COMMITTEE ON SAFETY OF MEDICINES

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CURRENT PROBLEMS

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CONTENTS

BENZODIAZEPINES, DEPENDENCE AND WITHDRAWAL SYMPTOMS

There has been concern for many years regarding benzodiazepine dependence (Br.Med. J, 1980: **280**, 910-912). Such dependence is becoming increasingly worrying.

Withdrawal symptoms include anxiety, tremor, confusion, insomnia, perceptual disorders, fits, depression, gastrointestinal and other somatic symptoms. These may sometimes be difficult to distinguish from the symptoms of the original illness.

It is important to note that withdrawal symptoms can occur with benzodiazepines following therapeutic doses given for SHORT periods of time.

Withdrawal effects usually appear shortly after stopping a benzodiazepine with a short half life, or up to several days after stopping one with a long half life. Symptoms may continue for weeks or months. No epidemiological evidence is available to suggest that one benzodiazepine is more responsible for the development of dependency or withdrawal symptoms than another.

The Committee on Safety of Medicines recommends that the use of benzodiazepines should be limited in the following ways:

USES

As Anxiolytics

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling or subjecting the

individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.

2. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate and unsuitable.

As Hypnotics

3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

DOSE

1. The lowest dose which can control the symptoms should be used. It should not be continued beyond four weeks.

2. Long-term chronic use is not recommended.

3. Treatment should always be tapered off gradually.

4. Patients who have taken benzodiazepines for a long time may require a longer period during which doses are reduced.

5. When a benzodiazepine is used as a hypnotic, treatment should, if possible, be intermittent.

PRECAUTIONS

1. Benzodiazepines should not be used alone to treat depression or anxiety associated with depression. Suicide may be precipitated in such patients.

2. They should not be used for phobic or obsessional states.

3. They should not be used for the treatment of chronic psychosis.

4. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

5. Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed, and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

THE "RED ALERT" SCHEME

The Committee on Safety of Medicines and the Drug Safety Research Unit have begun a trial of a new drug monitoring scheme called "Red Alert". Its aim is to encourage doctors to report serious adverse reactions to new drugs.

The scheme will cover every new drug (new active substance) marketed over the trial period. Inclusion of a drug does not imply any special concern about its safety at the present time.

During the trial, GPs in England who prescribe drugs included in the scheme will be sent specially modified yellow cards marked with red triangles. These "red alert" cards are printed with the patient's name and the name of the drug, and should be used only to report SERIOUS OR LIFE THREATENING adverse reactions or the death of the patient. Other reactions should be reported direct to the Committee on Safety of Medicines on an ordinary yellow card. Detailed guidance is given with each "red alert" card, and doctors are asked to follow it carefully.

SPIRONOLACTONE

It has become known to the Committee on Safety of Medicines that potential human metabolic products of spironolactone are carcinogenic in rodents.

As a result, the licences for all products containing spironolactone have been amended so that the drug is no longer indicated for essential hypertension and ideopathic oedema.

Products containing spironolactone remain licensed for use in cirrhosis with ascites and oedema, malignant ascites, nephrotic syndrome, and in the diagnosis and treatment of primary hyperaldosteronism and in congestive heart failure.

ORAL CONTRACEPTIVES AND BREAST CANCER

The following letter from the Chairman of the Committee on Safety of Medicines was published in the 28 November issues of the British Medical Journal, The Lancet, and the Pharmaceutical Journal:

"SIR, — By courtesy of the editor of the *British Journal of Cancer* and the authors concerned, the Committee on Safety of Medicines has been able to review the paper by McPherson and colleagues which is to appear under the title of "Early contraceptive use and breast cancer: results of another case-control study" in the November issue of the *British Journal of Cancer.**

The paper adds to the considerable body of knowledge which has now accumulated on this subject. At least eight substantial case-control studies in which the possible relation between oral contraceptive use and breast cancer was investigated have been published since 1980. Most of these studies, including the largest of them — the American Cancer and Steroid Hormone Study — have provided no cause for concern. Some, however, have raised questions about a possible adverse effect of prolonged oral contraceptive use early in life.

The forthcoming publication by McPherson and colleagues suggests that there may be a two and a half fold increase in the risk of breast cancer in women up to 45 years of age who have had four or more years of oral contraceptive use before their first full term pregnancy. The authors point out that their data do not directly reflect upon the use of the modern low dose oral contraceptive pills. In addition, this study has found no association between oral contraceptive use after first full term pregnancy and breast cancer either in women under 45 years of age or in older women. The paper extends the previously reported results of these authors (published in December 1983), which were fully considered by the Committee on Safety of Medicines at the time of their appearance.

The Committee on Safety of Medicines has considered the additional results now being made available in the light of all the current evidence. It will continue to monitor the several studies which are still in progress on this subject but agrees with the view of McPherson and others that the newly reported findings do not indicate the need to change at this time the current advice regarding the use of the presently available oral contraceptive agents. Thus the Committee remains of the view that women receiving oral contraceptives should be prescribed a product with the lowest suitable content of both oestrogen and progestogen.

A W ASSCHER"

* McPherson K, Vessey M P, Neil A, Doll R, Jones L, Roberts M. Early oral contraceptive use and breast cancer. Results of another case-control study. Br J Cancer 1987; **56**: 653-60

COMMITTEE ON SAFETY OF MEDICINES

ADR REPORTING: WHAT, HOW AND WHERE

What to Report

NEW Drugs ▼ Report **ALL** suspected reactions, that is any adverse or unexpected event, however minor, which could conceivably be attributed to the drug.

Please report even if the reaction is well recognised or if you are unsure of the causal relationship.

New drugs have an inverted black triangle '▼' in the British National Formulary, MIMS and the Data Sheet Compendium.

ESTABLISHED Drugs Report **SERIOUS** suspected reactions, including those which are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation.

Please report a serious reaction even if it is already well-recognised.

Please do *not* report *minor* reactions for established drugs.

How to Report

Two yellow cards are enclosed. Others can be found in:

- the British National Formulary
- FP10 prescription pads
- the ABPI Data Sheet Compendium
- by dialling 100 and asking for **CSM Freephone**

When reporting, please give details of BRAND NAME and BATCH NUMBER, especially for

- over the counter drugs
- slow or delayed release formulations
- biotechnology products, eg human growth hormone
- vaccines

Please print your name and address clearly, or use a legible stamp. A copy of the report will be returned to you in a window envelope.

Where to Report

CSM, FREEPOST, London SW8 5BR

or if you are in one of the following NHS regions:

CSM West Midlands, FREEPOST, Birmingham B15 1BR

CSM Northern, FREEPOST 1085, Newcastle-upon-Tyne NE1 1BR

CSM Wales, FREEPOST, Cardiff C44 1ZZ

(Yellow cards with red triangles *only* should be sent **FREEPOST** to the Drug Safety Research Unit at the address shown on them.)