

CSM/SSRIsWG/04/11th MEETING

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 28 APRIL 2004 AT 10AM IN CR1 AT MARKET TOWERS.

Members Present

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 Klaus Ebmeier	Professor of Psychiatry, University of Edinburgh
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

Professional staff of MHRA

Dr June Raine	Director, Post Licensing Division
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
Dr Frances Rotblat	CPMP Delegate, Post Licensing Division
Ms Claire Davies	Scientific Assessor, Pharmacovigilance Group
Dr Carlos Martinez	Head of Research, GPRD
Dr Stephan Rietbrock	Researcher, GPRD

Others

Professor Karen Facey	Consultant
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Observers

Dr Jane Moseley	Pharmacoepidemiology Team Leader, Pharmacovigilance Group
Dr Camilla Parikh	Medical Assessor, Pharmacovigilance Group
Dr Bill Richardson	Medical Assessor, Pharmacovigilance Group
Dr Martina Riegl	Medical Assessor, Post Licensing Division

Invited Experts

Dr Craig Whittington	National Collaborative Centre for Mental Health (present for items 1 to 5 only)
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1.0 INTRODUCTION

- 1.1 The Chairman welcomed members of the Group and thanked them for coming to the meeting.
- 1.2 The Chairman welcomed to the meeting Dr Craig Whittington from the National Collaborative Centre for Mental Health who along with his colleagues has been developing the NICE guideline on the identification and management of depression in children.
- 1.3 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 Chambers and Drummond and Drs Zwi and Jezzard.

3. MINUTES OF MEETING OF 27 FEBRUARY and 31 MARCH

- 3.1 The minutes of the meeting on 27 February were agreed as a correct record. However, the minutes of 31 March had only been circulated by email 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 26th May 2004.

4. DECLARATION OF INTERESTS

- 4.1 The Group confirmed that their interests were as declared at the meeting of 31 March 2004.

5.0 PRESENTATION FROM DR WHITTINGTON

- 5.1 The Group heard a presentation from Dr Craig Whittington on the findings of the meta-analysis of data from randomised controlled trials that compared an SSRI versus placebo in children and adolescents aged 5-18 years. Dr Whittington explained that the CSM's decision to publish a summary of the clinical trials of SSRIs in the treatment of depression in the paediatric population had allowed them to examine the safety and efficacy of SSRIs from unpublished data as well as studies that had been published in peer reviewed journals. They concluded that published data suggest a favourable risk-benefit

profile for some SSRIs in the treatment of depression, however, addition of unpublished data indicated that risks could outweigh the benefit of these drugs in paediatric depression, with the exception of fluoxetine.

- 5.2 Following his presentation Dr Whittington answered a number of questions and entered into general discussion about the data he had presented. The difficulty of taking publication bias into account in meta-analyses and the limitations of statistical analyses were discussed. It was agreed that it is important to be aware of the strengths and weaknesses of the different methods for statistical analysis when considering which is the most appropriate and also in interpreting the results.
- 5.3 Dr Ebemeir commented that he was aware of ongoing work by the Pittsburgh Group looking into a comparison of cognitive behavioural therapy and psychotherapy and offered to contact the Pittsburgh Group with a view to obtaining these data so that they may be considered by both NICE and the Group.
- 5.4 With regard to timescale of publication of the NICE guideline on childhood depression, Dr Whittington informed the Group that the first draft was likely to be available by October 2004. It was agreed that it was important to remain in regular contact with the NICE guideline groups both for adult and childhood depression.
- 5.5 The Chairman thanked Dr Whittington for his presentation.

6.0 PAPERS

6.1 Analysis of all adult clinical trials for Seroxat

- 6.1.1 The Group was reminded that the secretariat has reviewed all clinical studies of paroxetine with the exception of the pharmacokinetic studies on healthy volunteers. The Group was presented with a paper which provided an overview of the findings from all these studies. The Group was asked to advise on what, if any, further analyses should be conducted.
- 6.1.2 The Group advised that a formal meta-analysis of these data would be an important and logical next step.
- 6.1.3 The Group also commented that this exercise had been extremely important in highlighting potential areas of weakness in terms of definitions used by investigators for recording suicide-related events and also the definitions used by companies in searching databases for these events. Where possible, this information should be used to inform future regulatory guidance about adverse event reporting in clinical trials in this therapeutic area.

6.2 GPRD Study

6.2.1 The Group had a presentation on the latest results from the GPRD SSRI study, including results for both fatal and non-fatal outcomes.

6.2.2 Various factors affecting interpretation of the results were raised including:

General points:

i) Whether young people identified through free text search are different in terms of risk and exposure to those identified through Read codes.

ii) A disease severity code will be included in the analyses.

iii) Age at onset may be a confounder with type of disease varying with to age at onset and SSRI effect varying with underlying disease profile (eg bipolar disease).

iv) Confounding by indication may lead to an apparent increased risk.

v) Whether there is any increased risk in the elderly, the difficulty of defining incipient disease in the elderly was discussed.

Non-fatal outcomes:

i) Self laceration is likely to be a different outcome from other non-fatal outcomes.

ii) Whether serious non-fatal attempts should be included in this group. It was thought this is unlikely to introduce little noise as the proportion will be small.

iii) The signal for increased risk associated with SSRIs in children and adolescents and possibly young adults compared with TCAs reflects the clinical trial data.

6.2.3 The Group was informed that members of the Group, GPRD staff and members of the secretariat will compile a final draft report for consideration at the EWG June 2004.

6.2.4 The Chairman thanked the members of the Group and the secretariat for their continuing work on this study.

7. CURRENT LITERATURE

7.1 The Group was provided with recently published papers entitled 'Efficacy and safety of antidepressants for children and adolescents', 'Antidepressant medication in children' and 'Suicide by antidepressant intoxication identified at autopsy in Vienna'.

7.2 The Group noted this information.

8.0 ORAL UPDATES

8.1 Feedback from CPMP discussion of paroxetine referral

- 8.1.1 The Group was informed that at the April CPMP meeting there had been discussion on the MAH's responses to the key outstanding issues agreed in March. Two company hearings were also held in the confines of this CPMP meeting, prior to CPMP reaching an Opinion on the risk:benefit of paroxetine.
- 8.1.2 The Group was provided with a copy of the EMEA press release outlining the CPMP Opinion and the proposed changes to the product information for paroxetine. The Group noted that the CPMP Opinion was substantially in line with the CSM advice.
- 8.1.3 The Group was informed that that the CPMP Opinion will now forwarded to the European Commission for its agreement. Once the Commission Decision is received the product information for paroxetine products will need to be amended accordingly.
- 8.1.4 The Group was asked to comment on the need for further public communication, particularly on the possible increased risk in young adults. The Group commented due to differences in maturity and development there may be some young adult patients whose risk of suicidal behaviour may be similar to that in the paediatric population. The Group considered that this information should be communicated in a timely manner commensurate with the need to liaise with relevant colleagues including NICE to achieve consistent advice on what constitutes close monitoring.

8.2 Update on patient representation

- 8.2.1 The Group was informed that Jim Thomson, the Chief Executive of Depression Alliance, has been nominated as the lay representative. His nomination has been supported by all the other patient organisations that had been contacted.
- 8.2.2 The Group commented that it would also be helpful to have another patient representative. The Group advised that the Royal College of Psychiatrists patients and carers group should be contacted again regarding Eamonn O'Tierney's absence from meetings and whether in light of this they would wish to suggest another representative.

8.2 Media coverage

- 8.2.1 The Group was provided with a selection of press cuttings including i) the communication of CSM advice regarding the recommended dosage of paroxetine, ii) Mr Brook's resignation from the Expert Working Group and the

iii) the Whittington et al publication in the Lancet and the accompanying editorial.

- 8.2.2 The Chairman commented that there were two aspects of the media coverage surrounding Mr Brook's resignation that are factually incorrect. The first of these was the statement that the risk of suicide and suicidal ideation is dose-related, as the Group had concluded that there is no good evidence to suggest that this is the case. The second related to the circumstances which led to CSM issuing advice on the lack of additional efficacy for some indications at higher than the recommended dosages, when new usage data suggesting that patients were being started at doses higher than those recommended coupled with the likely timescale for the European referral for paroxetine led to the decision to issue the communication in March.

9.0 ANY OTHER BUSINESS

- 9.1 The Chairman informed the Group that the next meeting would be held at 10am on 26 May 2004. It was agreed that once the dates for the July and August meetings had been finalised these dates would be emailed to members of the Group.

MHRA
April 2004