SAFETY OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS

Dear Colleague

I am writing to tell you the advice of the Committee on Safety of Medicines (CSM) on the safe use in adults of selective serotonin reuptake inhibitor (SSRI) antidepressants in the light of CSM's Expert Working Group Report on SSRIs and new advice in relation to the antidepressant venlafaxine (Efexor).

Background

In December 2003 the CSM issued advice on the use of SSRIs in the treatment of major depressive disorder in children. Since then its Expert Working Group has examined a large body of safety evidence from a wide range of sources – spontaneous suspected adverse drug reactions, clinical trials, published literature and epidemiological databases. The key findings of the Expert Working Group are listed in Appendix 1.

Key Conclusions

SSRIs are effective medicines in the treatment of depression and anxiety conditions, and the CSM has concluded that the balance of risks and benefits of all SSRIs in adults remains positive in their licensed indications. Clear advice is to be given in all SSRI product information in 3 areas: withdrawal reactions, dose changes, and suicidal behaviour.

Summary of general prescribing advice

1. For the majority of SSRIs in the treatment of depressive illness, clinical trial data do not show any additional benefit from increasing the dose above the recommended daily dose. In the absence of evidence of a benefit from increasing the dose, good practice would be to maintain patients on the lowest efficacious dose. For patients currently on a dose above the recommended dose, the advice is to complete the course if the patient is well.

2. Careful and frequent patient monitoring by healthcare professionals, and where appropriate other carers, is important in the early stages of treatment, particularly if a patient experiences worsening of symptoms or if new symptoms arise after starting treatment.

3. If a patient is not doing well after starting treatment the possibility of an adverse reaction to the drug should be considered. Patients should be monitored for signs of restlessness or agitation, particularly at the beginning of treatment. Increasing the dose in these circumstances may be detrimental.

4. Evidence of a relationship between suicidal behaviour and increasing/decreasing dose is not robust, however patients should be monitored around the time of dose changes for any new symptoms or worsening of disease.

5. To minimise withdrawal reactions on stopping SSRIs, the dose should be tapered gradually over a period of several weeks, according to the patient's need.

6. There is no clear evidence of an increased risk of self-harm and suicidal thoughts in young adults of 18 years or over. But individuals mature at different rates and young adults are at a higher background risk of suicidal behaviour than older adults, so as a precautionary measure young adults treated with SSRIs should be closely monitored.

Venlafaxine (Efexor)

The CSM has additionally considered the balance of risks and benefits of Efexor because of concerns about cardiotoxicity and toxicity in overdose. CSM recommended that treatment with Efexor should only be initiated by specialist mental health practitioners, including GPs with a special interest, and there should be arrangements in place for continuing supervision of the patient.

Efexor should not be used in patients with heart disease, (e.g. cardiac failure, coronary artery disease, ECG abnormalities including pre-existing QT prolongation), patients with electrolyte imbalance or in patients who are hypertensive.
Patients currently doing well on treatment with venlafaxine can continue to the end of their course.

NICE Guidelines
The National Institute for Clinical Excellence (NICE) has today issued guidelines for the NHS on the treatment and care of people with depression and anxiety.
The key priorities for implementation for each guideline are set out in Appendix 2.
Electronic copies of the quick reference guides for both depression and anxiety can be found on the NICE website at www.nice.org.uk. Hard copies of both guidelines will be distributed to the NHS on 15th December.

Further information
Further information for prescribers and patients including questions and answers and the full report of the CSM's Expert Working Group Report on SSRIs will be available on the website of the Medicines and Healthcare products Regulatory Agency (MHRA), www.mhra.gov.uk, early next week.

Please report any suspected adverse reactions via the Yellow Card reporting scheme to the CSM/ MHRA.

Should you require any additional information, please telephone 020 7084 2000 at the MHRA.

Yours sincerely

Professor Gordon Duff
Chairman, CSM

Annex 1

CSM EXPERT WORKING GROUP ON SSRIS: KEY FINDINGS

Use of in SSRIs in adults

Suicidal behaviour – adults

- There is epidemiological evidence that the risk of self harm in depressed patients is greatest around the time of presentation to medical services. It is general clinical experience that the risk of suicide may increase in the early stages of treatment for depressive illness.

- **Careful and frequent patient monitoring by healthcare professionals, and where appropriate other carers, is important in the early stages of treatment, particularly if a patient experiences worsening of symptoms or new symptoms after starting treatment**.

- Studies indicate that increases in the prescribing of SSRIs have not been associated with an increase in population suicide rates, although interpretation of these findings is difficult as a range of factors influence population trends in suicide.

- From the available clinical trial data, both published and unpublished, a modest increase in the risk of suicidal thoughts and self-harm for SSRIs compared with placebo cannot be ruled out. There is insufficient evidence from clinical trial data to conclude that there is any marked difference between members of the class of SSRIs, or between SSRIs and other antidepressants with respect to their influence on suicidal behaviour.

- Evidence from non-experimental studies based on the General Practice Research Database indicates that there is no increased risk of suicidal behaviour with SSRIs compared with TCAs.

- There is no clear evidence that there is an increased risk of self-harm or suicidal thoughts when SSRIs are discontinued.

- Evidence of a relationship between suicidal behaviour and increasing/decreasing dose is not robust, however **patients should be monitored around the time of dose changes for any new symptoms or worsening of disease.**

Withdrawal reactions

- All SSRIs may be associated with withdrawal reactions on stopping or reducing treatment. Paroxetine and venlafaxine seem to be associated with a greater frequency of withdrawal reactions than other SSRIs. A proportion of SSRI withdrawal reactions are severe and disabling to the individual.

- The most commonly experienced withdrawal reactions are dizziness, numbness & tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances.

- **To minimise withdrawal reactions on stopping SSRIs, the dose should be tapered gradually over a period of several weeks, according to the patient's need.**

- There is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome according to internationally accepted criteria [either DSM-IV or ICD-10].

Dose response

- For the majority of SSRIs in the treatment of depressive illness, clinical trial data do not show an additional benefit from increasing the dose of an SSRI above the recommended daily dose.

- **In the absence of evidence of a benefit from increasing the dose, good practice would be to maintain patients on the lowest efficacious dose.**

- **If a patient is not doing well after starting treatment the possibility of an adverse reaction to the drug should be considered. Patients should be monitored for signs of restlessness or agitation, particularly at the beginning of treatment. Increasing the dose in these circumstances may be detrimental.**

Use of SSRIs in children and adolescents

- The balance of risks and benefits for the treatment of depressive illness in under 18s is judged to be unfavourable for paroxetine (Seroxat), venlafaxine (Efexor), sertraline (Lustral), citalopram (Cipramil), escitalopram (Cipralex) and mirtazapine (Zispin). It is not possible to assess the balance of risks and benefits for fluvoxamine (Faverin) due to the absence of paediatric clinical trial data. Only fluoxetine (Prozac) has been shown in clinical trials to be effective in treating depressive illness in children and adolescents, although it is possible that, in common with the other SSRIs, it is associated with a small increased risk of self-harm and suicidal thoughts. Overall, the balance of risks and benefits for fluoxetine in the treatment of depressive illness in under 18's is judged to be favourable.

- The safety profiles of the different products in clinical trials in children and adolescents differ across studies. However an increased rate of a number of events including insomnia, agitation, weight loss, headache, tremor, loss of appetite, self harm and suicidal thoughts were seen in those treated with some of the SSRIs compared with placebo.

Young adults

- There is no clear evidence of an increased risk of self-harm and suicidal thoughts in young adults of 18 years or over. However, given that individuals mature at different rates and that young adults are at a higher background risk of suicidal behaviour than older adults, as a precautionary measure **young adults treated with SSRIs should be closely monitored.**

Annex 2: NICE guidelines on depression and anxiety

Depression: management of depression in primary and secondary care

Key priorities

Screening in primary care and general hospital settings

- Screening should be undertaken in primary care and general hospital settings for depression in high-risk groups – for example, those with a past history of depression, significant physical illnesses causing disability, or other mental health problems such as dementia.

Watchful waiting

- For patients with mild depression who do not want an intervention or who, in the opinion of the healthcare professional, may recover with no intervention, a further assessment should be arranged, normally within 2 weeks ('watchful waiting').

Antidepressants in mild depression

- Antidepressants are not recommended for the initial treatment of mild depression, because the risk–benefit ratio is poor.

Guided self-help

- For patients with mild depression, healthcare professionals should consider recommending a guided self-help programme based on cognitive behavioural therapy (CBT).

Short-term psychological treatment

- In both mild and moderate depression, psychological treatment specifically focused on depression (such as problem-solving therapy, brief CBT and counselling) of 6 to 8 sessions over 10 to 12 weeks should be considered.

Prescription of an SSRI

- When an antidepressant is to be prescribed in routine care, it should be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects.

Tolerance and craving, and discontinuation/withdrawal symptoms

- All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly.

Initial presentation of severe depression

- When patients present initially with severe depression, a combination of antidepressants and individual CBT should be considered as the combination is more cost-effective than either treatment on its own.

Maintenance treatment with antidepressants

- Patients who have had two or more depressive episodes in the recent past, and who have experienced significant functional impairment during the episodes, should be advised to continue antidepressants for 2 years.

Combined treatment for treatment-resistant depression

- For patients whose depression is treatment resistant, the combination of antidepressant medication with CBT should be considered.

CBT for recurrent depression

- CBT should be considered by patients with recurrent depression who have relapsed despite antidepressant treatment, or who express a preference for psychological interventions.

Anxiety: management of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care

Key priorities

General management

- Shared decision-making between the individual and healthcare professionals should take place during the process of diagnosis and in all phases of care.
- Patients, and where appropriate, families and carers should be provided with information on the nature, course and treatment of panic disorder or generalised anxiety disorder, including information on the use and likely side-effect profile of medication.
- Patients, families and carers should be informed of self-help groups and support groups and be encouraged to participate in such programmes where appropriate.
- All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping or missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but occasionally can be severe, particularly if the drug is stopped abruptly.

Step 1: Recognition and diagnosis of panic disorder and generalised anxiety disorder

- The diagnostic process should elicit necessary relevant information such as personal history, any self-medication, and culture or other individual characteristics that may be important considerations in subsequent care.

Step 2: Offer treatment in primary care

- There are positive advantages of services based in primary care practice (for example, lower drop-out rates) and these services are often preferred by patients.
- The treatment of choice should be available promptly.
  Panic disorder
  - Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.
  - Any of the following types of intervention should be offered and the preference of the person should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order are: (a) psychological therapy (CBT); (b) pharmacological therapy (an SSRI licensed for panic disorder; or if an SSRI is unsuitable or there is no improvement, imipramine or clomipramine may be considered[1]); (c) self-help (bibliotherapy based on CBT principles).

  Generalised anxiety disorder
  - Benzodiazepines should not usually be used beyond 2-4 weeks.
  - In the longer-term care of individuals with generalised anxiety disorder, any of the following types of intervention should be offered and the preference of the person with

[1] Imipramine and clomipramine are not licensed for panic disorder but have been shown to be effective in its management.

generalised anxiety disorder should be taken into account. The interventions that have evidence for the longest duration of effect, in descending order, are: (a) psychological therapy (CBT); (b) pharmacological therapy (an SSRI); (c) self-help (bibliotherapy based on CBT principles).

Step 3: Review and offer alternative treatment

- If one type of intervention does not work, the patient should be reassessed and consideration given to trying one of the other types of intervention.

Step 4: Review and offer referral from primary care

- In most instances, if there have been two interventions provided (any combination of psychological therapy, medication or bibliotherapy) and the person still has significant symptoms, then referral to specialist mental health services should be offered.

Step 5: Care in specialist mental health services

- Specialist mental health services should conduct a thorough, holistic, reassessment of the individual, their environment and their social circumstances.

Monitoring

- Short, self-complete questionnaires (such as the panic subscale of the agoraphobic mobility inventory for individuals with panic disorder) should be used to monitor outcomes wherever possible.

Obtaining copies of the guidelines

Electronic copies of the quick reference guide to the **anxiety** guideline can be found on the NICE website at www.nice.org.uk/CG022quickrefguide and electronic copies of the information for the public leaflet that accompanies the guideline can be found at www.nice.org.uk/CG022publicinfo.

Electronic copies of the quick reference guide to the **depression** guideline can be found on the NICE website at www.nice.org.uk/CG023quickrefguide and electronic copies of the information for the public leaflet that accompanies the guideline can be found at www.nice.org.uk/CG023publicinfo.

Hard copies of both guidelines will be distributed to the NHS on 15th December and will be available to order from the NHS Response Line on 0870 1555 455 from that date, by quoting the following reference numbers:

- N0766 - depression quick reference guide
- N0767 - depression information for the public (English)
- N0768 - depression information for the public (English and Welsh bilingual)
- N0763 - anxiety quick reference guide
- N0764 - anxiety information for the public (English)
- N0765 - anxiety information for the public (English and Welsh bilingual)