget and particular lifestyle. And it really is rare that it would start at the age in the late forties. This is a condition that you would see in somebody in her twenties or even in her thirties, but rarely would it appear for the first time in somebody at this age group. Bipolar type 2, again, you look for the hypomanic symptoms, may not be as prominent as the manic symptoms, but they're there if you look. And they need to be sustained. So Anne, our patient, doesn't meet the criteria really for either bipolar 1, definitely not, and not for bipolar type 2.

So we revisited the diagnosis and then started peeling back those treatments that one would normally offer for a full bipolar disorder condition, which is that we started by instituting menopausal hormone therapy. And what I did for Anne was I actually started with transdermal oestradiol. I used 50 micrograms. And I also added in 100 milligrams of oral prometrium every day. I used these two in a regular format because what I'm trying to do is restabilise the hormonal fluctuations in the brain. Therefore my use of oestradiol transdermal, because it does cross the blood-brain barrier. This is pure oestradiol. Similarly, prometrium has an important effect on the GABA and glutamate system so that it actually does provide some anti-anxiety treatment.

Prometrium was my choice because it is a more natural progestin, and it doesn't have the depression that some of the other progestins are associated with. After Anne was stabilised, and she had no particular physical health contraindications to using MHT, after she was stabilised on MHT, we embarked on a course of down-titrating the olanzapine to get rid of that.

Then we down-titrated and ceased the lithium carbonate. And I also down-titrated the fluoxetine. Kept her on a very low dose in the end. And after about eight months, she was a very happy and well contained, in terms of mental health symptoms, very responsive to MHT, and she continued on a very low dose, that is 5 milligrams of fluoxetine, and my next step will be to see if we can get rid of that, but that is the hardest one to actually decrease, is the last step of a withdrawal from an SSRI. We also instituted psychotherapy for her, and we also instituted marital therapy because there were some big issues that had occurred between her husband and herself. And also we helped her regain her registration as a nurse. And although she did not want to go back to intensive care unit, she is working as a nurse in another area. And she feels very content.

So this is a story that has a happy ending, as we say, that the couple and the family sort of 'strode off into the sunset'. But of course many stories do not. And I think it's really important that we understand that women can have depression related to the menopause directly related to gonadal hormone fluctuations in the brain. And we mustn't over-diagnose bipolar disorder in this group. And we must be careful with our psychiatric medications because they are potent drugs with potent side effects in many directions, and that includes social impacts of an adverse nature, like losing registration as a nurse. So I might just finish up there.

**Dr Tessa King:** Yep, thank you so much, Jayashri, and thank you Rod for your talks. Very informative. I think that case study just really highlights how we as GPs are in a unique position when a woman presents for the first time in perimenopause, with perhaps symptoms of hot flushes and night sweats, along with clear mood or cognitive changes. We're in a unique place to start MHT, or the contraceptive pill if they're under 50 and it's safe, and see how their mood responds, and also their vasomotor symptoms respond, if this is a safe option to use hormonal therapy. So that we don't end up with a cascade of diagnoses and psychiatric prescribing.

So in terms of prescribing MHT as a GP, I just thought I'd run through a kind of brief overview of what I would tend to do. So it's really hard to remember all the different MHT products. So a good place to start, if you're using a contraceptive pill, is Zoely, generally. It has the lowest mood side effect profile. And for MHT, I would generally recommend a transdermal oestrogen. Both Rod and Jayashri have highlighted the stability of levels that this provides, and also it's much safer from a VTE perspective than oral oestrogen.

So generally start with a low to medium dose, either a 25 or a 50 microgram oestradiol patch, or one to two pumps of oestradiol gel daily, depending on the woman's preference. And Jayashri mentioned prometrium or micronised progesterone, providing some positive effects on GABA receptors. It's also the safest progesterone to use from a breast cancer perspective. We would use one tablet daily for a woman who's postmenopausal, so who ceased bleeding. For women still having periods, even if they're regular, the recommendation is two tablets on the same 12 days per month. And then sometimes oral progesterone can worsen mood symptoms, so you could consider a Mirena or other progesterone alternatives, but often it can be difficult to find the right progesterone if a woman is sensitive to progesterone from a mood perspective. If MHT isn't safe, or not the most appropriate option, you could consider, in a woman with vasomotor plus mood symptoms, escitalopram, citalopram, or fluoxetine. But just remember there are only about 35 to 60% effective for the treatment of vasomotor symptoms, and they are difficult to go on and come off.

In terms of key messages for tonight, the things that I hope people take away is that cognitive and mood changes are common symptoms of perimenopause and menopause. And just like vasomotor symptoms, they can be directly caused by the hormonal fluctuations during this time. And it's important to specifically ask women about mood and cognitive changes during perimenopause and menopause because they won't always volunteer this information. And just like vasomotor symptoms, mood changes can respond positively to MHT.

Rod asked me to just go through his, unless you want to go through them, Rod? I'm not sure he's there yet. Anyway, I'll go through Rod's. So all women should receive an individual assessment prior to treatment, and make sure, as I went through at the start of this talk, it's important to correctly diagnose the stage of the menopause transition. In a perimenopausal or recently postmenopausal woman with menopausal symptoms including vasomotor symptoms and mood changes, MHT should be considered as first-line therapy after appropriate evaluation of mental health. And when the only symptoms are mood disorders, MHT may also be appropriate. Progesterone-containing IUDs may induce mood disorders in a small number of women and is more likely if the woman's had premenstrual symptoms PMDD or postnatal depression in the past. Pharmacological intervention should be part of an overall plan to maximise the health of a woman in midlife and beyond. And I'll let you go through your key messages.

**Prof Jayashri Kulkarni:** So my key messages, and isn't it interesting, we're all three of us on the same page, is oestrogen, progesterone, testosterone, and their pituitary and hypothalamus related hormones are very potent steroids, and they do have an impact on mental health. And sometimes people forget that, and they sort of work in silos that these hormones are just below the waist. They're not. It's for all brain activity as well. Mental health changes of the perimenopause can occur from the mid-forties onwards, well before the body symptoms of hot flushes and other symptoms. And women with previous premenstrual depression, perinatal depression, or psychosis are more likely to experience menopausal depression. Women with significant early life emotional, physical, sexual abuse, trauma of all types in early life, and subsequent significant life stresses are more likely to experience menopausal depression. And thank goodness for MHT, which can actually improve a lot of mood symptoms.

**Dr Tessa King:** So, we'll move on to questions. I'll start with the first question. Jayashri, if you are happy to answer this. What factors would sway you to use antidepressants versus MHT?

**Prof Jayashri Kulkarni:** So really I think the biggest thing is, as we've all talked about, that there are some women where MHT is contraindicated. So that's a group that we would stay away from, you know, breast cancer themselves or a recent DVT or pulmonary embolus or some other type of clotting problem. That's a real no-no. Very big family story of breast cancer is also very problematic. But let's put those things aside, and we are looking at the symptoms that the woman is presenting with. My preference would be to go with MHT first if I can, but I might combine antidepressants and MHT. If she already is on an antidepressant, then I'm not going to make things worse by trying to get her off an SSRI, because then I'll have, the poor woman will be in withdrawal symptoms as well, and that's not good. So then in that case, I'd probably just add in the MHT. So I'm very favourable towards MHT as a first line, if we can, in this age group, as long as there's no physical contraindications.

**Dr Tessa King:** And Rod, regarding your case study, we had a question from one of the audience members. How long would you treat with oestrogen and testosterone, and what will happen to the symptoms when the treatment ceases?

**Prof Rodney Baber:** It's a good question. So oestrogen and testosterone or oestrogen and progesterone, or are we talking about libido?

**Dr Tessa King:** Yeah, I guess, by the end I think she was on all three. So oestradiol, progesterone, and testosterone.

**Prof Rodney Baber:** Okay. Well, I think first of all, the simple answer is you should review the need for those treatments on an annual basis, once you've established the patient on an appropriate treatment. And then you, as said, if she still has persistent vasomotor symptoms, then she needs to continue with her oestrogen. And if she tries coming off her testosterone therapy and finds that her problem reoccurs, then you would need to restart her therapy. But it's very important to review it on an annual basis.

**Dr Tessa King:** Yep. Thanks Rod. And Jayashri, I had a question from an audience member who has a patient who's 50 years old, perimenopausal, with low mood, agitation, who came to the audience member wanting to take prometrium alone for her mood symptoms. She has no vasomotor symptoms at this stage. I couldn't find any research or evidence for this, and I've recommended oestradiol, but I'd like to know your thoughts.

**Prof Jayashri Kulkarni:** Sure. So here's the problem with the lack of the clinical trials. What I want to do is a big head-to-head comparison of combined MHT versus an SSRI. But we haven't got there yet. But in this particular case, I think there's some evidence from the animal work that really does show that oestradiol in the brain is very neuroprotective. It has many, many different effects, and I won't bore everyone to tears with all the circuitry work and all the other different receptors that oestradiol has a positive impact on. So for someone who's got those kinds of symptoms, I think the combination would be better. I'd want to know why the patient was a bit worried about oestradiol, because I think there's still a lot of mythology about, 'Ooh, I can't have oestrogen because it'll cause this, this, and this,' from the Women's Health Initiative study back in 2000. So we need to be understanding of what that issue is about. I think the combination, as long as there's no particular physical issues for this patient, would be a better combo.

**Dr Tessa King:** Yep. Thanks Jayashri. Rod, a question for you. In someone who has a history of migraine with aura and hasn't been able to use the contraceptive pill, can you use MHT?

**Prof Rodney Baber:** You certainly can. There's very clear evidence to show that you can use hormones, postmenopausal hormones, for somebody who, correctly, should not use the oral contraceptive for her migraines. The best choice is a transdermal oestradiol preparation, because that will give you more stable hormone levels, and the fluctuations are one of the things that can cause the migraines. And of course use micronised progesterone as well, continuously if possible.

**Prof Jayashri Kulkarni:** How many times have we all had clients and patients who, one of the symptoms is that their migraines are right out of control, which is so awful for functioning, and it comes back into control once the hormones are readjusted.

**Dr Tessa King:** Yes. On that point—

**Prof Rodney Baber:** Interestingly enough, sorry. Interestingly enough, sometimes, almost counterintuitively, you actually need to use slightly higher levels of oestrogen to achieve that effect.

**Dr Tessa King:** Yeah. Thanks Rod. You mentioned, in terms of continuous progesterone, so daily progesterone or, say, prometrium if you're using that, I'm just wondering, normally the guidelines say in someone who is amenorrhoeic for 12 months, you can use daily progesterone. And for someone who's having irregular periods, you use cyclical progesterone. In someone where you want to maintain a stability for migraine perspective or from a mood perspective, in a woman who's having irregular cycles, could you use daily prometrium?

**Prof Rodney Baber:** You could, but you're likely to get more breakthrough bleeding. So I would definitely try her on the continuous oestrogen and sequential progesterone. And remembering you need to use double the dose, 200 milligrams for 14 days. But if that really fails, then you could perhaps look at using progesterone daily, but you're likely to get, or more likely to get unplanned and unexpected bleeding.

**Dr Tessa King:** Yeah. Jayashri, just a recent paper that's come out in relation to MHT and worsening mood symptoms. Do you have any thoughts on this paper at all?

**Prof Jayashri Kulkarni:** Yes, I do. Look, unfortunately what happens is there are association papers, which researchers who use an epidemiological kind of stand will go back and look at data in a public sort of register. So this is a classic paper that comes from the Denmark, the Danish registers. And Denmark is great because they do put everybody in various registers for various things. But the difficulty with that paper is it goes back to data from the late 1980s into even forward up into the 2000s, but things changed a lot. And so the difficulties are, and they talked about depression, but they didn't actually define what was depression. They didn't also define, when they talked about antidepressants, they didn't say what was involved. And there were comments in the paper about old style antidepressants and so on.

So here is the problem. I actually think that there's been so much trouble with association studies that they're really not helpful for the practicing clinician. What we need, I come back to it, what we need is good, big clinical studies that do head-to-head real-world data. And that's tough to do, as a researcher trying to do this, it's tough. But that way you can actually look at what's going on for individual patients. Because even in the menopause depression, we definitely have two groups. First time ever, versus someone who's got a lot of depression but it's come unstuck. So there's two differences already. So what happens when you give MHT to one group and the other? And so that's an example that would be washed out in an association study. So I don't wish to be particularly negative about colleagues in research, but I'm not a fan of the association epidemiological studies of that nature in mental health. Mental health is too vague and woolly, and association studies have their own problems. And so you put that together with wooliness, and then you get very, very difficult to make any sense out of it. And it scares people, too. So we mustn't put too much weight on association studies. There you go. I'm being very controversial.

**Dr Tessa King:** We're just running out of time, so I just thought I'd check. Rod, did you have anything you wanted to add at all tonight?

**Prof Rodney Baber:** I don't think so. I think you've probably covered it all very nicely. Thank you.

**Dr Tessa King:** And Jayashri, anything you wanted to add before we wrap up?

**Prof Jayashri Kulkarni:** No, thanks for the opportunity, and without us planning it, isn't it interesting, we've come from three different disciplines and come to the same conclusions and the same findings.

**Dr Tessa King:** Well, thank you so much both for talking tonight. We need to wrap up now, and if we have any unanswered questions, we'll aim to have them answered and pop them up with a recording in the coming weeks. Don't forget, if you need your CPD points or a certificate, just complete the evaluation and a link will pop up for you shortly. Thank you so much for attending tonight, and a huge thank you to both Rod and Jayashri for presenting tonight. We look forward to seeing you next time. Thank you.

**End of transcript**

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This podcast series has been made possible by the NSW Government's Menopause Awareness Campaign. For help talking about menopause, download the [Perimenopause and Menopause Symptom Checklist](https://www.jeanhailes.org.au/resources/perimenopause-and-menopause-symptom-checklist) and take it with you to your next medical appointment. For more information visit: <https://www.nsw.gov.au/women-nsw/toolkits-and-resources/perimenopause-and-menopause-toolkit>

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