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CARFAX

Addiction to Oestrogen and Progesterone

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Exogenous oestrogens, progesterone and progestogens are prescribed for a variety of conditions in spite of lack of proof of efficacy. Supraphysiological levels of oestrogen and progesterone have occurred in some individuals due to demands for increased doses. Brain function, amine metabolism and nutritional status can be altered by exposure to exogenous hormones. Direct and indirect mechanisms of psychoactivity may induce dependency. A doctor's severe 'menopausal type' withdrawal symptoms after exposure to oral conjugated oestrogens (Premarin 625 µg/day) are reported.

Keywords: addiction, exogenous steroid hormones, oral contraceptives, psychoactive, lack of efficacy, increasing doses, withdrawal symptoms, menopause, post-menopausal hormone replacement therapy.

INTRODUCTION

Over the last decade it has been suggested that several naturally occurring steroid hormones may be addictive when taken or applied exogenously. These include androgen anabolics in 1989 [1] and 1990 [2], oestrogens in 1994 [3, 4] and progesterone in 1996 [5]. Sex hormones are psychoactive. Oestrogen reduces the activity of monoamime oxidase (MAO) enzymes. Higher amine levels may induce feelings of well-being or even euphoria. Excessively high levels or over-response can result in feelings of irritability, anxiety or insomnia. Progesterone has the opposite effect. Increasing MAO activity and consequent lower amine levels can induce sedation or depression [6, 7].

OESTROGEN DEPENDENCY

Here is the personal experience of Dr Margaret White.

> I practised medicine for over 40 years and in the early days I believed all I was taught. About half way through my career I realised that my profession was by no means infallible. At one time Drinamyl was recommended as a first-line treatment for depression but "Purple hearts", the popular name for Drinamyl, soon became notorious as a common drug of addiction among the young. Such experiences were often repeated as I have seen many changes in prescribing fashions. When early oral contraceptive trials began to report sudden deaths in young women due to thrombosis and heart attacks I was interested, and rather surprised, to learn that these steroid hormones were immunosuppressive. More recently I discovered to my cost that in some cases they can be dependency-inducing.

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PSYCHOACTIVITY (well-being, euphoria)

A. DIRECT ACTION
By binding to the numerous oestrogen receptors in the brain.

B. INDIRECT ACTION
(1) By altering receptor sensitivity, e.g.
- affect of magnesium or essential fatty acid deficiencies on cell membranes;
- dopamine receptor density and limbic dopamine concentrations.

(2) Availability of tryptophan for serotonin synthesis affected by vitamin B_6 deficiency.
(3) Inactivation of serotonin and dopamine:
- monoamine oxidase (MAO) increase—zinc dependent;
- catechol-*o*-methyl transferase (COMT) increase or decrease—copper dependent

FIG. 1. Possible dependency mechanisms for oestrogen.

My personal story is interesting because I had a normal asymptomatic menopause when I was 50 with no hot flushes, giddy bouts or flooding. As a general practitioner, I was visited by a young, attractive, female drug company representative who eulogized on the wonderful effect oestrogen would have on me. It would do wonders for my skin, hair, sex life, etc. She persuaded me to take the smallest dose (Premarin 625 μg) just to see the improvements. Apart from making me so randy that I exhausted my husband, the only side-effect was weight gain. After about a year I was reminded of the dangers of taking hormones by an American specialist. He advised me to come off the drug very gradually. Within a short time I was suffering from every menopausal horror story including flushing, sweating, giddiness and severe depression. It was so ghastly that I went back on to Premarin. Soon I felt as well as I had been before I first took the hormones. Six months later and several pounds heavier I decided that I was not going to be a slave to any drug. Once more I had a miserable time which lasted for 9 months. I told colleagues who noticed my distress that the menopause that nature gave me was fine but the one that Premarin gave me was hell!

It may be said that I became addicted to Premarin because I have an addictive personality. I refute that. I started smoking at 21 in the post-mortem room and I smoked about 10 cigarettes a day for over 30 years. I finally realised that I must stop and did so much more easily and with far fewer withdrawal symptoms than when I stopped Premarin.

Usually, injections and implants which are rapidly absorbed are more likely to lead to dependency than tablets. Women who self-medicate are at greater risk and some apply skin patches at shorter intervals or use several at once. Oestrogen is prescribed either alone or in combination with progestogens for a variety of conditions including post-partum depression, pre-menstrual tension, anxiety states (a common complaint of smokers who are said to have addictive personalities), and menopausal depression. Oestrogen deficiency is not the underlying cause of any of these and depression is not a common feature of the menopause [8–10]. It has been found that from 3–15% of women having implants reach supraphysiological levels in their serum and symptoms return when these very high levels start to fall [11, 12]. The *Journal of Psychosomatic Research* reported in 1997 [13] that nearly half of 40 women seeking reimplantation met the criteria for being psychiatric cases. I certainly was. Interestingly enough, the only significant change over 2 months among the women given a placebo implant was an improvement in remembering, presumably due to an improvement in copper/zinc ratios.

Bewley and Bewley describe the trap that is laid for unwary women: "Powerful psychological maintenance factors also exist since hormone replacement is

PSYCHOACTIVITY (sedative, hypnotic)

(1) Progesterone is converted to ring A-reduced progestins. These are very potent bartiturate-like modulators of GABA receptors [20].
(2) Regulation of pro-opiomelanocortin neurons [21].
(3) Dopamine is involved in reinforcing and motivating behaviours [22]: levels regulated by MAO and COMT changes (zinc, copper) and vitamin B_6-dependent enzymes; receptor sensitivity affected by magnesium and essential fatty acid concentrations [23, 24].

FIG. 2. Possible dependency mechanisms for progesterone.

reported to prevent ageing". If Dr Faustus could not resist such a temptation, how can mere women? Whitehead and Stevenson wrote in a letter to the *Lancet* that women can be reassured that standard doses or oral or transdermal hormones are not addictive [14]. They are wrong. Compston believed that the only symptoms caused by the drug were those that had been there before and that "the normal ageing process should be treated and not tolerated" [15]. Neither comment was true in my case. Some doctors are like the early scientists who searched for the philosopher's stone which would turn everything to gold.
(See Fig. 1.)

PROGESTERONE and DEPENDENCY

Progesterone and progestogens are also given to menopausal women, either alone or added to oestrogens to prevent increases in oestrogen-induced endometrial cancers. Progesterone is prescribed for the pre-menstrual syndrome in spite of the evidence that progesterone levels are usually normal and that progesterone supplementation is ineffective [16–19].

Keefe and Sarrel described a 43-year-old woman with chronic anxiety [5]. After 3 years of implants, injections and suppositories, her serum progesterone level reached 400 μmol l^{-1}. She was admitted to hospital complaining of headaches, nausea and neuropathy in both legs, mild fever and slowing conduction on an EEG. When her levels were reduced to 250 μmol l^{-1}, these symptoms resolved but her anxiety symptoms returned with such severity that she demanded restitution of progesterone.

Progesterone is not indicated for women with a history of anxiety or drug dependency as they are at an increased risk of self-medication. The recent wild-fire spread of progesterone cream as a universal panacea and alternative to oestrogen hormone replacement therapy may be due to a steroid suppression of exogenous hormone-induced symptoms. After years of exposure to progestogen-dominant oral contraceptives, a poorly absorbed form, progesterone cream, is being substituted to the profit of some distributors [25].

As members of the medical profession, we believe that doctors too readily prescribe powerful drugs, such as hormones, to symptomless women. Even if they have symptoms, why give drugs with dangerous side-effects when essential nutrient supplementation and simple alterations to lifestyles are all that is usually required in our experience? (See Fig. 2.)

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