

## **Does Perimenopausal Progesterone Treatment of Hot Flushes/Night Sweats Cause Side Effects**

I've previously been discussing various aspects of this Peri-P trial with you and have provided you with its results (before they are published) so that you will have some benefit from your participation.

Last time we talked about night sweats and sleep improvements as being the most important and significant findings in this randomized controlled trial.

What if I told you that *helping sleep was progesterone's biggest side effect?*

How do we decide if a study medication causes side effects?

During a randomized controlled trial (RCT) it is customary to record side effects (that are officially termed "adverse effects" or "serious adverse effects"). Once something has been reported and recorded there are two further decisions that need to be made about the unwanted experience:

- 1) Is it related to the medicine being tested?
- 2) How serious a problem is it?

To determine if the side effect is related to the drug, before anyone knows who is taking the active medicine or placebo, researchers with expertise related to that drug grade that adverse effect as to whether it may be related to the medicine. This falls into categories of unlikely, possibly, very likely, or definitely related to the tested medicine.

To determine whether the side effect is a major medical problem or not we grade its severity as mild, moderate or serious. Moderate adverse effects might last a few days before getting better—like a bad flu. A serious adverse effect is one that causes hospitalization, long-term health problems or death.

We assessed adverse effects from what you told Andrea in response to her monthly email

Andrea asked how you were doing and if you were having any problem with the pills. We took your replies regarding adverse effects and assessed them for their relationship or not with progesterone based on previous controlled trials of progesterone and safety (1-5) studies.

What the Peri-P study found related to adverse effects of progesterone

Mysteriously more of you who were taking progesterone (22 of 93) than were taking placebo (8 of 96) replied that you had experienced something you thought might be a side effect. The only moderate adverse event was one woman who developed atrial fibrillation (a very irregular heart rate). That arrhythmia was considered unlikely related to progesterone (never been reported) but her family doctor told her to stop taking the study drug and withdraw participation. The variety of specific experiences was wide from heart burn to constipation and sprained ankles to headaches. None of these, except for one woman who had a dizzy spell was possibly related to progesterone.

Sleep improvement as progesterone's strongest "side effect"

Why on earth would I say that helping disturbed sleep is a side effect? It is the opposite of an adverse effect—it is a huge benefit. The reason is that you are taking progesterone to help hot flushes and night sweats. Its actions to improve sleep (as far as we know) act very differently and thus are not directly related to why you are using it. But the majority of women taking a morning dose of progesterone (even

as low a dose as 100 mg) would feel drowsy, dizzy, “drunk” or have distinct difficulties driving or operating dangerous machinery.

However, when taken at bedtime, 300 mg of progesterone shortens the time it takes to fall asleep, lengthens the time you stay in deep sleep, decreases sleep disturbance (for example if there is a noise, or change in temperature) and lengthens the total sleeping time. In short, it makes sleep more efficient. Multiple randomized controlled trials have shown that in both men (6) and women (7), after 3 weeks’ use has no negative effects on morning alertness, memory or other cognitive and performance tests. Interestingly, a nasal spray progesterone has also now been shown to improve sleep (although not as strongly as a full dose of the sleeping pill, zopiclone, and acting differently in the brain)(8).

#### Overview of progesterone and adverse effects

We have documented now that there were no serious adverse events in two studies of progesterone for hot flushes and night sweats, in a total of 322 women taking either progesterone or placebo for three months. We have also shown that progesterone doesn’t change weight, waist circumference, blood pressure, cholesterol or other lipids or fasting blood sugar (3). It also doesn’t increase or decrease inflammation (3). Importantly, progesterone is different than the pill form of estrogen and does not increase blood clots(9); it also doesn’t, as estrogen may, increase the risk for migraine headaches. After three months of taking progesterone, when women stopped it, their hot flushes did not get worse (1). In fact it took more than a month for hot flushes to increase to the level they were at during the baseline month. Also, evidence suggests that progesterone with estrogen in menopausal women’s hormone therapy prevents the increased risk of breast cancer that estrogen alone may cause (10;11).

Thus the study in which you participated showed that oral micronized progesterone caused no serious adverse effects and had the beneficial side effect of improving sleep.

**Note**—we are in the process of analyzing some of the other results of the Peri-P study related to quality of life, anxiety, depression and menstrual flow. It will take some months before we have new data to share with you.

In the meantime, have a lovely summer and keep your eyes peeled to see a news report that will tell you we have been successful in getting the results of this study published.

#### Reference List

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