Managing Menopausal Vasomotor Symptoms

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"The principal endocrine change of the menopause is loss of estrogen."

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Hello, my name is Rod Baber, and I'd like to talk to you today about the menopause and specifically about managing menopausal vasomotor symptoms.

We'll cover a bit on endocrinology of the menopause. We'll talk about symptoms associated with the menopause, a differential diagnosis of hot flushes, so-called vasomotor symptoms, the indications for the use of hormone therapy and contraindications to the use of menopausal hormone therapy. And then lastly, when to use non-hormonal treatments, which hormonal treatments work and don't work, and a little bit on new treatments for vasomotor symptoms. So let's start with the endocrinology of the menopause.

The menopause happens because the ovaries expend their supply of oocytes, eggs. It's the permanent cessation of ovarian follicular activity. So the principal endocrine change of the menopause is loss of estrogen. Women's estrogen levels go from a mean value of about 320 picomoles per mil during reproductive life to less than 100. Progesterone stops, of course, because ovulation stops. But the ovary after the menopause still produces some testosterone.

We now know that in the infundibular nucleus of the hypothalamus, there are a collection of neurons called KNDy neurons, not spelled the way you might think, but spelled K-N-D-y. These neurons secrete three neuropeptides, neurokinin B, kispeptin and dynorphin. The kispeptin is what triggers the release of GnRH and the release of pulsatile GnRH in turn leads to the release of pulsatile LH and FSH and a surge of LH, which triggers ovulation. That triggering of ovulation releases an oocyte, but it also releases estrogen into the circulation. And that serum estrogen feeds back to the KNDy neuron in the hypothalamus to control regulation of hormone output.

It also regulates the activity of other neurons in the KNDy neuron. It's actually supplying negative feedback. So when the menopause occurs and estrogen stops being produced by the ovaries, the KNDy neurons in the brain get bigger and they produce more kispeptin and they produce more of another peptide called neurokinin B. The neurokinin B in turn sends signals to the thermoregulatory center, which is in the preoptic area of the hypothalamus and that causes disruption of temperature control.

So compared to reproductive life, in post-reproductive life, this excess secretion of neurokinin B causes a narrowing of the thermoregulatory neutral zone and therefore the onset of thermoregulatory changes, which try to correct the problem and they do that by trying to get rid of heat, by sweating and by having hot flushes.

So the trigger for the hot flush is, first of all, the loss of estrogen from the ovary, which makes the KNDy neuron in the hypothalamus bigger, which produces more neurokinin B and we'll get on to how important that is a little bit later in this talk.

The loss of estrogen at the time of the menopause does other things other than cause flushes and sweats and mood changes and muscle and joint aches and pains. It can also lead to more rapid loss of bone and therefore an increased risk of osteoporosis and fracture in postmenopausal women and we also know that the loss of estrogen after the menopause increases every woman's risk of cardiovascular disease. Their risk never really catches up to men. But the rate of cardiovascular disease certainly increases after the menopause.

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Overall, the signs and symptoms of the menopause begin somewhat before the final menstrual period, perhaps as much as 10 years before. Once menstrual cycles become irregular, women will then develop intermittent vasomotor symptoms, hot flushes and night sweats, sleep disorders, which may be primary or secondary to the flushes, mood changes, depression, anxiety and often what they call brain fog, which is just a bit of difficulty sorting their thoughts out. It is not a sign of dementia in almost all cases.

It is caused by fluctuating hormone levels and the symptoms that arise from that. And as I mentioned before, muscle and joint aches and pains, arthralgias, if you like, are also very common. Also in this period of time, which is called the perimenopause, menstrual disorders occur.

Forty percent of presentations to gynaecologists occur for women between the ages of 40 and 50 and it's because of problems with dysfunctional uterine bleeding. Following the menopause, there are other symptoms which begin to present themselves.

One is urogenital atrophy or genitourinary syndrome of the menopause. This is caused by the loss of estrogen, which in turn leads to a change in the vaginal flora. So the normal lactobacilli, which dominate the vaginal flora in premenopausal years, disappear and are replaced by gut flora, which increase the risk of infection and, of course, of vaginal discharge.

The loss of estrogen also leads to reduced lubrication in the vagina and reduced elasticity of vaginal tissues. And all of those things also then contribute to pain with sex. And lastly, as time goes on and as women age and they will now spend at least a third of their lives after their final menstrual period, we know that there's an increased risk of osteoporosis and cardiovascular disease.

Don't forget there are other causes of hot flushes. Of course, if somebody is 50 or 51, hasn't had a period for a year and has hot flushes, then they're almost certainly due to the menopause. But physiological causes include hot drinks, emotional distress and anaphylaxis.

Drugs can cause flushing. I suppose the commonest one would be alcohol. But a number of different drugs can also do that including bromocriptine, levodopa and amyl nitrate and there are some diseases which will cause flushing as well. Probably the best known would be carcinoid syndrome or neuroendocrine tumours, systemic mastocytosis, leukemia and lymphoma. A pheochromocytoma will cause flushes, as will thyroid or renal cancer, diencephalic seizures and postural orthostatic tachycardia syndrome. So just have these in the back of your mind when you see somebody who's flushing, if you have any suspicion that it's not menopause. Menopausal vasomotor symptoms are, as I said before, heat dissipation mechanisms triggered when the core body temperature rises above the thermoneutral range. They are a sudden, intense sensation of heat in the upper body, usually in the face, the neck and the chest. Typically, they last between one and five minutes. But for some women, they can last much longer.

We regard them as moderate to severe if they occur more than seven times a day, let alone at night. They can be accompanied by sweating, by chills, by anxiety and by heart palpitations. In Western countries such as Australia, between 60 and 80 percent of women will experience some of these vasomotor symptoms, either during the perimenopause or after their final menstrual period.

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The U.S. Federal Drug Administration has defined these vasomotor symptoms as mild, moderate and severe. Mild symptoms are sensations of heat without any sweating. Moderate symptoms are sensations of heat with sweating, but not sufficient to interrupt daily activities and severe vasomotor symptoms are sensations of heat with sweating, which cause cessation of daily activities or interrupt sleep. These hot flushes are the most common menopausal complaint. About one in four women experience severe vasomotor symptoms, which do interfere with their ability to function.

We are not overprescribing hormones to treat the menopause. About one in four Australian women have severe hot flushes and one in five Australian women either use or have in the past used menopausal hormone therapy. One in seven use complementary therapies, which make no difference and many women, I'm afraid to say, use or are offered nothing.

Vasomotor symptoms are also important because they have links to other aspects of general health. They can affect cardiovascular disease risk. They can affect bone loss and they can affect epigenetic aging. They have an impact on sleep, on mood disturbances, on cognitive function, and obviously, because of all of the above, on interpersonal relationships. And they also have an economic burden.

They have a significant effect on work productivity, and it's estimated that Australian women leave the workforce quite prematurely because of these menopausal symptoms and because their problems are not being addressed or recognized in the workplace.

The most effective treatment for vasomotor symptoms is menopausal hormone therapy.
Compared to placebo, there is about an 87% reduction in the frequency and severity of vasomotor symptoms amongst women using menopausal hormone therapy. But the placebo response is usually of the order of 30%. And so a lot of alternative therapies show a short-term benefit similar to that seen with placebo.

But that benefit will wear off over the course of approximately 12 months. So the most effective treatment is the replacement of the missing hormone estrogen with or without progestogens, depending on whether or not the woman still has an intact uterus.

Why would you use menopausal hormone therapy? Well, the principal indication is alleviation of troublesome vasomotor symptoms. But as I've said before, we know it also reduces the risk of osteoporosis and related fracture. And it can reduce the risk of osteoporotic fracture to about the same magnitude as we see with bisphosphonates and rank-ligand inhibitors. In other words, other anti-resorptive agents.

Menopausal hormone therapy, particularly estrogen hormone therapy, may reduce the risk of cardiovascular disease, particularly when it's initiated within 10 years of the final menstrual period. The data we have on estrogen plus progesterone therapy is not as convincing, possibly because most of it was accumulated when synthetic rather than natural progestogen was used. For women who have symptoms of vulvovaginal atrophy or GSM, and that's about 50% of postmenopausal women and 70% of women who reach the age of 70, topical estrogen therapy is usually effective in alleviating those symptoms.

And for women who are taking oral systemic low-dose hormone therapy, it may still be necessary to use topical

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estrogens to achieve relief of these vaginal symptoms. But remember, we must always accompany advice on hormone therapy with appropriate lifestyle advice. By which I mean regular exercise, healthy diet, healthy weight, avoid smoking, minimize drug use and alcohol use, and try and identify triggers which might make your symptoms worse.

Menopausal hormone therapy is not appropriate for every woman, and I will talk to you later in this podcast about other options. Complementary therapies are, on the whole, no better than placebo.

Of course, there are some contraindications to hormone therapy. They include undiagnosed PV bleeding, any hormone-dependent cancer, active thromboembolic disease, active myocardial infarction, active severe liver disease, and porphyria cutanea tarda. Be cautious using hormone therapy in women who have a history of gallbladder disease, who are at increased risk of cardiovascular disease or breast cancer. And for those women, use a screening tool.

These are free. They're available online. They're incredibly easy to use, and it will be very beneficial to you and to your patient to do this and to let them understand which is safe for them and which is not.

Be careful with women who have migraine with aura. Menopausal hormone therapy is not contraindicated in this group, but normally we would recommend you use transdermal therapy. And we do not recommend that you initiate menopausal hormone therapy in women who are over the age of 65 and have never previously used hormones.

There are a few rules regarding the use of hormone therapy, which I won't go into in much detail, except to say that if a woman has had a hysterectomy, all that she needs is estrogen. If she still has an intact uterus, then unopposed estrogen will increase her risk of endometrial hyperplasia and cancer. So you must always use a progestogen to counteract the effect of estrogen on the endometrium.

The progestogen should be used in an appropriate dose for 10 to 14 days per month when therapy is sequential, and that will give a withdrawal bleed or period once a month, or continuously for women who are more than one year from their final menstrual period. They are therefore postmenopausal, and continuous estrogen and progestogen therapy affords them the benefit of not having to worry about any bleeding at all. For most women, oral therapy is okay, and it could be equally used as could transdermal therapy.

But for women who are at increased risk, for example, an increased risk of thromboembolic disease, an increased risk of cardiovascular disease, who are obese, who are diabetic, who suffer from migraines, then for those women or older women, it would be more appropriate to use transdermal estrogen with micronized progesterone. In other words, body-identical estrogen and progestogen transdermally. Let's move on now to women who can't use hormonal therapy.

When would you consider using non-hormonal treatments for menopausal symptoms? Well, certainly in anybody who had a hormone-dependent cancer. And the commonest group will be women who have had breast cancer. Women whose medical history suggests that perhaps they shouldn't use hormones, including

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those who previously had a thromboembolic event, who suffer from severe liver disease or acute severe cardiovascular disease.

Other considerations should be the older women. I've already mentioned you shouldn't initiate therapy for the first time with hormones over the age of 65. And in many cases, it would be advisable not to use hormone therapy in women who are at very high risk of breast cancer or very high risk of cardiovascular disease.

So there's quite a number of indications. But perhaps the largest group are women who prefer not to use hormones at all. At the turn of the century, there was a paper released from the United States called the Women's Health Initiative, which was scathing about the benefits and risks of menopausal hormone therapy.

Much of the data which was released at that time has since been reanalyzed and re-evaluated. And that view of the place of menopausal hormone therapy has changed completely; to the guidelines that I've just been talking to you about. But it has had a lasting impact on the psyche of many women and many women just do not want to take hormones, despite whatever we tell them, because of their fears.

So let's start with what doesn't work for vasomotor symptoms. It doesn't help if you stop having a curry. Spicy foods and hot drinks do not cause hot flushes. Yoga is a great thing for you to do. It's great for the mind. It's probably great for the body, but it doesn't do anything for hot flushes. Unfortunately, neither does acupuncture, neither does paced breathing, neither does vitamin E, and neither do herbal supplements in general. And the last thing that doesn't help again, unfortunately, is exercise. Exercise is great. Everyone should exercise regularly each week for their own peace of mind and for their cardiovascular health. But exercise doesn't improve hot flushes.

There are some remedies which do work, but none of them are as effective as medium doses of estrogen. In terms of efficacy, on the whole, they will reduce hot flushes and night sweats by about 60 percent compared to around 80 percent for menopausal hormone therapy. Of course, non-hormonal treatments have next to no effect on genitourinary symptoms, no effect on bone loss. But on the other hand, some of them will improve mood and sleep, and they're less likely to cause breast tenderness or vaginal bleeding.

Cognitive behavioral therapy has become really important in this area. CBT used to be something which you had to see the psychologist about, but these days there are a lot of online services available which patients and doctors can access readily and inexpensively.

Clinical trials of CBT have been shown to reduce the bother of vasomotor symptoms in healthy, symptomatic, postmenopausal women, in women who have suffered breast cancer and are postmenopausal, and in women who are having trouble with their work duties because of their menopausal symptoms. CBT has additional benefits in that it is often able to improve mood and to reduce anxiety. It can improve sleep and it will improve sexual function and the use of CBT for the treatment of menopausal symptoms is endorsed in national and international guidelines.

Interestingly, although acupuncture has no benefit in terms of relief of vasomotor symptoms compared to placebo, hypnosis does.

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There have been a number of substantial clinical trials conducted, mostly in the United States, which show that there is a reduction in the frequency of vasomotor symptoms by about 60% compared to control groups, and in physiologically measured vasomotor symptoms, a reduction again by about 60% compared to 10% for controls. So hypnosis or even self-hypnosis is another option which women can consider.

There are a number of pharmacological agents, several SSRIs, including citalopram, escitalopram and paroxetine. Only paroxetine is approved for this indication. The other medications are used off-label in low doses, usually of the order of 10 to 20 milligrams of citalopram or escitalopram and about 10 milligrams of paroxetine. Their effect on symptoms is a reduction in frequency of hot flushes of about 50 to 60%. Additional benefits are a decrease in anxiety, improvements in mood and improvements in sleep.

But side effects, adverse effects, include drowsiness, a dry mouth, and most importantly, and quite commonly, sexual dysfunction. And this is very important to remember because for many women, this is a time when sexual dysfunction becomes more common and they are wary about taking any medication which might further exacerbate that problem. Finally, on that topic, paroxetine is contraindicated in women who are currently using tamoxifen because it interferes with tamoxifen metabolism.

There are a couple of SNRIs which have been used and shown to be reasonably effective, slightly more effective than the SSRIs, and they are venlafaxine and desvenlafaxine.

A number of centrally acting agents have been shown to be quite effective. Again, a similar magnitude of benefit. They include gabapentin in doses of up to 900 milligrams a day and clonidine in doses of up to 0.2 milligrams per day. There is an improvement in quality of life and sleep, a reduction in flushes. But these medications are associated with dizziness, drowsiness and weight gain.

There's another anticholinergic agent which has been used recently and which is the subject of a renewed interest, and that is oxybutynin, which is a drug used to treat urinary urgency or overactive bladder. In a low dose of two and a half milligrams twice a day, it reduced hot flushes by about 70 percent and is also, of course, useful in reducing urinary urgency. Of course, it shouldn't be prescribed to women who have voiding difficulties and it must not be prescribed to women who have glaucoma. Side effects include dry mouth and blurred vision. So it's wise to induce a treatment in the evening with a low dose. And that brings me to the new agents, which are called neurokinin receptor antagonists.

And you'll remember I mentioned at the beginning of this talk how important it was for us to discover that neurokinin B, in excess, disrupted the thermoregulatory systems in the brain. So just to go over that again, the KNDy neuron in the hypothalamus releases kisspeptin, dynorphin and neurokinin B. Kisspeptin stimulates the release of GnRH and hence the release of LH and FSH, which causes ovulation. Kisspeptin release is regulated by negative feedback from estrogen and dynorphin and positive feedback from neurokinin B. When the estrogen loss occurs at the menopause, that results in hypertrophy of the KNDy neurons and increased production of kisspeptin and neurokinin B. The increase in kisspeptin increases GnRH, LH and FSH and the increase in neurokinin B acting on neurokinin 3 receptors in the thermoregulatory centre causes hot flushes and night sweats.

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There have been several clinical trials on different molecules trying to ascertain how effective they were. The first of these was called MLE4901. It had a short but spectacular life. It was better than estrogen at reducing hot flushes. But unfortunately, it also induced adverse changes in liver function. So before it really got out of phase one trials, it was done and dusted. But clever pharmaceutical chemists all around the world have been looking for variations of that molecule, which might still be effective at alleviating hot flushes and not have any effect on liver function. There are a couple of those in the pipeline.One is called elinzanetant. It's a neurokinin 1, neurokinin 3 receptor antagonist. And the other is called fezolinetant, which is a neurokinin 3 receptor antagonist.

Both of them, in randomized placebo-controlled trials, have shown a reduction in the frequency of menopausal vasomotor symptoms of about 60 percent and also a reduction in the severity of vasomotor symptoms of about 50 percent. This is particularly relevant in the fezolinetant trials because they were able to demonstrate that because of this significant reduction in the severity of symptoms, most women on the trial, even if they did not get rid of their hot flushes, reached a situation where they were able to function normally and sleep at night despite the presence of milder hot flushes, which still existed. These trials on both of these molecules also showed an improvement in sleep disturbance, possibly due to the reduction in flushes or possibly due to a direct effect on sleep mechanisms.

Side effects are not common. Gastrointestinal side effects were the most common. And the liver enzymes, which I mentioned to you before, were elevated in about 5 percent of women overall, compared to 2 to 3 percent of women on placebo.

Importantly, there were no cases of liver damage amongst women taking active medications in any of these trials. Liver enzymes changed. The women did not know that their liver enzymes had changed. Bilirubin levels did not go up and they did not have any symptoms suggestive of liver disease. Overall, in the trials, there were no changes in coagulation parameters, no changes in urine analysis, no changes in biochemistry, no changes in haematology. Importantly, Neurokinin 1 and 3 receptor antagonists do not affect the levels of estrogen progesterone in the circulation and therefore, their use in women who are suffering from hormone-dependent cancers would not be contraindicated.

It is contraindicated in some medications. These drugs are CYP1A2 substrates, and therefore they're contraindicated in uses of moderate to severe CYP1A2 inhibitors, which include ethanol, estradiol, ciprofloxacin and carbamazepine and a few antidepressants. They shouldn't be used in women with severe renal impairment, and they shouldn't be used in women, of course, with moderate to severe hepatic impairment.

So in summary, the most effective treatment for menopausal vasomotor symptoms is menopausal hormone therapy. Not all women can or even wish to take menopausal hormone therapy. And for those women, there are a range of treatment options which have been proven to be effective in clinical trials. The newest of these is the Neurokinin 3 receptor antagonist, fezolinetant.

When you're deciding on which hormonal or non-hormonal treatment to offer your patient for the alleviation of her menopausal symptoms, you need to take into account her medical history, her concurrent illnesses,

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her symptoms and of course, her own preferences and remember, your treatments may be multifactorial. It could be that you start with one treatment and switch to another. It could be that you combine more than one treatment and remember, too, your aim is to reduce the frequency and severity of menopausal vasomotor symptoms to permit normal daily activities.

That's it. Thanks for listening. I hope it was useful. Certainly gives you something to think about, doesn't it?