Drug dependence with oestrogen replacement therapy

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Dependence on some drugs can be hard to recognise. Hormone replacement therapy (HRT) has been widely prescribed only in the past two decades, and the indications for treatment and the risk/benefit ratio are still disputed. Oestrogens are psychoactive: they lift mood, can be given by injection, and their use has powerful psychological effects. Reports of women with supraphysiological oestradiol concentrations may represent tolerance and withdrawal. Dependence on substances occurring naturally in the body has been reported before. We propose that HRT dependence occurs.


Introduction

Hormone replacement therapy (HRT) with oestrogens (with or without added progestagen) is becoming widely used by menopausal and post-menopausal women. We suggest that HRT could be dependence-producing on the basis of the known actions of oestrogens and historical analogies.

Standard definitions of drug dependence have criteria in common with or without added progestagen use, tolerance, physical dependence, a physiological withdrawal state, and use to relieve withdrawal symptoms. Additional criteria include stereotypic patterns of use, impaired ability to control use, relapse after abstinence, recurrent drug cravings, and continued use despite evidence of harm. Dependence-producing drugs are psychoactive (producing pleasant or euphoriant effects). The likelihood and severity of dependence depend on dose and route of administration. Drugs that rapidly promote a feeling of wellbeing are more likely than other types of drug to induce dependence, and those taken by injection can produce dependence faster and more powerfully than substances taken orally. HRT can be given by injection (implant).

Psychoactivity and oestrogen

Postpartum depression, premenstrual syndrome, and depression at the menopause suggest that female hormones affect mood, although there is poor correlation between mental symptoms and circulating hormones. No convincing evidence has linked depression with the menopause per se. However, oestrogen treatment improves depression scores after surgical menopause and mood after the natural menopause, though there is a striking placebo response.

Oestrogen may act directly via brain binding sites or indirectly by altering dopamine receptor sensitivity or availability of tryptophan for serotonin synthesis. Oestradiol binds to numerous sites in the primate brain. There is substantial overlap with sites either modulated by other drugs of abuse or that mediate their effects. Many drugs modulate brain oestrogen receptors. Oestrogen affects antidepressant-induced down-regulation of 5-hydroxytryptamine-2 and imipramine binding. Chronic administration affects dopamine receptor density and limbic dopamine concentrations. A biphasic effect on dopamine receptors could indicate withdrawal. Oestrogen increases free tryptophan which is reduced in perimenopausal women. Whatever the mechanism is that lifts mood, it could provide the pharmacokinetic precondition for physical dependence. The complex mechanism of benzodiazepine action on the brain was elucidated only lately. Dependence is not only a matter of drug administration but also of drug/organism interaction. Perimenopausal women might be especially at risk of dependence if they show a changing sensitivity to oestrogen. Ageing affects cell nuclear oestrogen-receptor-binding capacity in rats. One study suggests that only perimenopausal women are predisposed to mood disturbance that responds to HRT. That a woman could become dependent on HRT seems improbable because oestrogen occurs naturally; however, people have become dependent on other naturally occurring substances. Endogenous opioids can produce dependence. Enkephalin, a brain opiate peptide, may have a role in the euphoria associated with so-called runners high. Anabolic steroids have also produced dependence.

Early signs of dependence

In some women receiving repeat oestradiol implants, intervals between administration become shorter. Others continue to have menopausal symptoms despite oestradiol concentrations many times higher than normal, which might indicate tolerance. Supraphysiological oestradiol concentrations have been found in 3-15% of women with implants. Symptoms ascribed to oestrogen deficiency recur with falling rather than low absolute values. Some workers have claimed that women with supraphysiological oestradiol concentrations belong to a special subgroup with conditions such as depression, premenstrual syndrome, or even "an addictive personality", such as the so-called heavy smoker. Such women, the argument goes, would need high oestradiol concentrations to allow them to overcome any dependence on psychoactive drugs. These findings can be interpreted with a dependence model. First, symptoms ascribed to oestrogen deficiency might be a withdrawal syndrome, and high oestradiol concentrations are then needed to overcome these symptoms. Second, HRT may be replacing or interacting with other

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dependence-producing drugs (such as benzodiazepines or nicotine), the perceived addictive quality being a property of HRT, rather than a personality trait. If some women have difficulty stopping HRT, this would suggest dependence. The return of symptoms might initially be thought of as being rebound.

Powerful psychological maintenance factors also exist, since HRT is reputed to halt ageing. On stopping HRT, recipients have to abandon hope of protection from ageing. Recurrent HRT cravings and relapse after discontinuation of treatment would suggest drug-reinforced behaviour.

Treatment practices
Is HRT used to treat abnormal conditions (eg, premature menopause or ophorectomy), is it a medication for symptomatic relief (eg, hot flushes), or is it prophylaxis for at-risk groups (eg, high risk of osteoporosis) or for all women? Indeed, some doctors advocate offering HRT to all women. The Medical Research Council general practice survey estimated that 9% of post-menopausal women in the UK take HRT. Even if only a small proportion were dependent, the numbers could be large. Dependence is not excluded even if most HRT users stop without difficulty, since most people taking dependence-producing drugs can do so—for instance patients prescribed morphine usually stop without difficulty, resulting in few therapeutic opiate addicts. Cautious prescribing of dependence-producing drugs for a specific reason over a limited time causes few difficulties. Prescribing on less clear-cut grounds over long periods, or indefinitely, is more likely to lead to dependence.

Recognising dependence can be difficult. One has to remember that heroin, cocaine, amphetamines, bromides, barbiturates, and other non-barbiturate sedatives, and agonist/antagonist opioids were all initially regarded as safe. Recognising dependence can be difficult. One has to remember that heroin, cocaine, amphetamines, bromides, barbiturates, and other non-barbiturate sedatives, and agonist/antagonist opioids were all initially regarded as safe.

Conclusion
Oestrogen is highly effective, but has risks and should have clear-cut indications before use. HRT can be injected (implanted) and promotes feelings of wellbeing, which raise concerns about its dependence potential. It is used to treat conditions that are part of the normal ageing process and it is promoted in the non-medical press and media as a drug that maintains youth. Those taking HRT might be investigated for DSM-III-R criteria of dependence. Clinicians should be aware of the possibility of dependence and the importance of reporting cases. If patients have difficulty stopping, withdrawal under medical supervision may be needed. Even after stopping HRT, prostogestagen might be needed since there can be oestrogenic stimulation of the endometrium for up to two years after the last implant. If HRT does cause dependence, this alone should not cause undue alarm and should not be a reason to withhold this treatment. Even powerful dependence-producing drugs are safe and valuable if prescribed in a careful and controlled way for clear-cut, specific reasons.

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REFERENCES

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Drunk in charge

The police mind is eminently ready and practical; but it is deficient in scientific caution. Because it has to deal with a great many drunken people, more or less insensible, it is apt to jump to the conclusion that insensibility signifies drunkenness and nothing else. Hence sometimes serious blunders arise, to which we have often drawn attention. Here is another. A brewer’s porter, after supping with his mates and turning down stairs, was found, at two o’clock one morning last week, sitting on a door-step; and, as he was insensible, he was taken by two constables to the police station and locked up in a cell. They did not notice that his head was bleeding. At six o’clock the man complained of being ill, and, as blood was drawn attention. Here is another. A brewer’s porter, after supping with his mates and tumbling down stairs, was found, at two o’clock on his head two inches and a half long, and with his mates and tumbling down stairs, was found, at two o’clock one morning last week, sitting on a door-step; and, as he was insensible, he was taken by two constables to the police station and locked up in a cell. They did not notice that his head was bleeding. At six o’clock the man complained of being ill, and, as blood was drawn attention.

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