

COMMITTEE ON SAFETY OF MEDICINES

EXPERT GROUP ON SAFETY OF SSRIs

MINUTES OF THE MEETING OF THE CSM EXPERT GROUP ON THE SAFETY OF SSRIS HELD ON WEDNESDAY 26 MAY 2004 AT 10AM IN CR1 AT MARKET TOWERS.

Members Present

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| Professor Ian Weller (Chairman) | Professor of Sexually Transmitted Diseases & Director of Centre of Sexual Health & HIV Research, Royal Free & University College Medical School |
| Professor Deborah Ashby | Professor of Medical Statistics, Queen Mary, University of London |
| Dr Jonathan Chick | Consultant Psychiatrist, Alcohol Problems Service, Royal Edinburgh Hospital & part time Senior Lecturer at Edinburgh University |
| Professor Mary Chambers | Professor of Mental Health, University of Ulster |
| Professor Colin Drummond | Professor of Addiction Psychiatry, St George's Hospital Medical School, London |
| Professor David Gunnell | Professor of Epidemiology, Department of Social Medicine, Bristol University |
| Dr Ross Taylor | Senior Lecturer in General Practice, University of Aberdeen & General Medical Practitioner Principal, Grampian Health Board |
| Dr Ann York | Consultant & Honorary Senior Lecturer in Child & Adolescent Psychiatry, Child & Family Consultation Centre, Richmond Hospital |
| Dr Morris Zwi | Consultant Child & Adolescent Psychiatrist, South West London & St George's Mental Health NHS Trust |

Professional staff of MHRA

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| Ms Sarah Wark | Unit Manager, Pharmacovigilance Group |
| Dr Julia Dunne | Specialist in Paediatrics, Pharmacovigilance Group |
| Dr Simon Day | Statistics Unit Manager, Licensing Division |
| Dr David Brown | Statistician, Licensing Division |
| Dr Julie Williams | Scientific Assessor, Pharmacovigilance Group |
| Dr Lesley Wise | Statistician/Epidemiologist, Pharmacovigilance Group |
| Ms Claire Davies | Scientific Assessor, Pharmacovigilance Group |
| Dr Carlos Martinez | Head of Research, GPRD |
| Dr Simon Amyes | Post Licensing Division(item 4.1) |

Observers

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| Dr Jane Moseley | Pharmacoepidemiology Team Leader, Pharmacovigilance Group |
| Dr Camilla Parikh | Medical Assessor, Pharmacovigilance Group |
| Dr Bill Richardson | Medical Assessor, Pharmacovigilance Group |

Invited Experts

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| Mr Stephen Pilling | Co-Director, National Collaborating Centre for Mental Health |
| Ms Rachel Burbeck | National Collaborating Centre for Mental Health |

1.0 INTRODUCTION

- 1.1 The Chairman welcomed members of the Group and thanked them for coming to the meeting.

The Chairman welcomed to the meeting Mr Stephen Pilling and Ms Rachel Burbeck from the National Collaborating Centre for Mental Health who along with their colleagues have been developing the NICE guideline on the management of adult depression in primary and secondary care.

The Chairman informed members that the issues considered by the Expert Working Group are confidential and that members should not speak directly to the press but should refer any enquiries to the Chairman, MHRA or Press Office. At scientific meetings, they should take care not to give the impression that they speak on behalf of the Group.

2. APOLOGIES AND ANNOUNCEMENTS

- 2.1 Apologies were received from Professors Ebmeier and Drs Mukaetova-Ladinska, Raine and Jezzard.

3. MINUTES OF MEETING OF 31 MARCH and 28 APRIL

- 3.1 The minutes of the meeting on 31 March were agreed as a correct record. The minutes of the meeting on 28 April had been tabled on the day and therefore it was agreed that a hard copy should be sent out with the papers for the next meeting and these minutes would be formally agreed at the meeting on 30 June 2004.

4. DECLARATION OF INTERESTS

- 4.1 The Group confirmed that their interests were as declared at the meeting of 28 April 2004.

5.0 MATTERS ARISING

- 5.1 The Group was reminded that at the last meeting it had recommended that a formal meta-analysis of the paroxetine adult clinical trial data. The Group was informed that following the meeting some members of the Group were to meet with the secretariat to discuss the best way to take this forward and to consider what if any further data would be required from the MAH in order to perform this meta-analysis.

6.0 PAPERS

6.1 GPRD STUDY – FIRST DRAFT OF FINAL REPORT

- 6.1.1 The Group considered the first draft report of the GPRD study and made the following comments:

- i) the lack of progress, extensive focus on subgroups and internal inconsistencies were of concern;

- ii) any deviations from the protocol should be clearly documented
- iii) generalisability of the study results will depend on the characteristics of the study cohort and accuracy of GP classification of depression;
- iv) information should be included on the proportion of total anti-depressant prescribing that is captured in the GPRD study;
- v) concern was expressed about the classification of some drugs within the TCA group, especially mianserin;
- vi) the number of patients exposed to each drug within a category should be presented in the study results;
- vii) concern was expressed about the accuracy of differentiation between minor and mild depression. The consensus was that patients should not be excluded if they are treated, as this is a primary care study;
- viii) Suicide rates are consistent with other studies and with the pattern seen in national statistics. Clarification of the case definition method for suicides should be provided;
- ix) overall effects should be presented as well as sub-group analyses in addition to formal heterogeneity tests;
- x) further evaluation should be made of the reasons for TCA/SSRI prescribing in young people, especially those identified through free text.

- 6.1.2 The Group was informed that the Steering Group will input into a further draft of the report and that this will be presented at the June meeting of the EWG.

7.0 CURRENT LITERATURE

- 7.1 The Group was provided with recently published papers entitled 'Relationship between alcohol use disorders and suicidality in a psychiatric population', 'Global burden of depression in the year 2000' and 'CYP2D6 genotype: Impact on adverse effects and nonresponse during treatment with antidepressants – a pilot study'.

- 7.1.2 The Group noted this information.

8.0 PRESENTATION FROM MS RACHEL BURBECK

- 8.1 The Group was informed that a meeting had been held on 14 May between Dr Pilling and his colleagues on the NICE Guideline Group, Professor Weller and members of the secretariat. The purpose of this meeting was to update one another on the progress and next steps in terms of the respective reviews.
- 8.2 The Group heard a presentation from Ms Burbeck on the development of the NICE Guideline on the management of adult depression in primary and secondary care and the conclusions and recommendations reached by the Group.
- 8.3 The Group was provided with a copy of the NICE Guideline (short version) and the Quick Reference Guide that will accompany the NICE Guideline, along with the information document for the public.

- 8.4 The Group commented that:
- i) the flat dose response curve seen with paroxetine may be common to all SSRIs and related antidepressants and therefore it may be advisable that any statement about increasing dose is broadly consistent with the changes that will be made to the paroxetine product information;
 - ii) it may be advisable that mention is made of the need for careful monitoring of young adults who may be at an increased risk of suicidal behaviour;
 - iii) consistent terminology should be used in the NICE guideline and the Group's final report to describe reactions which may occur on stopping treatment and ideally to avoid confusion should be in line with the product information which describes these reactions as withdrawal reactions;
 - iv) the stepped care approach used in the NICE Guideline appears to be a useful model, however, prescribers may not be familiar with this type of model and further information may be useful.
- 8.5 The Group noted the concerns expressed in relation to venlafaxine, including its potential toxicity in overdose, and recommended that these are considered fully by the Group in its reviewing of the available data on the use of venlafaxine in adults.

9.0 ORAL UPDATES

9.1 Update on patient representation

- 9.1.1 The Group was informed that concerns had been expressed about the links between Depression Alliance and the pharmaceutical companies and that in light of this it may be necessary to rethink patient representation on the Group.
- 9.1.2 The Group commented that one option that could be considered is to recruit patient representatives from local PCT or hospital patient groups rather than from the voluntary patients organisations.

9.2 Fluoxetine juvenile toxicity study

- 9.2.1 The Group was updated on the progress of the ongoing application to extend the indication of fluoxetine for its use in the treatment of depression in children. The Group was informed that during this European procedure the MAH had submitted preliminary data from juvenile rat toxicity studies, which have been conducted at the request of the FDA.
- 9.2.2 Only limited information has been submitted but the available data suggest that fluoxetine may affect growth rate and sexual maturation. The final report is expected in late August at which point these data will be considered by the Group and also by the CSM's paediatric group.
- 9.2.3 The Group was informed that the FDA has also requested that the MAHs for the other SSRIs and the related antidepressants conduct juvenile animal toxicology studies. The secretariat has written to the relevant MAHs asking them to provide information on likely timeframe for completion of these

studies and requesting that they submit the preliminary and/or final reports as soon as these are available.

10.0 UPDATED WORKPLAN

- 10.1 The Group was informed that the main body of the work still to be completed is the review of the adult data.
- 10.2 Letters have been sent to the Marketing Authorisation holders (MAHs) for the remaining SSRIs and the related antidepressants mirtazapine and venlafaxine requesting information on the key questions raised by the paroxetine evaluation. Initial responses received from all the MAHs indicate that they are unlikely to submit their complete response until end of July at the earliest.
- 10.3 The Group was informed that whilst it is important to receive all the data requested, rather than delay the progress of the review, it may be advisable to request that the MAHs provide some elements of the request as a priority.
- 10.4 The Group agreed in principle to this proposal but expressed concern as to whether limiting the information requested would enable the information to be submitted sooner. The secretariat agreed to keep the Group closely informed of progress.

11.0 FRAMEWORK OF FINAL REPORT

- 11.1 The Group was provided with a paper outlining the proposed framework of the final report and made the following comments:
- i) the chapter discussing the burden of depressive illness should include information on the natural history of depression and reflect that this is a recurrent relapsing disease;
 - ii) the chapter discussing the efficacy data should include information on the meta-analysis conducted by the NICE guideline group;
 - iii) the chapter on the potential for dependence and the risk of withdrawal reactions should be combined;
 - iv) a chapter should be included on any areas for further research that are highlighted during the ongoing review.

12.0 ANY OTHER BUSINESS

- 12.1 The Chairman informed the Group that the next meeting would be held at 10am on 30 June 2004 May 2004.

MHRA
May 2004