

Reports on Individual Drugs

Tamoxifen in the prevention and treatment of breast cancer

When diagnosed in time, breast cancer and all detectable cancer tissue can be removed surgically. However, because micrometastatic deposits of the disease can remain, adjuvant tamoxifen is routinely administered immediately following surgery. Although this practice has been shown to improve the 10-year survival rate of patients (1), uncertainty remains concerning which patients should receive treatment, and for how long.

In order to clarify this issue, the Early Breast Cancer Trialists Collaborative Group (EBCTCG) has carried out a meta analysis of 55 clinical trials conducted in 15 countries and involving 37 000 women diagnosed with early breast cancer (2). Results of the study showed that, when tamoxifen is started immediately following surgery and irrespective of age, relapse is prevented in 1 in 6 women and mortality in 1 in 12.

Furthermore, 5 years of tamoxifen therapy significantly reduced breast cancer recurrence by 42% and mortality by 22%. These results were similar for women under 50 years of age and older women. Among women who had received both chemotherapy and adjuvant tamoxifen for five years, 61% had no recurrence of disease after ten years, compared with 40% who were receiving chemotherapy alone. The results also showed an almost 50% reduction in new cancers in the contralateral breast during five year tamoxifen therapy.

However, for the 8000 women who had low or zero level estrogen-receptor protein in the primary tumour, the overall effects of tamoxifen appeared to be small. In the light of these results, the authors conclude that for women with estrogen receptor protein negative tumours, the benefit of adjuvant tamoxifen is not yet proved.

A recent clinical trial on the prophylactic use of tamoxifen in healthy women with a family history of breast cancer was terminated 14 months early when it was shown that tamoxifen reduced breast cancer incidence by 45% across all age groups compared with placebo. The trial, run by the Na-

tional Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project in the United States of America, was scheduled to last six years, and involved over 13 000 women (3).

It remains to be seen from the results of these latest trials, whether genetic screening for women at high risk for breast cancer might be beneficial in identifying those in need of prophylactic therapy (4).

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Selective serotonin re-uptake inhibitors and withdrawal reactions

Selective serotonin re-uptake inhibitors (SSRIs) are a relatively new class of antidepressants. Although the first product in this family of drugs was introduced as early as 1982, a significant increase in the use of SSRIs was observed only when fluoxetine, the third drug of this family, was launched in 1988 under the brand name, Prozac®. The success of fluoxetine resulted in a rapid expansion of the antidepressant market and, during the 1990s, additional SSRIs such as sertraline, paroxetine, venlafaxine, citalopram and nefazodone were also marketed.

However, despite a general belief that SSRIs did not create dependence or lead to symptoms of withdrawal when discontinued after long-term use, it was not long before case reports of withdrawal symptoms were received. The first reported case

involved a 32-year-old man who had experienced agitation, inability to concentrate and insomnia within 48 hours of discontinuation of fluoxetine (1). In the following year, a case was reported of a 30-year-old woman, treated with fluvoxamine 100 mg/day, who was overwhelmed by strong feelings of aggression when she tried to stop taking the medication (2). Similar isolated case reports continued to be received.

In an open study, when 14 patients were withdrawn from fluvoxamine after 7–8 months of treatment, new symptoms developed in 12 of the patients. These included dizziness, incoordination, headaches, nausea and irritability, and were distinguishable from the panic disorder for which the drug was prescribed. Symptoms usually peaked on day 5 after withdrawal (3).

Reports of withdrawal symptoms did not exclude the newer SSRIs. In 1993, the British Committee on Safety of Medicines cited 78 reports of symptoms occurring upon withdrawal of paroxetine, including dizziness, sweating, nausea, insomnia, tremor and confusion (4). A case of sertraline withdrawal was reported in 1994 (6) and the first reports on venlafaxine withdrawal were published two years later, citing such symptoms as muscle aches, fatigue, headache, nausea and dizziness (6). A substitution study suggested that nefazodone would not be an exception (7).

Isolated case reports of withdrawal symptoms associated with individual SSRIs have been supported by a number of observations. Several recent studies compare spontaneous reports of withdrawal symptoms from different SSRIs collected by adverse drug reaction monitoring programmes. According to data on adverse drug reactions from the United Kingdom, the rates of withdrawal reaction reports were different for different SSRIs: 0.3 per 1000 prescriptions for paroxetine, 0.03 per 1000 for sertraline and fluvoxamine, and 0.002 per 1000 for fluoxetine (8).

Drug surveillance data from France indicate that withdrawal reactions with fluvoxamine and paroxetine occur in a greater proportion of reports than with fluoxetine (9). A careful review of the WHO adverse drug reaction data base in relation to drug sales statistics converted into DDDs (defined daily doses) reveals that the reporting rate of withdrawal reactions for paroxetine was higher than that for sertraline and fluoxetine in Australia, the United Kingdom and the USA, which were selected for

detailed analyses, as well as for all 16 reporting countries combined (10). With an increasing number of reports of this kind, SSRI withdrawal has become the topic of several review papers. Although an early review concluded that withdrawal symptoms associated with the discontinuation of fluoxetine had not been established (11), more recent reviews explain the lower incidence of fluoxetine withdrawal symptoms in relation to its long half-life, the incidence appearing higher with shorter half-life agents (12). Common physical withdrawal symptoms appear as problems of balance, gastrointestinal and flu-like symptoms, and sensory and sleep disturbances. Psychological symptoms include anxiety, agitation, crying spells, and irritability. Some symptoms are similar to those reported with discontinuation of tricyclic antidepressants. However, SSRI discontinuation is also associated with novel symptom clusters, including sensory abnormalities and possibly aggressive and impulsive behaviour (13).

The clinical implications of SSRI withdrawal should be considered in the context of duration of treatment, clinical management of withdrawal, and risk of dependence and abuse. Because the symptoms of SSRI discontinuation include changes in mood, appetite and sleep, they are sometimes mistaken for signs of a relapse into depression (14). This can lead to continued prescribing even after depression has been treated. With regard to clinical management of withdrawal, gradual tapering is recommended, particularly for short half-life SSRIs (15). Concerning the risk of dependence and abuse, opinions are mixed. Some reviewers consider that SSRIs are not associated with dependence or drug-seeking behaviour. However, the same authors noted that SSRI discontinuation symptoms could be troublesome and there were several case reports where symptoms occurred consistently despite repeated attempts to taper therapy (12).

There is obviously some confusion about the concept of dependence in such discussions. The simplest definition of drug dependence given by WHO is "a need for repeated doses of the drug to feel good or to avoid feeling bad" (16). When the patient needs to take repeated doses of the drug to avoid the bad feelings caused by withdrawal reactions, the person is dependent on the drug. Those who have difficulty coming off the drug even with the help of tapered discontinuation should be regarded as dependent, unless a relapse into depression is the reason for their inability to stop the antidepressant medication.

In general, all unpleasant withdrawal reactions have a certain potential to induce dependence and this risk may vary from person to person. Dependence will not occur if the withdrawal reactions are so mild that all patients can easily tolerate them. With increasing severity, the likelihood of withdrawal reactions leading to dependence also increases. Although reporting rates of SSRI withdrawal are low in comparison with prescribed doses, it is prudent to recommend the monitoring of patient withdrawal symptoms even when SSRIs are prescribed at modest doses (17).

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Triclabendazole and fascioliasis

It is estimated that 2.4 million people suffer from fascioliasis infections worldwide, and a further 180 million are at risk of infection. Outbreaks can cause severe illness, and in some areas over 60% of the population can be infected. Typical symptoms include fever, abdominal pain, gastrointestinal disturbances, urticaria, hepatomegaly, anaemia and jaundice caused by the inflammatory response and lesions in the abdominal cavity and liver.

The liver flukes *Fasciola hepatica* and *F. gigantica* are flat worms which live in the bile ducts of their definitive hosts: either ruminants or man. Infection occurs through consumption of uncooked aquatic vegetables which have been contaminated with encysted parasitic larvae. Larvae migrate from the small intestine, across the intestinal wall, into the abdominal cavity. Within 24 hours of ingestion, the larvae have become immature worms and move to the liver to feed on liver tissue. While in the bile ducts, the worms mature into adult form. Each produces eggs which are then released into the biliary passages and are shed in the faeces.

Until recently, treatment of fascioliasis has been difficult because praziquantel — effective against most trematode infections — is inactive against

Fasciola species. Triclabendazole has been used effectively in veterinary practice for fascioliasis since 1983 and, following its successful use in humans during an outbreak in 1989 in the Islamic Republic of Iran, WHO concluded an agreement with the company Ciba-Geigy (now Novartis) to undertake human clinical studies to evaluate its effect. As a result of this agreement, a development programme of clinical trials in Bolivia, Chile, Cuba, the Islamic Republic of Iran and Peru has now been successfully concluded.

The most efficient dosage of triclabendazole for this indication was demonstrated to be 10 mg/kg given in two equal doses. During all trials, the drug was well tolerated and cases of transient biliary obstruction were attributed to the accumulation of dead worms during treatment. Triclabendazole was demonstrated to be highly efficacious and was not associated with serious adverse effects. As a result, the drug has been included in the WHO model list of essential drugs. On a population basis, treatment provides immediate relief to infected individuals and reduces the prevalence and intensity of the disease burden.