REPORT OF THE CSM EXPERT WORKING GROUP ON THE SAFETY OF SELECTIVE SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS

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Foreword

Introduction

During the course of the work of the Expert Group on the Safety of Selective Serotonin Reuptake Inhibitors (SSRIs), this important class of medicines has been in the glare of the media spotlight on a number of occasions.

Just as the Group was set up in the wake of particular public concerns about the safety of SSRIs, so the work of the Group has generated its own publicity. On the Group's first finding, resulting from clinical trial data on the use of paroxetine in the paediatric population, the Committee on Safety of Medicines (CSM) issued advice to patients and prescribers in June 2003. In September 2003, CSM advice on the use of venlafaxine in the same age group was issued and then in December 2003, when the Group's review of paediatric data was complete, further advice on the remainder of the eight medicines included in the Review was issued.

At each stage of the Group's work, its members have been very clear in their wish to release the evidence on which their advice has been based. In releasing this comprehensive report on the work undertaken by the Group, I hope the precedent set by the Group will be taken up by others.

The crucial role of the lay members of the Group has also set a precedent which I know the MHRA are taking forward in other ways. I know I echo the sentiments of the whole Group in saying that the patient perspective has been a key theme running though all our considerations, from reporting of suspected adverse drug reactions to the production of clear, meaningful patient information which supports the safe use of these medicines.

Both in relation to the continuing media attention, reflecting public concerns, and wider regulatory events, the work of the Group has not taken place in a vacuum. The Group has supported the European review of paroxetine and been informed by the work of the Food and Drug Administration in the United States. The Group has shared its conclusions with regulators world-wide and, we hope, informed the wider debate.

Conclusions of the Group

The conclusions of the Group and the evidence on which they are based are set out in the report. Inevitably, they represent a snap shot in time, based on the evidence available to the Group during the course of its work. Knowledge of drug safety develops as we learn more about the safety profile of medicines in use and, in that respect, SSRIs are no different to other medicines designed to treat potentially life-threatening illness.

If the Group has done its work well, this review will be recognised as the most comprehensive review of the available data this far. Its conclusions will have an impact on the regulation of these medicines and, together with those of the National Institute for Clinical Excellence, there will be implications for clinical practice. Importantly,

however, I hope the legacy of the Group will also be in looking forward, to identifying the further work necessary to establish safety, advising on study design and identifying the lessons to be learned.

Acknowledgements

As Chairman of the Expert Group, I am indebted to all the members of the Group. Their commitment has been unstinting and their resolve, carefully and painstakingly to look at all the evidence available, utterly determined.

I have already mentioned the lay members. My thanks also go to members of the Group who wrote large sections of the final report.

On behalf of the Committee, I also wish to thank those who gave evidence to the Group and whose contribution helped to shape the conclusions in the final report.

Finally, I should like to thank the secretariat the MHRA provided to support the work of the Group.

Professor Ian V D Weller MD FRCP – Chairman
December 2004

Executive summary

Context

Selective Serotonin Reuptake Inhibitors (SSRIs) and related antidepressants have been used in the treatment of depressive illness and anxiety disorders since the late 1980s.

The safety of SSRIs has been under close review by the Medicines and Healthcare products Regulatory Agency (MHRA) since the products were first marketed.

Background

In May 2003, in response to continuing public concerns about the safety of SSRIs, an Expert Working Group of the Committee on Safety of Medicines (CSM) was convened to investigate ongoing safety concerns with these medicines, in particular around suicidal behaviour and withdrawal reactions/dependence.

The Expert Working Group has studied all the available data including that from published and unpublished clinical trials, spontaneous reporting data from health professionals and patients, evidence from key stakeholders and data from the General Practice Research Database (GPRD). This included a study commissioned by the MHRA.

Output of the Working Group

The work of the Group resulted in CSM advice on the use of SSRIs in the paediatric population, advice to the European review of paroxetine, conclusions on the key issues relating to adult use which are general to all the medicines included in the review, and regulatory action in relation to particular medicines. This is the final report of the Group.

Use of SSRIs in children and adolescents

Based on the work of the Group, CSM issued advice on the use of SSRIs in the paediatric population in June, September and December 2003. In summary, that advice was that 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-18s 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, occurred in those treated with some of the SSRIs compared with placebo.

Young adults
The increased risk of suicidal behaviour seen in children and adolescents with depressive illness treated with SSRIs raised the question as to whether there was a similar increased risk in young adults. The clinical trial data for each product was reviewed in relation to a possible effect in young adults, and the GPRD study looked specifically at this age group. From these analyses, the Group concluded that 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. The Group also recommended that in further research on the safety and efficacy of SSRIs, young adults should be assessed separately.

Use of SSRIs in adults
In relation to the use of SSRIs in adults, the Group focused its attention on three areas of concern – suicidal behaviour, withdrawal reactions/dependence and dose.

Suicidal behaviour – adults
To address the question of a possible causal association between SSRIs and suicidal behaviour, the Group reviewed clinical trial data (published and unpublished), studies on the GPRD and spontaneous reports from health professionals and patients. The conclusions of the Group on this issue can be summarised as follows:

- 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 tricyclic antidepressants (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

It has been known for some time that, as with other antidepressants, the SSRIs and related antidepressants are associated with withdrawal reactions, although different SSRIs appear to cause withdrawal reactions to different extents. The Group considered data from clinical trials, the published literature and spontaneous reports from health professionals and patients. The Group's conclusions can be summarised as follows:

- 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 and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances.

- Awareness of the risk of withdrawal reactions associated with SSRIs needs to be increased amongst both prescribers and patients.

- There is evidence that withdrawal reactions are less severe when the dose is tapered gradually over a period of several weeks, according to the patient's need. Availability of low dose formulations to allow gradual titration is important.

- 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

During the detailed review of the risks and benefits of paroxetine, the Group looked at the information supporting the recommendation that patients not responding to the starting dose of paroxetine for depressive illness may benefit from dose increases.

Upon review, the Group considered that there was no evidence from clinical trials that increasing the dose above that recommended increases efficacy in the treatment of depressive illness. This review, combined with evidence from usage databases that a

proportion of patients were being started on paroxetine at doses higher than those recommended, led CSM to advise that a reminder of the recommended dose of paroxetine should be sent to health professionals. This communication took place on 11 March 2004.

It was considered appropriate that the effects of increasing the dose of all SSRIs, both in terms of efficacy and safety, should be investigated. The conclusions of the Group in relation to dose response can be summarised as follows:

- For the majority of SSRIs in the treatment of depressive illness, clinical trial data do not show an 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.

- 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.

Patient experience

The Group considered evidence from patients treated with SSRIs from a number of different sources, including written reports of patients' experiences and feedback from meetings with patient support groups. The reports provide a valuable insight into the experiences of patients and the impact these had on their lives. Feedback on the inadequacy of the patient information for SSRIs led the Group to advise extensive user testing for the Seroxat Patient Information Leaflet. The resulting leaflet will be used as a model for the leaflets of all other SSRIs.

Clinical implications

The Group has worked closely with NICE to ensure that their parallel work on the clinical management of depression and anxiety was informed by the conclusions of the Group.

Further work/next steps

The review has identified several areas for further research on the use of antidepressants.

1. INTRODUCTION

This is the final report of the work of the Committee on Safety of Medicines' (CSM) Expert Working Group (EWG) on SSRIs, which was established in May 2003 to investigate ongoing safety concerns with these medicines.

1.1 Background

Selective Serotonin Reuptake Inhibitors (SSRIs) have been used in the treatment of depressive illness and anxiety disorders since the late 1980s. The safety of SSRIs has been under review by the Medicines and Healthcare products Regulatory Agency (MHRA – formerly the Medicines Control Agency) since the products were first marketed. Two areas of public concern and scientific debate have been the issues of withdrawal reactions on stopping SSRIs and whether there is an increased risk of suicidal behaviour associated with treatment with SSRIs.

The CSM has considered the safety of SSRIs and, in particular, the issues of suicidal behaviour and withdrawal reactions on a number of occasions. Previous CSM considerations on SSRIs have led to harmonisation of the safety information provided for all SSRIs (2000); updated warnings about withdrawal reactions with all SSRIs; communications to prescribers in the drug safety bulletin 'Current Problems in Pharmacovigilance' in 1993 and 2000; and warnings added to the patient information leaflets (PIL) that, as with all antidepressants, suicidal thoughts may occur or increase in the early stages of treatment. These issues have also been considered by the European scientific committee, the Committee for Proprietary Medicinal Products (1998 to date).

Withdrawal reactions and suicidal behaviour have remained of public concern; this concern has recently focused on one SSRI, Seroxat (paroxetine). In May 2003 the CSM established an EWG to consider further the safety of SSRIs, with particular reference to suicidal behaviour and withdrawal reactions.

Very shortly after the EWG was established, clinical trial data on the use of paroxetine in children and adolescents were received. These data led the EWG to make its first priority a class review of the risks and benefits of all SSRIs in children and adolescents. This was completed in December 2003. The EWG then moved on to review the safety of SSRIs in adults in the key areas of concern.

1.2 Licensing status of SSRIs and related antidepressants in adults

Table 1.1 summarises the products included in the review and their licensed indications in the adult population:

Table 1.1: Current licensing status of antidepressants included in the review

Drug ***Brand name***	**UK launch**	**Current indications for treatment in the UK**
Fluvoxamine *Faverin*	1987	Major depressive disorder, obsessive compulsive disorder (OCD)
Fluoxetine *Prozac*	1989	Major depressive episodes, OCD, bulimia nervosa
Sertraline *Lustral*	1990	Depressive illness and accompanying feelings of anxiety, OCD, post-traumatic stress disorder (PTSD)
Paroxetine *Seroxat*	1991	Depressive illness accompanied by anxiety, OCD, panic disorder with or without agoraphobia, social anxiety disorder, PTSD, general anxiety disorder
Citalopram *Cipramil*	1995	Depressive illness, panic disorder with or without agoraphobia
*Venlafaxine *Efexor*	1995	Depressive illness and accompanying anxiety
**Mirtazapine *Zispin*	1997	Depressive illness
Escitalopram *Cipralex*	2002	Depressive illness, panic disorder with or without agoraphobia

*V*enlafaxine is a serotonin and noradrenaline reuptake inhibitor. While it is not an SSRI it is included in the review because it shares some of the properties of SSRIs.*

***Mirtazapine is a pre-synaptic alpha-2 antagonist which increases noradrenergic and serotonergic neurotransmission. It was included in the review because of the availability of recent clinical trial data in children and adolescents.*

1.3 Remit of the Expert Working Group on the safety of Selective Serotonin Reuptake Inhibitors

The remit of the EWG, which was agreed at its first meeting of 23 May 2003, was as follows:

- To consider the currently available evidence with regard to behavioural disorders, particularly suicidal behaviour, suicide attempt and suicide and a possible causal association with SSRIs;
- To consider the currently available evidence on withdrawal reactions and possible dependence associated with SSRIs and any implications for the risk:benefit balance;
- To consider the adequacy of the current product information for SSRIs and to make proposals to strengthen this if necessary;
- To consider the need for wider communication on the safety of SSRIs;
- To advise the Committee on Safety of Medicines of their conclusions.

Members of the EWG are listed in section 1.5 and include members with specialist expertise in psychiatry, child and adolescent psychiatry, epidemiology and statistics, as well as lay representation. The EWG met 17 times over the period May 2003 to November 2004.

1.4 Work of the Group

The following summarises the key data sources considered by the EWG.

Clinical trial data
The pharmaceutical companies which applied for the original licence for each of the SSRIs were asked to supply data from all the randomised controlled clinical trials (RCTs) (placebo-controlled and active-controlled) that the company had undertaken for that product. Each company was asked to analyse the results from all relevant company sponsored trials to a pre-specified protocol and to supply the case narratives for all reports of suicidal behaviour. These data were checked by the MHRA for consistency and completeness. Further information and additional data were requested as necessary.

These data were to be analysed as specified by the MHRA to evaluate i) the risk of suicide, suicidal thoughts and self-harm; ii) the risk of withdrawal reactions; and iii) information from dose response studies. The results of these analyses are provided in chapters 6 through to 9.

With regard to the risk of suicidal thoughts/behaviour, specific terms were identified by the MHRA in order that consistent results were available between companies. A brief review of the data supplied is provided in table 1.2.

Spontaneous reporting data from health professionals and patients
Reports of suspected adverse drug reactions (ADRs) received by the MHRA through the Yellow Card Scheme have been assessed during the review.

Patient reports have also been received via the BBC's *Panorama* programmes (in collaboration with the mental health charity, Mind) and from people who contacted the MHRA. These reports have formed part of the review by the EWG and are considered in chapter 10.

Commissioned study
The MHRA commissioned an observational study using the General Practice Research Database (GPRD), with advice from members of the EWG, to investigate the association between antidepressants and self-harm.

Evidence from experts
A number of experts were invited to give evidence to the EWG on specific aspects of the review, including Dr Andrew Herxheimer, Professor David Healy, Mr Charles Medawar and Professor Munir Pirmohamed.

Published literature
Regular searches of the scientific and popular media were made to identify all relevant literature that might be useful to the review. References to published literature are provided at the end of each chapter.

Table 1.2
Description of adult clinical trial data provided by the pharmaceutical companies for this review

Company	Drug	Number of studies examined for suicide-related events	Number of patients in controlled studies examined for suicide-related events	Comments on response to request for data on suicide-related events	Number of studies examined for withdrawal events	Number of dose response studies
Lundbeck	Citalopram	9 (26)	Citalopram 1,215 (4,500) Placebo 520 Active comparator (1,900)	9 GCP* studies in the initial analysis. Extended analysis provided data from 26 RCTs (numbers provided in brackets)	4 studies – 2 relapse prevention and 2 recurrence studies	4 fixed dose
	Escitalopram	34	Escitalopram 3,484 Placebo 1,800 Active comparator 1,800		6 studies – 4 of these used DESS checklist	2 fixed dose
Lilly	Fluoxetine	135	Fluoxetine alone 11,989 Placebo 5,141 Active comparator 4,160	Large number of RCTs performed outside the US were excluded from the suicide-related events database. Lilly have provided a proposal for retrieving these data, but this cannot be completed in the required time-frame for the report. Report to be updated when data are available	17 controlled trials – none specifically designed to examine withdrawal	4 fixed dose, 1 non-responder
Solvay	Fluvoxamine	48 (86)	Fluvoxamine 4,186 Placebo 3,396	Data from 48 RCTs were included, data from a further 38 active-controlled trials were provided separately	70 controlled trials – none specifically designed to examine withdrawal	0
Organon	Mirtazapine	41	Mirtazapine 2,618	In their initial analysis the MA holder was unable to include a full analysis of many	Examination of RCT data	2 fixed dose**

			Placebo 388 Active comparator 2,035	seemingly relevant studies. An interim analysis of all relevant studies has been provided by the MA holder. The MA holder has agreed to provide a revised combined analysis which is awaited.		
GlaxoSmithKline	Paroxetine	95	Paroxetine >13,000 Placebo 5,808 Active comparator 4,969	The MA holder provided anonymised patient data, which was used for a meta-analysis	13	6 fixed dose, 1 non-responder
Pfizer	Sertraline	156	Sertraline 11,548 Placebo 5,207 Active comparator 5,696		5 withdrawal trials	5 fixed dose
Wyeth	Venlafaxine Venlafaxine ER	42	Venlafaxine IR 2,730 Venlafaxine ER 3,423 Placebo 2,962 Active comparator 2,834	23 completed trials and 11 ongoing trials	28 controlled trials – none specifically designed to examine withdrawal	3 fixed dose, 1 non-responder 5 fixed dose

* GCP = Good Clinical Practice
** One study was terminated early

1.4.1 Output of the Group

An interim progress report of the EWG was published in September 2003[1]. The EWG also issued key recommendations during the period of the review as data became available. The following summarises the output of the EWG to date:

- Advice on the use of SSRIs and related antidepressants in children and adolescents was made available in June, September and December 2003[2 3 4].

- In June 2003, a revised Summary of Product Characteristics (SPC) and PIL for paroxetine, which included warnings about use in the paediatric population and updated warnings relating to withdrawal reactions and suicidal behaviour, was made available. This was available in the Electronic Medicines Compendium and pharmacists were alerted in the Pharmaceutical Journal.

- An article in the September 2003 edition of the MHRA/CSM drug safety bulletin 'Current Problems in Pharmacovigilance', which is sent to all doctors and pharmacists in the UK, reminded prescribers of CSM advice in relation to the use of paroxetine in under 18s and reminded prescribers of the licensing status in children of other SSRIs and related antidepressants[5].

- A fact sheet on SSRIs to aid discussion between prescribers and patients accompanied the September 2003 edition of 'Current Problems in Pharmacovigilance'[5].

- New advice was made available in the British National Formulary on paediatric use of paroxetine in September 2003.

- Advice reminding prescribers of the recommended dose regimen for paroxetine was issued in March 2004[6].

- A reminder of key prescribing advice for paroxetine was issued in the October 2004 edition of 'Current Problems in Pharmacovigilance'[7].

1.4.2 Report of the Group

This report provides background on the regulatory history of SSRIs in the UK, the burden of depressive illness, the sources of evidence considered, and pharmacological considerations. The report then outlines the key areas of concern examined by the EWG, provides a summary of the data considered and the key findings of the EWG in relation to those areas. Finally, the report looks forward to consider what lessons have been learned during the process of the review and what further research is required into the safety of SSRIs.

1.5 Membership of the Expert Working Group on the safety of SSRIs

Professor Ian V D Weller MD FRCP - Chairman
Professor of Sexually Transmitted Diseases and Director of Centre of Sexual Health and HIV Research, Royal Free and University College Medical School, University College, London

Professor Deborah Ashby BSc MSc PhD CStat Hon MFPH Hon MRCR
Professor of Medical Statistics, St Bartholomew's and the London, Queen Mary's School of Medicines and Dentistry, University of London

Mr Richard Brook (from May 2003 to March 2004)
Chief Executive of MIND

Professor Mary G A Chambers Bed (Hons) DPhil RN DN (Lond) RNT
Chief Nurse and Professor of Mental Health Nursing at South West London and St George's Mental Health NHS Trust

Dr Jonathan D Chick MA MB ChB MPhil FRCPsych FRCP (Ed)
Consultant Psychiatrist, Alcohol Problems Service, Royal Edinburgh Hospital, and part-time Senior Lecturer at Edinburgh University

Professor Colin Drummond MD FRCPsych
Professor of Addiction Psychiatry, St George's Hospital Medical School, London

Professor Klaus P Ebmeier MD
Professor of Psychiatry, University of Edinburgh

Professor David J Gunnell MB ChB MRCGP FFPH MSc PhD
Professor of Epidemiology, Department of Social Medicine, Bristol University

Ms Hilary Hawking (from October 2004 to date)
Clinical Governance User representative for South West London and St George's Mental Health NHS Trust

Dr Elizabeta Mukaetova-Ladinska MD PhD MRCPsych
Consultant Psychiatrist, Newcastle General Hospital, and Senior Lecturer in Old Age Psychiatry, Newcastle University

Mr Eamon O'Tierney MA (Cantab) ASA (from May 2003 to September 2003)
Member of the Royal College of Psychiatry's Committee for Patients and Carers

Dr Ross J Taylor MD FRCP (Edin) FRCGP DCH
Senior Lecturer in General Practice, University of Aberdeen

Dr Ann York MB BS MRCPsych
Consultant and Honorary Senior Lecturer in Child and Adolescent Psychiatry, Child and Family Consultation Centre, Richmond Hospital, Surrey

Dr Morris Zwi MBBCH FRCPsych
Consultant Child and Adolescent Psychiatrist, South West London and St George's Mental Health NHS Trust

Visiting experts for the meeting of 4 June 2003

Dr Santosh Paramala
Consultant Child and Adolescent Psychiatry, Guy's Hospital, London
Professor Peter Hill
Professor of Child and Adolescent Psychiatry, Great Ormond Street Hospital for Sick Children, London
Professor Eric Taylor
Professor of Child and Adolescent Psychiatry, Institute of Psychiatry, King's College, London

Invited experts who presented evidence to the EWG

Professor David Healy
Professor of Psychological Medicine, Hergest Unit, University of Wales, Bangor
Dr Andrew Herxheimer
Emeritus Fellow at the UK Cochrane Centre in Oxford
Mr Charles Medawar
Social Audit
Professor Munir Pirmohamed
Professor of Clinical Pharmacology, Liverpool University

Patients, relatives and their representatives who gave evidence to the EWG

Seroxat User Group
Online Seroxat Support Group
Mr Graham Aldred

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2 REGULATORY HISTORY

This chapter outlines the regulatory history of SSRIs in the UK with particular reference to the two mains areas of concern - withdrawal reactions and suicidal behaviour.

2.1 Withdrawal reactions in association with SSRIs

It has been known for many years that symptoms can occur on the withdrawal of antidepressants. Syndromes occurring on the withdrawal of tricyclic antidepressants (TCAs) have been defined and severe reactions have been noted on the withdrawal of monoamine oxidase inhibitors (MAOIs) [1]. Since the early 1990s, it has become clear that the SSRIs can also be associated with withdrawal reactions, although different SSRIs appear to cause withdrawal reactions to different extents[2]. The greatest number of spontaneous reports of withdrawal reactions have been associated with paroxetine. An article in 'Current Problems in Pharmacovigilance' in 1993 highlighted the risk of withdrawal reactions associated with paroxetine[3].

In late 1997, an article entitled 'The Antidepressant Web' by Charles Medawar raised concern that some people may become dependent on SSRIs[4]; this prompted a review of withdrawal reactions and dependence with these drugs. The related antidepressants venlafaxine and nefazodone (which is no longer marketed within Europe) were also included in the review. The CSM considered this issue in early 1998.

The issue was also discussed at European level by the Committee on Proprietary Medicinal Products (CPMP) and its Pharmacovigilance Working Party (PhVWP). At the December 1998 meeting of the PhVWP it was decided that France and Germany should carry out further evaluation of the issue of dependence associated with the SSRIs. The outcome of this review was a CPMP position paper which was published in April 2000[5]. The conclusion of the CSM and the CPMP was that all SSRIs are associated with withdrawal reactions; however, they are not drugs of dependence. Following the completion of a class review of the safety profile of SSRIs and a review of suicidal behaviour with SSRIs, a further article covering these aspects and the issue of withdrawal reactions was published in 'Current Problems in Pharmacovigilance' in September 2000[6].

The CPMP position paper (2000) contained key principles in relation to withdrawal reactions for inclusion in the product information for all SSRIs throughout Europe. The UK product information for all SSRIs and venlafaxine was updated accordingly.

Concern about withdrawal reactions with SSRIs continued and more recently has focused primarily on paroxetine. The BBC's *Panorama* programmes in October 2002 and May 2003 highlighted the level of public concern.

2.2 Suicidal behaviour in association with SSRIs

In the UK, this issue was first reviewed by the CSM following publication of a case series by Teicher et al (1990)[7] which stimulated scientific debate and intense media interest. In 1992, following further review, an article was published in the 'Current Problems in Pharmacovigilance' which stated "there is little to support the suggestion that fluoxetine induces suicidal or aggressive behaviour"[8].

Following close monitoring of spontaneous suspected adverse drug reaction reports, there was a UK exercise in 1998-2000 to develop harmonised safety information for all SSRIs. During this process, the CSM advised that the summary of product characteristics (SPC) should reflect the general clinical experience that suicidal behaviour may increase in the early stages of treatment with any antidepressant.

Dr (now Professor) David Healy raised the issue of suicidal behaviour with SSRIs in his publication 'A Failure to Warn' in 1999[9]. Concerns were also raised that SSRIs may be associated with the development of psychomotor restlessness/akathisia-like restlessness, which in turn may precipitate agitation and suicidal behaviour[10].

The CSM considered the available data in June 2000 and concluded that it was impossible to answer the question of whether SSRIs caused suicidal behaviour in a small subpopulation of patients. It was decided that the issue should be kept under review and formally reviewed every two to three years.

The CSM advised that patient information leaflets for the SSRIs, as with any antidepressants, should be updated to include a warning that suicidal thoughts may occur or increase in the early stages of treatment and that urgent medical advice should be sought in the event of such symptoms.

The UK presented the assessment on suicidal behaviour with SSRIs to the Pharmacovigilance Working Party (PhVWP) in 2000. All EU member states agreed with the scientific conclusions of the UK assessment.

The CSM considered data relating to suicidal behaviour, aggression and akathisia in December 2001 and concluded that:

- the evidence was not sufficient to confirm a causal association between SSRIs and suicidal behaviour, although an effect in a small high-risk population could not be ruled out;
- the risk of akathisia occurring in association with treatment should be added to the SPCs of all SSRIs.

This assessment report was then discussed at the PhVWP which agreed with the conclusions of the UK assessment report but considered that further discussion was required about the definition of the term akathisia.

On 21 November 2002, a group of CSM and external experts was called together to hear Dr (now Professor) David Healy present his research in relation to suicidal behaviour, including a reanalysis of human volunteer studies on fluoxetine.

The conclusions of this meeting were that:

- the evidence presented did not justify a change to the regulatory position;
- changes to the UK Seroxat PIL were required to clarify warnings on withdrawal reactions.

The meeting recommended the following further work to investigate suicidal behaviour:

- a study using the GPRD;
- reanalysis of clinical trial data on fluoxetine.

A further meeting of this expert group had been planned for March 2003. However, the Seroxat User Group, a group of 4,000 patients and former patients, called into question the independence of the members of the group in view of declarations of interest in the pharmaceutical industry by two members. Following legal advice, the meeting in March was cancelled and the group dissolved. It was important that this work was continued, and in May 2003 the CSM established its Expert Working Group on the Safety of SSRIs.

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3 BURDEN OF DEPRESSIVE ILLNESS AND SELF-HARM

This chapter outlines the burden of depressive illness and the epidemiology of suicide and self-harm.

3.1 Depressive illness

3.1.1 Definition of depressive illness

Depression is a term used to describe a persistent lowering of mood and, as such, encompasses a wide range of severity. Depression may be part of a unipolar or a bipolar disorder, the latter being also associated with at least one period of abnormal mood elevation. The main focus of this section and the report is on unipolar depression.

In order to ease communication about and research upon the disorder, specific definitions of depression have been developed within the ICD-10 (International Classification of Diseases - World Health Organisation (WHO)) and the Diagnostic and Statistical Manual for Mental Disorder (DSM IV, from the American Psychiatric Association). The ICD-10, the most frequently used classification in the UK, includes a number of conditions which are associated with depressive symptoms - mixed anxiety and depression within the anxiety disorders as well as mild, moderate and severe depressive episodes, recurrent depressive disorder (mild, moderate or severe), cyclothymia and dysthymia, mixed affective states and some other categories. The severe depressive disorders can additionally be categorised as with or without psychotic symptoms (see below). The classifications include descriptions of the sub-types of disorders which guide diagnosis.

Depression usually occurs in episodes lasting from weeks to months but occasionally can become chronic, lasting several years. Lowered mood, irritability, suicidal thoughts, plans and acts, reduced enjoyment of usually pleasurable activities including sexual activity, hopelessness, problems with concentration and memory, guilt, feelings of worthlessness, anxiety, reduced reactivity of mood, may all be present together or at different times. Depression is associated with a range of so-called biological symptoms such as alterations in sleep, alterations in appetite, sometimes restlessness and agitation or alternatively slowing of thoughts or movements, low energy levels, aches and pains with no apparent cause and greater sensitivity to physical pain or noise. Severe depression may be associated with psychotic symptoms such as hallucinations (abnormal perceptual experiences, as in hearing voices) and delusions (unrealistic and false beliefs, such as impending poverty, incurable illness or even death, and guilt or impending punishment).

3.1.2 Prevalence/incidence in the UK

Depression may begin at any age, including in childhood. Some people may have an isolated episode but more than half will have further episodes, some having increasingly frequent episodes as they get older. It is estimated that people with depressive illness on

average suffer four episodes in a lifetime. Severe depression is associated with increased morbidity and mortality. The overall suicide rate, if full life-time follow-up of all those with affective disorder (including depression) were achieved, has been estimated as 6%[1] . Those in general medical settings who also have depression tend to have more pain and worse physical, social and role functioning. There are high levels of comorbidity of other mental health problems with severe depression, such as substance misuse, anxiety, panic disorder, obsessive compulsive disorder (OCD), eating disorders and borderline personality disorder. Mood disorders are common in those with physical illness.

Data from the Office for National Statistics (ONS) survey of psychiatric morbidity[2] suggest that the prevalence of ICD-10 depression in males and females between 16 and 74 years is 2.6% and mixed anxiety/depression is 8.8% (Table 3.1).

Table 3.1: Rates of depressive and anxiety disorders (per 1,000 participants interviewed, ONS data)

	Males	Females	All
Mixed anxiety and depressive disorders	68	108	88
Generalised anxiety disorder	43	46	44
Depressive episode	23	28	26
All phobias	13	22	18
Obsessive compulsive disorder	9	13	11
Panic disorder	7	7	7
Any neurotic disorder	135	194	164

NB people may have more than one type of disorder
Cases identified using CIS-R and categorised into ICD-10 categories of disorder
N=8580

Thomas and Morris[3] estimated that in 2000 there were 2,660,000 cases of depression in England. In 20% of those with severe depression, symptoms persist for more than two years[4]. Almost a third of those recovering from severe depression suffer a relapse within three months and half suffer a further episode in the absence of continuation treatment[5].

3.1.3 Depressive illness in children and adolescents

In order to have their basic physical and emotional needs met, children are dependent on parents or carers. Therefore, environmental factors are likely to be more important in the development of depression in children compared to adolescents or adults. However, childhood depression does exist.

It is only since the 1970s that depressive illness in childhood and adolescence has been recognised. There are three main differences in depressive illness in children compared with adults:

- there are developmental issues that relate to the age differences in the presentation of affective disorders;
- children have different cognitive abilities, giving rise to differences in their experience of the cognitive features that are associated with adult depressive illness;
- to apply adult criteria to children assumes that they are correctly able to report their experience of depressive illness.

Depressed children may present with somatic complaints, suicidal behaviour, problems at school, school attendance difficulties and disruptive behaviour. The course of depressive episodes in children may involve fluctuating symptoms that can go unnoticed, but suspicion about depression needs to be followed up with direct interview and observation of the child as well as obtaining further information about the child's emotional state from parents and teachers[6].

The ONS survey of the mental health of children and adolescents in Great Britain[7] estimated that depressive illness occurs in 0.2% of boys and 0.3% of girls between the ages of five and 10 years, and 1.7% of boys and 1.9% of girls between the ages of 11 and 15 years.

The criteria for diagnosis of depressive illness in children and adolescents are the same as the criteria for adults. Depressive symptoms are very common in adolescents and depressive illness should therefore only be diagnosed when the following are present: significantly impaired social functioning, psychopathological symptoms such as a suicide attempt, and significant suffering from the symptoms. The aetiological factors of depressive disorder in young people appear to be related to early adverse experiences and certain temperamental features. These factors may predispose young people to develop depressive illness, especially in those genetically at risk.

3.1.4 International burden of depressive illness

Recent years have seen a focus on the burden of mental illness on health and productivity throughout the world. Data collected by the *Global Burden of Disease* study[8], conducted by the World Health Organization, the World Bank and Harvard University, revealed that mental illness, including suicide, accounts for over 15% of the burden of disease in established market ('western') economies such as the United States. This is more than the disease burden caused by all cancers. The burden on carers and the families of those with depression is probably as great as for those caring for people with dementia. The irritability and pessimism of a person with depression can have a profound impact upon family and carers. A general feeling of gloom, and the sense that care needs to be taken in interacting with the depressed person, can disrupt the family and its routine activities. Family members may feel they have to take on extra responsibilities and perhaps cope with a reduced family income if the depressed person is unable to work.

3.1.5 Treatment options

Treatment of depressive illness in adults

The National Institute for Clinical Excellence (NICE) (www.nice.org.uk) has developed a clinical guideline on the management of depression in adults in primary and secondary care. This guideline recommends a stepped care approach to treatment. For mild depression treated in primary care, the recommended approach includes watchful waiting, guided self-help, computerised cognitive behavioural therapy (CBT), exercise or brief psychological interventions, with drug treatment and longer psychological interventions normally being introduced only for moderate or severe depression. Psychological interventions include CBT which focuses on behavioural activation and dysfunctional thought patterns. An alternative approach is interpersonal psychotherapy which focuses primarily on difficulties in personal relationships. Combined psychological and drug treatment is recommended for severe or recurrent treatment-resistant depression.

Pharmacological approaches to the treatment of depression focus on the use of a range of antidepressants, including TCAs, MAOIs, and SSRIs and related antidepressants. Augmentation of antidepressants with lithium or another antidepressant is only recommended for treatment-resistant depression which should be treated by mental health specialists. Electro-convulsive therapy (ECT) was the subject of a recent NICE Technology Appraisal[9] and is recommended only for severe depression which is potentially life-threatening.

Treatment of depressive illness in children and adolescents

Treatment in children and adolescents is mainly based on psychosocial interventions such as CBT, interpersonal psychotherapy, family interventions and pharmacotherapy. Trials have investigated the efficacy of several forms of psychotherapy in depressed adolescents, but only trials of CBT have included pre-adolescents[6].

The National Institute for Clinical Excellence (NICE) is developing a clinical guideline for the management of depression in children and young people aged under-18[10], which is expected to be published in September 2005. The current version of this guideline is presently out for consultation and provides recommendations on a stepped-care model, with watchful waiting, non-directive supportive care and group psychological interventions for mild depression. The guideline also makes draft recommendations concerning the use of fluoxetine, but only in combination with psychological interventions and after a previous trial of psychological interventions has failed. However, as the guideline is subject to further development and consultation it is possible that these recommendations will change.

As there are currently no drugs licensed for the treatment of depressive illness in children in the UK, pharmacological treatment is based on the off-label use of drugs licensed for use in depressive illness in adults. Rigorous evidence for the efficacy of treatment of

depressive illness in children and adolescents has been lacking. A Cochrane systematic review of tricyclic antidepressants identified three trials of 64 pre-pubertal children. A weak trend favouring placebo over active treatment was found[11]. As it has become clear that tricyclic antidepressants are not an effective treatment in either children or adolescents, pharmacological treatment has tended to focus on the use of SSRIs.

3.2 The epidemiology of suicide and non-fatal self-harm

3.2.1 The incidence of suicide, self-harm and suicidal thoughts

Suicide accounts for only one to two percent of deaths in developed countries. In England and Wales the rate of suicide in the general population is around nine per 100,000 persons per year (Source: ONS, 2001). Suicide rates are approximately three times higher in males than females. Currently, the highest rates of suicide in England and Wales are in 25- to 34-year old men. The most commonly used method of suicide in males is hanging; self-poisoning by overdose of medicinal drugs is the second most frequently used method. Amongst females, around half of all suicides are from overdose; hanging is the second most frequently used method[12].

In England and Wales, the 'diagnosis' of suicide is arrived at as a result of a coroner's investigation. As coroners vary in their interpretation of official guidance for reaching a verdict of suicide, official suicide statistics usually combine suicide and undetermined (open verdict) deaths, as the latter category largely comprises suicides[13 14].

The incidence of self-harm presenting to hospital services is some 30 times higher than that for suicide. There are no national data on the incidence of self-harm ('deliberate' self-harm and 'attempted suicide'). The rate of hospital admission for self-harm in England was approximately 140 per 100,000 in 1999/2000[15] but fewer than half of the people who present to hospital are admitted[16]. The true rate of self-harm is therefore likely to be close to 300 per 100,000 and probably somewhat higher than this as people who self-harm do not all come to medical attention. Self-harm occurs more frequently in young people and in females. Rates are highest in 15- to 24-year old females and 25- to 34-year old males[17]; the incidence in these age groups is around five times higher than that amongst those aged over 55 years. Overdose accounts for the vast majority (over 80%) of episodes of self-harm; the second most frequently used method seen in hospital-presenting cases is self-laceration.

The incidence of suicidal thoughts is around 200 times higher than that for completed suicide. Recent data from the ONS National Survey of Psychiatric Morbidity suggest that around one in 38 women (2.6%) and one in 50 men (2.0%) in Britain develop suicidal thoughts in a year[18].

3.2.2 Time trends in suicide and self-harm

There have been marked fluctuations in suicide rates over the last 100 years[19]. The main factors underlying these variations are periods of economic recession, changes in the availability of commonly used methods of suicide, and periods of war[20 21]. Recent trends in the incidence of suicide in England and Wales are shown in figures 3.1 and 3.2.

Figure 3.1

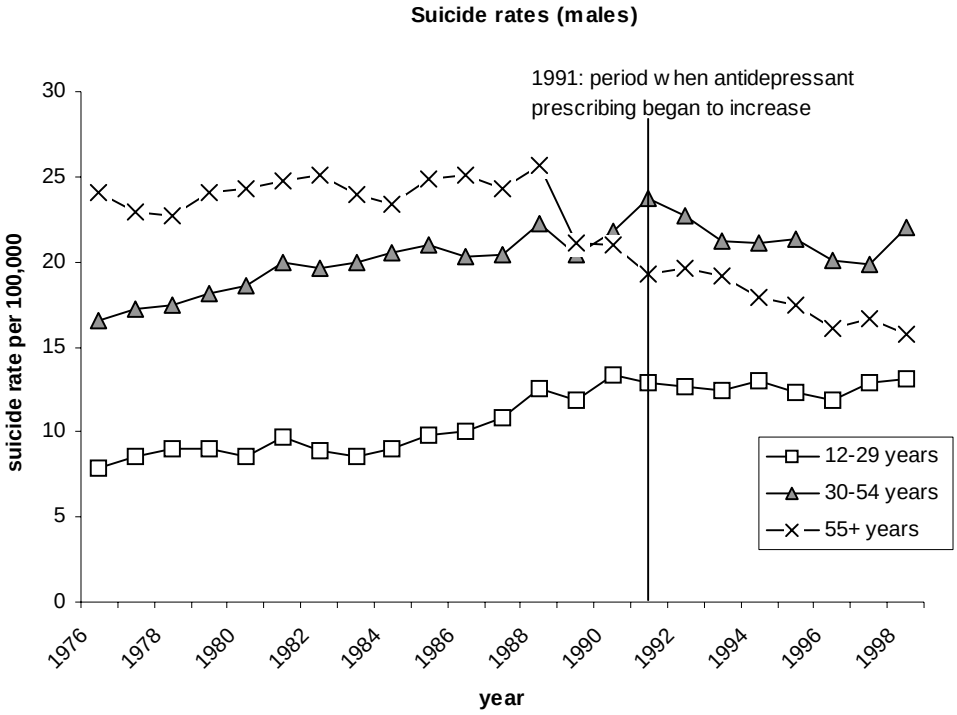

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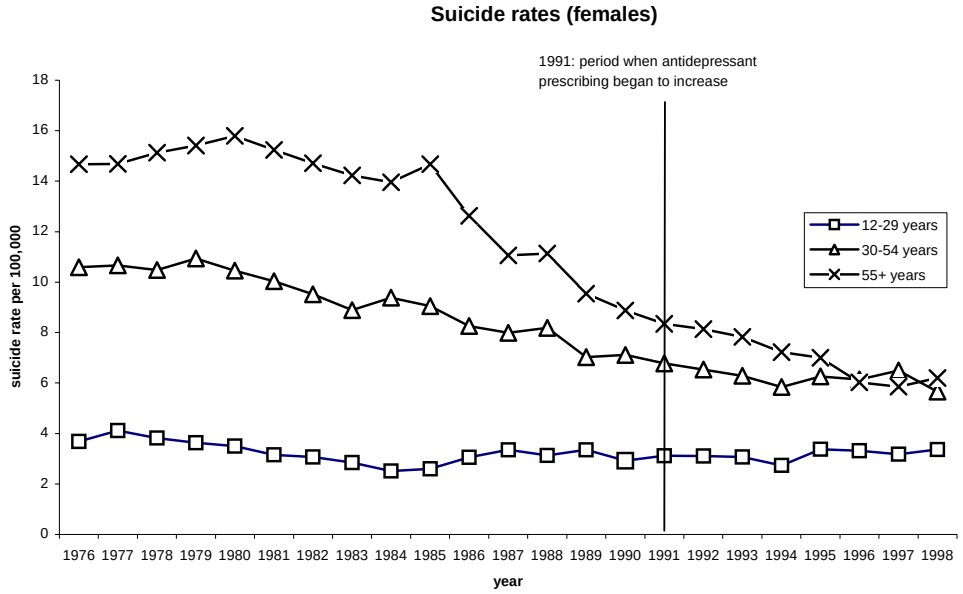
Figure 3.2



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In the last 40 years, rates of suicide have declined in older males whereas they have doubled in men under 45 years of age. In females, rates have declined in all age groups except those aged 15 to 24. The rise in suicide in young males has occurred in many, but not all, developed nations, many of which have also experienced rises in suicide amongst young females[20]. There are no definitive explanations for the rise in suicide in young adults. Possible explanations include adverse trends in a number of factors associated with suicide risk - increases in divorce, declines in marriage, rises in substance misuse and unemployment[21].

One influence on suicide rates is the ease of availability of lethal methods of suicide. Reductions in suicides in Britain in the 1960s are thought to be due to changes in the domestic gas supply. After the discovery of North Sea gas, domestic supplies in Britain were gradually converted from the highly toxic coal gas, with its high carbon monoxide content, to the relatively non-lethal natural gas. In the 1960s, domestic gas poisoning was the most commonly used means of suicide and its reduced lethality led to reductions in both method-specific and overall suicide rates[22]. A similar phenomenon was seen in Australia where restrictions on barbiturate prescribing led to reduction in its use for suicide and in overall suicide rates[23].

With respect to the safety of SSRIs, self-poisoning accounts for approximately a quarter of suicides in England and 20% of these deaths are antidepressant overdoses[24]. The TCAs are considerably more toxic in overdose than SSRIs. Consequently, it has been suggested that a switch from TCAs to SSRIs as first-line treatment for depression may prevent 300-450 overdose deaths a year through restricting access to the more toxic antidepressants[25].

Some authors have suggested that increased prescribing of antidepressants in recent years, possibly indicating improved detection and management of depression, may have led to reductions in suicide rates in some countries[26]. Evidence for this is controversial[27], and some have expressed concerns that antidepressants may, in fact, precipitate suicidal behaviour in some individuals[28].

Rates of deliberate self-harm appear to have increased over the last 40 years[29]. There are no national data on age and sex-specific trends in self-harm. However, the Oxford Monitoring System for Attempted Suicide has monitored rates of self-harm in Oxford since 1976[30]; data from this source suggest there was a rise in the rate of self-harm between 1976 and 2002. Rates have increased most in 15- to 24-year old males and females and in 35- to 54-year old males, and there have been modest reductions in the female:male ratio of self-harm[30].

3.2.3 Risk factors for suicide, self-harm and suicidal thoughts

Although suicide rates are around three times higher in males than in females in Britain, the incidence of self-harm and suicidal thoughts is highest in females. Furthermore, whilst 15- to 24-year old males and females have the lowest risk of suicide, the highest incidences of both self-harm and suicidal thoughts are in this age group.

The main risk factors for suicide are summarised in Table 3.2; with the exception of gender and age the main risk factors for self-harm and suicidal thoughts are similar to those for suicide[18 31]. The factor most strongly associated with suicide, self-harm and suicidal thoughts is psychiatric illness, particularly depression and psychosis[18 31 32]. Only a quarter of all suicides are under the care of mental health services at the time of their death[33]; the risk of suicide in the year after discharge from psychiatric hospital is around 100 to 200 times higher than the general population suicide rate[34]. Up to half of all successful suicides have previously made failed attempts. Of note, recent studies suggest that less than half of the people who die from suicide seek help from their general practitioner in the four weeks before their death[32 35]. Furthermore, a study in young adults who died from suicide found that approximately 70% were not taking antidepressants at the time of death[36].

Increased risk of suicide, self-harm and suicidal thoughts is associated with being unmarried, unemployed or misusing drugs/alcohol[19 31 37 38 39]. A family history of suicide is associated with a two- to threefold increased risk of suicide[40] and self-harm[41]. Whilst the prevalence of psychological disorders is higher after pregnancy, suicide risk in the first post-natal year is low[41 42].

Some occupational groups (eg vets and doctors) as well as those in social class V (unskilled, manual workers), and particularly the unemployed, are at increased risk of suicide [38 39]. The main high-risk occupations - vets, healthcare workers, pharmacists and farmers[43] - are characterised by having ready access to lethal methods of suicide, namely dangerous drugs and shotguns. This may, in part, explain their increased risk. The

increased risk in lower socioeconomic groups is likely to be due to a combination of factors including poverty, increased risk of unemployment and social drift as a result of severe mental illness.

Table 3.2 Groups at increased risk of suicide

High risk group	Estimated magnitude of increased risk
Current or ex-psychiatric patients	x10
Four weeks following discharge from psychiatric hospital	x 100-200
History of self-harm	x10-30
Drug/alcohol misuse	x20
Family history of suicide	2-3
Serious physical illness/handicap	N/K
Prisoners	x5
Doctors	x2
Farmers	x2
Unemployed	x2

Source: modified from Gunnell and Frankel, 1994[33]
N/K: not known

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4 INTRODUCTION TO PHARMACOVIGILANCE AND DATA SOURCES

The EWG has considered evidence from a wide variety of sources to evaluate the balance of risks and benefits for the SSRIs. Different types of evidence provide different perspectives on the relevant issues and each source has its own particular strengths and weaknesses. This chapter provides a brief introduction to pharmacovigilance and the strengths and weaknesses of the data sources reviewed by the EWG.

4.1 Pharmacovigilance

Any drug taken to treat a medical condition has potential risks and benefits. Prior to a company applying for a licence for a drug, RCTs are carried out to assess the efficacy and safety of the drug. By randomising patients to either the study drug or a comparator (which may be either another drug known to be effective in the treatment of the particular illness or a placebo), it is possible to assess whether the apparent beneficial effects of the drug are actually due to the drug, or may be due to the natural history of the disease or the effect of taking part in the study (placebo effect).

However, whilst RCTs may detect common adverse effects, they generally do not include sufficient people to detect rare adverse effects (such as suicide). Consequently, the safety of drugs is monitored after they are marketed to ensure that changes in the safety profile are identified and appropriate action taken, including amending the Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL). This monitoring is known as pharmacovigilance[1] and involves looking at data from a wide variety of sources and assessing the impact of new information on the balance of benefits and risks for patients taking the drug. Most drug regulatory agencies worldwide conduct pharmacovigilance. The MHRA has been at the forefront of the development of pharmacovigilance methods and of international efforts to improve pharmacovigilance planning prior to a drug launch[2]. A full guide to pharmacovigilance is outside the scope of this review, but a useful textbook for reference is 'Pharmacovigilance'[3].

There are a number of possible actions when a new drug safety issue is identified, in order to prevent or minimise the level of risk to patients. Rarely, if the risks of a medicine are found to outweigh the benefits, it may be necessary to remove the medicine from the market. More often, the risk of an adverse effect may be avoided or reduced by one or more of the following measures: including warnings in the product information (the SPC and PIL) or on the package label; restricting the indications for use of a medicine; changing the legal status of a medicine, eg from pharmacy to prescription only, to increase the level of professional supervision.

Communication of information on the nature of the risk to health professionals and patients supports informed choices about treatment options, and helps in the management of any ADRs, should these occur. It may be necessary to inform doctors and pharmacists by letter or fax cascade if the issue is urgent, or via the regular drug safety bulletin 'Current Problems in Pharmacovigilance'.

4.2 Approaches to pharmacovigilance at the MHRA

4.2.1 Spontaneous reports via Yellow Cards

The UK's spontaneous adverse drug reaction (ADR) reporting scheme (the Yellow Card Scheme) has been in operation since 1964. Reports of suspected ADRs are received from doctors, dentists, coroners, pharmacists, nurses and via Marketing Authorisation (MA) holders[4] (ie the companies that hold the authorisation to market the product). The scheme is voluntary for health professionals, but for MA holders there is a statutory requirement to report serious ADRs to the MHRA within 15 days of notification. Serious ADRs are defined as any that result in death or are life-threatening, lead to hospital admission or are disabling (eg blindness, deafness). Adverse reactions linked to a birth defect are also considered serious, irrespective of the severity of the birth defect[5].

Following a review of the Yellow Card Scheme in May 2004, Ministers accepted in principle a recommendation to enable patients to report ADRs directly to the MHRA. A CSM EWG on patient reporting of ADRs has been established to advise on pilot schemes to gauge the effectiveness of mechanisms for reporting.

Reporters are asked to send in 'suspected' ADRs, even if they are uncertain as to whether the drug caused the event. Therefore a report of an ADR does not necessarily mean that the drug caused it. Information on suspected ADRs is entered into a database which is regularly searched for reactions that are occurring more often than would be expected with a particular drug (signals). Methods for searching for these signals are well documented[6]. One such method is proportional reporting ratios (PRRs). These are a statistical aid to interpreting spontaneous ADR data. The PRR is calculated as the relative frequency of a specific suspected ADR versus all reported ADRs for that drug divided by the corresponding quantity for all other drugs on the database - a/a+b divided by c/c+d in the following two-by-two table:

	Reaction(s) of interest	All other reactions
Drug of interest	a	b
All other drugs in database	c	d

The expected (or null) value for a PRR is one, and the numbers generated are measures of association between the reaction and the drug; the higher the PRR, the greater the strength of the association. Measures of statistical significance for each value are calculated using the chi-squared test. Judgements may then be made on the basis of three key pieces of information - the PRR, the value of the chi-squared test and the number of reports. It is important to recognise that this is not a substitute for a detailed review of cases but an aid to identifying promptly those series of cases from a large database which warrant further review. The PRRs and chi-squared values provide measures of association between the reaction and the drug, and not causality. It may be extremely difficult to assess causality from spontaneous reports because prescribing decisions may be coincidentally associated with underlying disease progression independent of whether

any drug was given. This is a particular problem if the suspected drug effect is also related to the reason for prescribing the drug[7].

The EWG has reviewed data from the Yellow Card Scheme on suspected suicidal reactions and suspected withdrawal reactions (chapters 7 and 8).

Strengths

- This is a well-established UK-wide system for reporting suspected adverse drug reactions, with proven value in detecting previously unrecognised safety issues.

Weaknesses

- There is well-recognised under-reporting as with all spontaneous reporting systems.
- Some safety issues may go unrecognised by patients and prescribers, particularly if they are related to the condition for which the drug is prescribed.
- It may not be possible to conclude whether the suspected reaction is causal.
- Caution is necessary when comparing signals between drugs because a number of factors may influence reporting (eg length of time on the market, media interest).

4.2.2 Published research papers and case reports

The scientific and popular media provide a further source of information about new and emerging safety signals. Some scientific journals such as 'Drug Safety' and 'Pharmacoepidemiology and Drug Safety' have pharmacovigilance as their main theme, whilst others may provide published papers of specific pharmacovigilance interest from academic or commercial research. This research may be from randomised controlled trials, observational research, or specific case reports. A useful reference to observational research study designs, and their relative strengths and weaknesses, may be found in 'Epidemiology in Medicine'[8] and 'Pharmacoepidemiology'[9].

4.2.3 Literature reviews

Systematic literature reviews provide another source of information in pharmacovigilance. These are often carried out after a drug safety signal has been identified, and they provide an overview of the available published evidence up to that point. These formal reviews may be accompanied by meta-analyses of available trial results. A common weakness of systematic reviews and meta-analyses is the difficulty in identifying and including unpublished studies. The recent statement from the International Committee of Medical Journal Editors[10] on the need for registration of trials in a free, open-access registry emphasises the importance of both published and unpublished data in making clinical decisions. The pharmaceutical industry owns the data for a large number of clinical trials which should be available for review in the interest of public health. Where these remain either unpublished or selectively published, systematic reviews will be unable to reduce publication bias.

4.2.4 Expert opinion

The Sub-Committee on Pharmacovigilance (SCoP) is a sub-committee of the CSM. Evidence from new and emerging safety signals is considered by SCoP, which provides advice on the course of action to be taken. Advice from the sub-committee is then considered by the CSM as part of the ongoing monitoring of the benefit-risk balance of a medicine in its licensed indications.

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5 NEUROPSYCHIATRIC ADVERSE EFFECTS OF SSRIs AND RELATED ANTIDPRESSANTS: PHARMACOLOGICAL CONSIDERATIONS

SSRIs and the related antidepressants, venlafaxine and mirtazapine, have been associated with a number of adverse effects, the most controversial of which have been neuropsychiatric reactions such as suicidal thoughts and withdrawal reactions[1-7]. This chapter discusses the way in which the body handles and breaks down these antidepressants and how this may potentially affect an individual's chances of experiencing an adverse effect. It considers how the following may be important in determining the efficacy and safety of SSRIs and related antidepressants:

- the different liver enzymes involved in the breakdown of antidepressants and the differing levels of these enzymes between individuals;
- the time taken for a drug to be cleared from the body – this is likely to be particularly important with regard to the risk of withdrawal reactions occurring on stopping treatment;
- the extent to which SSRIs and related antidepressants cross the blood brain barrier and enter the central nervous system;
- the effectiveness of the different SSRIs and other antidepressants in increasing levels of serotonin and other chemicals in the brain, and how this differs between individuals and over time with changing levels of these chemicals in the brain.

Much of the information discussed assumes a basic understanding of pharmacology and therefore this chapter may not be suitable for all readers.

Key questions surrounding the psychiatric effects of the antidepressants include:

- possible mechanisms for differences between children and adults, and
- possible mechanisms explaining differences in action and adverse effect profile between the SSRIs and related antidepressants.

It may be difficult to disentangle the symptoms and patterns of the disease process itself from the neuropsychiatric adverse effects caused by these antidepressants, particularly since any increase in adverse effects, such as suicidal thoughts, may be very small compared with the background incidence[7]. Investigation of such adverse effects and the mechanisms underlying these effects has to take into account their multifactorial and complex nature.

5.1 Pharmacology of SSRIs and related antidepressants

The SSRIs are the first group of psychiatric drugs that have been designed to be selective for one neurotransmitter (cell messenger) system in the brain and thus to overcome one

of the specific transmitter deficits that are thought to be involved in the expression of depressive symptoms. When compared with tricyclic antidepressants, they are certainly more selective but still affect neurotransmitters other than serotonin in the central nervous system[8]. This can be illustrated with reference to their binding affinities to the different monoamine transporters (table 5.1)[9]. Furthermore, their effect is not limited to uptake inhibition. They have primary effects on many different receptors (see table 5.2), and also cause secondary changes in receptor numbers and receptor function at the synapse[8 10 11]. The same principles also apply to the related antidepressants venlafaxine (which is mixed serotonin and noradrenaline reuptake inhibitor) and mirtazapine (which acts as an antagonist at the α_2, $5HT_2$, $5HT_3$ and H_1 receptors).

This is important as the therapeutic effect of antidepressants is delayed suggesting that it cannot be equated with simple transporter inhibition, which occurs almost immediately. It is, however, poorly understood how the observed secondary changes lead to alleviation of depressive symptoms and signs. Together with the pathophysiology of depressive illness, this needs further investigation.

Table 5.1: Affinities of the antidepressants for the monoamine transporters

Antidepressant	Geometric mean (nM) of the dissociation constant (Kd)		
	5HT transporter	Noradrenaline transporter	Dopamine transporter
Amitriptyline	4.3	35	3250
Citalopram	1.2	4070	28100
Fluoxetine	0.8	240	3600
Fluvoxamine	2.2	1300	9200
Mirtazapine	>100000	4600	>100000
Norfluoxetine	1.5	1426	420
Paroxetine	0.1	40	490
Sertraline	0.3	420	25
Venlafaxine	152	9400	11700

A lower Kd indicates higher affinity for the transporter. Adapted from Tatsumi et al[9].

The pharmacokinetics of SSRIs also differ; many drugs have active metabolites with half-lives longer than the parent compounds. The half-lives of the parent compounds themselves differ widely, ranging from about 12 hours for venlafaxine to over four days for fluoxetine. The differences in pharmacokinetic parameters are shown in table 5.2.

5.1.1 Metabolism of antidepressants

Cytochrome P450 enzymes are responsible for the hepatic metabolism of many drugs. The P450 isoforms involved in the breakdown of SSRIs and the related antidepressants are CYP1A2, 2C9, 2C19, 2D6 and 3A4 (Table 5.2). Cytochrome P450 2D6 is, for example, responsible for the metabolism of approximately 25% of all drugs[12];

importantly, with respect to psychiatry, it is perhaps the major P450 isoform responsible for the metabolism of many of the antidepressants and antipsychotics used in current clinical practice[13]. It is expressed to a different degree in the human population, and is absent in 6-10% of people. The molecular basis of this has been fairly well-defined with over 80 allelic variants having been identified[13]. Individuals who are deficient in this enzyme are unable to metabolise certain drugs, leading to higher plasma concentrations and longer half-lives when given standard doses of the drug. This may predispose patients to dose-dependent adverse effects, although the picture is complicated by the fact that many of these drugs also have active metabolites[14].

Table 5.2: Pharmacological characteristics of the SSRI and related antidepressants

Drug	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Citalopram	Venlafaxine	Mirtazapine
Affinity	S>R 1.5x NF S>R 2.0x	Selective	Most potent Lower selectivity	Second most potent	Highly selective	NA and 5HT re-uptake blocker	
Half-life	1-4 days	15-28h	20h	26h	36h	5h	20-40h
Active metabolites.	Yes	No	No	Yes (5-10%)	Yes	Yes	Yes
Steady state	>4 weeks	10 days	7-14 days	5-7 days	6-10 days	3 days	4-6 days
Non-linear kinetics	Yes	Yes	Yes	No	No	No	No
Metabolising enzymes	2D6, 2C9, 2C19, 3A4	2D6, 1A2	COMT, 2D6	3A4, 2D6	2D6, 2C19, 3A4	2D6, 3A3/4	2D6, 3A4, 1A2
Enzyme inhibition	2D6	1A2, 2C19	2D6	minimal	Not relevant	Weak inhibitor 2D6	minimal
Receptor effects	$5HT_{2A}$, M, D_2, β	-	M	D, α_1	A_1, H_1	-	$5HT_2$, $5HT_3$, H_1, α_2

S=S enantiomer; R=R enantiomer; NF= Norfluoxetine; NA= Noradrenaline; 5HT= 5-hydroxytryptamine; COMT= Catechol-o-methyl transferase

CYP2D6 is involved in the metabolism of most of the antidepressants (including SSRIs), but its contribution is variable[8]. A drug that is cleared by more than one P450 isoform is less likely to cause adverse effects in patients who are deficient for CYP2D6 than a drug that is solely cleared by this isoform[14]. Many of the SSRIs are also metabolised by other P450 isoforms, in particular, CYP3A4[8]. There is a great deal of inter-individual variability in the acitivity of CYP3A4 – up to 50-fold in some studies – but this has not been related to any genetic polymorphisms. Taken together with the fact that CYP2D6 and CYP3A4 will have different affinities for the different antidepressants, and may result in the formation of different metabolites, the balance in the relative activities of CYP2D6 and CYP3A4 in each patient will be important in determining the kinetics of the drugs, and hence the inter-individual variability in kinetics.

To complicate matters, many SSRIs are also P450 enzyme inhibitors[15]. With respect to CYP2D6, such auto-inhibition is known to occur with drugs such as paroxetine and fluoxetine[16-18]. Paroxetine is such a potent CYP2D6 inhibitor that the majority of patients who were originally extensive metabolisers will appear to be poor metabolisers phenotypically after taking the drug. The degree of inhibition is dependent on the dose of

the drug and the pre-existing metabolic status[16]. The consequences of this effect are unknown, apart from its potential to lead to drug-drug interactions. Interactions may affect a wide range of drugs, particularly if the SSRI is capable of inhibiting more than one P450 isoform, as has been noted for fluoxetine.

It has recently been shown that CYP2D6 is involved in the metabolism of endogenous amines that may be precursors of neurotransmitters such as dopamine[19 20]. Theoretically, in extensive metabolisers of CYP2D6, drug administration may lead to inhibition of this P450 isoform with a consequent effect on endogenous metabolites, possibly leading to a relative deficiency of catecholamines in crucial areas of the brain. The relevance of this with respect to underlying personality, psychiatric disease and the pharmacology of the drugs used to treat these diseases is unclear and needs further investigation.

5.1.2 Half-life of SSRIs and related antidepressants

There seems to be an association between a drug's half-life and the presence of withdrawal reactions. Drugs such as paroxetine and venlafaxine, which have the shortest half-lives of all the drugs considered in the review, have been most commonly implicated in studies using spontaneous reports[21 22]. This may suggest that it is not the actual change that occurs in brain neurochemistry on drug administration that is important, but the rate of that change. One hypothesis is that inhibition of serotonin reuptake leads to increased serotonin levels in the synaptic space and desensitisation of serotonin receptors on the postsynaptic membrane. Abrupt withdrawal of an SSRI such as paroxetine will therefore lead to rapid changes in serotonin levels in the synaptic space. Taken together with the concurrent presence of desensitised receptors, this would lead to a relative deficiency of serotonin, which may be responsible for the withdrawal reactions. Drugs such as fluoxetine, which require four weeks to reach steady state because of their long half-lives, will lead to changes in brain neurochemistry at a slower rate than those drugs with a shorter half-life. It is therefore possible that adverse effects reported with paroxetine and venlafaxine could be circumvented by slower dose escalation and more gradual withdrawal than previously recommended in the product literature. However, it must be emphasised that this is a hypothesis that requires testing.

5.1.3 Brain uptake of SSRIs and related antidepressants

Kinetic studies carried out in patients or volunteers, or any studies investigating pharmacokinetic-pharmacodynamic relationships, rely on plasma level measurements. It is important to note that plasma levels give an indication of, but do not truly reflect, levels within the central nervous system, the main site of action of the SSRIs and related antidepressants[8]. For example, the brain to plasma concentration of fluoxetine is 2.6:1, while that for fluvoxamine is 24:1. For antidepressants to get into the brain, they have to cross the blood brain barrier. The blood brain barrier is rich in transporter proteins that actively transport drugs into and out of the brain[23]. However, the processes controlling active transport have not yet been investigated with respect to these drugs. Further work, therefore, needs to be carried out in this area. It is important to note that expression of these transporter proteins also varies amongst the human population. This variation in

protein expression may lead to inter-individual variation in the transport of drugs, and thereby may act as a pharmacogenetic determinant of efficacy and toxicity.

5.1.4 Downstream events of the antidepressants

SSRIs were designed to block the reuptake of serotonin in the synaptic space. The potency of different drugs to block reuptake varies, and it is also likely that there will be inter-individual variation in the degree of reuptake blockade achieved. The importance of this has recently been recognised in pharmacogenetic studies which have shown that the therapeutic response to SSRIs may depend on allelic variants in the 5HT transporter gene[24-27]. The SSRIs also have effects on other receptors, as indicated above. This may indeed be important with regard to their efficacy, especially since the reuptake blockade occurs almost immediately while the therapeutic response is not seen for about two weeks. In this respect, receptor desensitisation may be important in determining both efficacy and toxicity. Receptor desensitisation can vary between different individuals and may be genetically determined. This has clearly been seen with the β_2-adrenoceptor where genetic polymorphisms in encoding genes determine the degree of desensitisation on constant stimulation with drugs such as salbutamol[28]. Therefore, at least in part, for genetic reasons different patients respond differently to the same dose of the same drug.

5.1.5 Pharmacogenetic determinants of response to antidepressants

It can be seen from the above that the response to the SSRIs and related antidpressants is complex and depends on inter-individual variability in the kinetics of the drug, and on the actions of the drugs, which tend to affect more than one neurotransmitter pathway. Therefore, it is very unlikely that predisposition to the neuropsychiatric adverse effects is going to be determined by one gene. It is more likely that any predisposition will depend on multiple genes – this is in accordance with recent studies with other drugs that have shown that drug response is a complex phenotype, dependent on multiple genes and environmental factors interacting with each other[29]. Therefore, based on knowledge of how the drug is handled by the body, and the effects it has on the brain, the possible candidate genes that could be investigated with respect to these adverse effects include:

- Cytochrome P450 2D6 (CYP2D6);
- Serotonin (5HT) transporter gene;
- Serotonin receptor genes;
- Drug transporter genes.

It is important to state that any pharmacogenetic studies will require accurate and objective phenotypic characteristisation of all patients and controls included in the study for any results to be interpretable. Initial studies have suggested that the 5HT transporter gene polymorphism may affect tolerability with paroxetine and mirtazapine[30], although this needs to be replicated in other cohorts.

Conclusions

The pharmacology of the SSRIs and related antidepressants is complex and their exact mode of action is not entirely clear. The following areas of further research have been identified

Metabolism
Further research is necessary into the effect of specific enzymes such as CYP2D6 on the rate of metabolism of SSRIs, and the impact this has on adverse effects and withdrawal reactions.

Pharmacogenetics
There is emerging evidence that the risk of adverse drug reactions may be related to specific genotypes. There should be further research into the pharmacogenetic determinants of efficacy and toxicity associated with SSRIs.

Relationship between brain and plasma levels
Research into specific mechanisms involved in the passage of SSRIs across the blood brain barrier is needed, and also into the relationship between plasma drug levels and brain drug levels.

Receptors
Research into the effect of SSRIs on normal chemical receptors and whether this has a bearing on SSRI efficacy or toxicity is needed.

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6 SAFETY AND EFFICACY IN CHILDREN AND ADOLESCENTS WITH MAJOR DEPRESSIVE DISORDER

There has been increasing use of SSRIs and other newer antidepressants in the treatment of depressive illness in children and adolescents in the UK, although no medicines are licensed for this patient population. This chapter reports on the review carried out by the EWG on the safety and efficacy of SSRIs and related antidepressants in children and adolescents. Further data are available on the website[1 2].

In May 2003, the MHRA received from the MA holder a body of previously unseen clinical trial data on the safety of paroxetine in the treatment of major depressive disorder in children and adolescents. An urgent meeting of the EWG was held on 4 June 2003 to consider these data. Child and adolescent psychiatrists were invited to join the EWG as visiting experts for the discussion of the data. The advice of the EWG informed CSM's announcement on 10 June 2003 that paroxetine was contraindicated in patients under the age of 18 with major depressive disorder. This was on the basis of a lack of efficacy in this patient population and a risk of adverse events including suicidal thoughts and self-harm. The advice of CSM on paediatric use of venlafaxine was communicated on 19 September 2003 and the remaining medicines in the review on 10 December 2003.

The paroxetine paediatric data were the first clinical trial data to show an increased risk of suicidal behaviour with SSRIs and, on the basis of these data, CSM advised that the implications for paediatric use of other SSRIs, and for adult use of all SSRIs, be considered by the EWG. The decision was made to prioritise the review of paediatric data to ensure that comprehensive recommendations on the use of this class of medicines in children and adolescents were available as soon as possible.

Licensing status of antidepressants in children and adolescents

None of the tricyclic antidepressants has ever been authorised for treatment of depressive illness in children under 16 years in the UK or Europe. Amitriptyline and imipramine are authorised for use in children over seven years for nocturnal enuresis (bedwetting).

None of the SSRIs or the related antidepressants (venlafaxine and mirtazapine) are, or have ever been, authorised for treatment of depressive illness in children. Following a procedure to harmonise product information throughout the European Union in 2001, fluvoxamine has been authorised for use in children over eight years and adolescents for obsessive-compulsive disorder (25mg daily, increased if necessary in steps of 25mg every three to four days to a maximum 200mg daily in divided doses). Sertraline is also authorised for obsessive compulsive disorder in children from six to 12 years (25mg daily increased if necessary in steps of 50mg at intervals of at least one week, to a maximum 200mg daily) and adolescents over 13 years.

In the USA, fluoxetine was authorised on 3 January 2003 for the treatment of depressive illness and obsessive compulsive disorder in children aged seven to 17 years. Following previous consideration of the paediatric data for fluoxetine, the Paediatric Medicines

Working Group of the CSM had considered that the evidence for efficacy was robust for short-term use in major depressive disorder. This consideration was a preliminary one and not in the context of a formal licence application. In addition, there were concerns with regard to the long-term safety of fluoxetine, in particular with respect to possible adverse effects on growth and decreased alkaline phosphatase levels. Therefore, fluoxetine does not currently have a licence in the treatment of under-18s in the UK.

Despite the lack of licensed treatments there has been an overall increase in the number of prescriptions for SSRIs, venlafaxine and mirtazapine issued to children and adolescents in the last few years. Within the last 12 months (1/10/2003 to 30/9/2004) it is estimated that 58,000 under-18s were taking SSRIs in the UK, around half of whom were taking fluoxetine. Current prescribing data are provided in Annex A.

6.1 Clinical trial data on safety and efficacy in children under 18 years with major depressive disorder

Data reviewed by the EWG

The review included the following products:
Paroxetine (Seroxat), venlafaxine (Efexor), fluoxetine (Prozac), citalopram (Cipramil), escitalopram (Cipralex), sertraline (Lustral), fluvoxamine (Faverin), mirtazapine (Zispin).

The review focused on the risks and benefits of these products in the treatment of major depressive disorder. Following receipt of the analysis of the paroxetine data, and noting that a similar picture was emerging from venlafaxine clinical trials, marketing authorisation holders for all the SSRIs and mirtazapine were asked to carry out a standard analysis of their paediatric clinical trial data, as described at Annex B.

Double-blind, randomised, placebo-controlled trials in paediatric depressive illness were available for paroxetine, venlafaxine, fluoxetine, sertraline, mirtazapine and citalopram. In addition, a relapse prevention phase was available for fluoxetine, and the manufacturers of sertraline and citalopram submitted data from open-label extension studies. There were two ongoing studies with escitalopram. No RCTs in paediatric depressive illness had been conducted with fluvoxamine. Below is a summary of the safety and efficacy data considered for each product. Of note, no suicides were reported in any of the trials. Further details on the data are available on the MHRA website (www.mhra.gov.uk).

Limitations of the data

The RCT data on the use of SSRIs in the treatment of depressive illness in children and adolescents were difficult to assess and interpret. The clinical trial databases for the products were relatively small and therefore unlikely to detect rare adverse events. Also, the trials were predominantly conducted in the USA and there is uncertainty about whether the application of diagnostic criteria in some of the trials was comparable to criteria used in the UK.

6.1.1 Paroxetine

Efficacy in major depressive disorder

Efficacy was evaluated in three randomised, double-blind, placebo-controlled trials (one of which also had an imipramine arm) involving a total of 767 randomised patients aged seven to 18, treated for eight to 12 weeks. Of these 378 received paroxetine. Dose range of paroxetine was 10mg-50mg/day. Efficacy was not demonstrated.

General safety profile

Data from controlled clinical trials were available for 378 patients treated with paroxetine at doses of 10mg–50mg for 12 weeks. Of these, 263 completed eight to 12 weeks of treatment. No deaths occurred in the trials. There are no controlled data on long-term safety. Emotional lability, hostility, insomnia, tremor, dizziness and somnolence were reported more often by paroxetine-treated patients than by placebo-treated patients. Discontinuation due to adverse events occurred in 38 (10%) patients treated with paroxetine and in 15 (5%) of patients treated with placebo.

Incidence of suicide-related events (suicidal thoughts and non-fatal self-harm)

Table 6.1 Placebo-controlled trials in major depressive disorder

	Paroxetine % (n/N)	**Placebo n/N (%)**	**Crude Odds ratio (95% CI)**	**P value**
All suicide-related events	3.7 (14/378)	2.5 (7/285)	1.5 (0.6 3.8)	**0.5**

6.1.2 Citalopram

Efficacy in major depressive disorder

Efficacy was evaluated in two randomised, double-blind clinical trials involving a total of 407 patients treated for eight or 12 weeks. A total of 210 patients received citalopram. Dose range was 20mg-40mg/day. One involving 174 children and adolescents aged seven to 17 years provided some evidence of efficacy. No evidence of efficacy was found in the other trial involving 244 adolescents (13-18 years).

There was also an uncontrolled extension study (flexible dose over 24 weeks) involving 117 patients from the first study.

General safety profile

Safety data from controlled clinical trials are available for 210 patients treated with citalopram at doses of 20mg-40mg for up to eight or 12 weeks. Seventy-one patients in one study completed 12 weeks of treatment and 79 patients in the other study completed

eight weeks of treatment. There were no deaths. The following adverse events were reported at least twice as frequently in the citalopram-treated group than in those receiving placebo: anorexia, impaired concentration, diarrhoea, fatigue, influenza-like symptoms, migraine, dry mouth, vaginitis and weight loss.

Suicidal thoughts and self-harm

In the trial in adolescents, 14 in the citalopram group and nine in the placebo group required hospitalisation due to psychiatric disorders. There were 18 cases of self-harm/suicidal thoughts in the citalopram arm compared with 14 in the placebo group. In addition, it appeared the more serious suicide attempts occurred in the citalopram group. On analysis of item nine of K-SADS-P (suicidal thoughts item), citalopram was numerically better than placebo, ie citalopram showed a greater improvement in suicidal thoughts than placebo.

In the second trial involving children and adolescents, there was one event of self-harm/suicidal thoughts in each of the citalopram and placebo groups.

Incidence of suicide-related events (suicidal thoughts and non-fatal self-harm)

Table 6.2 Placebo-controlled trials in major depressive disorder

	Citalopram % (n/N)	**Placebo n/N (%)**	**Crude Odds ratio (95% CI)**	**P value**
All suicide-related events	9.0 (19/210)	7.6 (15/197)	1.2 (0.6-2.5)	**0.55**

6.1.3 Escitalopram

Efficacy in major depressive disorder

At the time of the review there were no completed trials in escitalopram for any indication in children and adolescents, although there are on-going trials for major depressive disorder.

As escitalopram is the active enantiomer of citalopram, and as there were no data, it was considered that the conclusions on citalopram should be extrapolated to escitalopram.

6.1.4 Fluoxetine

Efficacy in major depressive disorder

The efficacy of fluoxetine in the short-term (eight and nine weeks) treatment of major depressive disorder was demonstrated in two placebo-controlled clinical trials with 315 paediatric patients aged eight and above. The size of the effect was modest but consistent with that seen in the adult population.

On 18 August 2004 the Treatment for Adolescents with Depression Study (TADS) was published[3]. The TADS trial is a randomised controlled trial of 439 patients between the ages of 12 and 17 with a diagnosis of major depressive disorder. There were four arms: fluoxetine alone (n=109), placebo alone (n=112), CBT alone (n=111) and CBT with fluoxetine (n=107). On analysis of CDRS-R total score there was eveidence that fluoxetine+CBT was more effective than placebo (p=0.001). There was little evidence that fluoxetine alone was different to placebo or that CBT alone was different to placebo. On Clinical Global Impressions improvement responder analysis, the two fluoxetine-containing arms were more effective than placebo. The two fluoxetine-containing arms were also more effective than CBT alone. CBT alone was not superior to placebo (p=0.20)

General safety profile

The number of patients treated with fluoxetine at doses higher than 20mg/day and for periods longer than 10-19 weeks are small. Safety in paediatric patients of less than seven years has not been established. There were no studies that directly evaluate the long-term effects on sexual function and cognitive behavioural development.

In clinical trials, mania and hypomania were observed more frequently than in adults. Effects on growth rates and weight appear to be limited to subacute treatment and to abate with continued treatment. Decreases in alkaline phosphatase levels were observed in those receiving fluoxetine, but the clinical relevance is unclear.

Incidence of suicide-related events (suicidal thoughts and non-fatal self-harm)

Placebo-controlled trials in major depressive disorder including Treatment for Adolescents with Depression Study (TADS) data.

The analysis of the clinical trials conducted by the MA holder did not show an increased risk of suicide-related events (including suicide attempts and suicidal thoughts/ideation) with fluoxetine-treated patients compared with those in the placebo group. However, the TADs data demonstrated an elevated risk of suicide-related events in both fluoxetine arms compared with the placebo arm.

Table 6.3 Placebo-controlled trials in major depressive disorder

	Fluoxetine % (n/N)	**Placebo % (n/N)**	**Crude odds ratio (95% CI)**		**p value**
All suicide-related events (excluding TADS)	4.5 (8/178)	4.0 (7/177)	1.1	(0.4 – 3.1)	**0.80**
TADS	10.2 (22/216)	5.4 (6/112)	2.0	(0.8 - 4.9)	**0.14**
Overall	7.6 (30/394)	4.8 (14/289)	1.6	(0.9 – 3.1)	**0.14**

6.1.5 Fluvoxamine

The efficacy and safety of fluvoxamine in the treatment of depressive illness in children and adolescents aged <18 years has not been investigated.

6.1.6 Mirtazapine

Efficacy in major depressive disorder

Efficacy was evaluated in two randomised, double-blind, placebo-controlled clinical trials with a total of 259 paediatric patients aged seven to 17 years treated for eight weeks. A total of 170 patients received mirtazapine. Neither trial supported the efficacy of mirtazapine. Dose range was 15mg-45mg/day.

General safety profile

Data from controlled clinical trials were available for 170 patients who received mirtazapine and 88 patients who received placebo. There were no controlled data on long-term safety.

There were no deaths in the trials. In the controlled trials, a total of nine (5.3%) patients discontinued due to an adverse event in the mirtazapine group compared with three (3.4%) in the placebo-treated group. The most common adverse treated event leading to discontinuation in the mirtazapine-treated group was weight gain. Weight gain (31.8% vs 3.4%), somnolence (38.8% vs 6.8%), headache (35% vs 23%), fatigue (19.4% vs 11.4%), increased appetite (8.8% vs 2.3%), urticaria (11.8% vs 6.8%) and hypertriglyceridaemia (2.9% vs 0%) were reported more often for mirtazapine-treated patients than by placebo-treated patients.

Suicidal thoughts and non-fatal self-harm

One case of suicidal thoughts was reported in the mirtazapine-treated group. There was one case of self-mutilation in the placebo group

6.1.7 Sertraline

Efficacy in major depressive disorder

Efficacy was evaluated in two identically-designed randomised, double-blind, placebo-controlled clinical trials involving a total of 373 six- to 17-year olds treated for 10 weeks. A total of 189 patients received sertraline at a dose range of 25mg-200mg/day. These trials did not demonstrate significant efficacy.

General safety profile

In children and adolescents with MDD, those side-effects which occurred significantly more frequently with sertraline than placebo were agitation (6.3% vs 1.1%), anorexia (5.3% vs 1.1%), and insomnia (17.4% vs 6.8% in children).

Other (non-psychiatric) reactions in which the reporting frequency appeared to be markedly higher in sertraline-treated patients were dry mouth in adolescents, hyperkinesia in children, diarrhoea in both age-groups, nausea in adolescents, and urinary incontinence in children.

Incidence of suicide-related events (suicidal thoughts and non-fatal self-harm)

Table 6.4 Placebo-controlled trials in major depressive disorder

	Sertraline % (n/N)	**Placebo % (n/N)**	**Crude odds ratio (95% CI)**	**p value**
All suicide-related events	2.7 (5/189)	1.1 (2/184)	2.5 (0.5 - 13)	**0.28**

* Not estimated

Data from clinical trials appeared to show a consistently higher crude incidence of suicidal thoughts and self-harm in children and adolescents with MDD treated with sertraline, which was in the region of twice the placebo rate.

6.1.8 Venlafaxine

Efficacy in major depressive disorder

Efficacy was evaluated in two randomised, double-blind, placebo-controlled trials of eight weeks duration involving a total of 182 venlafaxine-treated patients aged six to 17, treated for eight weeks at doses from 37.5mg to 225mg per day, and one open-label six-month trial involving 86 patients. These trials did not demonstrate efficacy.

General safety profile

Data from controlled clinical trials in MDD were available for a total of 182 patients treated with venlafaxine at doses ranging from 37.5mg to 225mg per day for up to eight weeks of treatment. An open-label uncontrolled 24-week safety study involving 86 patients was also carried out. Of these, 36 patients completed the long-term study. No deaths occurred during the trials. Hostility and suicidal reaction, abdominal pain, anorexia, nausea and weight loss, dizziness and insomnia were reported more often by venlafaxine-treated patients than by placebo-treated patients.

Discontinuation due to adverse events occurred in 12% (33/268) of patients treated with venlafaxine and in 3% of patients treated with placebo. The most common adverse events leading to discontinuation in at least 1% of venlafaxine-treated patients and at a

rate twice that of placebo were (percentages listed for venlafaxine and placebo, respectively): hostility (2%, <1%) and suicidal thoughts (2%, 0%).

Hostility, manic reaction, overdose and suicidal thoughts were the commonest reasons for discontinuation due to an adverse event in the venlafaxine group. One percent of the venlafaxine patients discontinued due to a suicide attempt.

In the long-term study, the most common adverse event leading to discontinuation was hostility. Clinically important weight loss was also noted.

Incidence of suicide-related events (suicidal thoughts and non-fatal self-harm)

Table 6.5 Placebo-controlled trials in major depressive disorder

	Venlafaxine % (n/N)	**Placebo % (n/N)**	**Crude odds ratio (95% CI)**	**p value**
All suicide-related events	7.1 (13/182)	1.7 (3/179)	4.5 (1.4 - 15.0)	**0.01**

6.1.9 Discussion

With the exception of fluoxetine, the clinical trial data for the SSRIs and related antidepressants failed to demonstrate efficacy in the treatment of depressive illness in children and adolescents. This is the same with TCAs where efficacy in childhood depressive illness has not been demonstrated. This contrasts with the situation in adults where efficacy in depressive illness has been demonstrated for these products.

The fact that fluoxetine clinical trials alone had demonstrated efficacy in depressive illness in children and adolescents raised the question as to whether this was due to pharmacological differences between the SSRIs or due to differences in the clinical trial designs. The EWG considered a comparison of the study designs of paroxetine and fluoxetine paediatric depression trials in an attempt to see whether the apparent differences in efficacy with these products could be explained by the different study designs and/or conduct. Overall, the designs of the paroxetine and fluoxetine trials were fairly similar, although a more rigorous selection procedure was used for patients recruited to the fluoxetine trials. The additional effort to include only patients genuinely requiring treatment may have made the fluoxetine trials more sensitive to detect treatment effects. However, this does not mean that it was definitely the difference in the trial designs that led to fluoxetine demonstrating efficacy. It cannot be assumed that if the other SSRIs had used such a design they would have shown efficacy, and pharmacological differences may be the explanation.

It is possible that the SSRIs other than fluoxetine do work in the treatment of depressive illness in a subgroup of children and adolescents and this has not been demonstrated because of limitations in the trials conducted to date. In the absence of these data the EWG concluded that the efficacy of SSRIs other than fluoxetine in the treatment of depressive illness had not been demonstrated.

An increased risk of suicidal thoughts and self-harm in the SSRI-treated patients compared with those treated with placebo was seen fairly consistently across products in the trials. There were no suicides in any of the trials. Apart from the issue of suicidal behaviour, increased rates of other adverse events were of concern – particularly hostility, abdominal pain, anorexia, nausea and weight loss, dizziness and insomnia. Withdrawal reactions on stopping treatment were also identified. In weighing the risks and benefits of the SSRIs these other adverse events were considered important, as was the lack of information about the long-term effects of the use of these products in childhood/adolescence.

Faced with clinical trial data which did not demonstrate efficacy, and an increase of adverse events in the SSRI-treated groups, the EWG concluded that the balance of risks and benefits for the treatment of depressive illness in under-18s was judged to be unfavourable for paroxetine (Seroxat), venlafaxine (Efexor), sertraline (Lustral), citalopram (Cipramil), escitalopram (Cipralex) and mirtazapine (Zispin). It was 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. Subsequent to the CSM advice being issued, data from the Treatment for Adolescents with Depression Study (TADS)[3] were published. These data were consistent with previous trials in that they demonstrated efficacy for fluoxetine. Data from the trials indicate that, as with the other products, fluoxetine is associated with an increased risk of self-harm and suicidal thoughts. However, taking into account the demonstrated efficacy, the balance of risks and benefits for fluoxetine in the treatment of depressive illness in under-18s was judged to be favourable, as long as children are appropriately monitored for suicidal behaviour.

6.2 Studies using the UK General Practice Research Database

The UK General Practice Research Database (GPRD) is a computerised database of anonymised clinical records from primary care (GPs) which currently covers about 5% of the UK population. Each patient record has a unique encrypted identification number and contains demographic information, lifestyle factors, prescriptions with dosage instructions, medical symptoms and diagnoses, referrals, and dates of registration with the general practice. This database has provided information for a range of drug safety studies and is particularly useful when a drug is regularly prescribed in primary care. A previous study investigating whether there is an association between suicidal behaviour and antidepressants was carried out using GPRD by Jick et al (1995)[4].

Three studies have recently been conducted to look at the association between antidepressants and suicidal behaviour using the General Practice Research Database, each of which carried out analyses in children and young people. The studies are presented in greater detail in chapter 7; this section will discuss the results of the studies in relation to children.

Limitations of data

The data are recorded in GPRD for practice management as well as for research purposes. General practioners are trained in recording processes and the data are subject to quality assurance checks. However, some data are incompletely recorded meaning that in analyses of GPRD data it may not always be possible to completely control for all possible confounding factors or identify all relevant cases and study endpoints. A further limitation of the data is that there is no record of when or whether the patient started taking the medicine, as the date of prescribing is recorded rather than the date of dispensing. However, these should be non-differential between drug classes and this will tend to bias associations towards showing no difference between groups.

6.2.1 Antidepressants and the risk of suicidal behaviours (Jick et al, JAMA; 21 July 2004) [5]

This is a matched case-control study using GPRD between 1993 and 1999. The base population consisted of all patients with at least one prescription for the anti-depressants amitriptyline, fluoxetine, paroxetine or dothiepin between 1993 and 1999. The study was designed to consider whether the risks of non-fatal suicidal behaviour and suicide differed between these four antidepressants.

Non-fatal suicidal behaviour

Sixty-eight cases of non-fatal suicidal behaviour were identified in children and young people. These patients had a first time recorded diagnosis of suicidal thoughts or non-fatal self-harm at age 10-19 years during the study. All patients had received at least one prescription for either for amitriptyline, fluoxetine, paroxetine or dothiepin within 90 days before their index date and had at least two years recorded history in the GPRD before their index date. Patients with prescriptions for more than one antidepressant or a recorded history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia or attention-deficit disorder were excluded from the study. By implication, patients who were prescribed one of the four anti-depressants for reasons such as neuropathic pain or enuresis were included in the study.

Suicide

No children or young people aged under 18 years in the study committed suicide.

Controls

Controls (patients without suicidal behaviour) were identified from the same base population as cases and were matched to cases on age, sex, duration of recorded history in the GPRD and GP practice. The same requirements and exclusion criteria were applied to the controls as for cases.

The relative risk of suicidal behaviour for cases (fatal and non-fatal) compared to controls, adjusted for time since starting treatment, was calculated for;

- each of the anti-depressants compared to dothiepin (the most widely prescribed tricyclic antidepressant in the study period);
- time since first prescription (with "more than 90 days" as the reference group).

Results

Drug comparisons

There was no strong evidence of a difference in risk between the drugs for non-fatal suicidal behaviour. However, the odds ratio for non-fatal suicidal behaviour associated with paroxetine (Odds ratio=1.7 95% CI 0.7-4.1) approached conventional levels of statistical significance despite the low power of the study.

FDA re-analysis

A re-analysis of the data for under-19s was presented for the FDA Advisory Committee meeting in September 2004. In this re-analysis, amitriptyline was used as the comparator rather than dothiepin. The results are presented in Table 6.6 and show evidence of an increased risk for both fluoxetine and paroxetine compared to amitriptyline which reaches the conventional level of statistical significance despite the small numbers of young people in the study.

Table 6.6 Results for under-19s from Jick et al (2004)

Antidepressant	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)
Dothiepin	**Reference**	1.2 (0.9-1.6)
Amitriptyline	0.9 (0.3-2.8)	**Reference**
Fluoxetine	1.3 (0.6-3.0)	1.4 (1.0-1.9)
Paroxetine	1.7 (0.7-4.1)	1.6 (1.1-2.2)

The exclusion criteria and limited number of antidepressants studied limits the generalisability of this study. The study has very small numbers of children and young people and it is therefore difficult to draw firm conclusions from the results. Although the overall results show no strong evidence of an increased risk of suicidal events in young people exposed to either fluoxetine or paroxetine compared to dothiepin, the strongest odds ratios were in relation to paroxetine (table 6.6).

The use of dothiepin as the comparator group in this study means that the results cannot be compared with the controlled trials on which the prescribing advice for under-18s is based. The results of the study are, however, consistent with the possibility of a real increased risk in young people. The results of the re-analysis suggest that under-18s exposed to fluoxetine or paroxetine are at greater risk of suicidal behaviour than patients exposed to amitriptyline. However, these estimates may be affected by the range of prescribing indications for amitriptyline which include nocturnal enuresis (bed-wetting).

6.2.2 Antidepressant treatment and the risk of fatal and non-fatal self-harm in first episode depression – a population-based case-control study (MHRA-commissioned study)

This is a nested (matched) case-control study of patients receiving antidepressants for a first episode of depression between 1995 and 2001. All patients had a diagnosis for depression within 180 days prior to and 90 days after the first antidepressant prescription and had at least 365 days recorded history in the GPRD before study entry. There are a number of differences between the MHRA-commissioned study and the study by Jick et al. In particular, a different time period is covered, patients are restricted to those with a diagnosis of depression within a relatively short time from the first prescription, the list of codes used is far more extensive resulting in more cases being identified, suicidal thoughts/ideation were not included as the recording of these was difficult to validate.

A matched case-control analysis was used to compare the risk of non-fatal self-harm and suicide in (a) SSRI users compared with tricyclic antidepressant (TCA) users and (b) between different SSRIs and different TCAs, with paroxetine as the reference SSRI and dothiepin as the reference TCA. Cases were matched to controls on gender, year of birth and time in the study. The odds ratios were adjusted for severity of depression, referral to a psychiatrist or psychologist, past history of non-fatal self-harm, diagnosis or treatment for anxiety or panic disorder, diagnosis of schizophrenia, drug abuse, alcohol abuse, current lithium therapy, hypnotic medication, different antidepressants prescribed in the previous year, and whether the first depression diagnosis was before or after cohort entry.

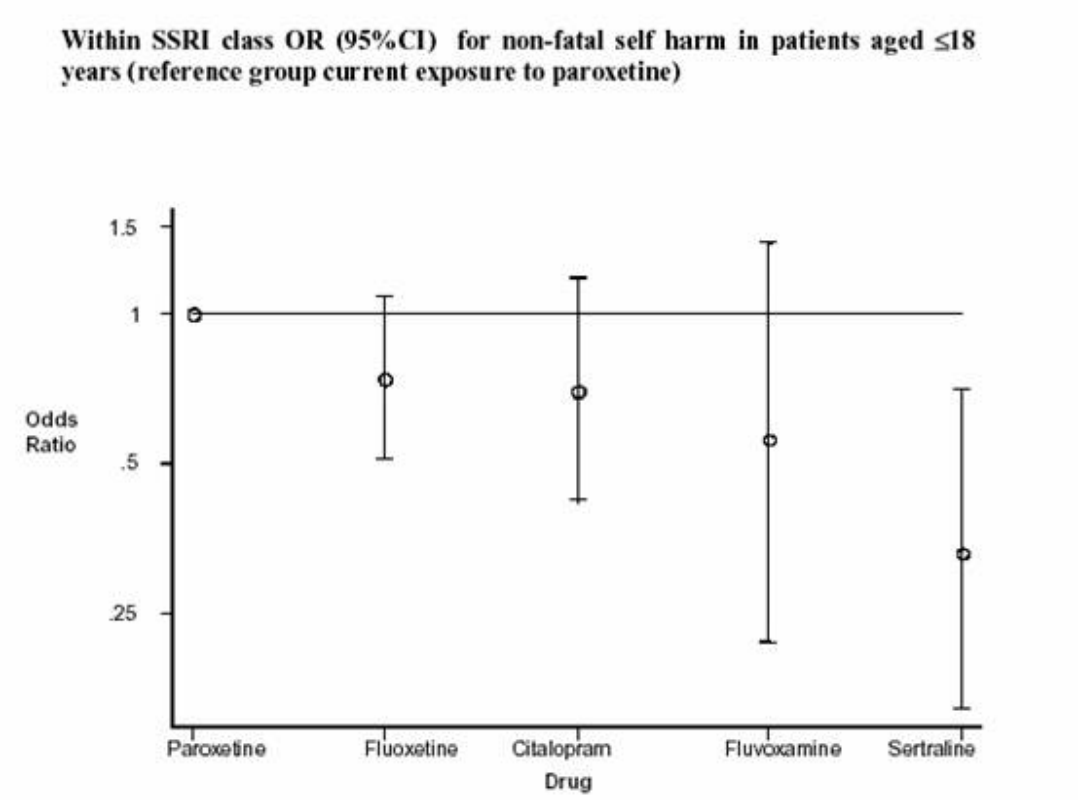
Results

There were 5287 patients with first-time depression eligible to enter the study in the age group 10-18 years. Amongst these patients were 285 non-fatal self-harm cases. There were no suicides. The adjusted odds ratio (OR) of non-fatal self-harm in this age group was 1.59 (95%CI 1.0-2.5), in SSRI users compared with TCA users. Within the SSRI class, the pattern of results suggest that the risk is highest in those who use paroxetine (see figure 6.1). There were no suicides in those aged ≤18 years currently or recently on TCAs or SSRIs.

This study included a greater range of antidepressants than the study by Jick et al and generally compared classes of antidepressants rather than individual drugs. This combined with the extensive search carried out to identify patients with non-fatal or fatal self-harm provided greater power to detect differences in risk. The study was limited to patients with a diagnosis of depression to ensure that there was homogeneity in the prescribing indications.

There was evidence of an increased risk of non-fatal self-harm for current SSRI use compared to current TCA use amongst those aged ≤18 years, which may be highest for those prescribed paroxetine compared to other SSRIs.

Figure 6.1



6.2.3 Paroxetine, SSRI use and the risk of suicidal behaviour (GlaxoSmithKline (GSK) study)

This was a cohort study with a nested (matched) case-control study of patients receiving first prescriptions for SSRI and non-SSRI antidepressants between 1988 and 2003. All patients had at least 18 months recorded history in the new full-feature GPRD before study entry and had a diagnosis for either major depression or an anxiety disorder in the 18 months prior to the initial antidepressant prescription. Patients were aged 10 years or older on the date of the initial AD prescription and were prescribed only a single antidepressant on the date of first prescribing.

The list of medical terms used to search for cases of non-fatal self-harm included suicidal thoughts and ideation as well as suicidal behaviour. The number of patients identified was similar to the MHRA study.

Cohort study

Demographic information and past medical history up to the time of cohort entry were compared across treatment cohorts (SSRI vs non-SSRI and paroxetine vs other SSRI (combined and separately)) to assess differences between treatment groups in the levels of suicide risk at the start of treatment.

Case control study

Analyses to compare the risk of suicidal behaviour associated with SSRIs and non-SSRI antidepressants included cases and controls drawn from the full cohort. A subset of cases and a separate set of controls drawn only from patients prescribed an SSRI were used in the analyses comparing paroxetine with other SSRIs. Cases were matched to controls on gender, age group, GP practice and duration of history within the database prior to study entry.

Results: children and adolescents (10-18 years)

Cohort study

This study contained 5,427 patients under 19 years who were new users of antidepressant drugs with a medical diagnosis for depression or anxiety or both in the 18 months prior to the first AD prescribing date.

Relative to non-SSRI users, SSRI users were more likely to have had a medical history of psychiatric referral or prior suicidal behaviour (table 6.7). These differences are not very large but conventionally statistically significant. Compared with patients receiving other SSRIs, patients receiving paroxetine were more likely to have a prior history of psychiatric referral.

Table 6.7 Prior medical history with SSRI use relative to non-SSRI use and paroxetine relative to other SSRIs among paediatric patients

Medical event	SSRI/non-SSRI Adjusted relative risk* (95% CI)	Paroxetine/otherSSRI Adjusted relative risk* (95% CI)
Prior suicidal event	1.3 (1.1-1.7)	1.2 (1.0-1.5)
Prior psychiatric referral	1.2 (1.1-1.4)	1.2 (1.0-1.4)
Prior psychiatric hospitalisation	0.7 (0.3-1.6)	1.2 (0.5-3.2)
Prior psychoses	1.3 (0.9-1.8)	0.9 (0.6-1.3)
Prior substance abuse	1.11 (0.7-1.8)	1.5 (0.9-2.5)
Prior stroke	.	.

* SSRI vs non-SSRI

Among children and adolescents, rates of suicidal behaviour were significantly higher in SSRI users than non-SSRI users (HR=1.9, 95%CI=1.3-2.8) and in paroxetine users compared with other SSRI users (HR=1.6, 95%CI=1.2-2.1).

Case control analyses

The analyses of cases and controls from both the SSRI and non-SSRI cohorts included 173 cases of suicidal behaviour; 140 paediatric cases were included in the case control analyses drawn from only the SSRI cohort.

Consistent with results from clinical trials and the MHRA study, there was a significant increase in the risk of suicidal behaviour in patients aged under 19 with a history of SSRI use compared to the use of a non-SSRI antidepressant (OR 1.8 95% CI 1.0-3.2). There

was weak evidence of an elevated risk of suicidal behaviour associated with paroxetine use relative to other SSRIs (OR = 1.4 95% CI 0.9 – 2.2).

Among those under 19 years, there was no evidence of a relationship between suicidal behaviour risk, duration of therapy and SSRI use relative to non-SSRI use. Whilst there was evidence of an increased risk with different durations of exposure to SSRIs, there was no evidence of a trend in risk with increasing duration of use: 1-30 days (OR=1.6, 95%CI=0.8-3.0); 31-60 days (OR=3.2, 95%CI=1.11-9.4); 61-90 days (OR=1.5,95%CI=0.3-9.4); 91+ days (OR=3.3, 95%CI=0.7-15.6).

There was some evidence of a trend of increasing risk associated with increasing duration of therapy with paroxetine relative to other SSRI use: 1-30 days (OR=1.1, 95%CI=0.6-2.1); 31-60 days (OR=1.5, 95%CI=0.6-4.1); 61-90 days (OR=1.6, 95%CI=0.4-7.7); 91+ days (OR=2.3, 95%CI=0.7-7.8). Although the estimates were not statistically different from one or statistically different from each other, this may have been due to small sample size in this age group.

The authors conclude that the study found no increased risk of suicidal behaviour associated with the use of SSRIs relative to non-SSRIs or paroxetine relative to other SSRIs in adults, and that the increased risk of suicidal behaviour associated with use of SSRIs and paroxetine was confined to adolescents (10-18 years). There was some evidence that this increased risk may differ by duration of SSRI use and paroxetine use among children, but there was no clear evidence of an association with increasing duration of use. The authors conclude "that children using SSRI medications may be at an increased risk of suicidal behaviour, and paroxetine users may be at a slightly elevated risk relative to users of other SSRI medications. However, because these increases are relatively small, they may be attributable to the unmeasured confounding by indication due to prescribing of SSRs and paroxetine to patients with an elevated background risk of suicidal behaviour."

Comments

This GPRD study covers a longer time period than the MHRA GPRD study (1988 to 2003 compared to 1995 to 2001), but has a comparable number of patients in the base cohort. The comparisons made in the study are of SSRIs vs non-SSRIs and then paroxetine vs other SSRIs either combined or individually. The drugs within the non-SSRI group include TCAs, MAOIs and new antidepressants such as venlafaxine. The effect of combining the non-SSRI drugs as a single group may be to reduce any apparent increase in risk due to SSRIs if patients exposed to newer antidepressants are at increased risk of suicidal behaviour.

The MHRA requested that GSK carry out a supplementary analysis excluding venlafaxine from the group of non-SSRIs. This resulted in a moderately higher relative risk among children exposed to SSRIs compared to non-SSRIs (OR=2.0, 95%CI=1.1-3.6) compared with the previous analysis (OR=1.8, 95% CI=1.0-3.2).

The study reinforces evidence from other GPRD studies about the increased risk of suicidal behaviour in adolescents exposed to SSRIs compared to non-SSRIs. This increased risk is present at all time points considered. The OR estimates are variable, but there is no evidence of a trend associated with increasing duration of therapy.

The results also suggest that there may be an increased risk in this age group for paroxetine compared to other SSRIs. There is some evidence of a trend in risk associated with increasing duration of paroxetine therapy compared to other SSRIs in adolescents, although all the confidence intervals overlap and there is no evidence that any differ from one. This finding is not inconsistent with the results of the MHRA study and the Jick study.

Discussion

These three GPRD studies contain overlapping sets of patients, but have employed different study designs. The results between the three studies are entirely consistent with each other. Overall there is evidence that children and young people exposed to SSRIs are at increased risk of suicidal behaviour compared to those exposed to other antidepressants. Furthermore, there is also consistent evidence from all three studies that children and young people exposed to paroxetine may be at increased risk of suicidal behaviour compared to those exposed to other SSRIs. It is possible that these results are due to confounding by indication where patients thought to be at greater risk of suicidal behaviour are preferentially treated with SSRIs due to their relative lack of toxicity in overdose. There is also some evidence from the GSK study that adolescents prescribed paroxetine may be more likely to have a previous history of suicidal behaviour than patients prescribed other SSRIs. The analyses controlled for previous history, however it remains possible that residual confounding may have contributed to the result..

The safety of SSRIs in adults is discussed further in chapter 7.

6.3 Conclusions

The EWG and CSM came to their conclusions based on the available clinical trial data. Subsequent data from the GPRD database were consistent with the safety concerns raised in the trials. The conclusions of the EWG and CSM for each product are as follows.

Paroxetine

Data on the safety and efficacy of paroxetine in MDD in children and adolescents under the age of 18 did not demonstrate efficacy in depressive illness in this age group, and showed an increase in the risk of harmful outcomes, including episodes of self-harm and potentially suicidal behaviour in the paroxetine group compared to placebo. The balance of risks and benefits in this population was negative.

Citalopram

Data on efficacy of citalopram in MDD in children and adolescents under the age of 18 did not demonstrate efficacy in depressive illness in this age group. There is a suggestion from the case narratives in one trial that there might be some harm from treatment as indexed by an increase in suicide-related events and serious suicide attempts. The balance of risks and benefits in this population was negative.

Escitalopram

Based on the available data for citalopram and the lack of any trial data in children and adolescents for the active enantiomer escitalopram, the balance of risks and benefits in this population was negative.

Fluoxetine

Efficacy in MDD has been demonstrated in short-term clinical trials. Initial data did not show an increased risk of suicide-related events. The MA holder was requested formally, on public health grounds, to submit an application for a paediatric indication in MDD.

Recently available data[3] suggest there is an increased risk of suicide-related events in children and adolescents treated with fluoxetine compared with placebo-treated patients. However, fluoxetine has been shown to be efficacious in MDD and therefore the balance of risks and benefits are considered to be favourable.

Fluvoxamine

No studies have been conducted in which the efficacy and safety of fluvoxamine in children and adolescents for the treatment of depressive illness has been investigated and therefore the balance of risks and benefits in this indication is unassessable.

Sertraline

The efficacy of sertraline in the management of MDD in children and adolescents has not been demonstrated, and clinical trials have shown a higher incidence of suicidal thoughts and suicidal behaviour in patients treated with sertraline compared with placebo in clinical trials. The balance of risks and benefits in this population was negative.

Venlafaxine

Data on the safety and efficacy of venlafaxine in MDD in children and adolescents under the age of 18 did not demonstrate efficacy in depressive illness in this age group, and showed an increase in the risk of harmful outcomes, including episodes of self-harm and potentially suicidal behaviour in the venlafaxine group compared to placebo. The balance of risks and benefits in this population was negative.

6.4 Key findings

In summary, the EWG concluded that 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-18s 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.

6.5 Regulatory options and clinical implications

The options for regulatory action in relation to the use of SSRIs for the treatment of major depressive disorder were viewed in the context of their unlicensed use in children (for background information on options for regulatory action see section 4.2.1, chapter 4). Because licences have not been granted for the use of SSRIs in children and adolescents with MDD, removal or restriction of indication or restriction to specialist use were not among the available regulatory responses. Both measures could have been interpreted as authorising the use of the product in a group of patients for which there was no licensed indication. Detailed consideration was given as to whether a warning or a contraindication was the appropriate regulatory response to the data reviewed by the EWG.

The EWG considered carefully the clinical implications of the recommendations not to use certain SSRIs and related antidepressants in the treatment of child and adolescent depressive illness, when considering the different regulatory options open to it. A contraindication sends the strongest signal that the balance of risks and benefits in the intended population is negative. Although evidence-based medicine relies on the availability of high quality trial evidence, it was acknowledged that doctors often have to make treatment decisions in the absence of such conclusive evidence and will, particularly in specialist settings, prescribe medicines that have not been licensed for a particular use. Therefore, the law allows doctors freedom to prescribe in the contraindicated population if they consider, from their knowledge and experience, it to be in the best interests of the patient. It remains possible that SSRIs and the related antidepressants may be effective in the treatment of depressive illness in some children, but the currently available evidence does not identify the population which may benefit.

6.6 Publication of advice on paediatric use

The EWG considered timely and transparent communication with all stakeholders to be of key importance. It also recommended that the clinical trial data on which regulatory decisions were made should be made available to the public. It considered this to be extremely important in relation to the data on the paediatric use of SSRIs where little clinical trial data were in the public domain.

Following CSM advice in June and September 2003 in relation to paroxetine and venlafaxine respectively, letters were sent to healthcare professionals through the Chief Medical Officer's Public Health Link cascade. In addition, there was a communication to Parliament and the press, and questions and answers were placed on the MHRA and CSM websites.

Communication of advice on the use of all SSRIs in children and adolescents took place in December 2003. A letter to doctors through the Public Health Link was accompanied by information aimed at children and adolescents who might be on treatment. Summaries of the clinical trial data on which the recommendations were based were added to the MHRA and CSM websites.

6.7 Further activity following CSM advice

Following the communications, members of the EWG and MHRA met with members of the Faculty of Child and Adolescent Psychiatry to discuss the Faculty's concerns about the regulatory action and the impact that it had had on the practice of child and adolescent psychiatry.

The publication of the paediatric clinical trial data informed the ongoing development of guidelines by NICE, and liaison meetings were held between members of the EWG and those working on the guidelines.

Further to the clinical trial data being published on the MHRA website, Whittington et al[6] conducted a systematic review of published versus unpublished data on the risks and benefits of SSRIs in children and adolescents with depression. They concluded that the published trials present a more favourable risk benefit profile for these products than the unpublished data.

Further data on the risks and benefits of SSRIs in children and adolescents emerged in 2004. In relation to fluoxetine, the Treatment for Adolescents with Depression Study (TADS) was published in JAMA in August 2004[3] and has been included in section 6.1.4. The Paediatric OCD Treatment Study (POTS), published in JAMA in October 2004[7], set out to evaluate cognitive behaviour therapy, sertraline, and their combination for children and adolescents with OCD. The authors concluded that children and adolescents with OCD should begin treatment with the combination of CBT plus a selective serotonin reuptake inhibitor or CBT alone.

There has been further debate in the literature and among regulators on the issue of the use of SSRIs in children and adolescents since the CSM advice. The Food and Drug Administration (FDA) in the USA has held two Public Advisory Committees on the subject and asked Columbia University to assemble an international panel of paediatric suicidality experts to undertake a blinded review of the reported behaviours using a rigorous classification system. Their conclusion, issued in October 2004 based on a pooled analysis of trials, was that the risk of suicidal behaviour with SSRIs and related antidepressants was on average twice that with placebo. The FDA has not restricted the use of these products in the USA but has added warnings about the risk of suicidal behaviour to the product labelling. There are ongoing discussions at a European level on this issue.

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[7] The Pediatric OCD Treatment Study **(**POTS**)** Team(2004) **'**Cognitive-Behavior Therapy, Sertraline, and Their Combination for Children and Adolescents With Obsessive-Compulsive Disorder: The Pediatric OCD Treatment Study (POTS) Randomized Controlled Trial' *JAMA*; 292: 1969 - 1976

7 SUICIDAL BEHAVIOUR

This chapter presents the key evidence considered by the EWG on the issue of suicidal behaviour. The chapter concentrates on the data in adults (for discussion of the data in children, see chapter 6).

Concern about a possible association between treatment with SSRIs and suicidal behaviour started in 1990 when Teicher et al[1] published a series of case reports of suicidal behaviour associated with fluoxetine. The most recent CSM advice (December 2001) on this issue has been that while the available study data did not suggest an increased risk of suicidal behaviour with SSRIs compared with other antidepressants, the possibility that SSRIs may cause suicidal behaviour in a subgroup of individuals could not be ruled out. The CSM has previously advised that it is general clinical experience that the risk of suicidal behaviour may increase in the early stages of treatment with any therapy for depressive illness. Product information for SSRIs was updated to reflect this in 2000; however, the debate as to whether SSRIs specifically increase the risk of suicidal behaviour, particularly in patients without depressive illness or previous history of self-harm, continued.

Key publications were identified through searches of electronic bibliographic databases and considered by the EWG; these are discussed in section 7.1. The EWG also considered expert opinion and data from Professor Healy, Mr Medawar and Dr Herxheimer, active researchers in this area.

Data received in May 2003 from GlaxoSmithKline on the use of paroxetine in children and adolescents were the first randomised controlled trials (RCT) data reviewed by the MHRA which clearly indicated that there was an increased risk of suicidal thoughts and self-harm in relation to an SSRI compared with placebo. These data led the EWG to prioritise the assessment of the use of SSRIs in children and adolescents (see chapter 6) but also raised concern about a possible increased risk in adult patients, particularly young adults.

Paroxetine was the first product to be considered in detail in view of the paediatric clinical trial data received from GlaxoSmithKline. The EWG's consideration was conducted in parallel with a Europe-wide review of its risks and benefits. The questions raised by the review of paroxetine and other SSRIs in children and adolescents in turn led the EWG to ask the marketing authorisation holders for the other SSRIs to conduct targeted analyses of their entire adult clinical trial databases. The clinical trial data are discussed in section 7.2.

A study to examine the possible association between SSRIs and suicide/suicidal thoughts and behaviour in children and adults using the General Practice Research Database was commissioned by the MHRA. Studies on the same database were conducted by other researchers[2] and the MA holder for paroxetine (GlaxoSmithKline). These studies are reviewed in section 7.3.

Spontaneous reports of suicidal behaviour received from health professionals through the Yellow Card Scheme as suspected adverse drug reactions and reports of patients' experiences are reviewed in sections 7.4 and 7.5, respectively.

7.1 Published evidence

Soon after the launch of fluoxetine (Prozac), the most frequently prescribed SSRI in UK, a series of reports appeared suggesting paradoxical worsening of depression and emergence of suicidal thoughts in some people [1 3]. The issue has been hotly debated[4 5]. Disentangling the evidence using published data alone is problematic as much research in this area is sponsored by the pharmaceutical industry[6]. Review of the paediatric trial data for SSRIs suggested that published findings present a more favourable risk-benefit profile than unpublished industry-sponsored trials, see table 7.1[7].

Table 7.1
Benefits and harms for fluoxetine, paroxetine, sertraline, citalopram, and venlafaxine versus placebo from both published and unpublished evidence, and the combination where available

Outcome	Publication status	Active treatment (n/N)	Placebo (n/N)	Relative risk (95% CI)
Fluoxetine*				
Non-remission	Published	33/48	37/48	0.78 (0.67-0.90)
		64/109	88/110	
Non-response	Published	46/109	69/110	0.67 (0.52-0.87)
Any serious adverse event	Published	1/109	4/110	0.25 (0.03-2.22)
Suicidal behaviour	Unpublished†	9/249	8/209	0.94 (0.37-2.40)
Suicide attempts	Unpublished†	6/249	4/209	1.26 (0.36-4.40)
Discontinuation because of adverse	Published	4/48	1/48	Random effects
events	Published	5/109	9/110	1.19 (0.18-7.85)
Paroxetine‡				
Non-remission	Published	36/93	47/87	0.72 (0.52-0.99)
Non-response	Published	33/93	39/87	0.79 (0.55-1.13)
	Unpublished	70/177	38/91	0.95 (0.70-1.28)
	Combined	-	-	0.88 (0.70-1.11)
Any serious adverse event	Published	11/93	2/87	5.15 (1.17-22.56)
	Unpublished	22/182	6/93	1.87 (0.79-4.46)
	Combined	-	-	2.55 (1.23-5.30)
Suicide attempt or ideation	Published	5/93	0/87	10.30 (0.58-183.53)
	Combined	14/378	7/285	1.51 (0.62-3.69)
Discontinuation because of adverse events	Published	9/93	6/87	1.40 (0.52-3.78)
Sertraline§				
Non-remission	Unpublished	60/97	51/91	Random effects
		31/92	44/96	0.92 (0.62-1.38)
Non-response	Published	74/189	92/187	0.80 (0.63-1.00)
Any serious adverse event	Published	7/189	6/184	1.14 (0.39-3.32)

Suicide attempt or ideation	Published	5/189	2/184	2.43 (0.48-12.39)
Discontinuation because of adverse events	Published	17/189	5/187	3.36 (1.27-8.93)
Citalopram¶				
Suicide attempt	Unpublished	1/89 14/121	2/85 5/112	1.99 (0.83-4.77)
Treatment emergent adverse events	Unpublished	75/89 91/121	59/85 79/112	1.13 (1.01-1.27)
Discontinuation because of adverse events	Unpublished Unpublished	5/89 13/121	5/85 9/112	1.20 (0.62-2.35)
Venlafaxine				
Suicide-related events	Unpublished‖	14/182	1/179	13.77 (1.83-103.61)
Discontinuation because of adverse events	Unpublished Unpublished	9/68 8/101	4/73 1/92	3.46 (1.30-9.21)

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n=number of patients with outcome: N=number of patients in the group: *Remission was defined as children's depression rating scale-revised (CDRS-R) <29: response was defined as at least 50% reduction in CDRS-R score from baseline to endpoint. †includes one trial of obsessive-compulsive disorder. ‡Remission was defined as Hamilton depression rating scale (HDRS) ≤8: response was defined as HDRS ≤8 or at least 50% reduction in HDRS/Montgomery-Asberg depression rating scale score from baseline to endpoint. §Remission was defined as no longer meeting DSM-IV criteria for current major depressive disorder at endpoint. ¶Suicide attempt included any of the following: suicide, suicide tendency, non-accidental overdose, and thoughts of self-harm. ‖Includes patients with major depressive disorder treated in a 24-week uncontrolled open-label study.

Limitations of published literature

Randomised controlled trials

Safety data from randomised controlled trials are not generally well reported, because the focus of the publication is usually on the efficacy of the drug. Furthermore, because suicide is a rare event, clinical trials do not generally contain sufficient patients to reliably estimate the risk in any particular treatment group.

Case studies/case series

These provide accounts of emergence of suicidal thoughts and worsening depression after starting treatment with SSRIs. It is very difficult to assess whether these reactions are due to the drug, would have occurred if the person was treated with any antidepressant, or are part of the underlying course of the disease.

Cohort/case control studies

Interpretation of the results of cohort and case-control studies is complicated by the possibility of missing information on potential confounders. For example, newly marketed drugs may be used in the treatment of depression resistant to previous antidepressants; drugs thought to be less toxic in overdose may be selectively prescribed to people perceived to be at greater risk of self-harm.

Time trends in prescribing

These studies are carried out at a population level. Whilst it is possible to deduce that there is no common side effect that increases the risk of suicide, it is not possible to

assess whether there may be an increased risk of suicide in a small number of patients exposed to an SSRI.

Fatal toxicity studies
These studies are also carried out at a population level. It is not possible to adjust the risks calculated for specific antidepressants for any factors such as disease severity that may be related to the decision to prescribe. The data are further limited by the extent to which the drugs taken in overdose are recorded on the death certificates and the fact that people who take fatal overdoses often take more than one drug.

Evidence from clinical trials and systematic reviews

A meta-analysis of data for fluoxetine (an SSRI) found no evidence that suicidal acts were less frequent amongst adults receiving active treatment: their pooled incidence was fluoxetine: 0.3%, placebo: 0.2% and TCAs: 0.4% [8]. In the most comprehensive synthesis of data from randomised trials, Khan and colleagues[9] found, if anything, that suicide rates in those treated with placebo (0.45 (CI 0.01 to 0.89) per 100 patient years) were lower than for SSRIs (0.59 (CI 0.31 to 0.87)) or other antidepressants (0.76 (CI 0.49 to 1.03)). These findings are difficult to interpret as this was not a formal meta-analysis and relative risks were not derived separately for each trial on an intention to treat basis or separately for placebo-controlled and active-controlled trials. There was no adjustment for differences in the severity of depression and follow-up time across the three comparison groups.

Suicide is rare, even amongst people with depression[10]. Thus, due to power limitations, the lack of clear clinical trial evidence of the effect of antidepressants on suicide is not surprising.

Gunnell and Ashby[11] recently considered the balance of benefits and harms of antidepressants with particular reference to suicide. Table 1 from the paper is reproduced below (Table 7.2). It summarises the clinical trial evidence released by the Medicines and Healthcare products Regulatory Agency (MHRA)[12] of the adverse effects of SSRIs on suicidal behaviour in children. Of note, there were no suicides in these trials. Using a Bayesian random effects model, the pooled estimate of increased risk of suicidal thoughts/behaviour using the data in this table is 1.66 (95% credible interval 0.83 to 3.50)[11]. Due to differences in case definitions, some of the figures in this table do not correspond with the figures provided in chapter 6.

Table 7.2 Risk of suicidal behaviour associated with use of SSRIs to treat depression

SSRI	*Comparison of suicidal behaviour*	Odds ratio (95% CI)
Fluoxetine vs placebo	Suicide attempts: 2.4% (6/249) vs. 1.9% (4/209)	1.3 (0.4 to 4.4)
Sertraline vs placebo	Suicide-related events (including suicidal thoughts): 2.7% (5/189) vs. 1.1% (2/184)	2.4 (0.5 to 12.4)
Citalopram vs placebo	Self-harm: 8.0% (17/213) vs. 4.9% (10/205)	1.6 (0.8 to 3.5)
Paroxetine vs placebo	"Possibly related to suicidality" 3.7% (14/378) vs. 2.5% (7/285)	1.5 (0.6 to 3.7)

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Since this review, two further RCTs of SSRIs in children have been published[13 14] and further paediatric trials have been identified[15]. In the TADS[13] trial – a four-arm trial of 439 adolescents (12- to 17-year olds) contrasting placebo vs fluoxetine alone vs fluoxetine plus cognitive behavioural therapy (CBT) vs cognitive therapy alone – there were 15 (6.9%) 'suicide-related events' in people receiving fluoxetine and nine (4.0%) in those receiving no fluoxetine. Seven patients 'attempted suicide' - six (2.8%) in those receiving fluoxetine and one (0.5%) receiving no fluoxetine. There were no suicides in this or other paediatric trials. These data are included in the analyses provided in chapter 6 (section 6.1.4).

In the smaller (n=112) four-arm POTS[14] trial of placebo vs sertraline alone vs CBT alone vs sertraline plus CBT in 7- to 17-year olds with obsessive-compulsive disorder, no episodes of treatment-emergent self-harm were reported.

Interpretation of the apparent increase in risk seen in the paediatric trials is problematic as it is conceivable that people taking SSRIs may simply be more likely to report adverse effects, perhaps due to a disinhibiting effect of the drugs. In addition, it has been suggested that response to treatment may lead to 'reactivation' amongst those whose depression previously prevented them from acting on suicidal impulses[16]. There is no published epidemiological evidence that provides clear evidence of this phenomenon.

Any early increased risk in suicidal behaviour may be counterbalanced by a longer-term reduction, but such benefits are not detected in the trials as their duration is generally 10 weeks or less whereas the mean duration of treatment in clinical practice is three to four months[17]. Reassuringly, time-trends for suicide (England and Wales)[18] and non-fatal self-harm (Oxford, UK)[19] in children and adolescents – the groups in whom the risks of SSRIs have been demonstrated – provide no consistent evidence of adverse trends paralleling increased prescribing in the 1990s, although there is some recent evidence of a rise in self-harm in young females[19]. Furthermore, in the USA, recent research suggests that geographic areas where antidepressant prescribing to 10- to 19-year olds has increased most have experienced the most marked declines in suicide[20].

Time trends in prescribing in relation to suicide

As depression is the main psychiatric condition leading to suicide it seems reasonable to infer that rises in antidepressant prescribing – indicating improved management of depression – should have a beneficial effect on suicide rates. Indeed, an intervention to improve GPs' management of depression in a Swedish community resulted in increased antidepressant prescribing and a short-term reduction in suicide[21].

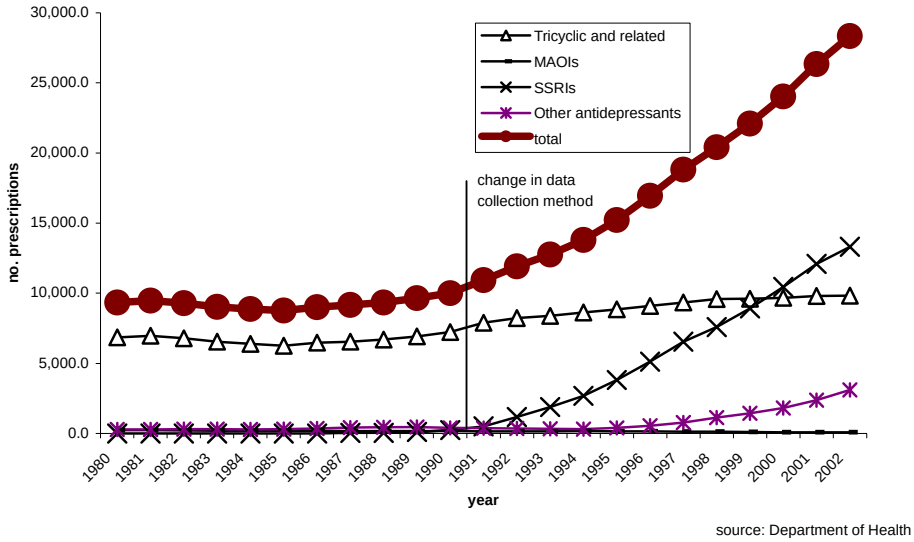
In the absence of clear evidence from clinical trials, researchers have investigated whether rises in antidepressant prescribing are associated with reductions in suicide at a population level[11 20 22 23 24 25 26 27 28 29]. With some exceptions[11 23 26 27], such studies conclude that recent rises in prescribing have contributed to declines in suicide. Interpretation of these findings is not straightforward[11]. A range of factors influence population suicide rates. It is therefore challenging to distinguish the discrete effects of increased antidepressant prescribing from changes in other risk factors. Furthermore, declining overall suicide trends may mask rises in some age/sex groups[28]. In Australia, recent rises in antidepressant prescribing were associated with declines in suicide in some age/sex groups but with increases in others[24]. In Britain, declines in suicide preceded increases in prescribing, and rises in antidepressant prescribing since 1991 in different age/sex groups do not consistently coincide with clear changes in previous suicide trends[11].

Studies of deaths due to overdose of antidepressants

The possible benefits of increases in antidepressant (SSRI) prescribing are not limited to their impact on depression. Self-poisoning accounts for around a quarter of suicides in England; 20% of these deaths are antidepressant overdoses[30 31]. The TCAs are considerably more toxic in overdose than SSRIs[32]. Consequently, it has been suggested that a switch from TCAs to SSRIs as first line treatment for depression may prevent 300-450 overdose deaths a year through restricting access to the more toxic antidepressants[33]. Of note in England, increased SSRI prescribing has not been accompanied by a fall in the prescribing of TCAs (Figure 7.1).

Figure 7.1

Figure 2 Trends in the number of antidepressant prescriptions issued 1980-2002, England



source: Department of Health

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7.2 Clinical trial data on suicide, self-harm and suicidal thoughts

Data reviewed

Paroxetine was the first SSRI to be considered in detail by the group in the context of a European review. The analysis of the paroxetine adult clinical trial data informed the focused questions which were then put to the MA holders for citalopram, escitalopram, fluoxetine, fluvoxamine and sertraline, and the related antidepressants mirtazapine and venlafaxine. In addition to the analysis provided by the MA holder for paroxetine, each clinical trial study report was sought and evaluated to confirm the consistency and completeness of the MA holder analysis.

The MA holder for all products were asked to provide all clinical trial data (both placebo-controlled and active-controlled studies) analysed to evaluate the risk of suicide, suicidal thoughts and self-harm with respect to age and gender, paying particular attention to the age group 18 to 29 years in view of the risks identified in the paediatric clinical trial data.

The MA holders were asked to include the following in their analyses:

i) examination of the risk in the first two weeks and first four weeks of treatment as well as overall risk;

ii) examination of the risk according to baseline suicidal risk so that studies which excluded patients with suicidal risk are analysed separately from those that did not;
iii) time to onset data as survival plots;
iv) narratives of the case reports for any suicides that occurred during these trials;
v) examination of possible risk factors (eg age, gender, severity of disease, dose, indications, previous psychiatric history, previous/concomitant pharmacotherapies) including table of odds-ratios and confidence intervals for each of the treatment risk factor interactions.

In identifying cases of suicidal events the MA holders were asked to search their databases using the list of terms used to analyse the paediatric clinical trial data (see Annex B). This text stream search was requested to identify potential cases of suicidal behaviour which had been recorded in the individual case record forms for the trial but may not have been identified as a drug-related or significant event by the investigator in the trials.

Cases identified were analysed overall and according to the following broad definitions:

- suicide - any fatal self-harm including intentional overdose and overdose (excluding accidental overdose);
- self-harm - any non-fatal self-harm;
- suicidal thoughts - any reports of suicidal thoughts or ideas.

Limitations of the data

There are a number of limitations to the use of randomised controlled trial evidence in determining the effect of SSRIs on suicide risk. As already discussed, because suicide is rare even in patients with depressive illness, most clinical trials have too few cases to confirm or rule out an increased risk of suicide with antidepressants. Estimation of the risk in specific subgroups, such as young adults, is more difficult because there are even fewer patients in separate age groups.

Cases of self-harm/suicidal thoughts may not be rigorously recorded in the trials as they may have been considered by investigators to be due to the underlying disease. In this review, the 'cases' identified by the text stream search have not been reviewed by an external panel of experts (this compares with the approach taken by the Food and Drug Administration in their analysis of the paediatric clinical trial data). However, differential mis-reporting in the different treatment or placebo groups is unlikely and therefore this should not bias the results.

The clinical trial data indicate that suicidal thoughts may have been under-reported in clinical trials. Data from studies in the general population suggest that they should outnumber acts of self-harm 5:1[34 35], but the reported incidence of thoughts and acts in the clinical trials is approximately 1:1 (see below). An alternative explanation for this finding could be that amongst people seeking treatment for depression, self-harm is disproportionately used as a means of coping with distressing symptoms (rather than

acting as a reflection of suicidal distress or intent as suicidal thoughts might better indicate)[36].

Despite the same questions being asked of all MA holders, the format and content of the submissions they returned differed. In particular, when trial data are synthesised, some MA holders did not take account of different durations of follow-up in different trials with different randomisation ratios – this may have led to over- or under-estimates of risk. A table summarizing the adult clinical trial data considered during the review is provided on page 9 of the report (table 1.2).

7.2.1 Paroxetine

More than 13,000 paroxetine-treated patients have been included in paroxetine clinical trials. The mean duration of placebo-controlled trials was 18 weeks, and the mean duration of active-controlled trials was nine weeks. Data from the placebo run-in phases of these trials have not been included in any of these analyses. The indications for which patients were treated in these studies included depressive illness, generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic, societal anxiety disorder (SAD) and pre-menstrual dysphoric disorder (PMDD). The adverse event data from these trials were also examined for possible suicide-related events and self-harm.

In the adult placebo-controlled trials there were a total of four completed suicides: one in the paroxetine group (on therapy) and three in the placebo group (all in the post-treatment period).

The incidence of possible suicide-related events occurring on therapy (including taper phase) is provided in Table 7.3 below. The comparison of the risk of events between the groups was performed using Fisher's exact test and the exposure adjusted data were compared using Poisson regression.

Adult placebo-controlled trials

Overall, the incidence of possible suicide-related events was similar in the paroxetine and placebo groups (0.8% vs 0.9%) (Table 7.3). The majority of these events occurred in the depression studies.

Table 7.3: Incidence of all suicide-related events by treatment group and indication: adult placebo-controlled trials

Indication	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	p value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.8 (0.6, 1.2)	0.31
Depression	58/3421 (1.7%)	41/2117 (1.9%)	0.9 (0.6, 1.3)	0.53
Generalised anxiety disorder (GAD)	2/1182 (0.2%)	2/985 (0.2%)	0.8 (0.1, 5.9)	1.00
Obsessive compulsive disorder (OCD)	1/542 (0.2%)	3/265 (1.1%)	0.2 (0.02, 1.6)	0.11
Panic	0/920 (0%)	3/780 (0.4%)		0.10
Post-traumatic stress disorder (PTSD)	3/786 (0.4%)	3/598 (0.5%)	0.8 (0.2, 3.8)	1.00
Pre-menstrual dysphoric disorder (PMDD)	0/760 (0%)	0/379 (0%)	-	
Social anxiety disorder (SAD)	2/870 (0.2%)	3/684 (0.4%)	0.5 (0.1, 3.1)	0.66

Adult active-controlled trials

Overall, the incidence of possible suicide-related events was lower in the paroxetine group compared with the comparator group (0.8% vs 1.3%; OR 0.66 (95% CI 0.46, 0.95) p=0.031), Table 7.4.

Table 7.4: Incidence of all suicide-related events by treatment group and control medication class: adult active-controlled trials

Indication	Paroxetine n/N (%)	Comparator n/N (%)	Odds ratio (95% CI)	p value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.7 (0.6, 1.0)	0.03
Tricyclic	26/2953 (0.9%)	32/2754 (1.2%)	0.8 (0.5, 1.3)	0.29
SSRI	14/1200 (1.2%)	24/1218 (2.0%)	0.6 (0.3, 1.1)	0.14
Tetracyclic	2/527 (0.4%)	4/518 (0.8%)	0.5 (0.1, 2.7)	0.45
Benzodiazepine	0/76 (0%)	0/77 (0%)		
Other	13/1766 (0.7%)	3/402 (0.7%)	1.0 (0.3, 3.5)	1.00

Risk in the first two and four weeks of treatment

In the placebo-controlled trials, approximately 20% of the events in patients on paroxetine and 30% of events in patients on placebo occurred within the first two weeks paroxetine. Almost 50% of events in each group had occurred within the first four weeks of treatment.

In the active-controlled trials, approximately 30% of the events in patients on paroxetine and 40% of events in patients on active control occurred within the first two weeks on paroxetine. Sixty-four percent of events in patients on paroxetine and 70% in patients in the active control group occurred in the first four weeks of treatment.

Risk according to baseline suicidal risk

Analyses were conducted on the risk of suicide-related events according to patients' baseline suicidal risk. Two analyses were performed.

The first analysis examined the risk of suicidal behaviour according to whether baseline suicidal risk was a study entry criterion. The highest incidence of suicide-related events occurred in the studies in which patients were required to have a recent episode and a history of suicidal behaviour on entry (Table 7.5). The incidence of possible suicide-related events in the paroxetine group was similar to that in the placebo group and lower than that in the active control group (Table 7.6) in all categories.

Table 7.5 Incidence of possible suicide-related adverse events by treatment group and study design criteria: adult placebo-controlled trials

Suicidality design criteria	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	p value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.8 (0.6, 1.2)	0.31
'Global' criteria				
Suicidal behaviour required	27/131 (20.6%)	29/136 (21.3%)	1.0 (0.5, 1.7)	1.00
No specific criteria	0/21 (0.0%)	0/10 (0.0%)	-	-
Severe or serious risks excluded	34/6180 (0.6%)	22/3984 (0.6%)	1.0 (0.6, 1.7)	1.00
Known, established or current risk excluded	5/2149 (0.2%)	4/1678 (0.2%)	1.0 (0.3, 3.6)	1.00

Table 7.6 Incidence of possible suicide-related adverse events by treatment group and study design criteria: adult active-controlled trials

Suicidality design criteria	Paroxetine n/N (%)	Comparator* n/N (%)	OR (95% CI)	p value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.7 (0.5, 1.0)	0.03
'Global' criteria				
No specific criteria	3/857 (0.4%)	5/850 (0.6%)	0.6 (0.1, 2.5)	0.51
Severe or serious risks excluded	37/4318 (0.9%)	35/2790 (1.3%)	0.7 (0.4, 1.1)	0.11
Known, established or current risk excluded	15/1347 (1.1%)	23/1329 (1.7%)	0.6 (0.3, 1.2)	0.19

*Comparator group includes those treated with other SSRIs, benzodiazepines, tricyclic and tetracyclic antidepressants and other antidepressants

For the second analysis, the presence of suicidal risk at baseline is defined as a score of ≥3 on either Item 3 of the Hamilton Depression Rating Scale (Ham-D) scale or on Item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS). In the adult placebo-controlled trials, for patients without suicidal thoughts at baseline or where baseline suicidal thoughts were not assessed, the incidence of possible suicide-related events in the paroxetine group was similar to that in the placebo group (Table 7.7). In the sub-group of patients who had baseline suicidal thoughts, the incidence in the paroxetine

group was lower than in the placebo group (paroxetine 15/444 (3.4%), placebo 21/291 (7.2%), OR 0.45, 95% CI 0.23, 0.89, p=0.023).

Table 7.7 Incidence of possible suicide-related adverse events by treatment group and baseline suicidal risk: adult placebo-controlled trials

Baseline suicidal risk	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	p value
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.8 (0.6, 1.2)	0.31
Absent*	51/8037 (0.6%)	34/5517 (0.6%)	1.0 (0.7, 1.6)	0.91
Present	15/444 (3.4%)	21/291 (7.2%)	0.5 (0.2, 0.9)	0.02

* Absent includes cases where baseline suicidal thoughts was not assessed.

In the adult active-controlled trials, the incidence of possible suicide-related events in the paroxetine treatment group was lower than in the active comparator group (Table 7.8). This difference reached conventional levels of statistical significance for the sub-group who did not have baseline suicidal thoughts (p=0.04) and also for the group overall (p=0.03).

Table 7.8 Incidence of possible suicide-related adverse events by treatment group and baseline suicidal risk: adult active-controlled trials

Baseline suicidal risk	Paroxetine n/N (%)	Comparator n/N (%)	Odds ratio (95% CI)	p value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.7 (0.5, 1.0)	0.03
Absent*	41/5787 (0.7%)	48/4387 (1.1%)	0.7 (0.4, 1.0)	0.04
Present	14/735 (1.9%)	15/582 (2.6%)	0.7 (0.4, 1.5)	0.45

* Absent includes cases where baseline suicidal thoughts was not assessed.

Examination of possible risk factors for suicidal outcomes

The effects of gender, age, severity of illness, indication, psychiatric history, psychotropic medication, baseline suicidal thoughts and baseline agitation on the risk of SSRI-related suicidal outcomes were examined. The analyses do not suggest that these factors increase the risk of suicide, non-fatal self-harm or suicidal thoughts in patients on paroxetine compared with those on placebo or active controls.

In the 18-29 years age group, the incidence of events in the paroxetine group (1.8%) was higher than that in the placebo group (1.4%) (OR 1.3 (0.7, 2.3), p=0.42), table 7.9. In the remaining age groups, with the exception of those over 70 years, the rate in the paroxetine group was lower than in the placebo group. In the over-70 age group, the number of events and the total number of patients in this age group are very small and therefore no firm conclusions can be reached.

Table 7.9 Incidence of possible suicide-related events by age group: adult placebo-controlled trials

	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	pvalue
Overall	66/8481 (0.8%)	55/5808 (0.9%)	0.8 (0.6, 1.2)	0.31
<18 years	0/5 (0.0%)	0/1 (0.0%)		
18-29 years	31/1727 (1.8%)	17/1204 (1.4%)	1.3 (0.7, 2.3)	0.46
30-39 years	18/2550 (0.7%)	18/1728 (1.0%)	0.7 (0.4, 1.3)	0.24
40-49 years	12/2270 (0.5%)	11/1515 (0.7%)	0.7 (0.3, 1.7)	0.52
50-59 years	3/1152 (0.3%)	9/807 (1.1%)	0.2 (0.1, 0.9)	0.03
60-69 years	0/530 (0.0%)	0/381 (0.0%)	-	-
≥70 years	2/247 (0.8%)	0/172 (0.0%)	-	0.51

In adult active-controlled trials (table 7.10), there were fewer possible suicide-related events in the paroxetine group compared with the active comparator group in most age categories. This difference was particularly marked in young adults (aged 18-29 years); (paroxetine 1.0% (10/969), comparator 2.6% (20/779; OR 0.40 (0.18, 0.85), p=0.02).

Table 7.10 Incidence of possible suicide-related events by treatment group and age group: adult active-control trials

	Paroxetine n/N (%)	Comparator n/N (%)	Odds ratio (95% CI)	p-value
Overall	55/6522 (0.8%)	63/4969 (1.3%)	0.7 (0.5, 1.0)	0.03
<18 years	0/4 (0.0%)	0/6 (0.0%)	-	
18-29 years	10/969 (1.0%)	20/779 (2.6%)	0.4 (0.2, 0.9)	0.02
30-39 years	13/1544 (0.8%)	10/1146 (0.9%)	1.0 (0.4, 2.2)	1.00
40-49 years	12/1647 (0.7%)	13/1182 (1.1%)	0.7 (0.3, 1.5)	0.31
50-59 years	9/1038 (0.9%)	14/835 (1.7%)	0.5 (0.2, 1.2)	0.14
60-69 years	7/831 (0.8%)	5/626 (0.8%)	1.1 (0.3, 3.3)	1.00
≥70 years	4/457 (0.9%)	1/390 (0.3%)	3.4 (0.4, 30.8)	0.38
Unknown	0/32 (0.0%)	0/5 (0.0%)	-	

To examine the effect of dose on risk, stratified analyses of possible suicide-related events from the fixed-dose, placebo-controlled studies were performed, including and excluding Study 057, in which the study population comprised suicidal patients. Study 057 compared a dose of 40mg paroxetine against placebo and accounted for all 27 possible suicide-related events seen with the 40mg paroxetine dose. These data do not suggest any dose-related risk of suicide-related events (Table 7.11). When the data from Study 057 are excluded, it is clear that the high incidences of events at 40mg is a reflection of the high incidence of events in this study which includes suicidal patients.

Table 7.11 Incidence of possible suicide-related events by dose: adult fixed-dose placebo-controlled trials, including and excluding Study 057

Including Study 057

Dose	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	p-value
5 mg	0/11 (0.0%)	0/9 (0.0%)	-	
10 mg	3/775 (0.4%)	1/737 (0.1%)	2.9 (0.3, 27.6)	0.62
20 mg	9/1405 (0.6%)	9/1324 (0.7%)	0.9 (0.4, 2.4)	1.00
30 mg	1/150 (0.7%)	0/101 (0.0%)	-	1.00
40 mg	27/874 (3.1%)	32/810 (4.0%)	0.8 (0.5, 1.3)	0.36
50 mg	0/57 (0.0%)	0/60 (0.0%)	-	
60 mg	0/182 (0.0%)	1/184 (0.5%)	-	1.00

Excluding Study 057

Dose	Paroxetine n/N (%)	Placebo n/N (%)	Odds ratio (95% CI)	P-value
5 mg	0/11 (0.0%)	0/9 (0.0%)		
10 mg	3/775 (0.4%)	1/737 (0.1%)	2.9 (0.3, 27.6)	0.62
20 mg	9/1405 (0.6%)	9/1324 (0.7%)	0.9 (0.4, 2.4)	1.00
30 mg	1/150 (0.7%)	0/101 (0.0%)		1.00
40 mg	0/743 (0.0%)	3/674 (0.4%)		0.11
50 mg	0/57 (0.0%)	0/60 (0.0%)		
60 mg	0/182 (0.0%)	1/184 (0.5%)		1.00

Meta-analysis of adult controlled trials for paroxetine

The MHRA has conducted a systematic review of the adult controlled trial data for paroxetine provided by the MA holder relating to the risk of suicidal events and, where appropriate, a meta-analysis. Due to the methods used for this meta-analysis, the numbers of patients and number of events included are not identical to those provided in the MA holder's analysis of trial data.

Method

Data from 116 controlled trials of paroxetine were used for this analysis. Indication-specific analyses were carried out using data from studies that did not have any open-label periods. The analyses were carried out separately for paroxetine vs placebo (88 studies) and paroxetine vs active comparator (66 studies), and were restricted to studies with at least 10 patients. Some trials were three-arm trials; these were included in both paroxetine vs placebo and paroxetine vs active comparator analyses. Formal meta-analyses[37] were carried out where there were more than two analysable studies in a group. Heterogeneity tests were carried out to determine whether fixed or random models were appropriate.

Risk differences and relative risks were calculated. Use of the risk difference allows all trials, even those with no events, to be incorporated within the analyses. The risk difference is the risk of a suicidal event for patients on paroxetine minus the risk of a suicidal event for patients on comparator (active or placebo). Accordingly, a positive risk difference implies a higher risk for paroxetine than placebo.

Similarly, a relative risk greater than one implies a higher risk for patients exposed to paroxetine than for those exposed to the comparator; however, estimates of relative risk are only possible if there are events in the comparator arm.

The difference in the risk of a suicidal event between patients on paroxetine and patients on placebo (or paroxetine and active comparator) was also calculated using a method recommended for small numbers[38]. This method gives slightly wider confidence intervals, but the point estimates are the same.

Paroxetine vs placebo

Data from all adult controlled trials of paroxetine vs placebo satisfying the criteria were included in this analysis. If the trial also contained an active comparator, this arm of the trial was ignored for the analysis of the data. A summary of the total numbers of patients in each arm of the placebo-controlled studies and the total number of suicidal events is provided in table 7.12.

Paroxetine vs active

Data from all adult controlled trials of paroxetine vs any actives satisfying the criteria were included in this analysis; no distinction was made between actives. If the trial also contained a placebo arm, this arm of the trial was ignored for the analysis of the data. This means that patients on paroxetine will appear in both the placebo and 'active' analyses if they are part of a three-arm trial. A summary of the total numbers of patients in each arm of the active-controlled studies and the total number of suicidal events is provided in table 7.13.

Results

Overall there were 20,914 patients included in the analyses. The summary of patient inclusion data is in tables 7.12 and 7.13 for placebo-controlled and active-controlled trials respectively.

Table 7.12 Summary of patient numbers for placebo-controlled trials and placebo arms of three-arm trials

Indication	Paroxetine		Placebo	
	Total	Events (%)	Total	Events (%)
Depression	3283	58 (1.8)	1974	39 (2.0)
GAD	904	2 (0.2)	697	2 (0.3)
OCD	284	1 (0.4)	146	2 (1.4)
Panic disorder	877	0 (0)	780	3
PMDD	760	0 (0)	379	0 (0)
PTSD	698	3 (0.4)	510	3 (0.6)
SAD	666	2 (0.3)	467	2 (0.4)

Table 7.13 Summary of patient numbers for active-controlled trials and active comparator arms of three-arm trials

Indication	Paroxetine*		Active comparator	
	Total	Events	Total	Events
Depression	4156	42 (1.0)	4154	56 (1.3)
OCD	220	1 (0.5)	134	2 (1.5)
Panic disorder	199	0 (0.0)	199	2 (1.0)

*These patients include some patients in three arm trials also in table 7.12

Heterogeneity tests showed no evidence of heterogeneity between studies, and the results from fixed and random effects models were identical in most cases. Therefore, only results from fixed effects models will be presented.

The indication specific results for the individual studies and fixed effects meta-analyses where appropriate are given in Annex C. The results from the meta-analyses are summarised in table 7.14.

Risk differences in Annex C are shown as proportions and therefore lie between –1 and 1. For clarity the risk differences in table 7.14 are presented as percentages. A risk difference of zero implies no difference in risk between the groups, a risk difference of 10% means that the risk in the paroxetine arm is 10% higher than in the placebo arm (eg 30% vs 20%).

The risk differences emphasise the rare nature of suicidal events in these studies, which is not immediately apparent from the relative risks. The absolute risks of these events are low and therefore the risk differences are low.

Table 7.14 Summary of fixed effects meta-analysis (Mantel Haenszel method) by indication and type of comparator

Indication	Risk difference (%)		Relative risk	
	Active controlled RCTs	Placebo controlled RCTs	Active controlled RCTs	Placebo controlled RCTs
Depression	-0.3 (-0.9, 0.3)	0.4 (-0.4, 1.2)	0.8 (0.5, 1.2)	1.2 (0.8, 1.7)
GAD	*	0.0 (-0.7, 0.7)	*	1.0 (0.2, 4.9)
OCD	*	-0.9 (-3.3, 1.5)	*	*
Panic Disorder	*	-0.4 (-1.1, 0.4)	*	*
PMDD	*	0.0 (-0.9, 0.9)	*	*
PTSD	*	-0.1 (-1.1, 1.0)	*	0.8 (0.2, 2.8)
SAD	*	0.0 (-1.0, 1.0)	*	*

* Less than 3 trials with analysable information

Overall, there is no strong evidence of an increased risk of suicidal events for adult patients with depression exposed to paroxetine compared to placebo, although the point estimates and confidence intervals are consistent with a possible increase in risk. The results of the meta-analyses for patients exposed to paroxetine compared to an active comparator suggest that the risks of suicidal events in these two groups are essentially similar. The low number of events in other indications means that the confidence intervals are very wide and it is therefore difficult to draw firm conclusions.

Discussion

The adult clinical trial data for paroxetine provided by the MA holder reinforces the relatively rare (approximate risk 1%) nature of suicidal events in these studies, and the increased risk of suicidal events in depression compared to other indications. Overall, these data show no conclusive evidence that adult patients exposed to paroxetine are at increased risk of suicidal events compared with patients exposed to either placebo or another active drug in any of the indications investigated. However, the data are consistent with the possibility of an increased risk of suicidal events in patients with depression exposed to paroxetine compared to placebo consistent with that suggested by paediatric trials.

The available data on the risk of suicidal behaviour in young adults do not provide clear evidence of an increased risk in this age group. Due to differences in maturity we cannot rule out the possibility that some young adults may have a risk of suicidal behaviour similar to that seen in children and adolescents.

Concerns have been raised that events occurring during placebo run-in or washout phases have inappropriately been counted against placebo as if they occurred during the randomised phase[4]. However, no examples of this have been found in a review of all of the paroxetine studies.

The meta-analysis has been restricted to data provided from trials conducted by the MA holder, and has not included any data from other randomised trials conducted by other groups or published studies. Consequently it is not a formal meta-analysis of all

available data. Whilst the results provide no clear evidence of an increased risk, the range of risk ratios included within the 95% confidence intervals are consistent with the possibility of a small increased risk of suicidal events for patients exposed to paroxetine compared with those exposed to placebo, but not paroxetine compared with other antidepressants. The confidence intervals are, however, also consistent with a small protective effect in relation to suicidal events.

It is known that depression is a major risk factor for suicidal thoughts and self-harm. Therefore, when considering the balance of benefits and harms for any antidepressant, it is important to consider the evidence for benefit of the antidepressant in relieving the symptoms of depression and thereby reducing the risk of suicidal thoughts or self-harm as well as the evidence for harm. The overall evidence of benefit for paroxetine is considered in a Cochrane review of studies of anti-depressants in dysthymia[39].

7.2.2 Other SSRIs and related antidepressants

As previously mentioned, the MA holders for the other SSRIs and related antidepressants were asked to provide all clinical trial data (both placebo-controlled and active-controlled studies) analysed to evaluate the risk of suicide, suicidal thoughts and self-harm with respect to age and gender, paying particular attention to the age group 18-29 years. The data submitted by the MA holder were reviewed and the key findings across the drugs and for each drug are provided in Table 7.15 below.

Table 7.15 Analysis of risk of suicide-related events (suicide, self-harm and suicidal thoughts)

	Drug vs placebo		**Drug vs active control**	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI) †	p value
Citalopram	1.3 (0.7, 2.5)	0.44	0.8 (0.5, 1.3)	0.41
Escitalopram	1.4 (0.4, 4.4)	0.61	1.0 (0.4, 2.3)	0.94
Fluvoxamine	1.6 (1.0, 2.7)	0.07	-	
Fluoxetine†*	0.9 (0.4, 2.0)	‡	TCAs : 1.4 (0.6, 3.2)	‡
			SSRIs : 2.0 (0.2, 19.9)	‡
Mirtazapine	1.3 (0.4, 6.9)	0.91	2.0 (0.9, 4.1)	0.08
Sertraline	1.5 (0.8, 2.9)	0.19	0.9 (0.6, 1.5)	0.68
Venlafaxine IR	1.3 (0.7, 2.1)	0.40	SSRI: 1.0 (0.6, 1.8)	0.99
			Other: 0.9 (0.5, 1.6)	0.66
Venlafaxine ER	0.8 (0.4, 1.3)	0.35	SSRI: 0.6 (0.3, 1.1)	0.11
			Other: 0.5 (0.3, 1.0)	0.05

†For fluoxetine statistical test employed was Mantel-Haenszel Incidence Difference test
* The statistical test was performed on events of suicide and self-harm
‡ Not provided

Citalopram

Two analyses have been conducted. The first was on nine GCP (Good Clinical Practice) compliant placebo-controlled trials in depressive illness. In these trials at least 1,215 patients received citalopram and 520 received placebo. Patients in these trials were treated for approximately 10 weeks. Most analyses were performed on the data from these trials (table 7.16).

As requested by the MHRA, the MA holder has expanded the database to include trials in other indications and active-controlled studies; some of these trials are not GCP-compliant. This expanded database comprises 29 controlled trials (placebo- and active-controlled). Approximately 3,300 patients received citalopram and 1,900 received an active control (clomipramine, sertraline, imipramine, fluvoxamine, fluoxetine, amitriptyline and mianserin). The indications for which patients were treated in these studies included depressive illness, panic and OCD.

Episodes of suicidal thoughts, non-fatal self-harm and suicide

Table 7.16 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide whilst on treatment and during a 30-day follow-up period – Nine GCP placebo-controlled trials (depressive illness)

	Citalopram % (n/N)	Placebo % (n/N)	Crude Odds ratio (95% CI)	P value
All suicide-related events				
Short-term	1.5 % (16/1063)	1.6% (7/446)	1.0 (0.4-2.3)	0.93
Relapse prevention	2.3% (6/257)	1.7% (3/176)	1.4 (0.4 5.4)	0.65
Suicide				
Short-term	0 (0/1063)	0 (1/446)	-	
Relapse prevention	0.4% (1/257)	0 (0/176)	-	
Non-fatal self-harm				
Short-term	0.6% (6/1063)	0.7% (3/446)	0.8 (0.2-3.1)	0.80
Relapse prevention	1.9% (5/257)	1.1% (2/176)	1.7 (0.4 - *)	0.51
Suicidal thoughts				
Short-term	0.9% (10/1063)	0.7% (3/446)	1.4 (0.4-4.8)	0.61
Relapse prevention	0 (0/257)	0.6% (1/176)	0 *	*

*estimates not calculable, 95% CI calculated using the Cornfield approximation to the standard error of the OR

In the placebo-controlled trials in depressive illness there was one completed suicide during double-blind treatment on citalopram, table 7.16. This occurred in a relapse prevention study and yielded an incidence of 0.4% with rate adjusting for person years exposure (PYE) of 0.01. The completed suicide in the placebo group occurred nine days after completing one day of placebo treatment.

Table 7.17 Event rates for episodes of suicide-related events whilst on treatment and during a 30-day follow-up period – all controlled trials (all indications)

	Citalopram % (n/N)	Placebo % (n/N)	Active % (n/N)	Odds ratio vs placebo (95% CI)	Odds ratio vs active (95% CI)
All suicide-related events	1.2% (54/4504)	0.9% (11/1180)	1.4% (29/2002)	1.3 (0.7-2.5) p- value = 0.44	0.8 (0.5-1.3) p- value = 0.41

95% CI calculated using the Cornfield approximation to the standard error of the Odds ratio

Risk in the first two and four weeks of treatment (placebo-controlled trials)

A total of 10 out of the 22 (45%) suicide-related events on citalopram and three out of 10 (30%) on placebo occurred within the first two weeks. Within the next two weeks a further seven and two events occurred in the citalopram and placebo groups, respectively.

Risk according to baseline suicidal risk (placebo-controlled trials)

Only one of the nine GCP-compliant placebo-controlled trials did not exclude patients with a risk of suicide. This was a relapse prevention study in depression. Therefore sub-group analyses by baseline suicide risk were not undertaken.

Examination of possible risk factors for suicidal outcomes (placebo-controlled trials)

Sub-group analyses were performed to examine possible risk factors and whether young adults (defined as those aged 18-29 years) treated with citalopram are at an increased risk of suicide, non-fatal self-harm or suicidal thoughts. These analyses were only performed on the nine GCP-compliant studies and so have limited power.

In relation to the severity of depression, a higher incidence of events was observed in those with severe depression (citalopram 2.5%, placebo 2.6%) compared with those with less severe depression (citalopram 0.9%, placebo 0.5%).

Concomitant psychotropic medication was not allowed in most studies and so the effect of this on the risk of suicidal outcomes cannot be assessed.

Escitalopram

Data from 34 controlled trials were analysed, of which 23 were completed trials and 11 were ongoing. In these trials approximately 3500 patients received escitalopram, at least 1800 received placebo and 1800 received an active control (citalopram, fluoxetine, paroxetine and venlafaxine). The indications for which patients were treated in these

studies included depressive illness, GAD, OCD, panic, PMDD and SAD. The study duration was approximately 10 weeks.

A relatively small number of events were identified, with a total of 10 suicide-related events in placebo-controlled trials and 13 and 20 in active-controlled comparisons. In the 11 ongoing studies, there have been six suicide-related SAEs.

Incidence of suicide-related events (suicide, suicidal thoughts, non-fatal self-harm)

Table 7.18 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide whilst on treatment – placebo-controlled trials (all indications)

	Escitalopram % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	P value
All suicide-related events				
Short-term	0.3% (6/2277)	0.2% (4/1814)	1.2 (0.4- 4.0)	0.78
Relapse prevention	0.3% (1/371)	0 (0/274)	*	
Suicide				
Short-term	0/2277	1/1814	*	*
Relapse prevention	0/371	0/274	*	*
Non-fatal self-harm				
Short-term	0.2% (5/2277)	0.05% (1/1814)	4.0 (0.6 - *)	0.17
Relapse prevention	0.3% (1/371)	0 (0/274)	*	*
Suicidal thoughts				
Short-term	<0.1% (1/2277)	0.1% (2/1814)	0.8 (*)	0.87
Relapse prevention	0 (0/371)	0 (0/274)	*	*

* Not estimated

95% CI calculated using the Cornfield approximation to the standard error of the odds ratio

As can be seen from the table above, there was just one completed suicide that occurred during the treatment period; this occurred on placebo.

A further suicide occurred six days after stopping treatment. This was in the citalopram group.

Table 7.19 Event rates for episodes of all suicide-related events - active controlled trials

	Escitalopram % (n/N)	Active % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0.5% (11/2252)	0.5% (9/1786)	1.0 (0.4-2.3)	0.94
	0.7% (6/923) *	0.8% (7/926)*	0.9 (0.3-2.4) *	0.8

(* Not including active controls from three-arm trials)

Risk in the first two and four weeks of treatment

The incidence of episodes of suicide, non-fatal self-harm and suicidal thoughts in the first two and four weeks of treatment were examined.
During the first two weeks of treatment two patients reported self-harm on escitalopram compared with one on placebo. During weeks three and four, two additional patients (one on escitalopram and one on placebo) reported self-harm. Three patients had suicidal thoughts in the first two weeks of treatment, all in the escitalopram group. No patients reported suicidal thoughts during weeks three and four.

Risk according to baseline suicidal risk

All studies excluded patients with a clinically significant baseline risk of suicide. Therefore sub-group analyses by baseline suicide risk were not undertaken.

Examination of possible risk factors for suicidal outcomes

The sub-group analyses were performed to examine possible risk factors for suicidal outcomes and whether young adults (defined as those aged 18-29 years) treated with escitalopram are at an increased risk of suicide, non-fatal self-harm or suicidal thoughts.

The majority of events (four out of six) in the placebo-controlled studies in depressive illness occurred in patients with more severe depression (MADRS baseline score of ≥30). The events occurred predominantly in patients with depression, with no events in the studies in panic and GAD.

Concomitant psychotropic medication was not allowed in most studies and so is not analysed. Information on psychiatric history was provided in the case narratives but not considered in the statistical analyses.

Fluoxetine

Data from 135 controlled trials were analysed. In these trials approximately 12,000 patients received fluoxetine, 5,000 received placebo and 4,000 received an active control (other SSRIs and TCAs), and 845 received fluoxetine combined with other medication. The indications for which patients were treated in these studies included depressive illness, OCD, bulimia nervosa, panic PMDD, obesity, bipolar disorder and a combined group of other indications (adjustment disorder, alcoholism, primary degenerative disorder, smoking, social phobia, PTSD, vasomotor instability and cognitive function).

The event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide are provided below. The events of suicide/self-harm were identified by searching adverse events preferred terms, actual text and comments for text strings possibly associated with self-harm. For suicidal thoughts, unlike the data provided by the other MA holders, these data are derived from Item 3 on the HAM-D scale. Data on emergence (change from 0 or 1 at baseline to 3 or 4) and worsening of suicidal thoughts (any increase from baseline in those with a score of less than 4 at baseline) have been provided.

Incidence of suicide-related events (suicide/self-harm, emergence of suicidal thoughts, worsening suicidal thoughts)

Table 7.20 Event rates for suicide-related events – placebo-controlled trials (all indications)

	Fluoxetine % (n/N)	Placebo % (n/N)	MHID† (95% CI)	p value	Mantel Haenszel odds ratio (95% CI)
Suicide/self-harm	0.2% (17/7010)	0.2% (11/4667)	-0.01 (-0.21, 0.18)	0.90	0.9 (0.4, 2.0)
Emergence of suicidal thoughts	0.8% (24/3078)	1.7% (31/1800)	-1.12 (-1.81, -0.42)	<0.01	0.4 (0.2, 0.7)
Worsening suicidal thoughts	12.9% (470/3643)	16.1% (353/2190)	-2.26 (-4.16, -0.36)	0.02*	0.7 (0.6, 0.9)

†Mantel-Haenszel Incidence Difference test
*DerSimonian-Laird test used due to heterogeneity across trials

Table 7.21 Event rates for suicide-related events - SSRI-controlled trials (depressive illness studies)

	Fluoxetine % (n/N)	SSRIs % (n/N)	MHID† (95% CI)	p value	Mantel Haenszel odds ratio (95% CI)
Suicide/ self-harm	0.8% (1/125)	0.4% (1/258)	0.41 (-1.34 to 2.15)	0.65	2.0 (0.2, 19.9)
Emergence of suicidal thoughts	3.9% (4/102)	1.5% (3/203)	2.44 (-1.68 to 6.56)	0.25	2.7 (0.6, 12.4)
Worsening suicidal thoughts	14.0% (17/121)	11.5% (29/252)	2.67 (-4.66 to 9.99)	0.48	1.3 (0.7, 2.4)

†Mantel-Haenszel Incidence Difference test

Table 7.22 Event rates for suicide-related events – TCA-controlled trials (depressive illness studies)

	Fluoxetine % (n/N)	TCAs % (n/N)	MHID† (95% CI)	p value	Mantel Haenszel odds ratio (95% CI)
Suicide/ self-harm	0.9% (16/1844)	0.5% (9/1776)	0.31 (-0.21 to 0.83)	0.25	1.4 (0.6, 3.2)
Emergence of suicidal thoughts	1.8% (20/1113)	2.3% (24/1023)	-0.61 (-1.82 to 0.60)	0.32	0.8 (0.4, 1.5)
Worsening suicidal thoughts	15.8% (281/1782)	13.5% (232/1715)	2.38 (-0.20 to 4.96)	0.07	1.2 (0.96, 1.4)

†Mantel-Haenszel Incidence Difference test

Risk in the first two and four weeks of treatment

In the placebo-controlled studies, four of the 17 episodes (24%) of suicide/self-harm in patients taking fluoxetine occurred in the first two weeks, this increased to 10 episodes (59%) in the first four weeks. No such events occurred in patients taking placebo in the first two weeks, but five of the 11 events (45%) occurred within the next two weeks.

Risk according to baseline suicidal risk

Analyses were performed for trials that had explicit suicidal risk exclusion criteria and those that had no such exclusions. Approximately half of the studies excluded patients at suicidal risk at baseline; hence reasonable numbers for analysis were included in each sub-group. The patterns seen within studies with or without exclusions for suicidal risk at baseline were similar to the overall results, which do not suggest that baseline suicidal risk has an impact on the incidence of completed suicide, non-fatal self-harm or suicidal thoughts.

Examination of possible risk factors for suicidal outcomes

The analyses performed do not suggest that young adults (defined as those aged 18-29 years) treated with fluoxetine are at an increased risk of suicide, non-fatal self-harm or suicidal thoughts compared with young adults on placebo or TCAs. There were too few events to permit statistical analysis of the studies involving clomipramine and SSRIs as active controls.

Approximately two thirds of the suicide-related events occurred in females. The rate of suicide/self-harm in females was 0.3% on fluoxetine and 0.3% on placebo; in males 0.2% on fluoxetine and 0.1% on placebo. In the TCA-controlled trials there was evidence of a difference between genders in the incidence of worsening suicidal thoughts which was

higher in females on fluoxetine (incidence difference =3%). No data were provided on concomitant psychotropic medication or psychiatric history.

Fluvoxamine

Data from 48 placebo-controlled trials were analysed. In these trials 4,186 patients received fluvoxamine and 3,396 received placebo. The indications for which patients were treated in these studies included depressive illness, OCD, panic and SAD.

There were a total of two completed suicides on fluvoxamine and an additional 47 episodes of non-fatal self-harm or suicidal thoughts. In the placebo group there were two completed suicides and 22 episodes of non-fatal self-harm or suicidal thoughts.

Incidence of suicide-related events (suicide/self-harm, emergence of suicidal thoughts, worsening suicidal thoughts)

Table 7.23 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide – placebo-controlled trials (all indications)

	Fluvoxamine % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	1.1% (48*/4186)	0.7% (24/3396)	1.6 (1.0 to 2.6)	0.07
Suicide	<0.1% (2/4186)	0.1% (2/3396)	0.8 (0.1 to 4.6)	0.83
Non-fatal self-harm	0.6% (24/4186)	0.3% (10/3396)	2.0 (0.7 to 4.0)	0.07
Suicidal thoughts	0.5% (23/4186)	0.4% (12/3396)	1.6 (0.8 to 3.1)	0.21

*Some patients had multiple events so total number with any event does not sum the individual events
95% CI calculated using the Cornfield approximation to the standard error of the Odds ratio

For all suicide-related events, when the event rate per year is examined the rate ratio is 1.85 (95% CI 1.07 to 3.21, p=0.03). The crude rate of each suicide-related event was approximately double that on placebo but there are no clear differences when treatment with fluvoxamine is compared to active control agents.

In exploratory analyses of active-controlled data, the rates of events for patients on active controls were similar to the rates for patients on fluvoxamine in placebo-controlled trials.

The following analyses have been conducted on the 32 placebo-controlled trials in the original submission.

Risk in the first two and four weeks of treatment

A total of eight out of the 63 (13%) suicide-related events on fluvoxamine and three out of 17 (18%) on placebo occurred within the first two weeks. Within the next two weeks a

further seven and five events occurred in the fluvoxamine and placebo groups, respectively.

Risk according to baseline suicidal risk

Analyses were conducted on the risk of suicide-related events according to whether baseline suicidal risk was an exclusion criterion for the trials. The highest incidence of suicide-related events occurred in the studies in which patients with baseline suicidal risk were excluded. Across the different categories, the incidence of possible suicide-related events in the fluvoxamine group was higher than that in the placebo group.

Examination of possible risk factors for suicidal outcomes

Despite small numbers in the age groups, it appears that the increased risk on fluvoxamine was consistent across all age groups (including the 18-29 year olds), with no evidence that it was heightened in young adults.

Two-thirds of the patients were female but within treatment groups the event rates for any suicide-related event were similar in each sex. A logistic regression analysis performed by the MA holder suggests that prescribing indication is an important predictor of the occurrence of a suicide-related event. Patients with panic disorder are less likely to experience a suicide-related event compared with patients with depressive illness (OR 0.10 95% CI (0.01, 0.72).

Mirtazapine

Data from 41 controlled trials were initially analysed. In these trials 2,618 patients received mirtazapine, 388 received placebo and 2,035 received an active control (maprotiline, sertraline, fluoxetine, fluvoxamine, citalopram). The average study duration was 4.4 weeks. These studies were conducted in patients with major depressive disorder. Trial data for mirtazapine are difficult to interpret because the MA holder has pooled mirtazapine event data regardless of whether this was from a placebo-controlled or active-controlled trial.

In their initial analysis the MA holder was unable to include a full analysis of many seemingly relevant studies. An interim analysis of all relevant studies has been provided by the MA holder. The MA holder has agreed to provide a revised combined analysis which is awaited.

There were a total of five completed suicides on mirtazapine and an additional 22 patients with non-fatal self-harm or suicidal thoughts. In the placebo group there were no completed suicides and three patients with non-fatal self-harm (but there were relatively few placebo-treated patients). In the group of all active controls there were three completed suicides and an additional eight patients with non-fatal self-harm or suicidal thoughts.

Event rates for all suicide-related events (suicide/self-harm, emergence of suicidal thoughts, worsening suicidal thoughts)

Table 7.24 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - placebo comparisons (all indications)

	Mirtazapine % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	1.0% (24/2349)	0.8% (3/388)	1.3 (0.4 to 6.9)	0.91
Suicide	0.2% (5/2618)†	0% (0/388)	*	
Non-fatal self-harm	0.4% (9/2349)	0.8% (3/388)	0.5 (0.1 to 2.8)	0.46
Suicidal thoughts	0.6% (13/2349)	0 (0/388)	*	

* Not estimated; † denominators will differ as 'suicide' was recorded in any trial where it occurred. Not all trials recorded non-fatal self-harm and suicidal thoughts

Table 7.25 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - active comparisons (all indications)

	Mirtazapine % (n/N)	Active % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	1.0% (24/2439)	0.5% (9/1766)	1.9 (0.9 to 4.1)	0.08
Suicide	0.2% (5/2618)	0.1% (3/2035)	1.3 (0.3 to 4.9)	0.72
Non-fatal self-harm	0.4% (9/2349)	0.1% (1/1766)	6.8 (1.1 to *)	0.04
Suicidal thoughts	0.6% (13/2349)	0.4% (7/1766)	1.4 (0.6 to 3.4)	0.47

95% CI calculated using the Cornfield approximation to the standard error of the OR
* Not estimated

Risk in the first two and four weeks of treatment

A total of 12 out of the 24 (50%) suicide-related events on mirtazapine, one out of three (33%) on placebo and six out of nine (67%) on active control occurred within the first two weeks. Within the next two weeks two more events occurred in the mirtazapine group and a further event in the placebo group.

Risk according to baseline suicidal risk

Analyses were conducted on the risk of suicide-related events according to patients' baseline suicidal risk. The presence of suicidal risk at baseline is defined as a score of ≥3 on either Item 3 of the Hamilton Depression Rating Scale (Ham-D) scale or on Item 10 of the Montgomery-Asberg Depression Rating Scale (MADRS).

There is a suggestion of a higher incidence of suicide-related events on mirtazapine in those with suicide risk at baseline (mirtazapine - 3.5% (4/114), placebo - 0 (0/35), active control 0 (0/95)), but this is driven by suicidal thoughts and based on just four patients.

Examination of possible risk factors for suicidal outcomes

The analyses performed do not suggest that young adults (defined as those aged 18-29 years) treated with mirtazapine are at an increased risk of suicide, non-fatal self-harm and suicidal thoughts compared with the overall population.

Sub-group analyses have been presented for incidence of suicide-related events by indication, gender, disease severity, previous psychiatric history and previous drug treatments. The available data do not allow examination of the effect of indication (too few patients treated for indications other than depression) or of gender (all suicide-related events on placebo occurred in females so no statistical analyses can be performed). Although the incidence of suicide-related events in each treatment group was higher in those with more severe depression at baseline, within the severity sub-groups the incidence in patients on mirtazapine was comparable to that in patients on placebo. Data from approximately 1,000 patients indicated that 50% of patients in each treatment group had psychiatric history and approximately 10% had received previous pharmacotherapy.

Sertraline

Data from 156 controlled trials were analysed, of which 56 were placebo-controlled, 70 were active-controlled and 30 were active- and placebo-controlled. In these trials approximately 11,500 patients received sertraline, 5,000 received placebo and 5,600 received an active control (amitriptyline, citalopram, clomipramine, desipramine, dothiepin fluoxetine, imipramine, lithium, lofepramine, mianserin, moclobemide, nortriptyline, paroxetine, trazadone, venlafaxine, maprotiline and pindolol). The indications for which patients were treated in these studies included depressive illness, OCD, PTSD, panic, SAD, PMDD.

Event rates for all suicide-related events (suicide/self-harm, emergence of suicidal thoughts, worsening suicidal thoughts)

Table 7.26 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide – placebo- controlled trials (all indications)

	Sertraline % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0.4% (30/7169)	0. 3% (14/5108)	1.5 (0.8 to 2.9)	0.19
Suicide	0.1% (4/7169)	0 (0/5108)	*	
Non-fatal self-harm	0.3% (20/7169)	0.2% (8/5108)	1.7 (0.8 to 3.9)	0.19
Suicidal thoughts	0.1% (6/7169)	0.1% (6/5108)	0.7 (0.2 to 2.1)	0.55

* Not estimated

Table 7.27 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide – active-controlled trials (all indications)

	Sertraline % (n/N)	Active control % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0. 6% (35/6281)	0.6% (35/5688)	0.9 (0.6 to 1.5)	0.68
Suicide	0.1% (4/6281)	0 (0/5688)	*	
Non-fatal self-harm	0.5% (30/6281)	0.6% (35/5688)	0.8 (0.5 to 1.3)	0.30
Suicidal thoughts	<0.1% (1/6281)	0 (0/5688)	*	

* Not estimated

Risk in the first two and four weeks of treatment

Approximately 60-75% of all the events observed in the treatment period occurred within the first two weeks of study treatment.

Risk according to baseline suicidal risk

Analyses were conducted on the risk of suicide-related events according to patients' baseline suicide risk. Two analyses were performed. The first examined the risk of suicidal behaviour according to whether patients were required to be at risk of suicide at study entry. In the second, the presence of suicidal risk at baseline is defined as a score of ≥3 on either ≥Item 3 of the HAM-D scale.

In both these analyses, generally the rate of suicide-related events in the sertraline group was similar to that in the placebo or active control groups, regardless of baseline suicidal risk. There was, however, strong evidence that placebo patients without suicidal thoughts at baseline had more suicidal thoughts on study than those on sertraline (p=0.01).

Examination of possible risk factors for suicidal outcomes

The analyses performed do not suggest that the risk of suicide, non-fatal self-harm or suicidal thoughts is different in young adults (defined as those aged 18-29 years) on sertraline compared with other age groups.

The effects of gender, age, severity of illness, dose and indication were also analysed. There was a higher incidence of non-fatal self-harm and suicidal thoughts in females across all treatment groups. The analyses do not suggest that these factors increase the risk of suicide, non-fatal self-harm or suicidal thoughts in patients on sertraline compared with those on placebo or active controls. The severity of illness and dose analyses, however, were limited due to incomplete information.

Venlafaxine

Data from 42 placebo-controlled trials were reviewed. In these trials, approximately 6,000 patients received venlafaxine (2,730 the immediate release (IR) formulation and 3,423 the extended release (ER) formulation,), 2,962 received placebo and 2,834 received an active control (of which 1,644 received another SSRI). The mean duration of the acute trials in MDD was approximately eight weeks. Trial data for venlafaxine are difficult to interpret because the MA holder has pooled venlafaxine event data regardless of whether this was from a placebo-controlled or active-controlled (which included fluoxetine, imipramine and amitriptyline) trial. The indications for which patients were treated in these studies included depressive illness, GAD and SAD.

There were a total of three completed suicides on venlafaxine IR and an additional 27 episodes of non-fatal self-harm or suicidal thoughts. For venlafaxine ER there was one completed suicide and an additional 22 episodes of non-fatal self-harm or suicidal thoughts. In the placebo group there were 26 episodes of non-fatal self-harm or suicidal thoughts.

Event rates for all suicide-related events (suicide/self-harm, emergence of suicidal thoughts, worsening suicidal thoughts)

Table 7.28 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - placebo comparisons (all indications) - Venlafaxine ER

	Venlafaxine ER % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0.7% (23/3423)	0.9% (26/2962)	0.8 (0.4-1.3)	0.35
Suicide	0.03% (1/3423)	0 (0/2962)	*	
Non-fatal self-harm	0.3% (10/3423)	0.3% (8/2962)	1.1 (0.4 to 2.7)	0.87
Suicidal thoughts	0.4% (14/3423)	0.6% (18/2962)	0.7 (0.3 to 1.3)	0.26

* Not estimated

Table 7.29 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - placebo comparisons (all indications) - Venlafaxine IR

	Venlafaxine IR % (n/N)	Placebo % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	1.1% (30/2730)	0.9% (26/2962)	1.3 (0.7 to 2.1)	0.40
Suicide	0.1% (3/2730)	0 (0/2962)	*	
Non-fatal self-harm	0.5% (15/2730)	0.3% (8/2962)	2.0 (0.9 to 4.7)	0.10
Suicidal thoughts	0.4% (12/2730)	0.6% (18/2962)	0.7 (0.4 to 1.5)	0.38

* Not estimated

Table 7.30 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - SSRI comparisons (all indications) - Venlafaxine ER

	Venlafaxine ER % (n/N)	SSRI controls % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0.7% (23/3423)	1.1% (18/1644)	0.6 (0.3 to 1.1)	0.11
Suicide	0.03% (1/3423)	0.06% (1/1644)	0.5 (*)	0.60
Non-fatal self-harm	0.3% (10/3423)	0.6% (10/1644)	0.5 (0.2 to 1.1)	0.09
Suicidal thoughts	0.4% (14/3423)	0.4% (7/1644)	1.0 (0.4 to 2.3)	0.93

* Not estimated

Table 7.31 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - active comparisons (all indications) - Venlafaxine ER

	Venlafaxine ER % (n/N)	Other active Controls % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	0.7% (23/3423)	1.3% (15/1190)	0.5 (0.3 to 1.0)	0.05
Suicide	0.03% (1/3423)	0.3% (3/1190)	0.1 (0 to 0.8)	0.02
Non-fatal self-harm	0.3% (10/3423)	0.6% (7/1190)	0.5 (0.2 to 1.3)	0.15
Suicidal thoughts	0.4% (14/3423)	0.4% (5/1190)	1.0 (0.4 to 2.6)	0.96

Table 7.32 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide - SSRI comparisons (all indications) - Venlafaxine IR

	Venlafaxine IR % (n/N)	SSRI controls % (n/N)	Odds ratio (95% CI)	p value
All suicide-related events	1.1% (30/2730)	1.1% (18/1644)	1.0 (0.6-1.8)	0.99
Suicide	0.1% (3/2730)	0.06% (1/1644)	1.8 (*)	0.30
Non-fatal self-harm	0.5% (15/2730)	0.6% (10/1644)	0.9 (0.4 to 2.0)	0.81
Suicidal thoughts	0.4% (12/2730)	0.4% (7/1644)	1.0 (0.4 to 2.6)	0.95

* Not estimated

Table 7.33 Event rates for episodes of suicidal thoughts, non-fatal self-harm and suicide – other active comparisons (all indications)- Venlafaxine IR

	Venlafaxine IR % (n/N)	Other active Controls % (n/N)	Odds ratio (95% CI)	P value
All suicide-related events	1.1% (30/2730)	1.3% (15/1190)	0.9 (0.5 to 1.6)	0.66
Suicide	0.1% (3/2730)	0.3% (3/1190)	0.4 (0.1 to 1.9)	0.29
Non-fatal self-harm	0.5% (15/2730)	0.6% (7/1190)	0.9 (0.4 to 2.3)	0.89
Suicidal thoughts	0.4% (12/2730)	0.4% (5/1190)	1.1 (0.4-2.9)	0.93

From the available analyses of suicide-related events taken from safety data, double-blind controlled trials show no obvious associations between venlafaxine and suicide risk. However, in the 18-29 age group there is some evidence of a slight increase in the risk of any suicide-related event on venlafaxine IR compared to placebo or venlafaxine ER.

Risk in the first two and four weeks of treatment

The incidence of episodes of suicide, non-fatal self-harm and suicidal thoughts in the first two and four weeks of treatment were examined. These results mirror the overall results, with fewer events on venlafaxine than on placebo or other SSRIs. Between 60% and 75% of all events observed in the treatment period occured within the first two weeks.

The MA holder has also provided data on worsening and emergence of suicidal thoughts as measured by HAM-D (Tables 7.34 and 7.35 below), which show similar results.

Risk according to baseline suicidal risk

Analyses were conducted on the risk of suicide-related events according to patients' baseline suicidal risk. The presence of suicidal risk at baseline was defined using the baseline HAM-D suicide severity item (0 vs ≥1). This analysis showed that significantly fewer patients on venlafaxine experienced a worsening of suicidal thoughts compared to placebo, and that this was consistent whatever the baseline suicidal risk.

Examination of possible risk factors for suicidal outcomes

Analysis of the available data show that in the 18-29 age group there is an increased incidence of episodes of suicide-related events in the patients on venlafaxine IR compared with those on placebo or venlafaxine ER, but these rates are comparable to those in patients on other SSRIs (venlafaxine IR - 2.3% (9/385), placebo - 0.7% (4/614), venlafaxine ER - 0.8% (6/734), other SSRIs -1.9% (7/361)) and are generally higher than those in patients aged over 29 years on venlafaxine IR.

In relation to dose, the analysis showed evidence of a trend ($p<0.02$) for both worsening and emergence of suicidal thoughts, with fewer events in patients receiving the higher doses (Tables 7.34 and 7.35).

Table 7.34 Incidence of worsening of suicidal ideation as measured by HAM D Dose group: number (%) of patients in dose-response studies

	Total daily dose, mg				
Time point	50 - 75 (n = 317)	150 – 200 (n=329)	225 (n=79)	375 (n=76)	p-Value[a]
Week 2	22 (6.9)	26 (7.9)	2 (2.5)	4 (5.3)	0.24
Week 4	34 (10.7)	31 (9.4)	3 (3.8)	4 (5.3)	0.03
Overall	37 (11.7)	37 (11.2)	3 (3.8)	4 (5.3)	0.02

a: Cochran-Armitage trend test

Table 7.35 Incidence of emergence of suicidal ideation as measured by HAM D Dose group: number (%) of patients in dose-response studies

	Total daily dose, mg				
Time point	50 - 75 (n = 214)	150 - 200 (n=228)	225 (n=54)	375 (n=49)	p-Value[a]
Week 2	21 (9.8%)	26 (11.4%)	2 (3.7%)	3 (6.1%)	0.17
Week 4	31 (14.5%)	31 (13.6%)	3 (5.6%)	3 (6.1%)	0.03
Overall	34 (15.9%)	34 (14.9%)	3 (5.6%)	3 (6.1%)	0.02

a: Cochran-Armitage trend test

A logistic regression analysis was performed to examine whether treatment, sex, age group and baseline severity of depression were risk factors. Treatment and baseline severity were the only factors found to be predictors of worsening or emergent suicidal thoughts.

Psychiatric history was not collected uniformly across the trials and so these data have not been analysed. Analyses of previous or concomitant medication have not been performed due to the diverse and unstructured nature of the data.

Discussion on clinical trial data for other SSRIs and related antidepressants

The clinical trial data in this section have consistently shown that the risk of suicide-related events in patients receiving placebo is slightly lower than the risk in patients receiving antidepressants across all trials.

Most clinical trial programmes also included studies against an active comparator, which may have been another SSRI or an antidepressant from a different drug class. The risks of suicide-related events are similar between the study SSRI and the active comparators, although as there are few events, it may be difficult to detect any real differences in risk. This suggests the possibility that the emergence of these events may be associated with treatment with any antidepressant rather than the specific drug in question.

The low frequency of suicide-related events, and the similarity in risks between the treated and placebo groups, make it difficult to assess whether there was an increase in risk early in treatment or in young adults (18-29 years). However, there do not appear to be any specific risk factors which clearly precipitate suicidal behaviour.

It is also important to balance any possible increase in the risk of suicide-related events against the evidence for a reduction in the symptoms of depression for patients treated with antidepressants compared with placebo, because treating depression is a major factor in reducing the risk of suicide-related events.

Examination of the data and conduct of the trials has suggested a number of areas where the design of the trials may be improved to provide better quality data of more relevance to post-marketing drug safety. These are addressed in the recommendations for the conduct of future trials in chapter 11.

7.3 Studies using the UK General Practice Research Database

The UK General Practice Research Database (GPRD) is a computerised database of anonymised clinical records from primary care (GPs) which currently covers about 5% of the UK population. Each patient record has a unique encrypted identification number and contains demographic information, lifestyle factors, prescriptions with dosage instructions, medical symptoms and diagnoses, referrals and dates of registration with the general practice. This database has provided information for a range of drug safety studies and is particularly useful when a drug is regularly prescribed in primary care. A previous study investigated whether there was an association between suicidal behaviour and antidepressants using GPRD by (Jick et al 1995)[10]. In this section we describe recent studies using this database to further investigate this association.

The MHRA are aware of three recent studies of the association between antidepressants and suicidal behaviour using the GPRD. As the majority of episodes of depression in the UK are managed in primary care, these studies provide a vital contribution to the evidence considered in this review.

Limitations of data

The data are recorded in GPRD for practice management as well as for research purposes. General practitioners are trained in recording processes and the data are subject to quality assurance checks. However, some data are incompletely recorded, meaning that in analyses of GPRD data it may not always be possible to completely control for all possible confounding factors or identify all relevant cases and study endpoints. A further limitation of the data is that there is no record of when or whether the patient started taking the medicine, as the date of prescribing is recorded rather than the date of dispensing. However, these should be non-differential between drug classes and this will tend to bias associations towards showing no difference between groups.

7.3.1 Antidepressants and the risk of suicidal behaviours (Jick et al[40])

This is a matched case-control study using GPRD between 1993 and 1999. The base population consisted of all patients aged between 10 and 69 years old with at least one prescription for the anti-depressants amitriptyline (TCA), fluoxetine (SSRI), paroxetine (SSRI) or dothiepin (TCA) between 1993 and 1999. The study was designed to consider whether the risks of non-fatal suicidal behaviour and suicide differed between these four antidepressants.

Incidence of suicidal behaviour

From the base population, 555 first episode cases of non-fatal suicidal behaviour and 17 cases of suicide were identified. All patients had received at least one prescription for either amitriptyline, fluoxetine, paroxetine or dothiepin within 90 days before their index date and had at least two years recorded history in the GPRD before their index date. Patients with prescriptions for more than one antidepressant or a recorded history of psychosis, panic disorders, phobias, obsessive-compulsive neurosis, manic-depressive disease, drug abuse, alcohol abuse, epilepsy, anorexia, bulimia or attention-deficit disorder were excluded from the study. By implication, patients who were prescribed one of the four anti-depressants for reasons such as neuropathic pain or nocturnal enuresis were included in the study.

Controls

Controls (patients without suicidal behaviour) were identified from the same base population as the cases and were matched to the cases on age, sex and duration of recorded history in the GPRD and GP practice. The same requirements and exclusion criteria were applied to the controls as for the cases. The relative risk of suicidal behaviour (fatal and non-fatal) for cases compared to controls, adjusted for time since starting treatment, was calculated for:

- each of the anti-depressants compared to dothiepin (the most widely prescribed tricyclic antidepressant in the study period);
- time since first prescription (with "more than 90 days" as the reference group).

Results

Drug comparisons

There was no strong evidence of a difference in risk between the drugs for either fatal or non-fatal suicidal behaviour, either overall or stratified by age. However, the odds ratio for non-fatal suicidal behaviour associated with paroxetine approached conventional levels of statistical significance (OR 1.29; 95% CI 0.97 –1.7) despite the low power of the study, table 7.36.

Table 7.36 Overall results from Jick et al (2004), based on 555 cases and 2062 controls

Antidepressant	Odds ratio (95% confidence interval)
Dothiepin	Reference
Amitriptyline	0.8 (0.6-1.1)
Fluoxetine	1.2 (0.9-1.5)
Paroxetine	1.3 (1.0-1.7)

Time periods

There were significant differences in the risk of both fatal and non-fatal self-harm for all four antidepressants according to the time since the patient commenced antidepressant therapy. These differences were seen for all four anti-depressants and the risk was much higher early in treatment rather than later (Table 7.37).

Table 7.37 Relationship between time since first prescription and non-fatal suicidal behaviours

Time since first prescription (days)	Odds ratio (95% CI)
1-9	4.1 (2.9-5.7)
10-29	2.9 (2.2-3.8)
30-89	1.5 (1.2-2.0)
≥ 90	Reference

7.3.2 Antidepressant treatment and the risk of fatal and non-fatal self-harm in first episode depression – a population-based case-control study (MHRA-commissioned study)

This is a nested (matched) case-control study of patients receiving antidepressants for a first episode of depression between 1995 and 2001. All patients had a diagnosis of depression within 180 days prior to and 90 days after the first antidepressant prescription, and had at least 365 days recorded history in the GPRD before study entry. There are a number of differences between the MHRA-commissioned study and the study by Jick et al[40]. In particular, a different time period is covered, patients are restricted to those with a diagnosis of depression within a relatively short time from the first prescription, the list of codes used is far more extensive resulting in more cases being identified; suicidal thoughts/ideation were not included as they appeared to be grossly under-reported.

The risk of non-fatal self-harm and suicide were contrasted between (a) SSRI users and tricyclic antidepressant (TCA) users and (b) different SSRIs and different TCAs, with

paroxetine as the reference SSRI and dothiepin as the reference TCA. The odds ratios were controlled for severity of depression, referral to a psychiatrist or psychologist, past history of non-fatal self-harm, diagnosis or treatment for anxiety or panic disorder, diagnosis of schizophrenia, drug misuse, alcohol abuse, current lithium therapy, hypnotic medication, different antidepressants prescribed in the previous year and whether the first depression diagnosis was before or after cohort entry.

Results

There were 146,095 patients with first-time depression eligible to enter the study. Amongst these patients there were 1,968 non-fatal self-harm cases and 69 suicides. The overall adjusted odds ratio (OR) of non-fatal self-harm was 1.0 (95% CI 0.9 - 1.1), and of suicide was 0.6 (95% CI 0.3 - 1.3) in SSRI users compared with TCA users, with little evidence that associations differed between drugs over time since starting or stopping treatment.

There was evidence that risks of non-fatal self-harm in SSRI users compared with TCA users differed by age group; the adjusted OR of non-fatal self-harm for SSRI users compared with TCA users for those ≤18 years was 1.6 (95% CI: 1.0-2.5). No association was apparent in other age-groups (Table 7.38), although there was weak evidence of a lower risk in SSRI users compared with TCA users in those over 30 years of age.

Table 7.38 Risk of non-fatal self-harm for patients exposed to SSRIs compared with TCAs

Age at study entry	Cases	Controls	Odds ratio (95% CI)
≤18 years	210	2809	1.6 (1.0-2.5)
19-29 years	482	7212	1.0 (0.8-1.3)
≥30yrs	652	9932	0.9 (0.7-1.0)

There was no overall evidence of an increased risk of suicide in patients exposed to SSRIs compared with TCAs (OR= 0.6 (0.3-1.3)). The number of cases of suicide identified (69 cases) made sub-group analyses unreliable.

7.3.3 Paroxetine, SSRI use and the risk of Suicidal behaviour (GlaxoSmithKline (GSK) study)

This was a cohort study with a nested (matched) case-control study of patients receiving first prescriptions for SSRI and non-SSRI antidepressants between 1988 and 2003. All patients had at least 18 months recorded history in the new full-feature GPRD before study entry and had a diagnosis of either major depression or an anxiety disorder or both in the 18 months prior to the initial antidepressant prescription. Patients were aged 10

years or older on the date of the initial antidepressant prescription and were prescribed only a single antidepressant on the date of first prescribing.

In the cohort study, demographic information and past medical history up to the time of cohort entry were compared across treatment cohorts (SSRI vs non-SSRI and paroxetine vs other SSRI (combined and separately)) to assess differences between treatment groups in the levels of suicide risk at the start of treatment. In the nested case-control study, analyses compared the risk of suicidal behaviour associated with SSRIs and non-SSRI antidepressants. A subset of cases and a separate set of controls drawn only from patients prescribed an SSRI were used in the analyses comparing paroxetine with other SSRIs. Cases were matched to controls on gender, age group, GP practice and duration of history within the database prior to study entry.

Results

Cohort study

This study comprised 158,530 patients with a medical diagnosis of depression or anxiety or both in the 18 months prior to the first antidepressant prescribing date. This resulted in a total of 55, 638 years at risk of which 34,147 were contributed by SSRI exposure. Fifty-nine percent of study patients received an SSRI as their first antidepressant treatment. More than 95% of all SSRI and non-SRRI users were over 18 and approximately 2/3 of the study cohort were female.

Relative to non-SSRI users, SSRI users were more likely to have had a medical history of psychiatric referral, prior suicidal behaviour, psychoses, acute cardio-vascular disease or stroke, and less likely to have had a major life event recorded in the past 18 months, insomnia or epilepsy (table 7.39).

Table 7.39 Risk of prior medical history in SSRI users vs non-SSRI users and paroxetine vs other SSRI users

Medical event	SSRI/non-SSRI Adjusted relative risk (95% CI) – under 19s	SSRI/non-SSRI Adjusted relative risk (95% CI) 19yrs and over	Paroxetine/ Other SSRI Adjusted relative risk (95% CI) – under 19s	Paroxetine/ Other SSRI Adjusted relative risk (95% CI) 19yrs and over
Prior suicidal event	1.3 (1.1-1.7)	1.0 (1.0-1.1)	1.2 (1.0-1.5)	1.0 (0.9-1.1)
Prior psychiatric Referral	1.2 (1.1-1.4)	1.1 (1.1-1.1)	1.2 (1.0-1.4)	1.2 (1.2-1.3)
Prior psychoses	1.3 (1.9-1.8)	1.4 (1.3-1.4)	0.9 (0.6-1.3)	0.8 (0.8-0.9))
Prior psychiatric hospitalisation	0.7 (0.3-1.6)	0.9 (0.8-1.1)	1.2 (0.5-3.2)	1.0 (0.9-1.2)
Prior substance abuse	1.1 (0.7-1.8)	1.0 (1.0-1.0)	1.5 (0.9-2.5)	1.1 (1.0-1.1)
Prior stroke	.	1.1 (1.0-1.2)	.	0.9 (0.8-1.1)

There was no evidence that event rates among adults were elevated in SSRI users compared to non-SSRI users (HR=1.0, 95%CI=0.9-1.1) or paroxetine users compared to other SSRI users (HR=1.1, 95%CI=0.9-1.2).

Nested case control analysis

These analyses included 1,271 of the 1,359 cases in the original cohort. Eight hundred and twenty cases were included in the case-control analyses drawn only from the SSRI cohort. Cases were excluded from the analyses where no matched controls could be found.

Among adults, there was weak evidence that the risk of suicidal behaviour was lower in SSRI users relative to non-SSRI users (OR=0.8, 95%CI=0.7-1.0), and was not significantly different with paroxetine relative to other SSRI use (OR=1.1, 95%CI=0.9-1.3).

There was no evidence of a relationship between suicidal behaviour risk, duration of therapy and SSRI use. There was also no evidence among adults of a trend of increased suicidal behaviour among SSRI users relative to non-SSRI users with increasing duration of therapy.

The authors conclude that the study found no increased risk of suicidal behaviour associated with use of SSRIs relative to non-SSRIs or paroxetine relative to other SSRIs in adults. See chapter 6 for a discussion of the study results in children and adolescents.

Discussion

These three GPRD studies contain overlapping sets of patients, but have used different inclusion and exclusion criteria.

The exclusion criteria and limited number of antidepressants studied limits the generalisability of the study by Jick et al. Although the overall results show no strong evidence of an increased risk of suicidal events in adults exposed to either fluoxetine or paroxetine compared to dothiepin, the strongest odds ratios were in relation to paroxetine (table 7.36).

The MHRA-commissioned study included a greater range of antidepressants than the study by Jick et al and generally compared classes of antidepressants rather than individual drugs. This combined with the extensive search carried out to identify patients with non-fatal or fatal self-harm provided greater power to detect differences in risk particularly for young people who form four percent of the study cohort (discussed in chapter 6). The study was limited to patients with a diagnosis of depression to ensure that there was homogeneity in the prescribing indications.

The GSK GPRD study covers a longer time period than the other two studies, but has a comparable number of patients in the base cohort. The comparisons made in the study are of SSRIs vs non-SSRIs and then paroxetine vs other SSRIs, either combined or individually. The drugs within the nonSSRI group include TCAs, MAOIs and other antidepressants such as venlafaxine. The effect of combining the non-SSRI drugs as a single group could be to reduce any apparent increase in risk due to SSRIs.

In common with the other studies, there is no evidence of an increased risk of suicidal behaviour in adults exposed to SSRIs compared to non-SSRIs or for paroxetine compared to other SSRIs.

The findings of the three studies are broadly consistent with each other. Overall, there is no evidence of an increased risk of suicidal behaviour in adults exposed to SSRIs compared to a range of other anti-depressants. However, there is evidence that children and young people exposed to SSRIs are at increased risk of suicidal behaviour compared to those exposed to other anti-depressants. Furthermore, there is also consistent evidence from all three studies that children and young people exposed to paroxetine may be at increased risk of suicidal behaviour compared to those exposed to other SSRIs.

It is possible that these results are due to confounding by indication where patients thought to be at greater risk of suicidal behaviour are preferentially treated with SSRIs due to their relative lack of toxicity in overdose[41]. This is supported by GSK's analysis which found that patients prescribed SSRIs are at higher baseline risk of suicidal behaviour than patients prescribed non-SSRIs. Furthermore, amongst people prescribed SSRIs, those prescribed paroxetine appear to have a more adverse suicide risk profile than those prescribed the other drugs in this class.

It is important to note that in none of these studies were patients treated with antidepressants compared with non treated patients with similar conditions because of concerns about confounding by indication whereby patients with more severe depression are more likely to be treated and likely to be at higher risk of suicidal behaviour.

The safety and efficacy of SSRIs in children and young people under 18 is discussed further in chapter 6, and recommendations for further research are in chapter 11.

7.4 Spontaneous reporting data from health professionals

The Yellow Card Scheme currently receives reports of suspected ADRs from health professionals. The database of Yellow Cards was searched (using data up to 11/09/2003) for all reports of suicide, suicidal thoughts, suicide attempt, overdose, non-accidental overdose and self-harm received in association with SSRIs.

For the health professional reports, as well as an overall analysis of the trends in reporting for suicidal thoughts and behaviour, the database was reviewed for patterns in the spontaneous reporting that may support a drug effect or may identify common risk factors in patients described in the reports.

7.4.1 Limitations of the data

Spontaneous reports are useful for highlighting potential 'safety signals' and in aiding identification of risk factors and nature of adverse events, ie qualitative data. However, the data are limited by inherent biases and cannot generally be used to establish a causal association. This is especially the case in situations where the suspected adverse drug reaction is a symptom of the disease being treated, as is the case here. Similarly the data cannot be used to quantify an adverse effect. There is a variable and unknown degree of under-reporting (again, this may be particularly true where the suspected adverse reaction is similar to the disease being treated). Furthermore, health professionals are asked to report 'suspected adverse reactions' regardless of doubts over a causal association with the drug. Therefore a report of an adverse reaction does not necessarily mean that it is due to the drug in question. A further limitation of spontaneous reporting from health professionals is that they may act as a 'filter', reporting only those details considered by them to be important rather than providing a direct account of the experiences of the patient.

7.4.2 Suicidal thoughts and self-harm

These analyses included the following terms which have been grouped under the overall term 'suicidal thoughts and self-harm': suicide accomplished, suicide attempt, suicidal ideation, aggravated suicidal ideation, parasuicide, non-accidental overdose and thoughts of self-harm. Data were analysed since marketing up to September 2003.

It is recognised that media interest can stimulate reporting through the Yellow Card Scheme, and the publicity surrounding the safety of fluoxetine in 1990 caused an increase in reporting of suicidal thoughts and self-harm associated with fluoxetine. There was also some effect on reporting rates for other SSRIs. The reporting rate of suicidal behaviour with fluoxetine then dropped between 1991 and 1993, and continued to fall gradually until 1998. In the years 1995 to 1998, the reporting rates for fluoxetine, paroxetine and sertraline were very similar, figure 7.2. This argues against this phenomenon being a particular adverse reaction to fluoxetine. Reporting rates for venlafaxine were comparatively higher between 1995 and 1998 (figure 7.3), although this coincides with the first few years of marketing of this drug. After 1998, reporting rates for venlafaxine fell to similar level as the other SSRIs.

Figure 7.2: Reporting rate for 1987 to 2002

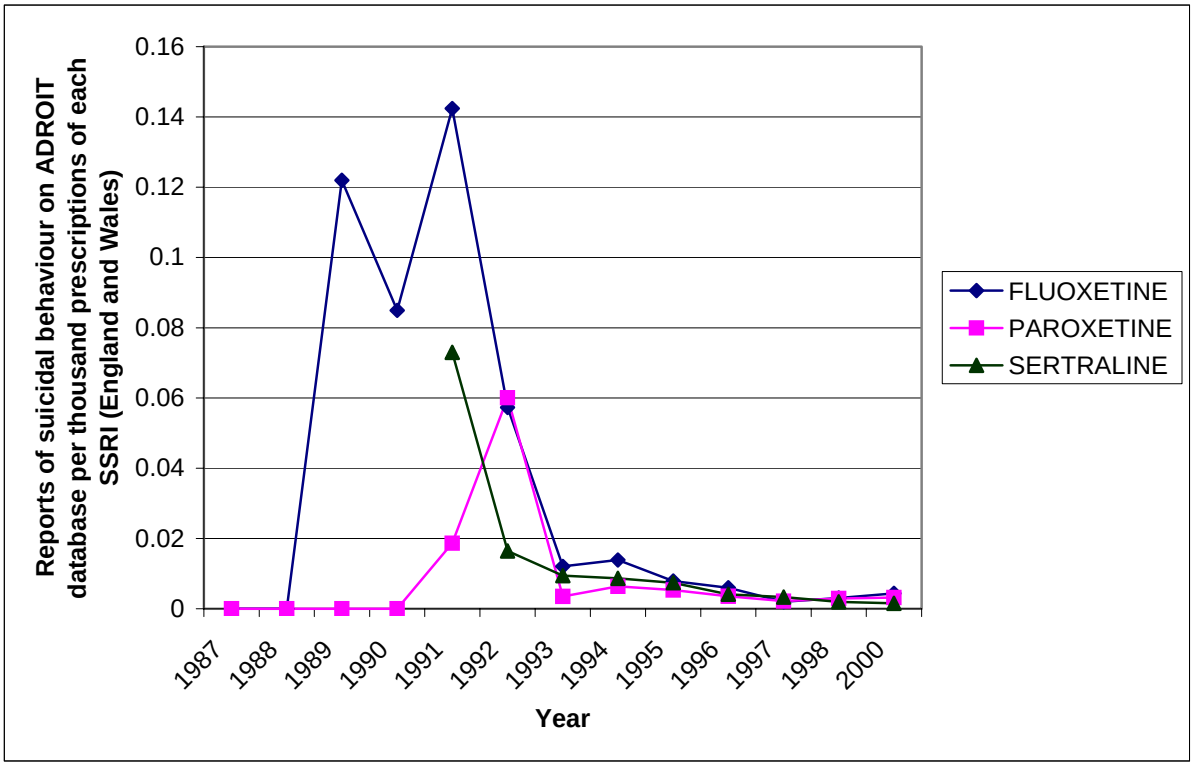
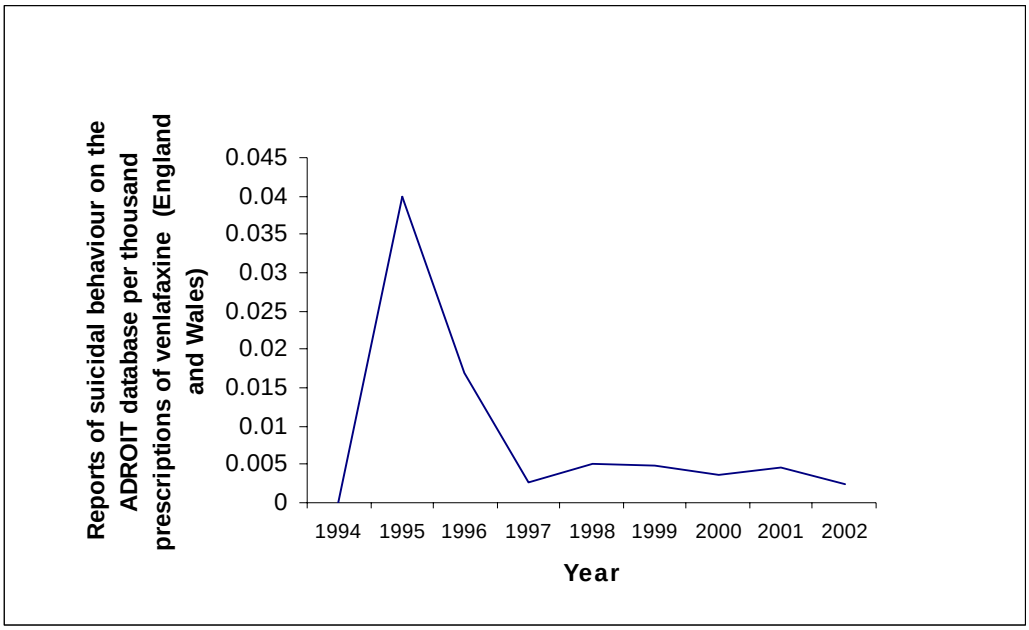


Figure 7.3: Reporting rate for 1994 to 2002 for venlafaxine



In the period from licensing of the drug up to September 2003, the highest number of reports of suicidal thoughts and self-harm were received for fluoxetine (n=274) and paroxetine (n=165). These reactions account for 3% and 2% of the total reports received for these drugs respectively. The proportional reporting ratio (PRR) for fluoxetine was 11.6 and for paroxetine was 4.2; see chapter 4 for discussion of PRRs.

When the individual cases of suicidal behaviour are examined, the majority show a close temporal relationship between drug intake and the adverse reaction. The reaction occurred within 15 days of starting the drug in 58% of reports and within one month in 77% of reports where this information is available. Of the reports of suicidal behaviour, six percent occurred on withdrawal of the drug.

Of the reports of suspected suicidal behaviour in association with an SSRI (where information was available), the majority (94%) listed depression as an indication for the suspected SSRI. Alternative indications reported included bulimia nervosa, anxiety and panic reaction.

Twelve per cent of cases of suicidal behaviour occurring on treatment with an SSRI were reported following a change in dose (increase or decrease). However, little or no information is provided on how soon after the change in dose the suspected reaction occurred. If there is a strong relationship between increases in dose and the onset of suicidal behaviour, one would expect to see a disproportionate number of events of suicidal behaviour on the higher doses of SSRIs and related antidepressants, which is not the case.

There are five cases in which a rechallenge of the suspected SSRI was documented (one percent of suicidal behaviour cases on treatment). Four of these were positive rechallenges (the symptoms settled when the drug was stopped but recurred on re-exposure) and occurred with fluoxetine (three cases) and paroxetine (one case). The fifth was a negative rechallenge with fluoxetine (the symptoms settled when the drug was stopped and did not recur on re-exposure).

For reports of suicide (accomplished), suicide attempt and suicidal thoughts where medical history is provided, approximately 24% (50/209) are reported to have a significant psychiatric history of one or more significant life events (terminal illness, death of spouse or child, schizophrenia, bipolar disorder, drug/alcohol abuse, previous history of suicide attempt, parasuicide, suicidal thoughts, self-harm or overdose).

A small proportion (seven percent) of cases reported co-suspect medication, 85% of which were other psychoactive drugs. Fifty-three percent of cases reported concomitant medication, a large proportion of which is also noted to be psychoactive. Benzodiazepines (particularly for cases associated with fluoxetine) were frequent concomitant medications.

The reports were analysed to establish whether symptoms relating to agitation, restlessness or akathisia accompanied the suicidal behaviour. Of reports of suicidal behaviour occurring on treatment with SSRIs and related antidepressants, three percent are associated with akathisia or restlessness. Fluoxetine and sertraline have the highest percentage of reports of suicidal behaviour associated with these terms, with 12% and six percent respectively. Eleven percent of cases were also associated with agitation.

Aggression and agitation were noted in 24% of reports of suicidal behaviour associated with the withdrawal of paroxetine. No cases were reported with the other SSRIs. No cases of suicidal behaviour associated with akathisia or restlessness were reported on withdrawal of medication.

Discussion

The fluctuation seen over time in the reporting rates of suicidal thoughts and self-harm with SSRIs serves to highlight the influence of publicity on the likelihood of an adverse reaction being reported. These and other limitations of the data need to be taken into account when considering the results.

The spontaneous reports generally demonstrate a close temporal relationship between the start of treatment and the suspected adverse reaction. This may be suggestive of a causal association but also may be due to the fact that an event occurring shortly after treatment initiation is far more likely to be linked to the treatment by the patient and the prescriber than an event occurring after some time on the drug. Furthermore, the patient tends to seek medical attention, and the drug is prescribed, at a point when depression is

worsening. That is to say that the risk of suicide may be greatest around the time medical attention is sought, even in those patients that do not receive treatment.

The vast majority of reports of suicidal behaviour listed depression as the indication for treatment. This may simply be a reflection of the background prescribing pattern for these products.

There were a small number of reports where a dose increase was mentioned. For most of these the temporal relationship between the dose increase and the suicidal thoughts or self-harm was unclear. A potential confounding factor that should be taken into account in this analysis is that a dose increase may be a sign that the patient's disease state has worsened. In these cases it would be difficult to disentangle whether any subsequent suicidal behaviour was due to the worsened underlying disease or an adverse reaction to an increasing dose. Overall, from spontaneous reports, there did not appear to be strong data linking the suspected adverse reactions with changes in dose – either increasing or decreasing.

A positive rechallenge provides good evidence of a causal association when considering individual spontaneous reports. There are reports (albeit very few) of positive rechallenges with fluoxetine and paroxetine. It is not particularly surprising that there are not many of these reports – if the prescriber suspected that the suicidal behaviour was due to the drug they are unlikely to want to expose the patient again and risk the event recurring.

A small proportion of the reports indicated that restlessness or akathisia had been associated with the suicidal behaviour; however, the majority did not report other symptoms and it is not possible from this data-set to assess what contribution these other symptoms played in the development of suicidal behaviour.

7.5 Patients' experiences

As described in chapter 8 (section 8.1.5), the patient reports reviewed by the EWG were obtained from two sources, the *Panorama*/Mind Yellow Cards and a questionnaire sent out to individuals who contacted the MHRA about the safety of the SSRIs.

7.5.1 Limitations of the data

Many of the limitations of spontaneous reporting data from health professionals also apply to reports from patients (see section 7.4.1). Our particular sample of patient reports will be subject to a greater degree of bias than health professional reports, as they were specifically sought following the *Panorama* programme on paroxetine. The vast majority of reports therefore relate to paroxetine rather than other SSRIs.

7.5.2 Panorama questionnaire: suicide, self-harm and suicidal thoughts in relation to paroxetine

A total of 129 patients experienced suicidal thoughts or self-harm (113 suicidal thoughts and 16 suicide attempts) in relation to paroxetine. Where information on indication was provided, over half of these patients received paroxetine for depression (58%; 60 out of 112 patients), approximately one quarter for depression and anxiety (25%; 28 out of 112 patients) and one eighth for anxiety disorders (13%; 15 out of 112 patients).

The majority (59%; 66 out of 112 reports) did not have a previous history of these feelings (or acts) prior to starting paroxetine. Where patients had experienced suicidal thoughts prior to paroxetine treatment, in some reports there is mention that the suicidal feelings they experienced were worse than those previously experienced. Information on time of occurrence in relation to treatment was provided in 80 reports. The majority of patients (62 reports) experienced these during treatment, with only eight patients experiencing these feelings on stopping and six patients experiencing them both during treatment and on stopping treatment.

In some reports patients also described experiencing a total change in characteror being told by friends/relatives that they had changed. These patients described feelings of violence, aggression and being extremely short-tempered.

7.5.3 MHRA questionnaire: suicide, self-harm and suicidal thoughts in relation to all SSRIs and related antidepressants

In 38 of the 55 reports received, patients experienced suicidal thoughts or behaviour (24 suicidal thoughts, 10 suicide accomplished, three suicide attempt and one self-harm).

Where information on indication was provided, one half of the patients were treated for depression (50%; 19 out of 38 patients), approximately one fifth for depression and anxiety (18%; seven out of 38 patients) and one tenth for anxiety disorders (10%; four out of 38 patients).

The majority (66%) did not have a previous history of these feelings (or acts) prior to starting treatment. Where patients had experienced suicidal thoughts prior to treatment, in some reports there is mention that the suicidal feelings they experienced were worse than those previously experienced. Information on time of occurrence in relation to treatment was provided in all 38 reports. The majority of patients (22 reports) experienced these during treatment, with only three patients experiencing these feelings on stopping and 13 patients experiencing them both during treatment and on stopping treatment. In eight reports, the suicidal behaviour was noted to have occurred within the first few days or the first week of treatment. In three reports, it is noted that the suicidal behaviour occurred after a change in dose (one after the dose was increased and two after the dose was decreased). In one report it was noted that the suicidal behaviour did not occur on the lower doses but only with the medium or higher doses. In two reports, specific mention of the term akathisia is made.

These reports also highlight the personality changes that patients experience with some describing a total change or being told by friends/relatives that they had changed in character. These patients describe feelings of violence, aggression and being extremely short-tempered. It is also of note that in five of the questionnaires, the patients appear to have experienced a depersonalisation disorder (where they experience a detachment from their own senses and surrounding events, as if they were outside observers), which may in part indicate a worsening of their underlying condition but is also listed as a side effect in the product information for some of the SSRIs.

7.5.4 Discussion

The reports reviewed in this section suggest that some people experience suicidal thoughts or self-harm following treatment with an SSRI. These reports should not be viewed as a random sample of patients on antidepressant treatment and cannot be used to try to establish the frequency of any adverse effect of SSRI treatment. It is likely that the patients' concerns about suicidal behaviour in association with the SSRIs have been heightened by the ongoing discussions of this issue in the media.

The strength of these data is that they provide patient accounts of suspected adverse drug reactions to SSRIs during normal clinical use and, particularly, verbatim patient reports help provide an overall picture which may be more informative than medical terms. The reports also provide powerful and detailed accounts of patients' experiences on treatment with SSRIs and the impact that these experiences have had on their lives and those of their relatives/carers.

7.6 Overall discussion

The assessment of a causal association between SSRIs and suicidal behaviour is difficult, because (1) suicide is a rare event, even in patients with depressive illness and (2) suicidal behaviour is a symptom of the underlying disease. All the data sources reviewed by the EWG have their own strengths and limitations in answering this question.

There is evidence that the risk of suicidal behaviour is highest around the time of presentation to medical services and starting treatment, possibly because the disease is at its worst before a patient will seek medical help. In addition it is common clinical experience that treatment with any active therapy for depression (pharmacological or psychological) can cause an increase in the risk of suicidal behaviour. Whether the same is true for anxiety states is not clear. 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, although neither can a modest benefit. 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.

If SSRIs are effective in treating depressive illness, why is there not less suicidal behaviour in the treated compared with the placebo group? Clinical trials are generally

not of a sufficient length for small or rare benefits of long-term treatment on depressive illness to be detected. These data may be reflecting an effect of SSRIs, an effect of antidepressants in general or the underlying disease. The evidence from the GPRD studies of the lack of any difference between the risk of suicidal behaviour with SSRIs compared with TCAs, supports a general antidepressant effect rather than an SSRI-specific effect.

Case reports from patients and health professionals which describe suicidal behaviour following SSRI treatment in patients with and without a previous history of suicidal behaviour are very compelling. They cannot on their own answer the question of causality, but they emphasise the need for close monitoring of patients, particularly in the early stages of treatment, and the need for patients and their families and care givers to be alert for symptoms which may be indicative of a worsening of the underlying disease or onset of suicidal behaviour.

The clinical trial data in children raise a concern that in some young adults there may also be a negative balance of risks and benefits for SSRIs. There is no clear evidence of this from the adult data considered – from clinical trials or from the GPRD studies. However, it is common sense that young adults differ in terms of maturity, so the findings in children and adolescents may be relevant to some young adults. In addition, young adults are at a higher background risk of suicidal behaviour and, as a precautionary measure, should be more closely monitored than older age groups. Apart from age - with under 19s being at increased risk compared to over 19s - no other possible risk factors for an effect of SSRIs in increasing the risk of suicidal behaviour were revealed by analysis of clinical trial or spontaneous reporting data.

7.7 Key findings

On consideration of all available data, the findings of the EWG can be summarised as follows:

- 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 a worsening of symptoms or new symptoms after starting treatment.

- Studies generally 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 adult clinical trial data, both published and unpublished, a modest increase in the risk of suicidal thoughts and self-harm in those taking 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 active comparators, with respect to their influence on suicidal behaviour.

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

- 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.

- 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.

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8 WITHDRAWAL REACTIONS AND POTENTIAL FOR DEPENDENCE

It has been known for many years that symptoms can occur on withdrawal of antidepressants[1]. Syndromes associated with the withdrawal of tricyclic antidepressants (TCAs) have been defined, and severe reactions have been noted on the withdrawal of monoamine oxidase inhibitors (MAOIs). It has since become clear that the selective serotonin reuptake inhibitors (SSRIs) and related antidepressants can also be associated with withdrawal reactions, although different SSRIs appear to cause withdrawal reactions to different extents[2].

It may sometimes be difficult to distinguish symptoms which reflect a return of the original illness because the treatment had been helpful but is now being withdrawn (ie a relapse), and symptoms which occur because the body is adjusting to the change as the drug is withdrawn. It is also important to note that withdrawal-like reactions are seen to occur on discontinuation of placebos where patients are not made aware whether they are taking a placebo or an active SSRI drug.

Withdrawal reactions are common to many psychoactive drugs (which act on the nervous system), however withdrawal is neither necessary nor sufficient for a medicine to cause dependence or abuse. While withdrawal reactions on discontinuation of SSRIs and related drugs are well recognised, there has been increasing public concern about the potential of SSRIs to produce drug dependence or abuse.

This chapter reviews data relevant to determining the frequency and severity of withdrawal reactions: data from clinical trials; published literature including case reports; prescription event monitoring; spontaneous reporting data; patient reports. This chapter also examines the factors that might influence the frequency and severity of withdrawal reactions including dose, length of treatment, rate of tapering of dose, and individual patient factors.

Limitations of data

Clinical trial data

There are a number of limitations to the use of randomised controlled trial evidence in determining the risk of withdrawal reactions in association with the SSRIs and related antidepressants. Often there is no standard approach to collection of data on potential withdrawal reactions occurring upon cessation of treatment – in particular with respect to a consistently employed definition of withdrawal symptoms and the time period over which these data are collected. Only recently standardised questionnaires, such as the Discontinuation Emergent Signs and Symptoms (DESS) checklist, have been employed to collect information on withdrawal reactions in clinical trials.

Differences in study design, patient population and the period over which data on potential withdrawal reactions are collected mean that caution is advised when using these data to compare the incidence of withdrawal reactions between antidepressants.

Prescription event monitoring study
Prescription event monitoring (PEM) studies provide an estimation of the frequency of an event which is not available from spontaneous reporting data. Questionnaires are sent to GPs asking for relevant clinical information on patients who have been prescribed a particular drug[3]. There are limitations to PEM data as not all the questionnaires are returned (the response rate in the PEM studies carried out to date has averaged 60%), they are limited to GP usage of drugs and there is no estimate of non-compliance with treatment.

Spontaneous reports from health professionals
Spontaneous suspected adverse drug reaction (ADR) reports are useful for highlighting potential 'safety signals' and in aiding identification of risk factors. The data are limited by a number of factors including incomplete patient histories and limited clinical details including co-prescribed medicines. There is a variable and unknown degree of under-reporting, and reporting may be stimulated by new drugs or media interest. Furthermore, health professionals are asked to report 'suspected adverse reactions' regardless of doubts over a causal association with the drug. Therefore a report of an adverse reaction does not necessarily mean that it is due to the drug in question. Likewise, if adverse events mimic symptoms of underlying disease, they may not be recognised as drug-related. A further limitation of spontaneous reporting from health professionals is that they may act as a 'filter', reporting only those details considered by them to be important rather than providing a direct account of the experiences of the patient. Therefore, these data cannot be used to establish a causal association or to quantify an adverse effect.

Patients' reports
Many of the limitations of spontaneous reporting data from health professionals also apply to reports from patients. The particular sample of patient reports considered by the EWG will be subject to a greater degree of bias than health professional reports as they were specifically sought following the *Panorama* programme on paroxetine. The vast majority of reports therefore relate to paroxetine, rather than other SSRIs.

8.1 Withdrawal reactions

8.1.1 Published literature

Case reports

There are a number of case reports of withdrawal reactions associated with SSRIs and related antidepressants in the published literature. The majority of the case reports identified in this review involved paroxetine. Others involve venlafaxine, sertraline fluoxetine and fluvoxamine. The majority of reports describe symptoms occurring after abrupt discontinuation of the drug.

In almost half of the cases in the literature, the withdrawal symptoms occurred up to three days after stopping the medication, although symptoms have been reported to occur

during tapering of the dosage of paroxetine[4], venlafaxine[5] [6] and fluvoxamine[7]. Symptoms on withdrawal have been found to occur more than one week after the final dose of fluoxetine[8] [9], paroxetine[10] and sertraline[11]. A delayed withdrawal reaction involving intense anxiety nine days after stopping venlafaxine has also been reported[12].

The symptoms reported to be experienced on withdrawal varied, although dizziness, vertigo, nausea and vomiting were commonly reported. Around one half (n=33) of the patients recovered from the withdrawal symptoms without restarting the original drug or receiving other treatment. Twenty-nine patients were restarted on the original drug (or the drug dosage increased if the reaction occurred during dose taper) with resolution of the symptoms. Of these, 17 patients then underwent gradual dose reduction in order to stop the drug.

The majority of reports in the literature do not describe severe withdrawal symptoms; however, a number of severe symptoms have been reported[4] [6] [7] [10] [12] [13] [14] [15] [16] [17]. The severity in each case was assigned by the reporter and the symptoms described as severe included nausea, vertigo, headache, fatigue, dizziness, anxiety and stomach cramps. Manic symptoms have been reported after stopping paroxetine[18] [19] and sertraline[20], and severe electric shock sensations have been reported on withdrawal of paroxetine[21]. It is probable, however, that the case reports in the literature represent the more severe end of the spectrum of withdrawal reactions occurring in practice.

Most symptoms have been reported to disappear within two weeks, although in some patients, symptoms lasted for several weeks[2].

Incidence of withdrawal reactions

A search of the literature identified a number of studies which specifically assessed the risk of withdrawal reactions with the SSRIs and related antidepressants. The incidence of withdrawal reactions on discontinuation found in these studies ranged from 0% to 86% of patients. Wide variations were found between studies measuring the incidence of withdrawal reactions with a particular drug. This may be due to a number of factors, including study design, the patient population and the definition of withdrawal reactions employed. These studies are summarised in Table 8.1.

Table 8.1: Studies of SSRI discontinuation reactions

Study	Drug withdrawn	Indication for treatment	Study design	Number of patients (N)	Withdrawal symptoms % (N)
Black et al (1993)[22]	Fluvoxamine	Panic disorder	Open-label	14	86 (12)
Mallya et al (1993)[23]	Fluvoxamine	OCD	Retrospective interview of patients completing open-label study.	17	24 (4)
Montgomery et al (1993)[24]	Citalopram Placebo	Depression	Double-blind, placebo- controlled	105 42	0 †
Barr et al (1994)[4]	Paroxetine	OCD	Open-label	6	50 (3)
Keuthen et al (1994)[25]	Paroxetine	OCD	Open-label	13	38 (5)
Holland [26](1995)	Fluvoxamine Placebo	Panic disorder	Double-blind, placebo- controlled	41 29	2 (1) 0
Oehrberg et al[27] (1995)	Paroxetine Placebo	Panic disorder	Double-blind, placebo- controlled	55 52	35 (19) 13 (7)
Bhaumik & Wildgust[28] (1996)	Paroxetine Fluoxetine	Depression	Retrospective case note analysis	12 not provided	42 (5) 0
Coupland et al (1996)[2]	Clomipramine Paroxetine Fluvoxamine Sertraline Fluoxetine	Anxiety disorder/ mood disorder	Retrospective chart review	13 50 43 45 20	31 (4) 20 (10) 14 (6) 2 (1) 0
Rauch et al (1996)[5]	Venlafaxine	OCD	Open-label	9	44 (4)
Fava et al [29](1997)	Venlafaxine (extended release) Placebo	Depression	Double-blind, placebo- controlled	9 9	78 (7) 22 (2)
Rosenbaum et al (1998)[30]	Fluoxetine Paroxetine Sertraline	Depression	Double-blind, placebo substitution	81 79 82	14 (11) 59 (47) 66 (54)
Dallal & Chouinard[31] (1998)	Venlafaxine	Depression	Open-label	8	75 (6)
Markowitz et al (2000)[32]	Citalopram Placebo	Depression	Double-blind, placebo- controlled	150 72	* see details in table footnote below
Bogetto et al (2002)[33]	Fluoxetine Paroxetine	Dysthymic disorder	Open-label	45 52	9 (4) 42 (22)
Judge et al (2002)[34]	Fluoxetine Paroxetine	Depression	Double blind placebo substitution	68 73	12 (8) 29 (21)

* Adverse events by body system that occurred during the first two weeks following abrupt discontinuation: body as a whole: citalopram 5 (3.3%) vs placebo 2 (2.8%); central nervous system: citalopram 15 (10.0%) vs placebo 16 (22.2%); psychiatric: citalopram 8 (5.3%) vs placebo 13 (18.1%); gastrointestinal: citalopram 4 (5.6%) vs placebo 7 (4.7%); miscellaneous citalopram 3 (4.2%) vs placebo 1 (0.7%). † Not reported

A number of the studies were open-label, and many involved very small numbers of patients, making interpretation of the results difficult. One study of note was by Coupland et al[2] who carried out a retrospective chart review of 352 patients treated in an outpatient clinic with either clomipramine, or one of the following SSRIs - fluoxetine, fluvoxamine, paroxetine or sertraline. Of these patients 171 discontinued treatment under supervision. The average length of treatment was - clomipramine 37 weeks (range 22-50 weeks), fluvoxamine 17 weeks (range 6-29 weeks, paroxetine 17 weeks (range 6-39 weeks), sertraline 13 weeks (range 5-29 weeks) and fluoxetine 12 weeks (range 6-15 weeks). Cases were defined as patients with at least one new symptom identified on stopping the antidepressant. Symptoms were found to occur more frequently in patients who had been treated with fluvoxamine (14%), paroxetine (20%), or clomipramine (31%), than in patients who had taken sertraline (2%) or fluoxetine (0%). No discontinuation symptoms were found in patients treated for less than seven weeks. Extending treatment beyond six months did not seem to increase the risk of withdrawal reactions compared with patients treated for less than six months.

In addition, there were a number of double-blind placebo-controlled studies. The study by Oehrberg et al[27] involved a 12-week treatment period with either paroxetine or placebo, followed by a two-week period on placebo during which all new symptoms were analysed. In this two-week period, symptoms after stopping treatment were identified in 19 (35%) of the paroxetine-treated patients and seven (14%) of the placebo-treated patients. Most of these patients reported only one adverse event on withdrawal and most of these were rated as of mild or moderate severity. The majority of patients in the study were able to discontinue paroxetine abruptly without ill effects.

Fava et al[10] carried out a study of withdrawal reactions during discontinuation of venlafaxine following a double-blind placebo-controlled study of the efficacy of the extended release formulation of venlafaxine. The rate of adverse events after discontinuation following eight weeks of treatment with venlafaxine was compared with that after discontinuation of placebo. During the three days after discontinuation of treatment, seven of the nine (78%) venlafaxine-treated patients and two of the nine (22%) placebo-treated patients reported adverse events.

An assessment of 70 patients who were withdrawn double-blind from fluvoxamine or placebo was carried out by Holland et al[26] as part of an eight week double-blind study of the efficacy of fluvoxamine in panic disorder. One patient in the fluvoxamine-treated group (2%) and no patients in the placebo-treated group developed adverse reactions on withdrawal of the study drug.

Markowitz et al[32] examined withdrawal from citalopram use for depression relapse prevention. In this study, 391 patients were initially treated in an open-label eight-week trial with a flexible dosing regimen of citalopram. Of this group, a total of 222 responders were randomised to receive either citalopram (n=150) or placebo (n=72) for 24 weeks. A similar proportion of patients in each group experienced one or more events on withdrawal from treatment. However, patients receiving placebo experienced more CNS and psychiatric symptoms compared with those patients who continued to receive

citalopram. A total of 22% of patients in the placebo group, compared with 10% in the continuing citalopram group, reported CNS symptoms, whilst 18.1% reported psychiatric symptoms compared with 5.3% in the continuing citalopram group. It is possible that some of the psychiatric symptoms experienced by patients on placebo may have reflected a return of the original illness. No patients who were abruptly switched from citalopram to placebo dropped out due to adverse events, suggesting that the symptoms associated with rapid withdrawal were mild and transient. The dosage of citalopram did not affect the incidence of withdrawal reactions.

The symptoms associated with discontinuation in the above studies included dizziness (most commonly), flu-like symptoms, nausea, headache, paraesthesiae, irritability and sleep disorders.

A study to compare withdrawal reactions associated with three SSRIs was carried out by Rosenbaum et al[30]. This involved a comparison of adverse events reported on double-blind placebo substitution of patients on fluoxetine, sertraline and paroxetine for five to eight days. The investigators' definition of a 'discontinuation syndrome' was an increase of four or more in the number of DESS checklist events from the beginning to end of the treatment interruption. This is a 43-item list based on the evaluation of signs and symptoms associated with discontinuation or interruption of SSRI treatment reported in the literature. Using this definition, the incidence of 'discontinuation syndrome' with fluoxetine was found to be 14% compared with 60% with paroxetine and 66% with sertraline.

The results of the study suggest a difference in symptomatology between the drugs studied. The most common spontaneously reported events with fluoxetine were headache, insomnia, abnormal dreams, asthenia and anxiety; with paroxetine and sertraline, the most common spontaneously reported events were nausea, dizziness, insomnia, headache and nervousness.

One relapse prevention study was identified where withdrawal reactions associated with citalopram were assessed by Montgomery et al [24]. This study involved patients who had received six weeks of treatment with either 20mg or 40mg citalopram. Those patients who responded to treatment with citalopram were then randomised to continue treatment (N=105) or put on placebo (N=42). Adverse events were elicited at assessment points of four, eight, 12, 16, 20 and 44 weeks. There was no evidence of any difference between the citalopram and placebo groups in the severity and frequency of any individual adverse event. The authors state that there was no evidence of withdrawal reactions to citalopram in the study.

Judge et al[34] examined the effects of a short treatment interruption time of three to five days with paroxetine and fluoxetine, as would occur if patients missed just a few doses. Patients successfully treated for depression with paroxetine (n=73) or fluoxetine (n=68) for between four and 24 months underwent treatment interruption in a double-blind fashion and emergent symptoms were assessed using the DESS checklist. All 43 DESS checklist events were reported as new or worsened in at least one patient in the

paroxetine group, whereas only 34 DESS checklist events were reported in at least one fluoxetine-treated patient. The most commonly reported symptoms were similar in both treatment groups and included dizziness, nervousness, irritability, agitation, trouble sleeping, sweating, fatigue and nausea. Furthermore, significantly more patients in the paroxetine-treated group spontaneously reported interruption-emergent adverse events than those in the fluoxetine group (21 (29%) and eight patients (12%), respectively).

Hindmarch et al (2000) [35] examined the effects of discontinuing and resuming antidepressant treatment with four different SSRIs (fluoxetine, sertraline, paroxetine and citalopram) on cognitive and psychomotor function (data not included in table 8.1). Patients whose antidepressant treatment had been continuous and remained constant for three months had their treatment interrupted for four to seven days using a double-blind placebo method. Aspects of cognitive and psychomotor performance were assessed using several methods. On discontinuing treatment, paroxetine-treated patients experienced significantly more disturbances in cognitive function ($p=<0.05$), poorer quality of sleep ($p=<0.05$) and an increase in depressive symptoms ($p=<0.05$), as rated by a patient-rated measure using the Zung scale and by the clinician using the MADRS scale. All changes were reversed on reinstatement of treatment.

In an open-label study, Bogetto et al[33] investigated the incidence and characteristics of the withdrawal reactions that occurred in patients following discontinuation from ≥8 weeks treatment with either paroxetine (n=52 patients) or fluoxetine (n=45 patients) following abrupt cessation of treatment. Patients were assessed using a checklist for withdrawal reactions, a semi-structured interview for withdrawal symptom characteristics, and the HAM-D and the MADRS scales. A total of 27% of patients enrolled in the study experienced withdrawal symptoms after discontinuation of treatment on the advice of their psychiatrist. Of these, 84.6% had received paroxetine and 15.4% had received fluoxetine. The mean onset time was two days after discontinuation and the mean duration was five days with the mean number of symptoms being four. The study only measured the presence and not the severity of symptoms.

Comparisons of spontaneous reporting of withdrawal reactions

Price et al[36], in a comparison of UK reports of withdrawal reactions associated with fluoxetine, fluvoxamine, paroxetine and sertraline received through the UK's spontaneous ADR reporting scheme, found a reporting rate for paroxetine of 0.3 reports per thousand prescriptions in comparison with rates for sertraline and fluvoxamine (0.03) and fluoxetine (0.002). However, they found no clear difference between the SSRIs in the nature of the symptoms reported.

Another study analysed data from the WHO Collaborating Centre for International Drug Monitoring database[37]. The WHO database collates spontaneously reported cases of suspected ADRs forwarded from 47 countries. The case reports are recorded using a common format and stored in the 1.6 million case record database maintained by the collaborating centre in Uppsala, Sweden. The authors of this study compared the reporting rates and symptoms of withdrawal reactions associated with fluoxetine,

paroxetine and sertraline. A much higher reporting rate was identified in this study for paroxetine in comparison with sertraline or fluoxetine

Blayac et al[38] (Centre de Pharmacovigilance du Languedoc-Roussillon, CHU, Montpellier) examined the French drug surveillance database for reactions associated with SSRIs. While they found that the psychiatric safety profiles of the three selected SSRIs (fluoxetine, fluvoxamine, paroxetine) to be relatively similar, they also found that withdrawal reactions with fluvoxamine and paroxetine occurred in a greater percentage of reports (13% and 14%, respectively) than with fluoxetine (1.5%).

In a further study in France, Trenque et al[39] scrutinised the French pharmacovigilance spontaneous reporting database for all reports received in association with each of the individual SSRIs and venlafaxine from launch until May 2000. Odds ratios were calculated as the odds of the association of reports of withdrawal reactions with SSRIs compared with that for all other drugs. The SSRIs were found to have a higher risk of withdrawal reactions, with the risks being particularly high with venlafaxine and paroxetine (Table 8.2).

Table 8.2: Number and odds ratios for reports of withdrawal reactions received in association with SSRIs and venlafaxine via the French pharmacovigilance spontaneous reporting scheme

	All reports (n)	Withdrawal reactions (n)	Odds ratio	95% CI
Any SSRI	4456	60	5.05	3.81-6.68
Venlafaxine	223	11	12.16	6.17-23.55
Paroxetine	1033	29	8.47	5.63-12.65
Fluvoxamine	616	8	4.45	2.21-9.0
Citalopram	270	2	1.87	0.46-7.55
Fluoxetine	1999	9	1.43	0.69-2.82
Sertraline	176	1	1.36	0.19-9.73

The Canadian regulatory authority (Health Canada) has also published the number of spontaneous reports of withdrawal reactions it has received in association with the SSRIs from launch up to 31 October 2002[40]. As shown in table 8.3, withdrawal reactions were reported more frequently with paroxetine.

Table 8.3: Spontaneous reports of withdrawal reactions in associations with SSRIs reported to Health Canada up to 31 October 2002

	Date marketed in Canada	**Total number of ADR reports**	**No (%) of reports of withdrawal reactions**
Citalopram	**1999**	**172**	**5 (2.9)**
Fluoxetine	**1989**	**1363**	**6 (0.4)**
Fluvoxamine	**1991**	**198**	**2 (1.0)**
Paroxetine	**1993**	**940**	**79 (8.4)**
Sertraline	**1992**	**480**	**10 (2.1)**

8.1.2 Clinical trial data

Paroxetine was the first of the SSRI class to be considered in detail by the EWG. The analysis of the paroxetine adult clinical trial data informed the focused questions which were passed in March 2004 to the Marketing Authorisation holders for citalopram, escitalopram, fluoxetine, fluvoxamine and sertraline, and the related antidepressants mirtazapine and venlafaxine.

The MA holder for each product was asked to provide all clinical trial data (both placebo-controlled and active-controlled studies) analysed to evaluate the risk of withdrawal reactions, and to include the following in their analyses:

i. an estimate of the incidence of withdrawal reactions;
ii. an indication of the severity of the withdrawal reactions and information on whether restart of medication or corrective therapy was necessary;
iii. examination of the impact of tapering of dose upon withdrawal;
iv. examination of the impact of duration of treatment.

The data submitted by the MA holders were reviewed and the key findings for each antidepressant are summarised below.

Paroxetine

Nature and frequency of withdrawal reactions

Data from clinical trials which employed a consistent mandatory taper regimen (tapering at a rate of 10mg/week until patients had completed one week at 20mg) show that 29.9% of patients in the paroxetine group and 20.1% of patients in the placebo group experienced adverse events on withdrawal from treatment. As can be seen from Table 8.4 below, the most common adverse events occurring were dizziness, headache, nausea, insomnia and anxiety.

Table 8.4: Number (%) of patients with adverse events in adult studies with a consistent taper and follow-up phase: all adverse events with an incidence ≥2%

	Paroxetine (n=2794)		Placebo (n=1892)	
	N	%	N	%
Dizziness	212	7.6	21	1.1
Headache	120	4.3	58	3.1
Nausea	97	3.5	42	2.2
Insomnia	84	3.0	36	1.9
Anxiety	75	2.7	32	1.7

The majority of events in both the paroxetine group (63%) and the placebo group (60%) occurred in the first week following cessation of treatment. Approximately 85% of events in the paroxetine group were mild to moderate, and approximately 15% were

severe. Most events resolved within 14 days in both treatment groups (78.5% in the paroxetine group and 79.1% in the placebo group).

Impact of tapering dose

The frequency of withdrawal symptoms following abrupt and gradual withdrawal of paroxetine suggests that gradual reduction reduces their frequency. Furthermore, where the incidence of withdrawal reactions in relation to the patients' dose of paroxetine has been examined, there is evidence to suggest the incidence of withdrawal reactions is higher in people taking higher doses (Table 8.5 below). This also supports the idea that if a patient's dose of paroxetine is gradually tapered at the end of treatment, this may reduce the risk of withdrawal reactions.

Table 8.5: Analysis of adverse event rates upon tapered withdrawal from treatment according to paroxetine dose

Paroxetine Dose	% (n/N) patients with adverse events	
	Any event	More than one event
10mg	9 (4/46)	4 (2/46)
20mg	16 (9/55)	9 (5/55)
30mg	18 (11/61)	12 (7/61)
40mg	17 (10/60)	13 (8/60)

Impact of treatment duration

Examination of the adult clinical trial data indicates that the overall incidence of adverse events that occur upon withdrawal from paroxetine treatment appears to increase with longer treatment duration (overall trend p value <0.001). As can be seen in table 8.6, the likelihood of a withdrawal adverse event in the paroxetine group increases with longer treatment duration. In the placebo group, this increase is still evident but the degree of increase is lower.

Table 8.6: Analysis of adverse event rates upon tapered withdrawal from treatment according to treatment duration

Treatment duration	% (n/N) patients with adverse events		
	All patients	Paroxetine	Placebo
1-28 days	6.0 (41/678)	6.4 (29/455)	5.4 (12/223)
29-56 days	15.6 (200/1285)	18.1 (129/712)	12.4 (71/573)
57-84 days	18.9 (313/1655)	22.7 (218/960)	13.7 (95/695)
≥85 days	25.9 (277/1068)	33.1(221/667)	14.0 (56/401)

Citalopram

Nature, frequency and severity of withdrawal reactions

The available data from four studies involving approximately 1,250 patients were provided by the MA holder. In these studies, adverse events which occurred were collected either via spontaneous reporting of adverse events or a symptom checklist. The data from these studies suggest that approximately 40% of patients will experience at least one adverse reaction upon abrupt discontinuation from citalopram treatment compared with 20% in the placebo group, and that in both groups approximately 8% of these will be severe. The most commonly reported reactions upon withdrawal were anxiety, dizziness, headache, nausea and/or vomiting, paraesthesia and sleep disorders including insomnia, and tremor.

Impact of tapering dose

All of these studies involved abrupt discontinuation from citalopram and therefore it is not possible to examine the impact that tapering of the dose may have had on the incidence of withdrawal reactions. As it is recognised that withdrawal reactions may be more likely following abrupt withdrawal, it is recommended that withdrawal from treatment with citalopram should be tapered.

Impact of treatment duration

Due to differences in the length of the observation periods after stopping treatment between the short-term (six to eight weeks) and longer-term studies (≥ 24 weeks), it is difficult to examine the impact that treatment duration may have on the risk of withdrawal reactions. There is evidence from the escitalopram studies that patients are at an increased risk of withdrawal reactions following longer-term treatment (see section below). As escitalopram is the active enantiomer of citalopram, there is no reason to believe that this would not equally apply to citalopram-treated patients.

Escitalopram

Nature and frequency of withdrawal reactions

Data from six studies involving approximately 800 patients who received escitalopram for major depressive disorder, social anxiety disorder and generalised anxiety disorder have been provided by the MA holder. All studies assessed adverse events which occurred during the escitalopram discontinuation or down-titration period of up to two weeks. In four of these studies, this involved use of DESS checklist. The data from studies suggest that approximately 30% of patients will experience withdrawal reactions upon abrupt withdrawal from treatment with escitalopram compared with approximately 10% in the placebo group. The most commonly reported reactions upon abrupt withdrawal were dizziness, nausea, insomnia, nervousness and sweating.

Impact of tapering dose

To examine the impact that a gradual tapering of dose may have on the risk of withdrawal reactions, the percentage of patients who experienced withdrawal reactions following abrupt withdrawal has been compared with the percentage of patients who experienced withdrawal reactions following a gradual tapering of dose. As can be seen from Table 8.7, the overall incidence of withdrawal reactions was generally lower following tapered withdrawal from treatment (between 6 and 25%) compared with the incidence following abrupt withdrawal (between 30 and 32%).

Impact of treatment duration

Although there are no strong data to suggest that patients are at an increased risk of withdrawal reactions following longer-term treatment with escitalopram, the available data from the studies in depressive illness provide some indication that the risk of withdrawal reactions may increase with longer duration of treatment (Table 8.7).

Table 8.7: Percentage of patients who experienced adverse events (AEs) upon discontinuation from escitalopram according to treatment duration

Method of discontinuation	Indication	Treatment duration (weeks)	% of patients experiencing AEs upon withdrawal
Abrupt	SAD	12	32
Abrupt	SAD	24	30
Tapered	Depressive illness	8	15
Tapered	Depressive illness	26	25
Tapered	Depressive illness	8	6
Tapered	GAD	24	11

Fluoxetine

Nature and frequency of withdrawal reactions

The available data from 17 studies have been examined. Approximately 60% of patients experienced at least one adverse event upon stopping treatment in both the fluoxetine and the placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature. The most commonly reported reactions were dizziness, paraesthesia, headache, anxiety, nausea and/or vomiting and asthenia (weakness, loss of energy).

Impact of tapering dose

Patients were abruptly discontinued from treatment in all fluoxetine studies; therefore these data do not permit comparison of the incidence of withdrawal reactions following abrupt withdrawal with that in association with a gradual tapering of dose.

Impact of treatment duration

To examine whether longer treatment duration increases the risk of withdrawal reactions, data from a single study were considered most relevant and therefore examined. In this study there were three arms. In the first arm, patients were treated with fluoxetine for 12 weeks; in the second arm 28 weeks, and in the third arm 50 weeks. As can be seen from Table 8.8 below, these data do not provide strong evidence to suggest that the risk of adverse events upon withdrawal increases following longer duration of treatment.

Table 8.8: Percentage of patients who experienced adverse events (AEs) upon discontinuation from fluoxetine according to treatment duration

Treatment duration (weeks)	% (n/N) of patients experiencing AEs upon withdrawal from fluoxetine
12	75 (72/96)
28	89.7 (87/97)
50	82.0 (82/100)

Fluvoxamine

Nature and frequency of withdrawal reactions

Two sources of data have been been provided by the MA holder. The first is a pooled analysis of 70 fluvoxamine clinical trials (32 placebo-controlled, with or without an active comparator group, and 38 active comparator-only trials) involving approximately 8,000 patients of which approximately 4,000 were treated with fluvoxamine. Possible withdrawal events were obtained from post-study contacts. However, not all protocols specified such an assessment; therefore these data were not systematically collected and so may underestimate the number of patients who are likely to experience adverse events upon withdrawal from fluvoxamine. The second is data from two depression relapse prevention studies in which fluvoxamine 'responders' were randomised either to continue treatment with fluvoxamine or to receive placebo.

The data from the pooled analysis suggest that approximately 6% of patients will experience withdrawal reactions when stopping treatment with fluvoxamine and 27% of these reactions may be severe in nature. The relapse prevention studies suggest that up to 24% of patients may experience withdrawal reactions upon stopping treatment and 10% of these reactions may be severe. The most commonly reported reactions upon withdrawal were headache, dizziness, nausea, and sleep disorders (including insomnia and abnormal dreams). Overall, therefore it estimated that approximately 12% of patients will experience adverse events on withdrawal, of which approximately 10% will be severe.

Impact of tapering dose

The MA holder states that the database was examined for information concerning dose-tapering regimens provided in the study protocols but that no useful information could be obtained.

Impact of treatment duration

Information on the percentage of patients who experienced adverse events upon stopping treatment with fluvoxamine according to duration of treatment is provided in Table 8.9 below. Patients who were treated for less than two weeks experienced a higher percentage of adverse events upon stopping treatment compared with the patients in the other groups; however, it is possible that these were events that led to discontinuation of treatment as opposed to events that occurred upon withdrawal. Overall, these data do not suggest that patients are at an increased risk of withdrawal reactions following longer duration of treatment with fluvoxamine.

Table 8.9: Adverse events upon stopping treatment with fluvoxamine according to duration of treatment

Treatment duration	Fluvoxamine %	Placebo %
< 2 weeks	11.1	7.8
2-6 weeks	5.7	4.2
7-10 weeks	4.1	4.1
> 10 weeks	5.5	14.9

Mirtazapine

Nature and frequency of withdrawal reactions

A pooled analysis of mirtazapine clinical trials, which involved approximately 2,600 patients, has been provided by the MA holder to determine the nature and frequency of adverse events which occurred upon discontinuing treatment. Approximately 15.3% in the mirtazapine group and 10.3% in the placebo group experienced at least one adverse event upon stopping treatment. For approximately 20% of patients in each group these adverse events were severe. The most commonly reported adverse events upon withdrawal from mirtazapine were somnolence, fatigue, headache, nausea, insomnia, sweating and dizziness.

Impact of tapering dose

As patients were abruptly discontinued from treatment in all mirtazapine studies, it is not possible to compare the incidence of withdrawal reactions following abrupt withdrawal with that in association with gradual tapering of dose. However, it is recognised that withdrawal reactions may be more likely following abrupt withdrawal and hence it is recommended that withdrawal from treatment with mirtazapine should be done gradually.

Impact of treatment duration

The available data do not strongly suggest that patients are at an increased risk of withdrawal reactions following longer duration of treatment with mirtazapine (Table 8.10). Due to differences in study design, however, the pooled analysis which has been conducted may not be the most appropriate manner in which to examine this. Therefore, the possibility that patients may be at an increased risk of withdrawal reactions following longer duration of treatment cannot be excluded.

Table 8.10: Incidence of withdrawal reactions upon stopping treatment with mirtazapine according to treatment duration

Treatment duration	Mirtazapine % (n/N)	Placebo % (n/N)
≤ 42 days	6.3 (17/271)	5.0 (12/242)
> 42 days	9.1 (31/340)	13.1 (18/137)
Total	7.9 (48/611)	7.9 (30/379)

Sertraline

Nature and frequency of withdrawal reactions

The available data from five controlled, randomised withdrawal trials were provided by the MA holder. In these studies, approximately 1600 patients were treated with sertraline followed by double-blind treatment with either sertraline or placebo. The data from these studies suggest that approximately 20% of patients will experience withdrawal reactions upon discontinuation from sertraline, and that around 20% of these reactions will be severe in nature. The most commonly reported adverse events upon withdrawal from sertraline in these clinical trials were dizziness, nausea, nervousness, anxiety, agitation, paraesthesia and emotional lability.

Impact of tapering dose

Data from one of the five studies show that when patients gradually discontinue sertraline, approximately 11% of patients experienced at least one adverse event within the first seven days following withdrawal compared with 38% of patients when treatment is abruptly stopped. This confirms that patients may be at an increased risk of withdrawal reactions following abrupt withdrawal, and supports the recommendation of gradual tapering of dose on stopping treatment.

Impact of treatment duration

As can be seen from Table 8.11, the available data do not suggest that patients are at an increased risk of withdrawal reactions following longer duration of treatment. However, differences in study design and patient population mean the data in these two studies may not be comparable.

Table 8.11: Percentage of patients who experienced adverse events in the double-blind phase by group and study

Study no	Duration of sertraline treatment (weeks)	Placebo % (n/N)	Sertraline % (n/N)
320	8	33.6* (37/110)	49.7* (91/185)
STL-NY-94-004C	24	34.8† (9/25)	18.5† (5/25)
93CE21-0615	28	11.4† (13/114)	9.2† (10/109)
96CE21-0703	28	2.0† (1/50)	2.2† (1/46)
96CE21-0631	52	38†(34/89)	17.4†(68/92)

* % of patients who had at least one adverse event within the entire double-blind phase

† % of patients who had at least one adverse event within the first seven days of the double-blind phase

Venlafaxine

Nature and frequency of withdrawal reactions

The clinical trials in the venlafaxine (Efexor) development program were not specifically designed to assess the nature and frequency of withdrawal reactions. However, retrospective analyses have been conducted by the MA holder to evaluate the adverse events that occurred upon discontinuation of venlafaxine by examining adverse events at the end of venlafaxine treatment in pooled double-blind studies and at the beginning of the double-blind phase in depression relapse or recurrence studies.

The data from 28 studies suggest that approximately 30% of patients will experience withdrawal reactions upon stopping venlafaxine treatment, of which up to approximately 12% will be severe in nature. The most commonly reported adverse events upon discontinuation from venlafaxine were dizziness, headache, nausea and/or vomiting, sleep disturbances (including insomnia and abnormal dreams), diarrhoea, agitation, anxiety, sweating, tremor, paraesthesia, palpitations and emotional instability.

Impact of tapering dose

Whilst this has not been directly examined in any of these studies, the available data do suggest that patients who receive higher doses of venlafaxine are at an increased risk of withdrawal reactions (Table 8.12). Therefore it is not unreasonable to assume that tapering the dose at the end of treatment may reduce the risk of withdrawal reactions.

Table 8.12: Number and % of patients who experienced at least three new symptoms upon discontinuation from venlafaxine treatment

Treatment arm	n/N (%)
Placebo	2/77 (3)
Venlafaxine ER 37.5mg	11/92 (13)
Venlafaxine ER 75 mg	9/92 (11)
Venlafaxine ER 150mg	20/98 (24)

Impact of treatment duration

Although there are no strong data to suggest that patients are at an increased risk of withdrawal reactions following longer duration of treatment with venlafaxine, the available data from depression studies provide some indication that the risk of withdrawal reactions increases with increasing duration of treatment. For example, 14% of patients following short-term treatment (eight weeks) and 29% of patients following longer-term treatment (24 weeks) experienced dizziness upon abruptly stopping treatment with venlafaxine.

Summary

Overall, the available data from these randomised controlled trials suggest that adverse events upon withdrawal from treatment occur commonly with all SSRIs and related antidepressants, and that generally they may be more likely to occur following abrupt withdrawal, with higher doses and longer duration of treatment.

Whilst these studies provide a crude approximation of the incidence of adverse events upon withdrawal, due to the differences in study designs (in particular, non-standardised approach to collection of data on potential withdrawal reactions, inconsistent definition of withdrawal reactions, period over which data were collected) caution is advised when comparing incidence between antidepressants.

These studies highlight the need for standard study designs to assess the incidence of adverse events upon withdrawal so that comparisons can be made between drugs and between indications, and availability of appropriate dosage strengths and formulations to enable gradual tapering of dose.

8.1.3 Prescription event monitoring

Prescription event monitoring (PEM) is a scheme run by the Drug Safety Research Unit (DSRU) in Southampton used to monitor the safety of newly marketed medicines in general clinical practice[3]. The scheme differs from spontaneous reporting in that forms requesting information are sent by the DSRU to the prescribing doctor requesting information at defined periods after a prescription has been dispensed. The doctor is requested to provide event data - ie any new diagnosis or reason for referral, any ADR or anything else significant enough to be entered in the patient's notes.

Each first prescription for a drug being monitored will lead to the DSRU issuing a form to the practitioner who wrote the prescription. The forms that are completed and returned are assessed by a medical doctor and serious suspected ADRs are followed up. Aproximately 60% of forms are returned.

Mackay et al. compared the results from a number of PEM studies of SSRIs.[41] The numbers of patients reported as experiencing withdrawal symptoms on stopping the SSRIs in the PEM studies are summarised below.

Table 8.13: Summary of PEM study results

Drug	No of patients	No of reports of withdrawal reactions	% reported as experiencing withdrawal reactions
Fluoxetine	12692	2	0.02
Fluvoxamine	10983	2	0.02
Paroxetine	13741	15	0.17
Sertraline	12734	2	0.03

[Adapted from Mackay et al[40]]

The symptoms associated with the withdrawal reactions for the SSRIs studied were agitation, anxiety, tremor, dizziness, loss of balance, nausea, vomiting, paraesthesia and restlessness.

The frequencies of withdrawal reactions obtained from PEM are 0.02% to 0.03% for patients stopping fluoxetine, fluvoxamine and sertraline, and 0.17% for patients stopping paroxetine. These are much lower than the rates seen in clinical trials, PEM is likely to produce an underestimate of frequency as not all withdrawal reactions will be reported to doctors. If symptoms are reported, they may not be recognised as withdrawal reactions by the doctor and therefore may not be entered as such in the patient's notes or reported.

8.1.4 Spontaneous reporting data from health professionals

The total number of reports of drug withdrawal reactions received through the Yellow Card Scheme for the SSRIs and the related antidepressants up to 31 August 2003 are listed in the table below. The reports included are those where the reporter has indicated that the symptoms were due to the cessation of treatment and these reports have therefore been classified as 'drug withdrawal reactions'. The percentage of total reports comprising drug withdrawal reaction reports was also calculated for each drug.

Table 8.14: Overview of reports of drug withdrawal

	Total number of reports of suspected adverse reactions	Total number of drug withdrawal reactions	Withdrawal reactions as % of total reports
Citalopram	1757	70	4.0
Escitalopram	142	2	1.4
Fluoxetine	7990	95	1.2
Fluvoxamine	2445	13	0.5
Mirtazapine	1395	16	1.1
Paroxetine	8831	1423	16.1
Sertraline	2438	85	3.5
Venlafaxine	3614	327	9.0

The highest number of drug withdrawal reaction reports has been received for paroxetine and venlafaxine, with withdrawal reactions accounting for 16.1% and 9.0% of the total reports of suspected adverse reactions received for these medicines, respectively. For escitalopram, since only two reports of withdrawal reactions had been received up to 31 August 2003, no further analyses of these reports were conducted.

Looking at the time to onset of the withdrawal reactions, between 52% (for sertraline) and 76% (for venlafaxine) occurred within three days of stopping the drug. For all drugs, the majority of withdrawal reactions (80%-90% for all drugs) started within the first week of stopping treatment. Longer onset times were calculated in isolated reports of citalopram (n=1), venlafaxine (n=1), paroxetine (n=2) and fluoxetine (n=5). Some symptoms were reported to have started before the drug was stopped but where tapering of dose had begun. In a small proportion of cases, the withdrawal reactions occurred when patients inadvertently missed a dose: 3% (n=38) of paroxetine reports, 3% (n=10) of venlafaxine reports, 5% (n=4) of sertraline reports, 1% (n=1) of citalopram reports, and none of the reports for the other drugs analysed.

The most commonly reported reactions that occurred upon withdrawal are shown in figures 8.1 to 8.6 below. Dizziness was amongst the most commonly reported reaction with all drugs, except for mirtazapine. For mirtazapine, the most commonly reported reaction upon withdrawal was anxiety. Other commonly reported reactions include paraesthesia (tingling or pins and needles), nausea and/or vomiting, headache and anxiety.

Between 32% and 54% of people who experienced withdrawal reactions had recovered or were recovering at the time of the report (without restarting the drug). Between 15% and 31% of patients had restarted the drug and recovered from the withdrawal reaction at the time of the report. There is a procedure for MHRA staff to follow-up reports of withdrawal reactions where the individual is not known to have recovered or where the patient restarted the drug. These attempts to obtain further information are not always successful and, in some cases, the eventual outcome remains unknown.

It was possible to calculate duration of the withdrawal symptoms for around one half of the reports. Between 41% (for fluoxetine) and 64% (for citalopram) recovered from the withdrawal symptoms within eight days and between 67% (for fluoxetine) and 88% (for citalopram) recovered within 14 days.

Most commonly reported symptoms on withdrawal from SSRIs and related antidepressants (spontaneous reporting data from health professionals)

Figure 8.1

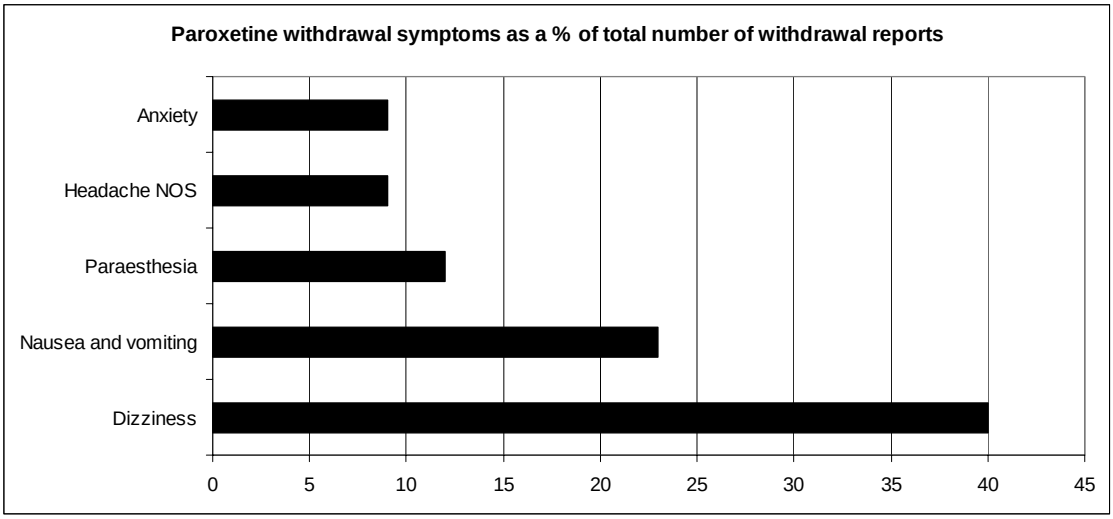


Figure 8.2

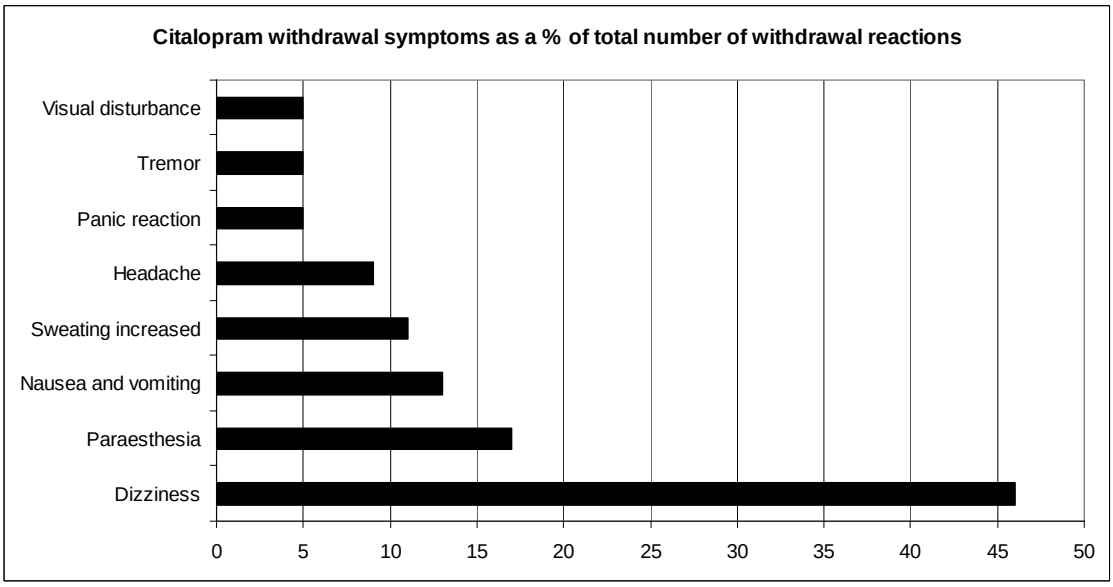


Figure 8.3

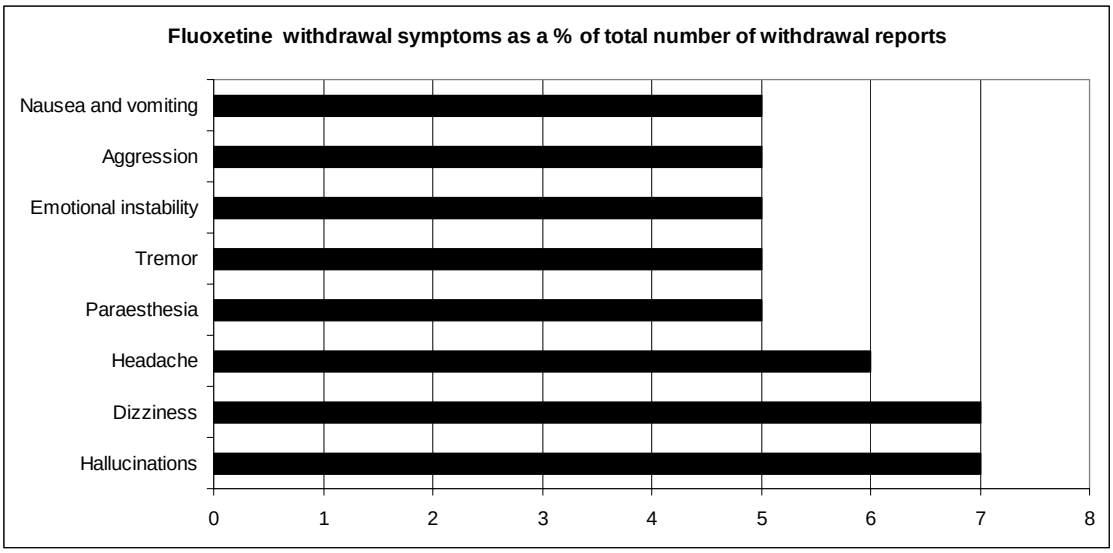


Figure 8.4

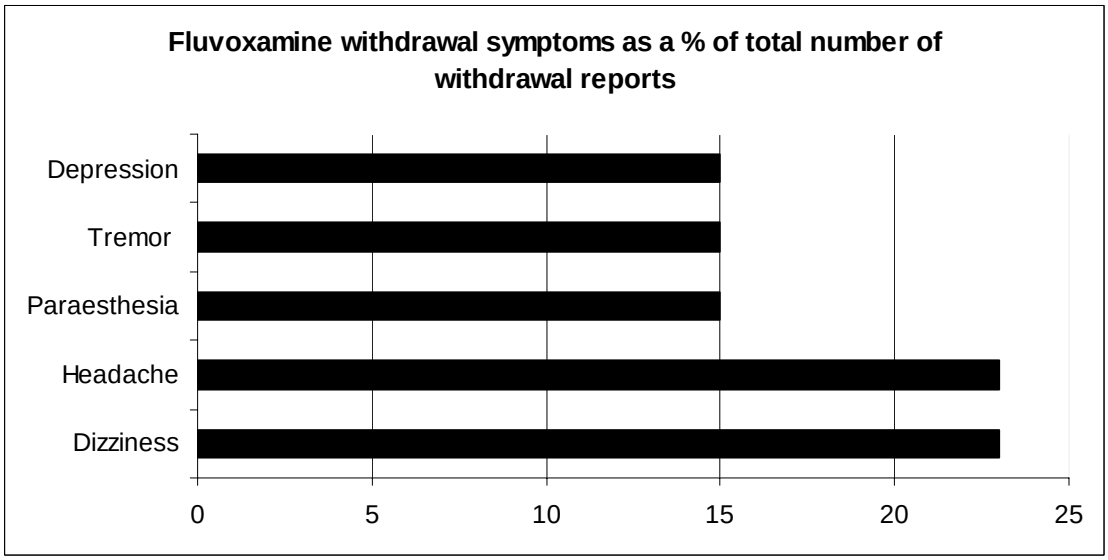


Figure 8.5

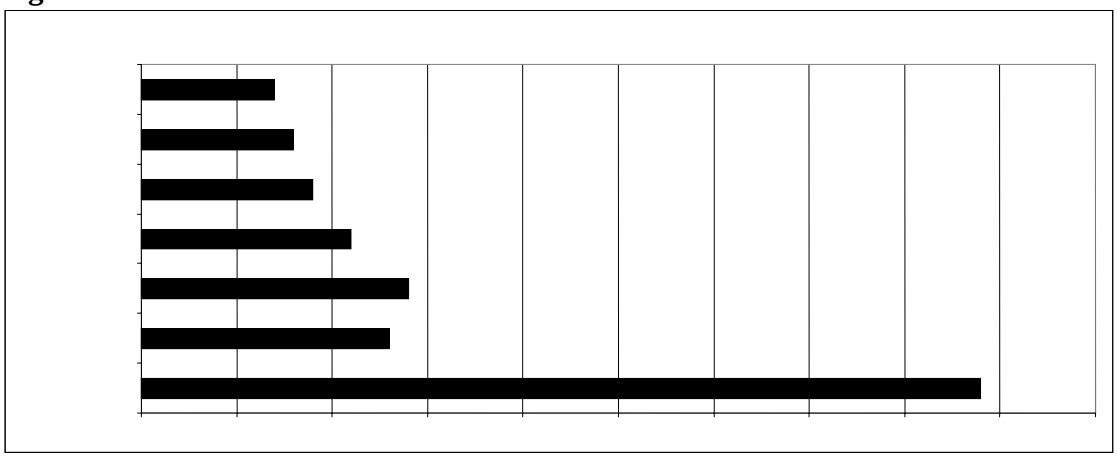
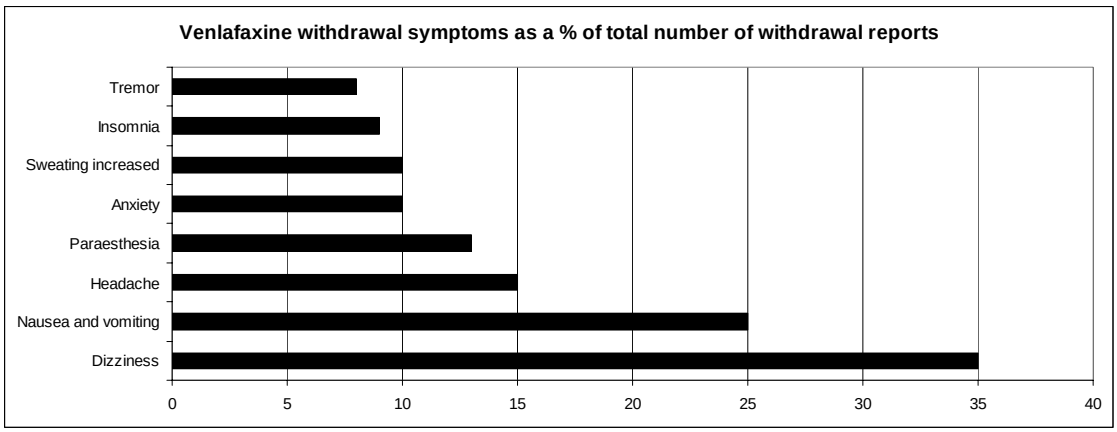


Figure 8.6



8.1.5 Patients' experiences

Over the time of the review, the Yellow Card Scheme did not include direct patient reporting, although work is ongoing to implement such a scheme (see section 4.2.1, chapter 4). The patient reports reviewed by the EWG were obtained from two sources. Following the BBC *Panorama* programme entitled 'Secrets of Seroxat', broadcast on 13 October 2002, *Panorama,* in collaboration with Mind, developed a *Panorama*/Mind Yellow Card or questionnaire to obtain information about patients' experiences, or their friends/relatives' experiences, in relation to the use of paroxetine (Seroxat). Following the *Panorama* programme screened on 12 May 2003, these *Panorama*/Mind Yellow Cards were provided to the MHRA. Subsequently, upon the advice of the CSM's EWG on the safety of SSRIs, a questionnaire was developed to capture all relevant information relating to patients' and/or their relatives' experiences. Where appropriate this questionnaire was sent out to individuals who contacted the MHRA about the safety of the SSRIs.

***Panorama* questionnaire: withdrawal reactions from paroxetine**

Of the 223 individuals who completed these questionnaires, a total of 203 reported at least one adverse reaction upon withdrawal from paroxetine. In some cases withdrawal symptoms occurred if paroxetine was taken a few hours later than usual or if a dose was accidentally missed. The most frequently reported withdrawal symptoms were dizziness, anxiety, disturbed sleep, agitation, sweating, nausea, tremors, confusion, numbness, and electric shock-like sensations.

One half of the individuals felt the most serious of these symptoms was intolerable and a further third felt the most serious of these symptoms was severe. Due to the severity of the withdrawal reactions individuals seemed genuinely afraid of experiencing these symptoms and therefore continued on paroxetine. For some, this had a considerable impact on their lives.

The majority (63%) of the individuals completing these questionnaires had made more than one attempt at trying to stop paroxetine. When questioned as to what they understood by the term 'dependence', the general response was that it meant having to carry on taking paroxetine to prevent the symptoms of withdrawal from returning. However, only two reports mentioned the need for increasing doses to achieve the desired effect, and there was no indication of drug-seeking behaviour.

Many patients seemed unaware that withdrawal reactions could occur upon stopping treatment with paroxetine and felt that there should be better information on the possible effects on stopping treatment. This, coupled with their doctor's apparent lack of awareness of the nature and possible severity of withdrawal symptoms, was an understandable concern for many patients.

MHRA questionnaire: withdrawal reactions from SSRIs and related antidepressants

Fifty-five completed questionnaires were received. Information on the occurrence of withdrawal symptoms was provided in 45 reports. In 34 of these reports the patients experienced withdrawal symptoms on stopping Seroxat. A list of possible withdrawal symptoms was provided and the patients indicated which of these they experienced. The most frequently experienced withdrawal symptoms were disturbed sleep (n=25), dizziness (n=22), agitation (n=22), sweating (n=22), anxiety (n=21), electric shock sensation (n=20) and tremors (n=20).

Patients were also asked to provide information on any other suspected ADRs they experienced. The suspected ADRs most frequently described in this section were anger/aggression/violent thoughts or behaviour, depression, mood swings, suicidal behaviour and flu-like symptoms.

In 29 of the reports information on severity of withdrawal reactions was provided. Two thirds of patients (19 out of 29 reports) felt the most serious of these symptoms was intolerable and for the remaining third almost all patients felt the most serious of these symptoms was severe.

8.1.6 Discussion

The SSRIs and related antidepressants are recognised to cause withdrawal reactions and recent attempts have been made to define these. The mechanisms involved in these reactions are still not clear.

In general, small controlled clinical trials in which specific enquiries have been made suggest that such reactions are quite common[2 22 27]. In contrast, post-marketing data from spontaneous ADR reporting using prescription denominators[36] and prescription event monitoring (PEM)[41] suggest much lower frequencies. These differences probably reflect the strengths and weaknesses of each type of data. Clinical trials in which small numbers of patients are closely observed and questioned about symptoms on withdrawal are unlikely to underestimate such effects. On the other hand, post-marketing data do reflect real life, and reactions which are recorded and reported are likely to be considered clinically important. However, spontaneous reporting data can only give a limited indication of frequency because of the problem of under-reporting and under-recognition because patients do not complain or doctors do not correctly attribute or record such symptoms.

Although the data suggest that withdrawal effects are common to all SSRIs and the related antidepressants, there are indications of different frequencies between drugs. They appear to occur most commonly with paroxetine and venlafaxine and least often with fluoxetine. Apart from the shorter half-life of paroxetine, its affinity for muscarinic receptors has also been suggested as a possible reason for the increased risk of withdrawal reactions for this drug (see section 5.1.2, chapter 5).

Fluvoxamine has an elimination half-life similar to paroxetine and inhibits its own metabolism in the same way as paroxetine, although to a lesser extent. Fluvoxamine has been associated with high rates of withdrawal reactions in published open-label studies; however, this is not reflected in the spontaneous reporting data, or in the data from PEM.

Fluoxetine has a long half-life and an active metabolite which, in turn, has a long half-life. Withdrawal reactions have been reported with fluoxetine and some case reports suggest that the delay between stopping fluoxetine and the onset of withdrawal symptoms may be up to two weeks. This may partly explain the relatively few reported withdrawal reactions with fluoxetine as they are not associated with discontinuation of the drug by patient or reporter. There is some suggestion that the symptoms associated with discontinuation of fluoxetine may be slightly different from those associated with paroxetine.

Data from clinical trials, spontaneous reporting from health professionals and the published literature suggest that many of the symptoms of withdrawal reactions associated with the SSRIs are mild and self-limiting, although reports of more severe reactions have been identified. The reports from patients suggest that, at least in some cases, not all patient experiences are reported by the health professional. While the symptoms experienced upon withdrawal may not in themselves be serious or life threatening, for a proportion of individuals they are severe and impact significantly on their quality of life. Much of the data received direct from patients relates specifically to paroxetine and it is not known at the moment to what extent this can be extrapolated to the other SSRIs and related antidepressants.

Data from spontaneous reports suggest that in some patients, withdrawal reactions may occur if they are late in taking their dose or forget to take a dose. This may be a particular problem for the SSRIs and related antidepressants with a short half-life.

8.2 Drug dependence and abuse

Concern has been expressed about the dependence-producing potential of SSRIs. The available data from animal studies, spontaneous reporting data and the published literature have been reviewed to determine whether there is evidence of dependence with SSRIs and the related antidepressants.

"Drug abuse" can be defined as “the use of a drug for non-medical purposes". Some drugs have properties that reinforce self-administration, because of their effects on mood (euphoria, or alleviation of dysphoria or distress), leading to the potential for abuse. Such drugs may be “addictive” or “dependence producing” such that the drug abuser will gradually increase the amount of the drug taken (with the development of tolerance), and will often continue to take the drug in spite of increasingly serious adverse consequences.

There are three main ways in which we can examine the potential of a drug, such as an SSRI, to produce dependence: animal self-administration studies; human drug abuse liability studies; clinical studies of the prevalence of symptoms of the "dependence syndrome" in humans as defined by internationally recognised diagnostic classification (ie the Diagnostic and Statistical Manual, 4th revision (DSM-IV; American Psychiatric Association, 1994) and the International Classification of Diseases, 10th Revision (ICD-10; World Health Organisation, 1992)).

Definitions of dependence

ICD-10

Three or more of the following manifestations should have occurred together for at least one month or, if persisting for periods of less than one month, should have occurred together repeatedly within a 12-month period:

1) a strong desire or sense of compulsion to take the substance;

2) impaired capacity to control substance taking behaviour in terms of its onset, termination, or levels of use, as evidenced by the substance being often taken in larger amounts or over longer periods than intended, or by a persistent desire or unsuccessful efforts to reduce or control the substance use;
3) a physiological withdrawal state when substance use is reduced or ceased, as evidenced by the use of the same (or closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
4) evidence of tolerance to the effects of the substance, such that there is a need for significantly increased amounts of the substance to achieve intoxication or the desired effect, or a markedly diminished effect with continued use of the same amount of the substance;
5) preoccupation with substance use, as manifested by important alternative pleasures or interests being given up or reduced because of substance use, or a great deal of time being spent on activities necessary to obtain, take or recover from the effects of the substance;
6) persistent substance use despite clear evidence of harmful consequences as evidenced by continued use when the individual is actually aware, or may be expected to be aware, of the nature and extent of harm.

DSM-IV

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1) tolerance as defined by either of the following:
    a. a need for markedly increased amounts of the substance to achieve intoxication or the desired effect;
    b. markedly diminished effect with continued use of the same amount of the substance;
2) withdrawal, as manifested by either of the following:
    a. the characteristic withdrawal syndrome for the substance;
    b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;
3) the substance is often taken in larger amounts or over a longer period than was intended;
4) there is a persistent desire or unsuccessful efforts to cut down or control [the] substance use;
5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects;
6) important social, occupational, or recreational activities are given up or reduced because of substance use;
7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

There are clearly many similarities between the two internationally recognised systems of diagnostic classification, but there are also important differences of content and emphasis. These will be examined separately in the discussion to examine the extent to which available clinical data supports the existence of dependence in relation to the SSRIs.

8.2.1 Available data on the abuse and dependence liability of SSRIs and related antidepressants

Pre-clinical data

Fluvoxamine

The dependence liability of fluvoxamine was reviewed in two studies involving monkeys. The studies failed to show dependence liability and drug-seeking behaviour with fluvoxamine.

Paroxetine

Evidence was presented from four pre-clinical studies performed in monkeys, one designed to assess psychological dependence (with amphetamine as the control drug), one designed to assess physical dependence (with diazepam as the control drug), and two designed to assess the ability of paroxetine to suppress the abstinence signal of morphine or phenobarbitone dependency. The studies concluded that paroxetine had no physical or psychological dependence liability, in contrast to diazepam which had mild to moderate physical dependence liability, and amphetamine which induced drug-seeking behaviour. Administration of paroxetine did not alleviate morphine or phenobarbitone withdrawal, suggesting that paroxetine did not share the same physiological mechanisms as the withdrawal dependence associated with these agents.

Venlafaxine

In monkeys trained to discriminate phenobarbital or dextroamphetamine from saline, venlafaxine doses up to 30mg/kg produced no discriminative stimulus effects to either drug - suggesting that venlafaxine would not produce subjective effects in humans like those caused by phenobarbital or amphetamine.

Published literature

In their review of the literature on the subject of antidepressants and abuse potential, Pagliaro and Pagliaro[42] identified only five antidepressants reported as being directly associated with substance abuse or dependence (amineptine, amitriptyline, fluoxetine, phenelzine and tranylcypromine). Three other antidepressants (citalopram, clomipramine and moclobemide) were described as being indirectly associated (ie a combination of drugs was used to create the desired effect). Twenty-seven separate cases were identified (not including 155 cases reported in France in association with amineptine).

Tranylcypromine was identified as the antidepressant used in one half of the reported cases (tranylcypromine is structurally similar to amphetamine). The authors concluded that antidepressants do not appear to carry a high risk of inducing substance use disorders as defined by DSM-IV. Abuse (ie taking more than the prescribed dose, or taking it in a non-prescribed pattern) was found to occur mainly in those patients with a previous history of substance use disorder.

The current review of the literature has revealed six case reports of abuse of fluoxetine and one case report of abuse of sertraline. All patients described in these reports had a history of substance abuse. In most cases, the drugs were abused for the effect of mood elevation, although Wilcox[43] reported a woman with anorexia nervosa who took fluoxetine for its appetite-suppressing effects. Two of the reports of abuse of fluoxetine described patients using fluoxetine in the same way as they used illicit drugs[44]. The intravenous injection of fluoxetine by an intravenous drug-user may have been related to the development of behavioural associations between intravenous drug use and pleasure . Similarly, in the report of ritualistic use of fluoxetine[45], the authors suggest that the re-enactment of the illicit drug use may explain the effect on the user rather than any pharmacological effect of the drug.

In the two cases of abuse of fluoxetine reported by Tinsley et al[46], the authors commented that although both patients abused fluoxetine neither experienced physical dependence as evidenced by tolerance or a withdrawal syndrome. They suggested that the mechanism involved in the abuse of fluoxetine might be due to its serotonergic effects which, if they sufficiently resemble those of amphetamines, may elicit a conditioned drug response, thereby enhancing the pharmacological effect of fluoxetine.

In addition to these cases of drug abuse, Castaneda et al[47] have reported three patients who experienced drug craving when switched from fluoxetine, paroxetine and venlafaxine to nefazodone. All patients had a history of opiate, cocaine or alcohol dependence; however, they were all abstinent at the time. The introduction of nefazodone precipitated relapse into cocaine or alcohol use in two patients and abnormally strong cravings in the third. The authors suggest that the mechanism of this craving may be a disturbance in serotonergic transmission or altered metabolism of nefazodone started after the use of paroxetine and fluoxetine (both potent inhibitors of the P450 2D6 system) leading to increased levels of a minor metabolite of nefazodone which may trigger the development of anxiety, dysphoria and impulsivity in some patients.

Spontaneous reporting data from health professionals

Up to 31 August 2003, a total of 20 reports of drug dependence and three reports of drug abuse had been received in association with the SSRIs and the related antidepressants.

The 20 reports of drug dependence were reported in association with paroxetine (n=20), fluoxetine (n=12), venlafaxine (n=4), sertraline (n=3) and fluvoxamine (n=2) (Annex C). Despite the use of the term ‘dependence’ or ‘addiction’ by the reporter, none of these reports describes features of dependence other than withdrawal. It is of note that six of

these reports are from two reporters, indicating that the submission of these reports may have been stimulated by media interest or the reporter's interpretation of the term 'dependence'.

Patients have reported that they found it 'impossible' to discontinue the drug because of withdrawal effects on repeated attempts.

Three spontaneous reports of drug abuse were received in association with fluoxetine (n=1), paroxetine (n=1) and sertraline (n=1). Two of these patients had a past history of alcohol and/or drug abuse and the third patient was reported to 'self-medicate' with a number of drugs including heroin, benzodiazepines and anticonvulsants.

Discussion

With reference to ICD 10 criteria, SSRIs do not appear to lead to craving in comparison with other drugs of dependence such as opiates, heroin, cocaine and alcohol (criterion 1). There is no clear evidence of impaired control (criterion 2) apart from isolated single case studies in individuals who misuse other substances. There is clear evidence of withdrawal symptoms on discontinuation of SSRIs (criterion 3); also some patients take care not to run out of the drug, possibly to avoid withdrawal symptoms (criterion 3). However, this is not nearly as marked as in typical drugs of dependence. Tolerance does not appear to be significant compared with other drugs such as benzodiazepines (criterion 4). There is some evidence of preoccupation, or rather patients making sure they have a supply of SSRI drugs (criterion 5), but this does not appear to be prominent and may be more a feature of withdrawal avoidance. Finally, there does not appear to be evidence of persistence despite harmful consequences, partly perhaps because the harmful consequences related to SSRI use are relatively minor, and the benefits to the individual greater, compared with other typical dependence-producing drugs (criterion 6). So although SSRIs meet two out of the six ICD 10 criteria (numbers 3 and 5), the evidence for criterion 5 is limited compared with other typical drugs of dependence.

In relation to DSM IV criteria, as stated above tolerance is rare (criterion 1), withdrawal is common (criterion 2), and the substance is sometimes taken over a longer period than intended because of difficulties in stopping SSRIs (criterion 3). Sometimes, a desire to cut down can be unsuccessful (criterion 4). However, it is uncommon for a great deal of time to be spent in obtaining SSRIs (criterion 5), activities are seldom given up in favour of SSRIs (criterion 6), and SSRIs are seldom continued in the face of drug-related problems (criterion 7) in comparison with other typical dependence-producing drugs. Overall, in relation to DSM IV there is evidence that three out of the seven criteria are sometimes met. However, the extent to which SSRIs meet these criteria is much less than with other typically dependence-producing drugs.

Both animal and human research show that SSRIs have a considerably lower abuse potential than most other dependence-producing substances, including benzodiazepines. The abrupt cessation of any psychoactive drug after a significant duration of use is likely to result in a withdrawal reaction. This can be expected from the pharmacological

actions of the drug on the brain and the changes that occur when it is withdrawn. Withdrawal reactions are significant in SSRIs, with differences between individual SSRIs in terms of frequency and the severity of withdrawal reactions. However, withdrawal reactions alone are not sufficient reinforcers of continued drug use in general terms, and in SSRIs in particular, on the basis of the current evidence. The SSRIs do not have an equivalent dependence potential to benzodiazepines on the basis of the existing evidence, although they both produce characteristic withdrawal reactions following chronic exposure. Furthermore, the WHO Expert Committee on Drug Dependence (2002) clearly distinguishes between substance dependence and abuse liability in the sense that one does not necessarily define the other. The WHO committee concluded that withdrawal is neither necessary nor sufficient for a diagnosis of dependence.

A review of the available published and unpublished data revealed no evidence that these drugs were associated with dependence, and the results of clinical and pre-clinical studies indicate that dependence, and the abuse potential of these drugs, is low.

There are a small number of UK spontaneous reports of dependence associated with some of the SSRIs. Those with any detail generally describe withdrawal reactions but no other features of dependence.

There are a small number of reports in the literature and UK spontaneous reports of abuse of fluoxetine and one report of tolerance to fluoxetine. The reports of abuse are all in known drug abusers and these reports should be seen in the context of the large usage of these drugs.

Analysis of usage data has shown that the vast majority of patients receiving SSRIs and related antidepressants have only a few prescriptions. Dependence amongst large numbers is not suggested by the patterns of prescribing shown. There are small numbers of patients who have large numbers of prescriptions. Some of these patients appear to have continuous prescriptions but some, for unknown reasons, have gaps between treatment periods.

8.3 Neonatal withdrawal symptoms/complications

8.3.1 Published literature

Case reports

There are 15 published case reports of withdrawal syndrome in neonates born to mothers who had taken SSRIs and related antidepressants during pregnancy – 10 with paroxetine, two with fluoxetine, and one each for citalopram, sertraline and venlafaxine. These cases are described below.

Kent & Laidlaw[48] describe a baby born to a mother who had taken sertraline throughout pregnancy but stopped the drug abruptly three weeks after birth (the baby had been breastfed). After one day, the baby developed signs of agitation, restlessness, poor

feeding, constant crying, insomnia and an enhanced startle reaction. The symptoms began to recede after 48 hours.

Spencer[49] reports fluoxetine toxicity in a neonate, reported by the author to demonstrate the long half-life of the active metabolite of fluoxetine. The reactions in the baby were not thought to be due to the withdrawal of fluoxetine.

Dahl et al[50] report that a 36-year old woman had been treated with clomipramine for several years and was commenced on paroxetine during the sixth month of pregnancy. A normal male baby was delivered at 39 weeks and initially appeared alert. At the age of 12 hours he developed increased respiratory rate and jitteriness. During the next hour he developed increased muscle tone and tremor. The symptoms decreased during the third and fourth day and the child was discharged at the age of four days.

Gerola et al[51] report the occurrence of suspected neonatal withdrawal symptoms (hunger, jitteriness, insomia, mild hypertension and diarrhoea) from maternal use of paroxetine during pregnancy. The symptoms appeared 48 hours after birth but spontaneously subsided and disappeared within two days.

Stiskal et al[52] report four cases of neonatal withdrawal reactions after paroxetine use throughout pregnancy. These neonates were exposed to the drug in utero at maternal doses ranging from 20mg to 120mg/day. The symptoms and abnormalities included, but were not limited to, jitteriness, vomiting, irritability, hypoglycaemia and necrotising enterocolitis.

Nijhuis et al[53] describe a baby born to a mother who had received paroxetine before and during her pregnancy. The baby did not experience any problems in the first few days but thereafter became irritable, lethargic and needed tube feeding. The baby improved spontaneously.

Nordeng et al[54] report five cases (three paroxetine, one citalopram, one fluoxetine) of neonatal withdrawal reactions after third trimester in utero exposure. Withdrawal symptoms occurred within a few days of birth and lasted up to one month after birth. Four of the infants needed treatment with chlorpromazine. Withdrawal symptoms were irritability, constant crying, shivering, increased tonus, difficulties with eating and sleeping, and convulsions. The authors concluded that neonatal withdrawal syndrome can occur after third trimester in utero SSRI exposure.

De Moor et al[55] describe withdrawal symptoms in a neonate after maternal use of venlafaxine during pregnancy. The symptoms were restlessness, hypertonia, jitteriness, irritability and poor feeding. The diagnosis was confirmed by temporary improvement after administration of low dose venlafaxine. The symptoms eventually began to decline spontaneously and the neonate recovered after eight days.

Isbister et al[56] questioned whether reports of neonatal events experienced after birth following the discontinuation of exposure to paroxetine were compatible with a

withdrawal syndrome, or perhaps more consistent with serotonin toxicity. The authors noted that reports concerning paroxetine were described as 'neonatal withdrawal syndrome', while reports concerning fluoxetine were described as 'serotonin toxicity'. They concluded that the reports reviewed were more consistent with serotonin excess than with withdrawal syndrome.

Published studies

Chambers et al[57] conducted a prospective study in 228 pregnant women taking fluoxetine. The outcome of their pregnancies was compared to that a matched group of 254 women not taking fluoxetine. There was no significant difference between the rate of spontaneous pregnancy loss or incidence of major structural anomalies in the fluoxetine group compared with the control group. Infants exposed to fluoxetine in the third trimester had higher rates of premature delivery (relative risk, 4.8; 95% CI 1.1-20.8), admission to special-care nurseries (relative risk, 2.6; 95% CI 1.1-6.9) and poor neonatal adaptation, including respiratory difficulty, cyanosis on feeding and jitteriness (relative risk, 8.7; 95% CI 2.9-26.6).

In a prospective, controlled cohort study, Costei et al[58] investigated whether there was a clinically important withdrawal syndrome in neonates exposed in utero to paroxetine. This study compared 55 women using paroxetine in the third trimester with 27 women using paroxetine during the first or second trimester, and 27 women using non-teratogenic drugs (a teratogen interferes with normal prenatal development causing one or more developmental abnormalities in the foetus). The groups were matched for maternal age, gravity, parity, social drug use and non-teratogenic drug use. Of the 55 neonates exposed to paroxetine in the third trimester, 12 (22%) required hospitalisation for complications. The most common problem was respiratory distress (n=9), followed by hypoglycaemia (n=2) and bradycardia, tachycardia and jaundice (n=1). In the comparison group, only three (5%) infants experienced complications (p=0.03). The authors concluded that when paroxetine is used near term, it is associated with a high rate of neonatal complications, possibly caused by its withdrawal reactions. The study has some limitations. It relied on information collected directly from the mother by telephone interview without any validation from medical records, and severity of depression may have been an important confounder (patients in the cohort exposed to paroxetine in the third trimester were more likely to have had more severe depression or anxiety than women in the control group). Severe maternal depression is a risk factor for poor perinatal outcomes.

A cohort study by Simon et al[59] involving 209 infants was designed to evaluate the effects of prenatal antidepressant exposure on perinatal outcomes, congenital malformations and early growth and development. The authors concluded that an association between SSRI exposure and lower gestational age and birth weight was detected, and suggested that the effects on Apgar scores were attributable to third trimester exposure. The authors acknowledged the limitations of the study, including the reliance on pharmacy records for drug exposure and on routinely collected clinical data rather than specific examination for malformations or developmental delay. They also

stated that their matching for depression treatment history may not have completely accounted for differences between exposed and unexposed infants in risk factors for poor perinatal outcomes, such as severity of maternal depression or other psychiatric disorders.

Laine et al[60] conducted a prospective, controlled, follow-up study in 20 mothers taking 20mg to 40mg per day of either citalopram or fluoxetine and their infants, and 20 matched controls. Perinatal sequelae of the infants and the relationship of these symptoms to cord blood monoamine and prolactin concentrations were investigated. The serotonergic symptoms score during the first four days of life in the SSRI group was four-fold higher than that in the control group (p=0.008). The SSRI-exposed infants had lower cord blood 5-hydroxyindoleacetic acid (5-HIAA) concentrations (p=0.02) compared with the control group. The authors concluded that infants exposed to SSRIs during late pregnancy are at an increased risk of serotonergic central nervous system adverse effects, and that the severity of these symptoms is related to cord blood 5-HIAA levels.

In a further study, Hendrick and colleagues[61] concluded that there was not an increased rate of congenital abnormalities or neonatal complications in infants exposed to SSRIs in utero, in comparison with rates observed in the general population (Hendrick 2003).

8.3.2 Spontaneous reporting data from health professionals

Up to 31 August 2003, a total of 31 cases of neonatal drug withdrawal syndrome had been reported in association with the SSRIs and related antidepressants. Of these, 17 were associated with paroxetine, five with fluoxetine, four with venlafaxine, two with sertraline and one with citalopram. In one report, the mother took both paroxetine and fluoxetine during pregnancy. The most commonly reported symptoms experienced by the infants were jitteriness, irritability and muscle twitching. More serious symptoms, such as jaundice, seizure and breathing problems, were reported in four of these reports.

8.3.3 Discussion

There is increasing evidence from clinical studies, published case reports and spontaneous reports to suggest that maternal use of SSRIs and related antidepressants, particularly during the third trimester, may lead to neonatal withdrawal reactions. The most convincing evidence is that for paroxetine.

8.4 Overall conclusions

Withdrawal reactions have been reported with all SSRIs and related antidepressants. The extent to which they cause these reactions appears to vary between drugs and they appear to occur most commonly with paroxetine and venlafaxine.

There is some uncertainty about the true frequency of withdrawal reactions with the SSRIs, with much higher frequencies being found in studies than are suggested by spontaneous reporting or PEM data. Despite difficulties in interpretation, the data

presented in this review suggest that withdrawal reactions are sufficiently common and in some cases severe enough to justify reinforcing the necessary steps to minimise their occurrence to doctors, and increase efforts to ensure that patients are adequately advised about them.

The SSRIs have been associated with a large number of spontaneous reports of withdrawal reactions. However, review of these reports and the published literature do not provide clear evidence that the SSRIs and related antidepressants have a significant dependence liability or show development of a dependence syndrome by meeting the criteria for either DSM-IV or ICD-10. Furthermore, although there are isolated reports of the abuse of fluoxetine and sertraline by known drug abusers, these comprise a very small number in relation to the usage of these drugs. In this review no evidence has been identified to suggest that abuse of SSRIs occurs in patients without a prior history of substance abuse.

In contrast, benzodiazepines have been clearly established as drugs which may produce dependence and withdrawal reactions. Current evidence does not support the view that SSRIs and related antidepressants have a comparable dependence. This is not to mimimise the distress that individuals may experience as a result of SSRI withdrawal reactions, which can in some cases be disturbing or disabling to the individual; rather the existence of withdrawal reactions alone is not sufficient to support the existence of an SSRI dependence syndrome or to provide evidence of dependence potential.

The available evidence shows that on discontinuation of treatment, gradual tapering of the dose of SSRI over several weeks or months significantly reduces the frequency and severity of withdrawal reactions. Further, certain SSRIs appear less prone to produce withdrawal reactions than others.

8.5 Key findings

- 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 and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety and sleep disturbances.

- Awareness of the risk of withdrawal reactions associated with SSRIs needs to be increased amongst both prescribers and patients.

- There is evidence that withdrawal reactions are less severe when the dose is tapered gradually over a period of several weeks according to the patient's need. Availability of low dose formulations to allow gradual titration is important.

- 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.

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9 DOSE RESPONSE

In common with other classes of antidepressants, the SSRIs and related antidepressants are licensed for use with a flexible dosing scheme.

The product information for prescribers and patients for each product states the dose that should be used for initiation of treatment. The option is then given that if the response is inadequate and further improvement is required, the dose can be increased and a maximum dose that can be used is generally given. For treatments that can be used to treat more than one condition, separate dosing instructions are given for each.

This chapter examines the available evidence to support the recommendations to increase the dose if the initial response is inadequate.

9.1 Background

During the detailed review of the risks and benefits of paroxetine, the EWG looked at the information supporting the recommendation that patients not responding to the starting dose of paroxetine may benefit from dose increases.

Upon review the EWG considered that the data to support the dose increases was inadequate. They considered that there was no evidence from clinical trials that increasing the dose above the recommended dose increases efficacy in the treatment of depression, SAD, GAD, PTSD and panic disorder. This review, combined with evidence from usage databases that a proportion of patients were being started on paroxetine at doses higher than those recommended, led CSM to advise that a reminder of the recommended dose of paroxetine should be sent to health professionals. This communication took place on 11 March 2004.[1]

It was considered appropriate that the same issue be investigated for other SSRIs. As such, the following request was then passed to the MA holders for other SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine and sertraline) and the related antidepressants mirtazapine and venlafaxine.

"*Please provide evidence to justify the use of doses above* [usual starting dose] *mg for* [product name] *in its licensed indications. Include tabulations of efficacy and safety data from fixed and variable dose studies.*"

The data submitted by each MA holder were reviewed, and the key findings for each drug are summarised in section 9.3 below.

9.2 Types of clinical trials for assessing dose reponse

There are three main types of clinical trial which are used when studying dose-response effects.

Studies to establish the optimal dose of a treatment are usually done in the early stages of a programme of trials. Fixed dose trials (see section 9.2.3) are the trials most commonly used to investigate dose response. When SSRIs were first being developed the importance of only moving patients slowly up to higher doses was not appreciated, so in many of the early fixed dose trials patients were placed directly onto higher doses rather than having their doses gradually titrated. This makes the interpretation of these trials difficult as many patients dropped out early on the high dose because of adverse events. More recent fixed dose trials where doses are titrated do not have this problem.

Recent developments in clinical trial design make it clear that randomised non-responder trials (see section 9.2.2) are more appropriate than fixed dose trials for investigating titration schemes. Trials with this design should be carried out in the future.

Once the dose, or dose range, has been selected, larger trials are run to confirm the efficacy and safety of this scheme. For antidepressants where a range of doses is usually recommended, these confirmatory trials will have a flexible dose design (see section 9.2.1).

9.2.1 Flexible dose trials

The majority of clinical trials investigating the efficacy of antidepressants are flexible dose trials.

Patients in these trials can have their daily dose of treatment increased or decreased based upon their response to treatment and how well they tolerate the treatment. For example, if a patient has an inadequate response to the initial dose the investigator might decide, in conjunction with the patient, to increase the dose. These trials replicate the way that antidepressants are used in practice, and when the trial includes another group of patients who are taking placebo or another antidepressant, can provide evidence which tells us whether a treatment works.

However, such trials do not provide evidence which tells us whether a dose increase was beneficial. This is because we do not know what would have happened if the dose had not been increased. In clinical trials of antidepressants it is recognised that patients are more likely to respond to treatment as the trial continues. Even patients receiving a placebo generally see their condition improve over the course of the trial. So in these trials the effect of dose increases is mixed up with the effects of time. In addition, the patients and investigator know that the dose was increased and so their assumptions may influence the assessment of future improvement.

These trials do not have a control group where the dose was not increased and as such they cannot tell us whether increasing the dose is a beneficial thing to do. Flexible dose studies will not be considered further in section 9.3.

9.2.2 Randomised non-responder trials

These are the ideal trials to assess the benefit of increasing the dose but, unfortunately, they are rarely performed.

In these trials patients are all treated with the same starting dose. Those that fail to respond are then randomly allocated to either have their dose increased or to remain on the same dose. The trial is blinded, meaning that patients and investigators do not know which group they were assigned to and so their assumptions cannot affect the responses. At the end of the trial the dose increase group can be compared with the group that did not have their dose increased, and the benefit of the dose increase can be assessed.

9.2.3 Fixed dose trials

In fixed dose trials, patients are randomly allocated to different doses of the medication. This is not ideal as in practice patients only use the higher doses if lower doses seem not to be working. However this design does allow comparison between doses, and if we see an advantage for higher doses in such a trial it provides support for the idea that some patients need the higher doses to achieve the desired response.

There can be problems with these trials if patients randomised to the higher doses are started immediately on those doses or moved up too quickly, rather than having their dose gradually increased. If this is done the trial can be biased against the high doses because of adverse experiences and early withdrawals caused by the sudden dose increase.

9.3 Data considered

Clinical trials for antidepressants usually use as their main efficacy measures the scores on psychiatric scales, where a decrease in score indicates an improvement in condition. These scores are generally analysed by looking at the change from the baseline score (the score the patient had before treatment was started). Therefore in the summaries of efficacy data that follow, larger negative numbers reflect a better response over the course of the trial.

9.3.1 Paroxetine (Seroxat)

Dose statements in the SPC at the time of the review:
Depressive illness: *Recommended dose: 20mg/day. Some patients not responding to a 20mg dose may benefit from dose increases in 10mg/day increments, up to a maximum of 50mg/day according to the patient's response.*

Obsessive compulsive disorder: *Recommended dose: 40mg/day. Patients should start on 20mg/day and the dose can be increased weekly in 10mg increments. Some patients will benefit from having their dose increased up to a maximum of 60mg/day.*

Panic disorder: *Recommended dose: 40mg/day. Patients should start on 10mg/day and the dose increased weekly in 10mg increments according to patient's response. Some patients may benefit from having their dose increased up to a maximum of 50mg/day.*

Social anxiety disorder: *Recommended dose: 20mg/day. Some patients not responding to a 20mg dose may benefit from dose increases in 10mg/day increments, up to a maximum of 50mg/day according to the patient's response.*

Generalised anxiety disorder: *Fixed dose of 20mg/day.*

Post-traumatic stress disorder: *Recommended dose: 20mg/day. Some patients not responding to a 20mg dose may benefit from dose increases in 10mg/day increments, up to a maximum of 50mg/day according to the patient's response.*

Data supplied

Table 9.1 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	10mg	20mg	30mg	40mg	60mg
MDD	6 weeks	HAM-D	398	-10.1	-8.9	-12.4^{+}	-11.5	-11.5	
OCD	12 weeks	Y-BOCS	338	-3.36		-4.02		-6.33*	-7.27*
Panic disorder	10 weeks	#attacks / 2 weeks	248	-5.5	-5.9	-5.7		-8.2*	
SAD	12 weeks	L-SAS	365	-15.0		-31.4*		-24.5*	-25.2*
GAD	8 weeks	HAM-A	565	-9.6		-12.5*		-12.2*	
PTSD	12 weeks	CAPS-2	551	-25.3		-39.6*		-37.9*	

** p<0.05 vs. placebo; + p<0.10 vs. placebo*

Depressive illness: A trial was conducted in patients with moderate to moderately severe major depressive disorder. Patients randomised to 30mg and 40mg were started on these doses at day one, as opposed to the current practice of starting on a lower dose and titrating up. This could bias the trial against the higher doses. To address this problem the analysis includes only patients who completed at least 10 days on medication. The 10mg dose seems sub-optimal and similar to placebo, while doses above 10mg show a separation from the other two arms. This supports the choice of 20mg as the recommended dose. However, the data provide no evidence that there is an efficacy advantage from using doses above 20mg; in fact, the results on 20mg were

numerically better than those for the higher doses. A randomised non-responder trial was also provided, where non-responders either stayed on 20mg or increased their dose to 40mg. No significant difference in response was seen between the groups.

Obsessive compulsive disorder: The 40mg dose was the lowest to demonstrate a separation from placebo, supporting the choice of 40mg as the recommended dose. There is also evidence of a dose response, with the trend favouring 60mg over 40mg. Hence there is some justification for concluding that some patients gain more benefit from 60mg than 40mg.

Panic disorder: Both the 10mg and 20mg doses failed to separate from placebo, but there is evidence of efficacy at 40mg, so the choice of 40mg as the recommended dose seems justified. Doses above 40mg were not included in the trial so there is no data to support an efficacy advantage for titrating to 50 or 60mg.

SAD, GAD and PTSD: The 20mg fixed dose achieved a clear statistically significant advantage over placebo, supporting the choice of 20mg as the recommended dose. There was no evidence of any additional benefit from using doses over 20mg; in fact, the results on 20mg were numerically better than those for the higher doses.

Conclusions

Depressive illness, SAD, GAD, PTSD: the recommended dose is 20mg daily. Titration above 20mg is not supported by clinical trial data.

OCD: the recommended dose is 40mg daily. Some patients will benefit from having their dose increased to 60mg daily.

Panic disorder; the recommended dose is 40mg daily. Titration above 40mg is not supported by clinical trial data.

9.3.2 Citalopram (Cipramil)

Dose statements in the SPC at the time of the review:
Depressive illness: *Citalopram should be administered as a single oral dose of 20mg daily. Dependent on individual patient response this may be increased to a maximum of 60mg daily.*

Panic Disorder: *A single oral dose of 10mg daily is recommended for the first week before increasing the dose to 20mg daily. The dose may be further increased, up to a maximum of 60mg daily dependent on individual patient response, however an optimum dose of 20-30mg daily was indicated in a clinical study.*

Data supplied

Table 9.2 Fixed dose trials: change in scores from baseline

Indication	Duration	Endpoint	n	Placebo	10mg	20mg	40mg	60mg
Depression	6 weeks	MADRS	200	-15.7		-16	-18.2*	
Depression	6 weeks	MADRS	274	-15.8		-17.9+	-16.0	
Depression	6 weeks	HAM-D	650	-9.5	-11.2	-10.1	-12.6*	-12.4*
				Placebo	10-15mg	20-30mg	40-60mg	CLO
Panic disorder	8 weeks	#	475	33%	44%	59%*	51%*	51%*

** p<0.05 vs. placebo; + p=0.051 vs. placebo*
 # = Clincal anxiety scale panic attack item - % patients with a score of 0 or 1 (no panic attacks)

Depressive illness: Three fixed dose trials were conducted. In two of the three trials there was some advantage for 40mg over 20mg, giving some evidence of a dose response. In the one trial where it was included, 60mg was no better than 40mg.

Panic disorder: A single dose finding study was provided, which included clomipramine 60-90mg/day as an active comparator. This was principally a fixed dose trial, but a small amount of flexibility was allowed within each fixed range. There was evidence that 20-30mg had improved efficacy compared to lower doses, but no evidence that doses higher than this provided additional benefit.

Conclusions

Depressive illness: the recommended dose is 20mg daily. Some patients will benefit from having their dose increased to 40mg daily. Titration above 40mg is not supported by clinical trial data.

Panic disorder: the starting dose is 10mg daily. Some patients will benefit from having their dose increased to 20-30mg daily. Titration above 30mg is not supported by clinical trial data.

9.3.3 Escitalopram (Cipralex)

Dose statements in the SPC at the time of the review:
Major depressive episodes: *Usual dosage is 10mg daily. Depending on individual patient response, the dose may be increased to a maximum of 20mg daily.*

Panic disorder with or without agoraphobia: *An initial dose of 5mg daily is recommended for the first week before increasing the dose to 10mg daily. The dose may be further increased, up to a maximum of 20mg daily dependent on individual patient response.*

Social anxiety disorder: *Usual dosage is 10mg once daily. Usually 2-4 weeks are necessary to obtain symptom relief. The dose may subsequently, depending on individual patient response, be decreased to 5mg or increased to a maximum of 20mg daily.*

Data supplied

Table 9.3 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	5mg	10mg	20mg
MDD	8 weeks	MADRS	485	-9.4		-12.8*	-13.9*
SAD	24 weeks	LSAS	825	-34.0	-44.5*	-41.5*	-49.1*

** p<0.05 vs. placebo;*
+ = percentage change from baseline in weekly binge eating episodes
 # = % change from baseline in weekly binge eating episodes

Depressive illness: A single fixed-dose trial in major depressive disorder was provided. There was evidence of a small efficacy advantage for 20mg over 10mg, but the number of withdrawals because of adverse events was also higher in the 20mg group.

Panic disorder: No trials were provided to justify the dose in this indication. It should be noted that no clinical trial data at all were supplied in this indication. The licence was granted based upon an argument of bioequivalence to citalopram. The conclusions might therefore be based upon those noted for citalopram above.

Social anxiety disorder: A single fixed-dose trial was provided. There was no evidence of an efficacy dose response across the 5, 10 and 20mg doses, while more patients withdrew because of adverse events on the higher doses.

Conclusions

Depressive illness: the recommended dose is 10mg daily. Some patients will benefit from having their dose increased to 20mg daily, although there is an increased potential for undesirable effects.

Panic disorder the starting dose is 5mg daily. Some patients will benefit from having their dose increased to 10mg daily. Titration above 10mg is not supported by clinical trial data.

Social anxiety disorder: the recommended dose is 5mg daily. Titration above 5mg is not supported by clinical trial data.

9.3.4 Fluoxetine (Prozac)

Dose statements in the SPC at the time of the review:
Major depressive episodes: *20mg/day to 60mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for undesirable effects at higher doses, a dose increase may be considered after three weeks if there is no response.*

Obsessive compulsive disorder: *20mg/day to 60mg/day. A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential for*

undesirable effects at higher doses, a dose increase may be considered after two weeks if there is no response.

Bulimia nervosa: *A dose of 60 mg/day is recommended.*

Data supplied

Table 9.4 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	5mg	20mg	40mg	60mg
Depression – mild	6 weeks	HAM-D	362	-5.35		-5.91	-5.72	-4.92
Depression – moderate/severe	6 weeks	HAM-D	351	-5.85		-9.67*	-9.24*	-7.40
Depression	6 weeks	HAM-D	354	-7.55	-11.64*	-10.31*	-11.66*	
OCD	13 weeks	Y-BOCS	349	-0.84		-4.61*	-5.76*	-6.75*$^{+}$
Bulimia nervosa	8 weeks	#	382	-14.39		-26.22		-45.38*$^{+}$

** p<0.05 vs. placebo; + p<0.05 vs. 20mg*
 # = % change from baseline in weekly binge eating episodes

Depressive illness: Two fixed dose trials were conducted. The first of these was analysed as two trials; one in mild depression and one in moderate/severe depression. There was no evidence that fluoxetine was efficacious in mild depression, with none of the doses being superior to placebo. For moderate/severe depression, there was evidence that the 20mg dose was more efficacious than placebo, however the data provided no evidence that there is an efficacy advantage from using doses above 20mg, with the results on 20mg being numerically better than those for the higher doses. The second trial mainly contained moderate/severe patients. In this trial all three active doses produced similar efficacy, again providing no evidence that titrating above 20mg provides additional benefit, and suggesting that 5mg may be an efficacious dose, although it has been studied in too few patients to be confidently recommended. In both trials there were more withdrawals because of adverse events on higher doses, however this may be partly because patients were started on those doses and not titrated to them.

A randomised non-responder trial was also provided, where non-responders either stayed on 20mg or increased the dose to 60mg. No significant difference was seen between the groups. More patients in the up-titrated group withdrew because of adverse events.

Obsessive compulsive disorder: There was a trend for improved efficacy with increasing dose, with the 60mg dose demonstrating superiority over 20mg. This is despite patients being placed straight onto the top doses rather than being titrated to them. There were also more withdrawals because of adverse events on the higher doses.

Bulimia nervosa: There was clear evidence that 60mg is superior to 20mg. The number of withdrawals because of adverse events was higher on the 60mg group, but this may be partly because patients were started on those doses and not titrated to them.

Conclusions

Depressive illness: the recommended dose is 20mg daily. Titration above 20mg is not supported by clinical trial data. Doses as low as 5mg daily may be efficacious.

OCD: the recommended dose is 20mg daily. Some patients will benefit from having their dose increased to 40mg and 60mg daily, although there is an increased potential for undesirable effects.

Bulimia nervosa: the recommended dose is 60mg daily.

9.3.5 Fluvoxamine (Faverin)

Dose statements in the SPC at the time of the review:
Depressive illness: *The recommended starting dose is 50 or 100mg, given as a single dose in the evening. It is recommended to increase the dose gradually until an effective dose is reached. The usual effective dose is 100mg per day and should be adjusted on individual patient response. Doses of up to 300mg per day have been given.*

Obsessive compulsive disorder: *The recommended starting dose is 50mg per day for 3-4 days. The effective dose usually lies between 100 mg and 300 mg per day. The dosage should be increased gradually until the effective dose is achieved, with a maximum of 300 mg per day for adults.*

Data supplied

All trials had a flexible dose design, so no evidence is available to support the recommendations to increase the dose.

Conclusions

No clinical trials were conducted to investigate the dose response of fluvoxamine.

9.3.6 Mirtazapine (Zispin)

Dose statements in the SPC at the time of the review:
Depressive illness: *Treatment should begin with 15mg daily. The dosage generally needs to be increased to obtain an optimal clinical response. The effective daily dose is usually between 15 and 45mg.*

Data provided

The applicant carried out two fixed-dose studies. One of these was prematurely terminated before many patients had been included. The other study included doses of 5, 10, 20 and 40mg but no placebo. All doses were similar to each other in terms of efficacy, but without a placebo arm it is not possible to interpret these data. However the trial clearly does not provide evidence to support a dose response relationship.

Conclusions

No clinical trials were conducted to investigate the dose response of mirtazapine.

9.3.7 Sertraline (Lustral)

Dose statements in the SPC at the time of the review:
Depressive illness (including accompanying symptoms of anxiety): *The starting dose is 50mg daily and the usual antidepressant dose is 50mg daily. In some patients, doses higher than 50mg may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level.*

Obsessive compulsive disorder: *The starting dose is 50mg daily, and the therapeutic dose range is 50-200mg daily. In some patients doses higher than 50mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level.*

Post traumatic stress disorder: *Treatment for PTSD should be initiated at 25mg/day. After one week the dose should be increased to 50mg once daily. In some patients doses higher than 50mg daily may be required. In patients with incomplete response but good toleration at lower doses, dosage adjustments should be made in 50mg increments over a period of weeks to a maximum of 200mg daily. Once optimal therapeutic response is achieved the dose should be reduced, depending on therapeutic response, to the lowest effective level.*

Data provided

Table 9.5 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	50mg	100mg	200mg	400mg
MDD	4 weeks	HAM-D	120	-8.8	-5.9	-8.1	-4.0	-2.5
MDD	4 weeks	HAM-D	171	-9.4	-10.4	-9.0	-7.6	-8.9
MDD	6 weeks	HAM-D	347	-7.6	-10.6*	-9.8	-9.2	
MDD	10 weeks	HAM-D	190	-9.7	-11.7	-9.2	-10.9	-8.0
OCD	12 weeks	Y-BOCS	324	-3.45	-6.08*	-4.67	-6.22*	

** p<0.05 vs. placebo*

Depressive illness: There were four fixed-dose studies conducted in MDD. Generally the 50mg dose showed numerically better efficacy than the higher doses. The rate of withdrawals because of adverse events was generally higher on the higher doses, but this is complicated by the fact that in the first three trials patients were placed immediately onto the higher doses rather than being titrated to them.

OCD: There was no evidence of increased efficacy with increased dose in the single fixed dose trial.

PTSD: All trials had a flexible dose design, so no evidence is available to support the recommendations to increase the dose.

Conclusions

Depressive illness, OCD and PTSD: the recommended dose is 50mg daily. Titration above 50mg is not supported by clinical trial data.

9.3.8 Venlafaxine (Efexor)

Dose statements in the SPC at the time of the review:
Depressive illness: *For initiation and maintenance the recommended dose is 75mg/day given in two divided doses (37.5mg twice daily). If after several weeks further clinical improvement is required, the dose may be increased to 150mg/day given in two divided doses (75mg twice daily).*

Severe depressive illness and hospitalised patients: *If, in the judgement of the physician a higher dose is required, for example in more severely depressed or hospitalised patients, a starting dose of 150mg may be given in two divided doses (75mg twice daily). The daily dose may then be increased by up to 75mg every two to three days until the desired response is achieved. The maximum recommended dose is 375mg per day. The dose should then be gradually reduced to the usual dosage, consistent with patient response and tolerance.*

Data provided

Table 9.6 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	25mg	75mg	150mg	200mg	225mg	375mg
Depression	6 weeks	HAM-D	324	-7.2		-11.0*			-12.0*	-10.8*
		MADRS		-7.5		-11.6*			-13.1*	-14.4*^
		CGI-S		-0.5		-1.0*			-1.4*+	-1.4*+
Depression	6 weeks	HAM-D	302	-9.3	-10.3	-11.0		-11.9*		
		MADRS		-10.5	-11.5	-12.5		-14.8		
		CGI-S		-1.2	-1.3	-1.4		-1.6		
Depression	12 weeks	HAM-D	353	-7.1		-11.6*	-10.4*	-12.1*		
		MADRS		-7.5		-13.1*	-12.4*	-13.4*		
		CGI-S		-0.7		-1.3*	-1.2*	-1.3*		

** p<0.05 vs. placebo; + p<0.05 vs. 75mg; ^ p=0.052 vs. 75mg*
For the second depression trial some flexibility was allowed in dosing: the 75mg arm received 50-75mg, while the 200mg arm received 150-200mg

Table 9.7 HAM-D: change from baseline to end of trial

	Venlafaxine		Fluoxetine		
	n	**Change**	**n**	**change**	**p-value**
Week 2					
Remained on low doses	74	-10.1	71	-10.1	p=0.93
Increased to high doses*	74	-6.1	88	-5.6	p=0.56
Week 8					
Remained on low doses	74	-15.7	71	-16.6	p=0.48
Increased to high doses*	74	-16.4	88	-12.4	p=0.007

** Venlafaxine patients increased to 150mg, fluoxetine patients stay on 20mg*

Depressive illness: There were three fixed dose trials conducted. In the first trial the 225 and 375mg doses showed superiority over 75mg on the CGI-severity scale, and a trend for increasing efficacy with dose was shown on other endpoints. In the second trial a trend for increasing efficacy with dose was seen for HAM-D. The third trial did not provide evidence to support a dose response. An increased number of patients withdrew because of adverse events at doses above 200mg.

A non-responder trial was conducted against fluoxetine where patients who had not responded to venlafaxine 75mg had their dose increased to 150mg, while patients who had not responded to fluoxetine 20mg stayed on 20mg. The groups were similar before titration while the venlafaxine group was superior after titration, providing some unorthodox but persuasive indirect evidence of a benefit of titrating those who do not respond to 75mg up to 150mg.

Severe depressive illness and hospitalised patients: All trials in these patients used a flexible dose scheme. These trials established efficacy, but the benefit of dose increases cannot be established. There is no evidence to support starting on 150mg rather than 75mg in these patients.

Conclusions

Depressive illness: the recommended dose is 75mg daily. Some patients will benefit from having their dose increased to 150mg daily.

Severe depressive illness and hospitalised patients: no clinical trials were conducted to investigate the dose response in these patients.

9.3.9 Venlafaxine ER (Efexor XL)

Dose statements in the SPC at the time of the review:
Depressive illness: *For initiation and maintenance the recommended dose is 75mg once daily. If after two weeks further clinical improvement is required, the dose may be increased to 150mg once daily. If needed the dose can be further increased up to 225mg once daily. Dose increments should be made at intervals of approximately 2 weeks or more, but not less than four days.*

Generalised anxiety disorder: *Fixed dose of 75 mg/day.*

Data provided

Table 9.8 Fixed dose trials: change from baseline to end of trial

Indication	Duration	Endpoint	n	Placebo	37.5mg	75mg	150mg	225mg	Active
MDD	8 weeks	HAM-D	323	-12.2		-15.4^	-13.8		-10.8
GAD	8 weeks	HAM-A	349	-9.5		-11.1	-11.7	-12.1*	
GAD	8 weeks	HAM-A	365	-8.0		-10.6*	-9.8		-9.5
GAD	8 weeks	HAM-A	535	-12.3		-14.2	-13.1		-14.3
GAD	24 weeks	HAM-A	528	-11.0	-13.8*	-15.5*	-16.4*		

** p<0.05 vs. placebo; ^p=0.059 vs. placebo*

Depressive illness: A single fixed dose study was provided, which included paroxetine 20mg/day as an active comparator. There was no evidence of a dose response, however a dose response for venlafaxine ER in this indication might be inferred from the venlafaxine data (venlafaxine ER is merely an extended release formulation of venlafaxine).

GAD: Four fixed dose trials were provided, trial 2 included buspirone 30mg as an active comparator and trial 3 included diazepam 15mg. Overall there was no evidence of a dose response above 75mg. In two trials the trend favoured 75mg over 150mg, while the ordering was reversed in the other two.

Conclusions

Depressive illness: the recommended dose is 75mg daily. Some patients will benefit from having their dose increased to 150mg or 225mg daily.

GAD: the recommended dose is 75mg daily. Titration above 75mg is not supported by clinical trial data.

9.4 Overall conclusions

For some treatments in some indications, data have been provided to support the statement that patients not responding to their starting dose may receive benefit from an increase in dose. However, for the majority of drugs and indications this is not the case.

It is important that patients and prescribers are aware, as appropriate, that clinical trials have not shown any additional benefit associated with increasing the dose.

For the majority of SSRIs and related antidepressants there is no evidence that increasing the dose above the recommended dose provides additional benefit in depressive illness.

There is no evidence for any the products of additional benefit from increasing the dose above that recommended in SAD, GAD or PTSD.

This general lack of evidence of a dose response may, in part, reflect the difficulty of demonstrating efficacy in these indications against placebo in clinical trials, particularly in depressive illness. It may also reflect the inadequacy of the study designs.

The trials conducted to look at dose response are not large enough, nor of a long enough duration, to identify whether there is a dose response relationship for serious adverse events. In the absence of good evidence it is a prudent assumption that some adverse events may increase with an increase in 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.

9.5 Key findings

- 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.

REFERENCES

[1] http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/paroxetine_11304.htm

10 THE PATIENT EXPERIENCE

10.1 Background

Work by Mr Charles Medawar and Dr Andrew Herxheimer has drawn attention to the reports by patients of their experiences on SSRIs[1].

The current product information for the SSRIs and related antidepressants contains warnings about the risk of withdrawal reactions and the possibility that patients may experience a worsening of their depression or suicidal thoughts, particularly in the early stages of treatment.

In September 2003, the CSM/MHRA published an SSRI Factsheet in its safety bulletin 'Current Problems in Pharmacovigilance'[2] with the aim of providing an aide-memoire of key information to support interactions between patients and health professionals.

This chapter describes the concerns expressed by patients on the quality of information for patients on SSRIs and describes the work carried out on the patient information leaflet (PIL) for Seroxat (paroxetine) to address these concerns.

10.2 Patient reports

As described in chapters 7 and 8, the EWG reviewed data on patients' experiences from two sources: the *Panorama*/Mind Yellow Cards and a questionnaire sent out to individuals who contacted the MHRA about the safety of the SSRIs. As well as capturing information on withdrawal reactions and suicidal behaviour (data reviewed in chapters 7 and 8, respectively), these questionnaires also invited people to provide any additional information that they considered important about their experience.

Concerns expressed by patients included:

i. the limited discussion between prescribing doctors and the patients about possible side-effects;
ii. the apparent lack of knowledge amongst health professionals about the potential side-effects both on treatment and on withdrawal;
iii. the difficulty experienced upon withdrawal from treatment;
iv. the perceived inadequacy of product information for patients;
v. concerns about suicidal behaviour, and also the personality changes that patients experienced while on treatment.

In four of the questionnaires, the patients described the benefits of their treatment (two on paroxetine, one each citalopram and sertraline) and the positive impact it had on their lives. In one of these reports, the SSRI was compared favourably with the patient's previous treatment with lorazepam.

Patients who completed either the MHRA questionnaire or the *Panorama*/Mind Yellow Cards are unlikely to be a random sample of patients on antidepressant treatment; however, the reports provide a valuable insight into the experiences of patients and the impact that these experiences had on their lives.

The Yellow Card Scheme has, until 2003, only accepted spontaneous reports of suspected ADRs from health care professionals. An Independent Review of Access to the Yellow Card Scheme which reported on 4 May 2004 recommended that a system should be set up for patients to report ADRs directly to the MHRA[3], in order to obtain the patient's own perspective on ADRs.

10.3 Improving the quality of patient information

The review of the responses to the questionnaires highlighted the need to improve the PILs. In particular:

i. improved warnings in the PIL about possible side-effects on treatment, with greater prominence given to those considered by the patients to be the most severe (however rare) and any that should lead to treatment being stopped;
ii. improved warnings in SPC and PIL about management of withdrawal or possible withdrawal symptoms;
iii. provision of detailed information on withdrawal symptoms and management of withdrawal to prescribing doctors;
iv. improved warnings in the PIL about the possibility of an increase in suicidal thoughts/worsening depression, particularly in the initial stages of treatment;
v. prominent warnings in the PIL about the action that should be taken if patients experience suicidal thoughts;
vi. the need for advice in the PIL that patients may wish to discuss their illness and its treatment with relatives/carers/friends and ask that they tell them if they notice any changes in personality/behaviour that may be indicative of a worsening of suicidal thoughts, particularly in the early stages of treatment.

Wider issues with the quality of PILs

There have been a number of general criticisms of PILs, focusing particularly on the accessibility and readability of the information. In 2003, the CSM established the Patient Information Working Group to review the content of the PIL and to make recommendations on how to improve this within the current legislative framework. One of the key work items for this group has been the development of guidance on a better expression of risk within PILs. Any misperception or failure to understand the risks of possible adverse drug reactions, both qualitatively and quantitatively, can affect a patient's ability to make rational decisions about the acceptability of medicines. The guidance advises on the presentation of information in PILs in order to optimise the communication of risk.

User testing

An additional mechanism for improvement in the quality of the information provided is the application of a user test. User testing was first proposed in the early 1990s in Australia. It is performance-based and relies on outcomes which will identify barriers to people's ability to use the information presented. User testing is a flexible development tool which aims to identify whether or not the information as presented conveys the correct messages to those who read it. Testing itself does not improve the quality of the information, but it will indicate where there are problem areas which should be rectified. It is particularly powerful when used as part of an iterative leaflet development process.

As requested by the MHRA, GlaxoSmithKline (GSK) commissioned diagnostic user testing on the PIL for Seroxat (paroxetine). The PIL for Seroxat was subjected to two full rounds of user testing. The intention was to explore patients' understanding of the use of paroxetine as a treatment for depression and anxiety disorders, and to test the usability of the patient information leaflet.

In round one, test scores showed the leaflet was working reasonably well; all but three of the 14 questions achieved the 80% benchmark level of leaflet performance stipulated by the European Commission. The three that failed to meet the benchmark were:

Q7: on missing a dose;
Q9: about symptoms not improving after two weeks;
Q11: about akathisia.

Changes made to the leaflet based on the round one results and conclusions included:

- **simplified language and layout;** several users had commented that the test PIL was too long and detailed;
- **briefer introductory information;** the summary section was restyled so that, while retaining the key points, it was briefer, it acted as an index and it was clearly distinct from the main text;
- **consolidated and clarified information on how to stop;** all important information on stopping Seroxat was consolidated in a dedicated section which simplified the explanation of possible effects;
- **clarified information on missed doses;** new clearer wording;
- **advice on procedure when no improvement perceived; a** new subsection in *How to take your tablets* advised patients on what to do if they did not start to feel better;
- **highlighted possible side-effects;** the presentation of side-effects was altered to make them more consistent and eye-catching.

The round two test scores showed that the leaflet was working more consistently than in round one, with all of the 14 questions achieving the 80% benchmark level of leaflet

performance stipulated by the European Commission. In this round all questions scored at least 8/10 correct.

Focus group

As recommended by the EWG, further user input, in addition to the user testing by GSK, was sought. As a result, a focus group meeting involving representatives from patient interest and user groups and staff from the MHRA's Product Information Unit was held on 13 October 2004. A member of the EWG, Professor Mary Chambers, facilitated this group.

The aim of this focus group was to obtain the views of attendees on a draft version of the Seroxat PIL, and to determine whether it would meet the needs of users for written information provided with the medicine. The focus group considered all sections of the PIL and the report of the group's discussion is attached at Annex D.

The focus group raised many valid and important points in relation to the Seroxat PIL. The focus group also raised general concerns about accessibility and readability of the PIL. This is a matter that is currently being considered in detail by the CSM's Working Group on Patient Information. Many of the recommendations made by that group in terms of ways to improve the information contained within PILs in general and, in particular, risk communication have been conveyed to GSK and, where possible, have been incorporated in the new Seroxat PIL.

The advice of the focus group and the results of the user testing are provided on the Seroxat PIL as an exemplar for PILs for other SSRI products. The good practice identified in communications with patients in this PIL will also be used to inform the MHRA's consideration of PILs for other products in the class.

10.4 Conclusion

The reports from patients via *Panorama*/Mind Yellow Cards and the MHRA questionnaire have provided valuable information on the nature and seriousness of patient experiences on SSRIs. They reinforced the need to introduce a system of direct reporting of ADRs from patients and this is being developed as a follow-on to the Independent Review of the Yellow Card Scheme. Secondly, the reports were a stimulus for work to improve the quality and accessibility of information in the PIL, as this plays a key role in safe use as well as supporting informed decision- making by patients.

REFERENCES

[1] Medawar C, Herxheimer A, Bell A Jofre S (2002) ' Paroxetine, *Panorama* and user reporting of ADRs: Consumer intelligence matters in clinical practice and post-marketing drug surveillance' *Int J Risk & Safety Medicine* 15: 161-169

[2] http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpsept2003.pdf

[3] Report of an Independent Review of Access to the Yellow Card Scheme (2004) The Stationery Office

11 THE WAY FORWARD AND FURTHER RESEARCH REQUIRED

This review of SSRIs has considered a wide range of data from meta-analyses, randomised controlled clinical trials (RCTs), epidemiological studies and from spontaneous suspected ADR reports, including reports from patients. This chapter summarises the key findings of the review and considers what further research would be desirable to provide better information to patients and prescribers.

11.1 Main findings

The main findings of the review are as follows.

Use of 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 and 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-18s 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.

11.2 Research requirements

The review has identified several areas for further research on the use of antidepressants.

- The effectiveness of SSRIs in mild depression has not been clearly demonstrated in RCTs. Without clinical trials in mild depression it is not possible to assess the balance between benefit and harm for these drugs in this indication.

- Many TCAs have not been subjected to the same level of assessment in clinical trials as have modern antidepressants (eg SSRIs). A systematic review of published and unpublished placebo-controlled RCTs of TCAs is required to assess whether there is any evidence of an increased risk of suicidal thoughts, self-harm and suicide in association with these drugs.

- Primary care research is required to investigate the patterns of use for the most commonly prescribed antidepressants, and factors governing GPs reasons for prescribing them.

- Questionnaire-based measures should be developed and evaluated for use in primary care to help GPs identify those patients who would most benefit from antidepressant treatment.

Psychiatric adverse effects of SSRIs: pharmacological considerations

- Further research is necessary into the effect of specific enzymes such as CYP2D6 on the rate of metabolism of SSRIs, and the impact this has on adverse effects and withdrawal reactions. Likewise, there is emerging evidence that the risk of

adverse drug reactions may be related to specific genotypes. There should be further research into the pharmacogenetic determinants of efficacy and toxicity associated with SSRIs.

- Research is needed into the effect of SSRIs on other chemical receptors and whether this has a bearing on SSRI efficacy or toxicity.

- Clinical trials should be conducted to study pharmacological and other approaches to offset the worsening of symptoms described by some patients around the time of commencing treatment.

Safety and efficacy in children and adolescents

- There should be further research on the epidemiology of depressive illness in children and young people**.**

- Research is required to better understand why antidepressants generally appear to be ineffective in children and adolescents**.**

- There should be clinical trials of antidepressants or non-drug interventions in children and adolescents, which include regular monitoring for the occurrence of self-harm, suicidal thoughts and other adverse effects.

- Large randomised controlled trials should be conducted comparing psychological interventions in depressed children and young people to placebo medication and antidepressants.

- There should be studies to estimate the rate and nature of withdrawal effects in children and adolescents.

- Cochrane systematic reviews on drug and non-drug treatments of depressive illness in children and young people should be conducted, incorporating published and unpublished data.

Withdrawal reactions and potential for dependence

- There should be trials in adults, adolescents and children to determine the best way to withdraw from antidepressants; such research might include an assessment of the substitution of short-acting SSRIs with long-acting SSRIs during withdrawal.

- Further research is needed to determine the relationship of withdrawal reactions with dose and duration of treatment.

- Studies are required to quantify the abuse liability of SSRIs and related compounds.

Suicidal behaviour

- There is anecdotal evidence of an increased risk of self-harm early in antidepressant therapy; further investigation and quantification of this phenomenon will help inform the monitoring requirements for patients initiating antidepressant therapy.

11.3 Recommendations for the conduct of future clinical trials of antidepressants

- To enable comparison between substances, consideration should be given to developing standard clinical trial protocols for assessment of dose, withdrawal reactions, and duration of therapy for antidepressants.

- Safety and efficacy should be assessed separately for age groups 18-30 years and >30 years.

- Study results should be presented using 'time to event' analyses to assess whether there is an excess risk early in treatment.

- All clinical trials should be carefully monitored for an excess risk of self-harm.

- Suicidal behaviour is rare in clinical trials; therefore many trials are too small to reliably detect any difference in the risk of self-harm and suicide between treatment groups. Standardisation of clinical trial protocols should enable results from future studies to be combined, and should enable the detection of any increased risk within particular sub-groups or at any specific time-points.

- Information on patients leaving a study for 'lack of efficacy' should be closely examined for suicidal events prior to unblinding.

- Information on patients experiencing suicidal events during the 'run-in' period should be clearly identified.

- Clinical trials of the same substance in a range of indications should be designed in such a way that any safety concerns relating to specific indications should not be confounded by the study design.

- Trials should be of long enough duration to reflect likely use in practice.

- Whilst placebo-controlled trials provide important information on efficacy, studies against an active comparator should be a requirement for all new antidepressants. The clinical trial protocol must have an appropriate and relevant comparator for the indication prescribed at an appropriate dose; it would be

preferable if clinical experts could design a set of standard protocols which could be used in clinical trial design.

- These studies should be designed to provide clear evidence of any efficacy of increased doses. The most appropriate trial is the randomised non-responder trial where patients are all treated with the same starting dose. Those that fail to respond are then randomly allocated to either have their dose increased or to remain on the same dose. The trial is blinded, meaning that patients and investigators do not know which group they were assigned to and so their assumptions cannot affect the responses. At the end of the trial the dose increase group can be compared with the group that did not have their dose increased, and the benefit of the dose increase can be assessed. The studies should be designed to be large enough to provide accurate information for each proposed dose level. The minimum effective dose should also be ascertained.

GLOSSARY OF ACRONYMS

5HT	5-hydroxytryptamine
ADR	Adverse drug reaction
ADROIT	Adverse Drug Reactions On-line Information Tracking
CBT	Cognitive behavioural therapy
CDRS-R	Children's Depression Rating Scale - revised
CNS	Central nervous system
COMT	Catechol-o-methyl transferase
CPMP	Committee on Proprietary Medicinal Products
CSM	Committee on Safety of Medicines
DALY	Disability adjusted life year
DDD	Defined daily dose
DESS	Discontinuation emergent signs and and symptoms
DSM-IV	Diagnostic and Statistical Manual for Mental Disorder
DSRU	Drug Safety Research Unit
ECT	Electro-convulsive therapy
EWG	Expert Working Group
FDA	Food and Drug Administration (USA)
GAD	Generalised anxiety disorder
GCP	Good clinical practice
GPRD	General Practice Research Database
HAM-D	Hamilton depression score
HRT	Hormone replacement therapy

ICD-10	International Classification of Diseases
K-SADS-P	Kiddie-SADS-Present episode
MA	Marketing authorisation
MADRS	Montgomery-Asberg Depression Rating Scale
MAOIs	Monoamine oxidose inhibitors
MDD	Major depressive disorder
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Noradrenaline
NF	Norfluoxetine
NICE	National Institute for Clinical Excellence
NOS	Not otherwise stated
OCD	Obsessive compulsive disorder
ONS	Office for National Statistics
OR	Odds ratio
PCA	Prescription cost analysis
PEM	Prescription event monitoring
PhVWP	Pharmacovigilance Working Party
PIL	Patient information leaflet
PMDD	Premenstrual dysphoric disorder
PPA	Prescription Pricing Authority
PRR	Proportional reporting ratio
PTSD	Post traumatic stress disorder
R	R enantiomer

RCTs	Randomised (controlled) clinical trials
S	S enantiomer
SAD	Social anxiety disorder
SCoP	Sub-Committee on Pharmacovigilance
SH	Self-harm (deliberate self-harm/attempted suicide/parasuicide)
SNRI	Serotonin and noradrenaline reuptake inhibitor
SPC	Summary of product characteristics
SRIs	Serotonin reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants
WHO	World Health Organisation