

Reports on Individual Drugs

Hormone replacement therapy and breast cancer

It is now an accepted fact that women with a family history of breast cancer have a higher risk of developing this condition during their lifetime. With the increased use of hormone replacement therapy (HRT), it has become important to advise such patients of the risks involved in taking perimenopausal or postmenopausal hormone therapy.

Documented evidence is available that hormone replacement therapy relieves menopausal symptoms and its long-term use seems to prevent or delay osteoporosis. It may also protect against ischaemic heart disease and partially prevent or delay the onset of Alzheimer disease (1). General risks of HRT show that there is a slightly increased risk of deep vein thrombosis and/or pulmonary embolism (2, 3, 4). However, concerning the risk for breast cancer, there is a considerable body of literature which discusses the association, but supporting data are not consistent. Previously, two meta-analyses have found a positive association, two others found no association, and additional recent studies have failed to clarify the situation (5). The Iowa Women's Health Study, has now been published which extensively examines the risk of postmenopausal breast cancer, case fatality, and total mortality in women with and without a family history of breast cancer (5).

Participants in the study were selected from a random sample of women aged between 55 and 69 years in 1986. In this prospective cohort of 41 837 women, data were collected on HRT use as well as on family history of breast cancer in first-line relatives, which was reported as 12.2%. The study showed that among women with a family history of breast cancer, currently using HRT and who had done so for at least 5 years previously, breast cancer at an age-adjusted annual rate was 61 cases per 10 000 person-years (95% CI, 28 to 94 cases). Statistically, this rate was not higher than the rate of 46 cases per 10 000 person-years in women who had never used HRT.

Among women without a family history of breast cancer, the rate in those who are currently receiving HRT and had done so for at least 5 years was 41

cases per 10 000 person-years; a rate not significantly greater than the 36 per 10 000 person years seen in women without a history of breast cancer who had never received HRT.

Although the study was quite extensive in terms of patient data, it had some limitations. No validation was made of the history of breast cancer, and no data were provided on the particular HRT formulation which was being used in terms of hormone ingredient, or the reasons for taking HRT. It is also disputable whether a period of five years is long enough to demonstrate tendencies in the development of breast cancer. However, despite its limitations, the study has provided some interesting information on questions of benefit and safety.

The study suggests that, for most women, HRT is not associated with a statistically significant increased risk of breast cancer. A woman with a family history of breast cancer may constitute an exception, although the modest increased risk in this study was consistent with chance. The mortality rate in women with a history of breast cancer seemed to show a decreased risk, and evidence also suggested an inverse association with the rate of death from coronary heart disease, stroke and from cancers other than breast cancer. Further studies with similar objectives and conducted in a representative sample of HRT users and non-users will help to determine conclusions.

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Mefloquine effectiveness impaired by high withdrawal rates

Mefloquine for prophylaxis of malaria has now been prescribed to over 8 million travellers worldwide since its introduction onto the market in 1985, despite being relatively expensive (1). Tolerability of weekly mefloquine prophylaxis in travellers was originally based on two uncontrolled, observational studies (2, 3). However, this tolerability is now in doubt as more observational data become available showing an excess of neuropsychiatric or neuropsychological side-effects in travellers taking mefloquine compared with travellers taking other standard antimalarial prophylaxis (4–8). In fact, evidence is accumulating that mefloquine is more toxic than was previously thought, although as early as 1989 some drug regulatory authorities introduced restrictions on prophylactic use based on spontaneous reporting of adverse drug reactions (9–10). Drug regulators in other countries — Australia, Ireland, Malaysia, the Netherlands, and the United Kingdom — introduced similar restrictions between 1994 and 1997. This controversy has now prompted public debate in the United Kingdom, Canada and the Netherlands (12).

A systematic review has been conducted (12) to assess evidence from randomized controlled trials of the efficacy, tolerability and overall effectiveness of mefloquine prophylaxis in preventing malaria infection in non-immune adult travellers. Information has been obtained from clinical trial consulting registers, data bases, indexes, pharmaceutical industry sources and key scientists and has resulted in 37 trials being identified as eligible, with 10 meeting the inclusion criteria. These 10 trials provide information on a total of 2750 non-immune adults randomized to mefloquine or to a control group. One placebo-controlled trial examined malaria incidence directly and showed mefloquine to be highly effective as prophylaxis for malaria in a drug-resistant area. However, four placebo-controlled trials showed that mefloquine was not well tolerated, as demonstrated by withdrawal of the drug, which was consistently higher than with placebo. Five studies covered field trials comparing mefloquine with other chemoprophylaxis, and mefloquine was shown to be as well tolerated as other chemoprophylaxis, although there was a trend towards higher withdrawals in the mefloquine group.

This review generates clear uncertainty with regard to the tolerability and effectiveness of mefloquine in conventional malaria prophylaxis because of the

high withdrawal rates. Withdrawal from, and non-compliance with, malaria prophylaxis are hazardous because they leave travellers incompletely protected. Studies suggest that women more commonly report adverse effects from mefloquine (6, 8) and one study has shown that adult women experience twice the toxicity from mefloquine chemoprophylaxis as do adult men (11). Male soldiers are less likely than ordinary travellers to withdraw from mefloquine (12).

Thus, based on available evidence, the usefulness of mefloquine in prophylaxis may be limited to highly motivated occupational subgroups or individual travellers at high risk of infection in areas of chloroquine-resistant malaria. It may also be advisable to prescribe mefloquine for travellers only when the destination is one where reliable diagnostic and treatment facilities for malaria are not readily available. In such circumstances, the traveller should be informed of the potential neurological or neuropsychiatric adverse reactions. Because they are rare, observation by a co-traveller or someone close may be advisable to detect these symptoms at an early stage (12). Recommendations for travellers, including the advisability of initiating mefloquine prophylaxis 2–3 weeks before travel, are issued by WHO (13).

In light of this situation, it would seem preferable not to approve candidate drugs for routine unrestricted use until large randomized controlled clinical trials have documented the efficacy, safety and tolerability of a product in the anticipated target population.

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Zopiclone and zolpidem hypnotics and drug dependence

Benzodiazepines were first introduced as anxiolytics and hypnotics more than 30 years ago. It soon became evident, however, that they cause dependence and that discontinuation can lead to withdrawal symptoms which often mimic the very same illness for which the treatment was initiated. For these reasons, most benzodiazepines are scheduled under the international Convention on Psychotropic Substances, and some physicians are reluctant to prescribe them for insomnia or anxiety.

Given this situation, alternative treatment and new innovative drugs were sought and the hypnotics, zopiclone and zolpidem, were introduced ten years ago. Although they are unrelated chemically to benzodiazepines, they act via the benzodiazepine/gamma aminobutyric acid receptor complex. They have been marketed in many countries for the short-term treatment of insomnia and early clinical trials showed that zopiclone and zolpidem do not cause a rebound effect, dependence, or withdrawal phenomena and that they are a safe option for treating insomnia (1–3). Some drug regulatory agencies have received reports on neuropsychiatric reactions similar to those observed during benzodiazepine use, but symptoms rapidly disappeared on discontinuation of the drug (4).

In 1987, a study involving 10 normal healthy volunteers was carried out to test whether zopiclone was likely to produce rebound after short-term use (5). A comparison was made with placebo and a standard benzodiazepine hypnotic, temazepam. The study also tested whether tapering the dosage lessened any potential rebound symptoms. Zopiclone tended to be associated with some dysphoric effects such as feelings of being troubled, tense, antagonistic or bored whereas temazepam produced drowsiness, clumsiness, dreaminess and sadness. An increase in these symptoms was noted after stopping temazepam, but this effect was lessened when the dose was tapered. Zopiclone was associated only with minimal effects. However, in a recent report of four cases (3), situations were described where patients — because they had increased their intake of zopiclone above the dose prescribed — suffered symptoms on withdrawal which included craving, anxiety and insomnia. For reasons not explained in the report, three of the patients took the hypnotic even in daytime, and one patient had a previous history of benzodiazepine dependence.

The dependence liability of zopiclone and zolpidem remains somewhat unclear based on the available studies and data. It would seem that, with the products currently available, any effective treatment of insomnia is bound to cause some kind of dependence during treatment for chronic sleep problems and is more likely to occur in certain types of personality or in patients dealing with difficult life crises and will depend on whether the patient is or has been drug or alcohol dependent. Caution should therefore be exercised when prescribing hypnotics, and this should be limited to short-term treatment only.

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