The New Yellow Card

The new Yellow Card has been designed to comply with data protection legislation and recent guidelines from the General Medical Council on confidentiality. It also simplifies reporting. The changes include:

- Use of the patient's initials and age at the time of the reaction instead of the full name and date of birth.
- Requirement for inclusion of a local identification code (e.g. practice number, pharmacy number or hospital number) for the patient. This will aid your identification of the patient in future correspondence and facilitate the inclusion of the report in the patient's notes.
- Tick boxes to help establish the seriousness of the reaction and also to indicate outcome.

Copies of the new Yellow Card are available:
- By post from CSM Mersey
- From the back of BNF 40
- From the CSM Mersey website http://www.liv.ac.uk/~druginfo/csm

We will continue to accept the old cards but please only include the patient’s initials and age. A new card will be supplied when the report is acknowledged.

SSRIs and Galactorrhoea

Drug therapy is a common cause of hyperprolactinaemia with antipsychotics and antidepressants being frequently implicated. The selective serotonin reuptake inhibitors (SSRIs) are believed to increase prolactin levels both directly at the pituitary and also by inhibiting dopamine receptors at the hypothalamus. There are few reports of SSRI-induced hyperprolactinaemia in the literature, but galactorrhoea has been identified as a class effect of SSRIs and is being added to all of the SSRI Summary of Product Characteristics (SPCs).

CSM Mersey has received four reports of galactorrhoea associated with SSRIs including fluoxetine, paroxetine and venlafaxine (2 reports). In two cases prolactin levels were measured and found to be high, but they returned to normal over several weeks. All four patients continued taking antidepressants and galactorrhoea persisted.

St John’s Wort

All herbal medicines have the potential to cause adverse reactions. However, because many of them are unlicensed, there is often little information on their side-effect profiles. St John’s Wort is a herbal medicine increasingly being used by patients in the UK, and suspected reactions are beginning to be reported via the Yellow Card scheme. CSM Mersey has received five such reports in recent months. They include three reports of skin reactions (burning of the scalp, exacerbation of psoriasis and a viral-type rash) and two reports of serious drug interactions which are detailed below:

- A patient with supraventricular tachycardia, well controlled on verapamil, experienced an exacerbation of symptoms when self-medicating with St John’s Wort.
- A patient taking the immunosuppressants tacrolimus and prednisolone for ocular sarcoid experienced increased disease activity about two weeks after starting St John’s Wort.

Hyperforin, the constituent of St John’s Wort responsible for most of its antidepressant activity, induces cytochrome P450 CYP3A, CYP2C9 and CYP1A2 activity, and increases the metabolism of many drugs. The CSM highlighted some of the resulting interactions in a letter to prescribers and pharmacists in February 2000. A copy of the letter and the accompanying patient information leaflet can be found on the CSM website at http://open.gov.uk/mca/aboutagency/regframework/csm/csmhome under the heading 'Important safety messages'.

Please report any suspected adverse reactions or drug interactions with St John’s Wort, or any other herbal preparation, via the yellow card scheme.

Zybanτ (bupropion)

Since bupropion was launched for smoking cessation in July 2000, CSM Mersey has received 81 yellow cards reporting suspected adverse reactions. Most of the reported reactions are recognised and are included in the product's SPC. Nationally, the most frequently reported reactions to bupropion have been skin disorders (1608 reactions), including rash (297) and urticaria (491). The CSM has received
37 reports of angioedema so far, plus 132 reports of face oedema and 38 reports of tongue oedema. CSM Mersey has received 7 cards for swelling of the face, mouth or extremities, 6 cases of urticaria and 10 cases of allergic or hypersensitivity-type rash.

Bupropion can cause chest pain and we have received two reports of this reaction locally. In addition, there have been two reports of left arm pain associated with indigestion, and one of chest tightness.

We have also received two reports of mouth ulcers in association with bupropion. This reaction is not currently included in the SPC, but this is being reviewed as part of ongoing safety monitoring.

**Venous thromboembolism and antipsychotics**

There is some evidence from as early as the 1950s that antipsychotic drugs are possibly associated with the development of venous thromboembolism (VT). However the reaction is not well recognised and is included in few of the SPCs for antipsychotics.

A research letter originating in Sweden described 12 cases of VT during clozapine treatment over the last decade. Five patients died and in three of these there were no other contributory factors. Based on these spontaneous reports, the risk of VT in clozapine-treated patients was estimated to be at least one in 2000-6000. The mechanism by which clozapine might induce VT remains to be confirmed.

A subsequent letter detailed the results of a surveillance programme of severe adverse reactions in all inpatients of 35 psychiatric hospitals in Germany and Switzerland. There was no significant difference in the incidence of VT between those patients on clozapine (0.038%), other antipsychotics (0.029%) and those receiving no antipsychotic treatment (0.026%). This raises the possibility that VT may be related to other factors such as reduced motor activity during psychiatric illness.

In the USA, the risk of pulmonary embolism (PE) appears in the data sheet for clozapine and the FDA has received 83 reports including 63 deaths in the last 10 years.

In the UK, the CSM have received 32 reports of VT and 19 of VT in clozapine-treated patients. Reports for other atypical antipsychotics are: olanzapine (6 VT, 3 PE), risperidone (5 VT, 3 PE), quetiapine (3 VT, 2 PE) and zotepine (1 PE). CSM Mersey has received one report of a fatal PE in a patient who had recently begun taking olanzapine for the treatment of schizophrenia. This patient had no other predisposing factors for the reaction.

A recent study suggests that current exposure to conventional antipsychotic drugs also significantly increases the risk of idiopathic venous thromboembolism in men and women younger than 60 years of age.

The association between antipsychotic agents and venous thromboembolism remains unclear. Please report any suspected cases to the CSM. This will help characterise the association, if any, and enable more specific advice to be given to prescribers.

### Pergolide - serosal fibrotic reactions

A recent report describes retroperitoneal fibrosis as a complication of pergolide therapy in a 63-year old woman with Parkinson's disease. She developed shortness of breath and ankle swelling 8 months after initiation of pergolide. At the time, investigations, including a chest X-ray, were normal. However, 10 months later her serum urea and creatinine levels were raised and a chest X-ray showed an enlarged heart. Two months later a CT scan confirmed the diagnosis of retroperitoneal fibrosis.

CSM Mersey has also received the following reports:

- **Retroperitoneal fibrosis** in a 60-year-old man who had been taking pergolide for approximately two and a half years before symptoms developed. The patient presented with bilateral lymphoedema of the legs but no back pain or renal dysfunction and a slight eosinophilia.
- **Fibrosing alveolitis** in a 48 year old woman who had been taking pergolide for over 6 years before developing shortness of breath and reduced exercise tolerance. CT scan found evidence of hypersensitivity pneumonitis/fibrosing alveolitis.
- **Pulmonary fibrosis and effusion** in a 44 year old man presenting as shortness of breath and chest discomfort 6 months after starting pergolide. Chest X-ray showed pleural effusion and lower lobe shadowing and CT of the thorax showed diffuse interstitial fibrosis.

Nationally there have been 9 cases of retroperitoneal fibrosis, 6 of pulmonary fibrosis, 6 of pleural fibrosis, 1 of fibrosing alveolitis and 1 of pneumonitis associated with pergolide reported to the CSM (from a total of 466 reported reactions).

Serosal fibrotic reactions are recognised idiosyncratic adverse reactions to ergot derivatives, and are mentioned in the SPC for pergolide. Symptoms can be non-specific, often do not develop until many years after initiation of treatment, and hence may easily be missed, leading to a delay in diagnosis. Reactions occur even after small doses, are often irreversible and appear to occur more commonly in women than men.

Patients taking pergolide who have a history of this type of reaction with ergot derivatives should be carefully monitored clinically and with appropriate radiographic and laboratory studies.

### References

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