THE UNIVERSITY OF SOUTHAMPTON

ADVERSE EVENTS DURING ANTIDEPRESSANT TREATMENT: PRESCRIPTION EVENT MONITORING STUDIES WITH MIRTAZAPINE AND PAROXETINE IN GENERAL MEDICAL PRACTICE IN ENGLAND

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ABSTRACT

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The research described within this thesis aimed to evaluate the profile of adverse events during treatment with the antidepressant mirtazapine in general medical practice in England. The method employed was Prescription Event Monitoring (PEM), which is non-interventional, and provides 'real world' clinical data: patients included within this method are considered more representative of the wider population exposed to the drug, than patient samples included within clinical trial databases.

Using the Drug Safety Research Unit PEM database, events reported during treatment with mirtazapine were analysed and compared with events reported with the selective serotonin reuptake inhibitor paroxetine. Incidence densities (IDs) for reported events were calculated, during the first month of treatment (ID_1) and during months two to six (ID_2) for mirtazapine and paroxetine, The profile of reported adverse events was compared to the description within the Summary of Product Characteristics (SPC) for mirtazapine and previously unrecognised events are described.

The most frequently reported suspected adverse drug reactions (ADRs) were 'unspecified' side effects (n=177), drowsiness/sedation (116) and malaise/lassitude (71). Events with highest incidence density in the first month (ID_1 per 1000 patient-months treatment) were: drowsiness/sedation (58.1), malaise/lassitude (27.8) and dizziness (15.6). The most frequently reported events for stopping mirtazapine were: not effective (2432), drowsiness/sedation (800) and weight gain (362). Adverse events possibly due to mirtazapine but not included within the SPC were agitation (73), aggression (70), dizziness (122), rash (20), hallucinations (13), abnormal dreams (31), oedema (30), palpitations (10) and tremor (14).

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PREFACE

Having worked at the Drug Safety Research Unit (DSRU) for five years, I had been at the heart of an important international institution. During my time at DSRU, I hoped to undertake an original research project that might lead to scientific publications and possibly be linked to study for a higher degree. At DSRU, I worked as a Clinical Research Fellow and this position provided an ideal opportunity to carry out such a piece of research.

Being the only independent international pharmacovigilance centre in the UK, the unit can make significant contributions in the field of pharmacovigilance and pharmacoepidemiology. The Prescription Event Monitoring database (PEMbase) has more than four million reports from all over England. This information source is the basis for the core operations of the unit, in finding new safety signals for prescribed medication and in the development of risk management plans.

Pharmacovigilance as a scientific discipline is a relatively new area, and therefore the work of the DSRU and the studies I undertook is relatively uncharted water. I feel privileged to have had the chance of working in this great institution, from where I have experienced the challenges and successes in working in the area of pharmacovigilance and pharmacoepidemiology.

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I am also grateful for the funding that I received from the Drug Safety Research Unit in completing my DM, and to the many colleagues who showed interest in my studies within the Drug Safety Research Unit, particularly Dr Nayan Acharya, Dr Emma Heely and all the other staff. I would like to specially extend my thanks and gratitude to Dr Kiyoshi Kubota, who had originally collected and analysed the data for the Paroxetine PEM study, which I used for comparison with findings from the mirtazapine database.

Finally, I am grateful to my husband, Arun and my two lovely children Shyamaleena and Himal for their tolerance and support whilst the thesis was being written.

CHAPTER 1:
DEPRESSION AND PHARMACOVIGILANCE OF ANTIDEPRESSANT DRUGS

Introduction to depression

Depression has been termed by a variety of names in medical and popular literature for hundreds of years. Early English texts refer to "melancholia," which was for centuries the common term for all emotional disorders. Depression is now referred to as a mood disorder, and the primary subtypes are major depression (either unipolar or bipolar), chronic and usually milder depression (dysthymia), and 'atypical' depression. Other forms of depression include premenstrual dysphoric disorder, recurrent brief depression, and seasonal affective disorder. Therefore, the term 'depression' covers a broad spectrum, ranging from severe forms of normal sadness at one end, to severe illness at the other.

Epidemiological surveys indicate that the depressive disorder known as major depression is common in nearly all countries. Reported rates differ substantially, partly due to variations in study methodology, but also to real differences in prevalence probably attributable to social factors[1].

The annual prevalence in Western countries is reported as between 3% and 10% with a weekly prevalence in the United Kingdom (UK) of 2.3%[2]. Milder depressive states are more common with a UK weekly prevalence of 7.7%. The prevalence of depressive disorders is approximately 2 – 3 times higher in women than men, although this difference was less marked in adults over 55 years of age in one survey[3].

In 1990 major depression was estimated as the fourth leading specific cause of disability on a global scale, second only to ischaemic heart disease in developed countries[4]. These

epidemiological findings are reflected in rates of presentation in general practice, where 5 – 10% of consecutive patients fulfil criteria for major depression with a similar number having milder depressive states[5,6].

Types of depressive disorder

Depressive disorders come in different forms, distinguished by the severity of symptoms, the course of illness, and the specific cause of the symptoms, if known. There are three major types -

- Major Depression (or unipolar major depression): This is the most common depressive disorder, in community and primary care surveys;
- Bipolar depression (or manic-depressive illness): episodes of major depression in patients who have also experienced episodes of mania;
- Dysthymic disorder: a low to moderate level of depression that persists for at least two years, and usually longer. The symptoms are not as severe as in major depression, but they are more enduring and as impairing.

Symptoms of depression

Not everyone who is depressed experiences every symptom, and the severity of symptoms varies between individuals and episodes. The main depressive symptoms, included within current diagnostic criteria[7] are as follows:

- Persistent sad, anxious, or 'empty' mood.

- Feelings of hopelessness and pessimism.
- Feelings of guilt, worthlessness and helplessness.
- Loss of interest or pleasure in hobbies and activities that were once enjoyed, including sex.
- Insomnia, early-morning awakening, or oversleeping.
- Appetite and/or weight loss or overeating and weight gain.
- Decreased energy, fatigue, being "slowed down".
- Thoughts of death or suicide; suicide attempts.
- Restlessness, irritability.
- Difficulty concentrating, remembering, making decisions.
- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain

Causes of depression

***Neurotransmitter disturbances*:** Depression has been linked to abnormalities in the availability of key neurotransmitters (chemical messengers in the brain) - most importantly, serotonin (5-hydroxytryptamine, 5-HT), acetylcholine, dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline). Norepinephrine and serotonin transmit signals across synaptic gaps between brain cells. Relative depletion of neurotransmitters within synapses may be a cause of depressive symptoms. Antidepressants may alleviate depression by increasing the levels of these neurotransmitters within brain synapses. The degree to which these chemical messengers are disturbed may be determined by other factors such as adversity, ambient light and genetic

susceptibility: for example, a defect in a gene known as SERT, which regulates serotonin has also been linked to depression[8].

***Hormones*:** The role of hormones in depression is not clear, but ovarian hormones may play roles in the pathophysiology of premenstrual dysphoria and postpartum depression. Disturbances of the hypothalamo-pituitary-adrenal endocrine axis may play a role in the development and maintenance of depression.

***Changes in Brain Structure*:** Neuorimaging studies have shown that a particular area of the brain known as the prefrontal cortex, which influences emotional control, is less active and smaller in elderly depressed people than in those who do not suffer from depression, greatest atrophy being seen in those with the most severe depression[9].

***Medications*:** Many prescribed drugs, such as beta-blockers, corticosteroids, antihistamines, analgesics, and anti-parkinsonism medications, have been implicated in the development of depression. In addition, withdrawal from some medications can also cause depressive symptoms[10].

Genetic susceptibility: The tendency for depression to run in families indicates that a there may be a hereditable biological vulnerability in bipolar disorder and unipolar depression.

Psychosocial factors: People with persistent low self-esteem, or who have characteristic cognitive distortions, are prone to depression. In addition a serious loss, chronic illness,

difficult relationships, financial problems, or limited social network have all been implicated as aetiological factors in the development of depression.

Guidelines for Treating Depression

In spite of the effectiveness of current pharmacological and psychological treatment approaches, more than two-thirds of people with major depression do not receive treatment. Antidepressants are clearly effective in the treatment of major depression and dysthymia; the majority of patients with major depression will improve with good compliance and adequate doses of the right antidepressant drug[11]. Side effects can be minimised if the regimen is started at low doses and built up over time. Lack of compliance is a major barrier to success: as many as 70% of elderly depressed patients do not adhere to antidepressant drug regimens[11]. Some patients with accompanying problems, such as anxiety, may require additional drugs that treat those symptoms.

For people experiencing a first episode of depression, antidepressants are usually continued for at least six months after resolution of symptoms. Some patients may require long-term maintenance treatment – such as those who have had three or more episodes of depression; people aged over 50 years who have never had major depression before; those with two episodes and a family history of depression or bipolar disorder; and people who have experienced particularly severe or life-threatening depressions. Most patients have a recurrence of depression within five years after treatment has stopped[12].

Current antidepressant drugs

The principal classes of antidepressants include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and a mixed group of other compounds.

Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) were among the first antidepressants to become available. Examples of MAOIs include phenelzine and tranylcypromine. MAOIs are presumed to relieve depression by elevating the levels of key neurotransmitters (norepinephrine, dopamine, 5-HT) through the inhibition of the enzyme monoamine oxidase. Unfortunately MAOIs also impair the ability to break down tyramine, a substance found in aged cheese, wines, most nuts, chocolate, and other foods. Ingestion of tyramine-containing foods whilst taking a MAOI drug can cause a pressor response to tyramine, with the development of tachycardia and hypertension. MAOIs also can produce the same effects when used in combination with sympathomimetic drugs contained within over-the-counter cold and cough medications. For these reasons, MAOIs are usually only prescribed after other options have failed, although they have been found effective in 'atypical' depression (with prominent anxiety symptoms), social phobia, and post-traumatic stress disorder.

MAOIs commonly cause orthostatic hypotension (a sudden drop in blood pressure upon standing), drowsiness, dizziness, sexual dysfunction, and insomnia. They can also cause birth defects and should not be taken by pregnant women. Very dangerous side effects can occur from interactions with other prescribed medications including pethidine and some other

antidepressants. There should be at least a two week interval between stopping MAOIs and starting most other antidepressants.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) (for example amitriptyline, protryptyline, nortriptyline and trimipramine) were developed in the 1950s and 1960s and represented the principal treatment for depression for many years.

TCAs work mainly by increasing the level of norepinephrine and 5-HT within brain synapses, to varying degrees. Most TCAs also have 'anti-cholinergic' side effects, due to effects on the autonomic nervous system, causing dry mouth, blurred vision and constipation. Anti-cholinergic side effects can also aggravate narrow angle glaucoma, urinary obstruction due to benign prostrate hypertrophy, and cause delirium in the elderly. TCAs can cause life-threatening heart rhythm disturbances when taken in over-dose, and orthostatic hypotension with dizziness upon arising. TCAs should also be avoided in patients with seizure disorders, due to a reduction in the epileptic threshold.

The most common side effects of TCAs include dry mouth, blurred vision, sexual dysfunction, weight gain, difficulty in urinating, disturbances in heart rhythm, drowsiness, dizziness and orthostatic hypotension.

TCAs may pose a danger for some patients with certain heart diseases. One study comparing nortriptyline with paroxetine, a selective serotonin reuptake inhibitor (SSRI), reported nine times more adverse cardiac events with the use of the tricyclic than with the SSRI[13]. Also of concern is a recent study reporting that tricyclics, particularly imipramine, may be responsible

for 10% of cases of a lung disease called idiopathic pulmonary fibrosis, which can cause lung inflammation and scarring[14].

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) increase the amount of serotonin within synapses. SSRIs have been used successfully for over a decade to treat depression, and have fewer side effects than TCAs or MAOIs. SSRIs do not interact with tyramine in food, and do not produce orthostatic hypotension or heart rhythm disturbances. In most European countries SSRIs have become the first-line treatment for depression. The most well-known SSRIs are fluoxetine, paroxetine, sertraline, fluvoxamine and citalopram.

SSRIs are generally well tolerated and side effects are usually mild. The most common side effects are nausea, diarrhoea and headache, but these side effects generally dissipate within the first few weeks of use. Some patients experience sexual side effects such as decreased libido or delayed or inability to have an orgasm. 'Serotonin syndrome' is a serious but rare medical condition associated with use of SSRIs in combination with other medication (for example, MAOIs), and is characterized by high fevers, seizures, and heart rhythm disturbances.

SSRIs are efficacious in major depression, dysthymia, premenstrual dysphoric disorder and a range of anxiety disorders, including obsessive-compulsive disorder, panic disorder, generalised anxiety disorder and social phobia. Fluoxetine appears to be safe for during pregnancy, but SSRIs are often avoided in pregnant and breastfeeding women.

As with other antidepressants, it takes a few weeks for SSRIs to become effective in most adults, and longer in the elderly and those with dysthymia. SSRIs are effective in the prevention of recurrence of depressive illness: one recent study of patients taking fluoxetine suggested that patients should continue taking fluoxetine for 38 weeks to prevent relapse; another study examined patients using paroxetine and found that those who continued with the full dose of paroxetine for 28 weeks had half the chance for relapse when compared to those who reduced their dose[15].

Elderly people taking SSRIs should take the lowest possible dose, and those with heart problems should be monitored closely. Rarely, patients taking SSRIs develop extrapyramidal symptoms, such as parkinsonism and akathisia. Death from overdose is extremely rare. Adverse interactions with other prescribed (antidepressants, some antihistamines) or illicit drugs may cause confusion, changes in blood pressure, stiffness, and irregular heart beats.

Other antidepressants

Bupropion is an effective treatment for major depression and aids smoking cessation. It causes less sexual dysfunction than SSRIs, but side effects include restlessness, agitation, sleeplessness, headache, rashes, and stomach problems. Weight loss occurs in about 25% of patients. High doses increase the risk for seizures, particularly in those with eating disorders or other risk factors for seizures.

Venlafaxine is a serotonin-nordrenaline reuptake inhibitor, efficacious in major depression, generalised anxiety disorder and some other anxiety disorders. The efficacy of venlafaxine is marginally greater than that of most SSRIs, in severely depressed patients. Side effects include

the tendency to raise blood pressure when prescribed at high dose, and symptoms after treatment discontinuation may be distressing.

Nefazodone (now withdrawn in the UK and many other European countries) is associated with less sexual dysfunction than SSRIs but case reports suggest that it may be hepatoxic in an minority of patients.

Mirtazapine

Mechanism of action

Mirtazapine differs from other dual-acting antidepressants by not being a reuptake inhibitor, its antidepressant activity probably being related to a direct enhancement of noradrenergic neurotransmission by blockade of alpha2-autoreceptors. A rapid increase in serotonin synaptic levels through blockade of alpha2-heteroreceptors on serotonergic neurones indirectly enhances 5-HT1A-mediated neurotransmission. In addition, mirtazapine has antagonist properties at the 5-HT2 and 5-HT3 receptors, resulting in less insomnia and nausea than is seen with SSRIs.

Pharmacokinetics

Mirtazapine is rapidly and well absorbed from the gastrointestinal tract after single and multiple oral administrations, and peak plasma concentrations are reached within 2 hours. It binds to plasma proteins (85%) in a non-specific and reversible way. The absolute bioavailability is approximately 50%, mainly because of gut wall and hepatic first-pass metabolism. Mirtazapine shows linear pharmacokinetics over a dose range of 15 to 80mg.

The presence of food has a minor effect on the rate, but not the extent, of absorption. The pharmacokinetics of mirtazapine is dependent on gender and age: females and the elderly show higher plasma concentrations than males and young adults.

The elimination half-life of mirtazapine ranges from 20 to 40 hours, which is in agreement with the time to reach steady state (4 to 6 days). Total body clearance as determined from intravenous administration to young males amounts to 31 L/h. Liver and moderate renal impairment cause an approximately 30% decrease in oral mirtazapine clearance; severe renal impairment causes a 50% decrease in clearance[16]. There were no clinically or statistically significant differences between poor (PM) and extensive (EM) metabolisers of debrisoquine [a cytochrome P450 (CYP) 2D6 substrate] with regard to the pharmacokinetics of the racemate.

The pharmacokinetics of mirtazapine appears to be enantioselective, resulting in higher plasma concentrations and longer half-life of the (R)-(-)-enantiomer (18.0 +/-2.5h) compared with that of the (S)-(+)-enantiomer (9.9+/-3. 1h). Genetic CYP2D6 polymorphism has different effects on the enantiomers. For the (R)-(-)-enantiomer there are no differences between EM and PM for any of the kinetic parameters; for (S)-(+)-mirtazapine the area under the concentration-time curve (AUC) is 79% larger in PM than in EM, and a corresponding longer half-life was found. Approximately 100% of the orally administered dose is excreted via urine and faeces within 4 days.

Biotransformation is mainly mediated by the CYP2D6 and CYP3A4 isoenzymes. Inhibitors of these isoenzymes, such as paroxetine and fluoxetine, cause modestly increased mirtazapine plasma concentrations (17 and 32%, respectively) without leading to clinically relevant consequences. Enzyme induction by carbamazepine causes a considerable decrease (60%) in mirtazapine plasma concentrations. Mirtazapine has little inhibitory effects on CYP isoenzymes and, therefore, the pharmacokinetics of coadministered drugs is hardly affected by mirtazapine. Although no concentration-effect relationship could be established, it was found that with therapeutic dosages of mirtazapine (15 to 45 mg/day), plasma concentrations range on average from 5 to 100 microg/L[17].

Efficacy of mirtazapine

A meta-analysis of 20 short term comparative studies of 5 selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) has shown no difference in efficacy between individual compounds but a slower onset of action of fluoxetine[18]. There were suggestions that fluoxetine caused more agitation, weight loss and dermatological reactions than the other SSRIs. More patients discontinued fluvoxamine, and fewer patients stopped sertraline because of adverse effects than their comparator SSRIs. The most common adverse events with the SSRIs were gastrointestinal (especially nausea) and neuropsychiatric (particularly headache and tremor).

Pharmacovigilance and its importance

Pharmacovigilance is the process of identifying, evaluating and responding to adverse drug reactions (ADRs) and safety issues about medicinal products. The goal is the safer use of medicines and is usually achieved by dissemination of accurate, timely and clinically relevant information. Thus the objectives of pharmacovigilance are concerned with identifying, validating, quantifying and evaluating adverse reactions associated with the use of drugs. The need for pharmacovigilance and postmarketing surveillance is partly due to the limited exposure of patients to medicines prior to their launch. When a new drug is first licensed, the information about its clinical safety is incomplete[19]. After a new drug is marketed, it is often used in markedly different populations from those included in clinical trials.

Several studies have shown that ADRs are a leading cause of death. It has been estimated that ADRs could account for more than 100 000 deaths in the USA each year, amounting to the fourth commonest cause of death after heart disease, cancer and stroke[20]. A meta-analysis of 39 prospective studies, covering a period of 2 years in the US hospitals showed a 6.7% incidence of serious and fatal ADRs; and a 0.32% death rate among patients either admitted to hospital because of an ADR or experiencing an ADR while in hospital. This analysis examined only ADRs attributed to medicines that were "properly prescribed and administered", and therefore excluded ADRs arising due to overdose, drug administration errors, drug abuse, therapeutic failures and non-compliance. The authors suggested that ADRs are considerably under-reported, and that the incidence of ADRs is the same now as it was over 30 years ago.

A study performed in the UK has estimated that ADRs account for 1 in 16 hospital admissions, and cost the National Health Service (NHS) £466m a year. A total of 1,225 admissions were related to an adverse drug reaction, giving a prevalence of 6.5%. The average stay was eight days, which accounted for 4% of the hospital bed capacity. The projected annual cost to the NHS of such admissions was £466m[21].

Objective of these studies

The objectives of the research described within this thesis were to evaluate the adverse events associated with the antidepressant drug mirtazapine during treatment in general medical practice in England, using the technique of prescription event monitoring (PEM), and to compare the profile of these events with that seen with paroxetine. I had already gained wide experience of pharmacovigilance and PEM through my role in a number of previous investigations of prescribed medications, including a number of psychotropic drugs, and wished to gain a greater understanding of the principles of pharmacovigilance, and consider the relative advantages and disadvantages of the PEM system. My involvement in these other pharmacovigilance studies is summarised in the following paragraphs.

Pharmacovigilance study of alendronate in England[22] (published in Osteoporosis International, 2003;**14**:507-514).

Alendronate sodium is an aminobiphosphonate, an analog of inorganic pyrophosphate, indicated for the treatment of osteoporosis in post-menopausal women. We analyzed events reported in patients prescribed alendronate by general practitioners in England. A non-

interventional observational cohort study was conducted using prescription event monitoring. Exposure data were obtained from dispensed prescriptions issued between October 1995 and January 1997. Outcome data were obtained by sending questionnaires to prescribing GPs.

The cohort comprised 11,916 patients. Events most frequently reported as suspected adverse drug reactions and reason for stopping alendronate were recognized gastrointestinal events listed in the Summary of Product Characteristics. These included nausea/vomiting, abdominal pain, dyspepsia, esophagitis and esophageal reflux. Events with the highest incidence density (ID1 per 1000 patient months treatment) were dyspeptic conditions (32.2), nausea/vomiting (20.8) and abdominal pain (13.8). The term dyspeptic conditions included dyspepsia, esophagitis, esophageal reflux, duodenitis, gastritis and heartburn. Serious suspected adverse reactions possibly related to alendronate were single reports of angioedema, erythema multiforme, hypercalcemia and hypocalcemia. There were 540 deaths in this elderly cohort. This study suggested that alendronate was well tolerated, though there may be risk of developing gastrointestinal side effects including esophagitis and esophageal ulcers.

The Pharmacovigilance of Mirtazapine: results of a prescription event monitoring study on 13554 patients in England[23] (Published in *Journal of Psychopharmacology* 2003;**17(1):**121-126).

We monitored the safety of mirtazapine as reported in primary practice in England. The exposure data were provided by monitoring the dispensed prescriptions issued between September 1997 and February 1999. Questionnaires

sent to GPs provided outcome data. Drowsiness/sedation and malaise/lassitude were the most frequent ADRs (116, 71 respectively) and had the highest incidence density (per 1000 patient-months) in the first month of treatment (58.1, 27.8 respectively). Agitation (73), aggression (70), rash (20), hallucinations (13) and abnormal dreams (31) were unlabelled AES while abnormal liver function tests (12), syncope (8), abnormal behaviour (4) and visual disturbance (3) were labelled AES possibly due to mirtazapine use. Serious suspected ADRs reported were facial oedema (5), allergy (3), bone marrow toxicity (2) and myelodysplasia (1). The results of this study are described in more detail in subsequent chapters of this thesis.

Pharmacovigilance of Valsartan: Results of a Post-Marketing Surveillance Study on 12 881 Patients in England[24] (Published in *Journal of Human Hypertension* 2002;**16:**795-803).

We monitored the safety of valsartan using the Prescription Event Monitoring, in patients prescribed this drug by general practitioners in England. Exposure data were obtained from dispensed prescriptions issued between December 1996 to November 1998. Outcome data were obtained by sending questionnaires to prescribing GPs.

The cohort comprised 12 881 patients. Events most frequently reported as suspected adverse drug reactions were malaise/lassitude (37; 0.3% of total cohort), dizziness (19; 0.1%) and unspecified side effects (57; 0.4%). Events with highest incidence density (ID1 per 1000 patient-months of treatment) in the first

month of treatment were: malaise/lassitude (15.6), dizziness (11.8) and headache/migraine (10.9). The most frequent reasons for stopping valsartan were: not effective (847; 6.6% of total cohort), malaise/lassitude (265; 2.1%) and dizziness (146; 1.1%). No unexpected serious adverse events were identified. Other events assessed as possibly related to valsartan use were: impotence (37), dizziness (19), cough (9), facial oedema (5), hyperkalemia (3) and angioneurotic oedema (1). There were four reports of exposure during pregnancy and 203 deaths (1.5%) in this cohort. No untoward features other than dizziness were identified that had not been mentioned in the prescribing guidance.

Troglitazone and Liver Function Abnormalities[25] (Published in *Drug Safety*, 2001;**24:**(2).149-154).

We wished to investigate whether there were any cases of liver function abnormalities possibly associated with troglitazone use in general practice in England, through conducting a prescription-event monitoring study between October and December 1997.

Event data were obtained for a total of 1344 patients. Troglitazone was effective in 394 (75%) of the 529 patients for whom an opinion was given. The major cause of stopping troglitazone was because the drug was withdrawn from the market (1101 reports). The most frequent reasons for stopping treatment related to drug tolerability were malaise or lassitude (16 reports), abnormal liver function tests (I 1 reports) and nausea/vomiting (9 reports). 30 patients with liver dysfunction

were identified from the cohort. In 9 of these patients there were alternative explanations for the liver dysfunction and hence these patients were not followed up further. 21 patients were followed up, for whom 19 questionnaires were returned. In 5 patients their liver dysfunction was assessed as possibly related to troglitazone, in 6 patients the liver dysfunction was unlikely to be attributed to troglitazone, while in 7 patients it was difficult to assess the causality because of limited information and confounding factors. The remaining patient was not included as this individual did not fit the inclusion criteria of the study. The cohort was small (as the drug was available for only 3 months in the UK), but 5 patients with abnormal liver function, considered possibly related to troglitazone were detected in this study.

The incidence of adverse events and risk factors for upper gastro-intestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study[26]. (Published in *British Journal of Clinical Pharmacology*, 2000;**50:**35-42).

Meloxicam is a novel nonsteroidal anti-inflammatory drug (NSAID) which may be associated with fewer adverse upper gastrointestinal events than other NSAIDs because it preferentially inhibits the inducible enzyme cyclo-oxygenase-2 relative to the constitutive isoform, cyclo-oxygenase-1. The aims of the study were to: determine the rate of adverse events associated with meloxicam in general practice, stratify these rates by selected risk factors, and to identify signals of previously unsuspected adverse events associated with meloxicam. All patients

prescribed meloxicam in England between December 1996 and March 1997 were identified by the central Prescription Pricing Authority. We sent short questionnaires to all prescribers asking about adverse events experienced within 6 months of the last prescription.

There were 19,087 patients in the study. The rate of dyspepsia during the last month of exposure was 28.3 per 1,000 patient-months. There were 33 reports of upper gastrointestinal haemorrhage during treatment (rate: 0.4 per 1,000 months). A history of gastrointestinal disorder in the previous year was associated with an increased rate of dyspepsia (rate ratio: 3.0; 95% confidence interval: 2.6, 3.4), abdominal pain (2.1; 1.6, 2.6), and peptic ulcer (4.0; 1.4, 13.2). Prior NSAID use was associated with a 20-30% decrease in the rate of dyspepsia and abdominal pain in patients starting meloxicam, while patients prescribed concomitant gastroprotective agents had a two to three-fold increased rate of dyspepsia, abdominal pain and peptic ulceration. Other rare events were thrombocytopenia (n=2); interstitial nephritis (n=1) and idiosyncratic liver abnormalities (n=1). We concluded that in the absence of gastro-intestinal risk factors the incidence of gastrointestinal disturbance was low.

Montelukast and improvement of eczema: observations from a prescription event monitoring study in England[27]. (Published in *International Journal of Clinical Pharmacology and Therapeutics*, 2001;**39**:529-533).

Montelukast is a cysteniel receptor antagonist indicated for the treatment of asthma. The objective of this study was to determine whether there are any

beneficial effects of montelukast on eczema and urticaria. A non-interventional observational cohort study was conducted between February 1998 and December 1998 using Prescription-Event Monitoring. In this study, events reported as eczema or urticaria improved were identified.

The cohort comprised 15,612 patients, in which 16 reports of eczema or urticaria improved were identified. Questionnaires were sent to the GPs for additional information. Fifteen of the 16 questionnaires were returned. In 5 cases the GPs thought that there was an improvement of eczema or urticaria with montelukast treatment in patients who had history of long-standing eczema or urticaria. Of the remaining 11 cases there was an alternative explanation for the improvement of eczema or urticaria in 10 cases and one was unassessable. Although the number of cases of improvement of eczema or urticaria in this cohort was small, there was evidence that leukotriene inhibitors may be helpful in the treatment of these diseases. We concluded that further studies were needed to provide evidence as to whether montelukast could have a role in the treatment of these conditions.

The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England[28]. (Published in *Journal of Psychopharmacology*, 2001;**15:**(4).265-271).

Olanzapine is an 'atypical' antipsychotic indicated for the treatment of schizophrenia and biolar disorder. We analysed adverse events reported in primary practice in England. Dispensed prescriptions issued between December

1996 and May 1998 provided exposure data; questionnaires sent to general practitioners provided outcomes. Frequently reported adverse events were: drowsiness/sedation (n = 19), extrapyramidal disorder (n = 13) and unspecified side-effects (n = 33). Events with the highest incidence density (ID) in first month and reason for stopping were: drowsiness/sedation (n = 153, ID 18.91), weight gain (n = 117, ID 8.9) and malaise/lassitude (n = 65, ID 5.2). Extrapyramidal disorders were more common in the elderly population (more than 70 years, ID, 3.6, risk 26.0 per 1000 patients) compared to those aged less than 70 years (ID, 1.1, risk 8.4 per 1000 patients). Serious suspected adverse reactions were neuroleptic malignant syndrome (n = 1) and angioneurotica (n = 2). There were eight reports of diabetes mellitus assessed as possibly due to olanzapine. Diabetes mellitus was an unlabelled AE and represented a possible signal generated by prescription-event monitoring.

The pharmacovigilance of tamsulosin: event data on 12,484 patients[29]

(Published in *British Journal of Urology International* 2000;**85:**446-450).

We wished to determine drug effectiveness and adverse effects in a non-interventional observational cohort study of over 10,000 patients treated with tamsulosin in general medical practice. Using prescription-event monitoring, data were collected of all prescriptions for tamsulosin issued nationally during June 1996 to January 1998. For each patient entered into the cohort a computerized longitudinal record of exposure was constructed. The outcome data, patient information and an opinion about the effectiveness of the drug were provided by

the prescriber, using a standard questionnaire sent 6 months after the initial prescription for tamsulosin. The incidence of each of almost 2000 events listed in the Drug Safety Research Unit computerized dictionary was calculated and scrutinized by medical assessors for possible adverse reactions, and any difference determined between the incidence of each event in the first month and subsequent months of exposure. All deaths were followed up to detect possibly drug-related causes.

Event data were obtained on 12,484 patients, from the 52.9% of questionnaires returned that contained valid event data. Tamsulosin was reported to have been effective in 7428 (78.3%) of the 9,487 patients in whom the general practitioners expressed an opinion about effectiveness. Suspected adverse drug reactions were reported in only 171 (1.4%) of the cohort. Dizziness, headache, malaise and hypotension were common to the reported adverse reactions, reasons for stopping the drug and events of greatest incidence density. None of the 282 deaths that occurred in this elderly cohort were attributed to the drug. This study suggested that tamsulosin has a highly acceptable benefit-to-risk ratio. No untoward features not already mentioned in the prescribing guidance were identified.

Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies[30]. (Published in British Journal of Clinical Pharmacology, 1998;**46**:505-551).

We investigated age and sex specific incidence rates of suspected adverse drug reactions recorded by general practitioners in England after the prescription of selected newly marketed drugs. Information was collected from 48 national cohort studies of newly marketed drugs studied by prescription-event monitoring. Questionnaires were sent to prescribers asking for details of events and suspected adverse drug reactions recorded in the patients' notes occurring after the drugs were prescribed.

During the 48 cohort studies, a total of 513 608 patients were investigated, of which 221,781 (43.2%) were males and 285,862 (55.7%) were females. The overall incidence of suspected adverse drug reactions in males was 12.9 per 10,000 patient-months of exposure (95% confidence limits 12.3 to 13.5), and in females was 20.6 per 10,000 patient-months of exposure (95% confidence limits 19.9 to 21.3). The overall age-standardized relative risk of an adverse drug reaction in females compared to males was 1.6 (1.5-1.7). This sex difference was significant in all age groups above 19 years of age, and was relatively consistent across all age groups (X^2 test for heterogeneity=9.2, P=0.3). The highest rate of recording in males was in the 50-59 year age group, and in females was in the 30-39 year age group.

We concluded that in general practice in England, suspected adverse drug reactions to newly marketed drugs are recorded more often in adults between 30 and 59 years of age and are 60% more common in women than in men. The sex difference occurs in all age groups over 19 years of age.

CHAPTER 2: METHODLOGY OF PRESCRIPTION EVENT MONITORING

PRESCRIPTION EVENT MONITORING (PEM)

The Drug Safety Research Unit (DSRU) at Southampton uses Prescription Event Monitoring (PEM)[31], to monitor selected newly marketed drugs with widespread use in general practice in England, in particular those that are intended for long term use. Mirtazapine was licensed in September 1997 and a PEM study was conducted immediately after its launch in the UK.

Prescription Event Monitoring is a non-interventional, observational cohort form of post-marketing surveillance. It is non-interventional because nothing happens to interfere with the doctor's decision regarding which drug to prescribe for each individual patient. Thus, the method provides 'real world' clinical data involving neither inclusion nor exclusion criteria: the patients studied are those who receive the drug in everyday medical practice. This ensures that data are generalisable into the UK primary medical care population.

In the UK, virtually all persons are registered with a general practitioner (GP) who provides primary health care. A GP issues prescriptions ('FP10s') for the medicines deemed medically necessary. The patient takes the prescription to a pharmacist who dispenses the medication and then sends the FP10s to a central Prescription Pricing Authority (PPA) which arranges the pharmacist's reimbursement. The DSRU has a long standing and confidential arrangement with the PPA, which provides the electronic copies of all those prescriptions issued nationally for the drugs being monitored by PEM.

Procedure

The data for the mirtazapine PEM study was collected and analysed by me. Patients were identified by means of data from prescriptions (FP10s) written by GPs in England and supplied in confidence by the PPA between September 1997 and February 1999. Simple questionnaires (so-called 'green forms'), as shown in Figure 1, were posted to the prescribing doctors between March 1998 and September 1999, approximately six months following the first prescription identified by the DSRU. These forms requested information on the age, diagnosis and duration of treatment and other details, including events that may have occurred after the drug was prescribed. Only one green form was sent for each patient. No doctor was sent more than four green forms in any one month. These four green forms could be for any of the studies (approximately 20) which were in progress at the time of this study.

In PEM studies an 'event' is defined as *including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter into patient's notes.*

Figure 1. Copy of the 'green form'.

PLEASE REMOVE THIS SECTION OF THE FORM SO THAT THE BOTTOM HALF BECOMES ANONYMOUS

DRUG SAFETY RESEARCH UNIT
PRESCRIPTION EVENT MONITORING

MEDICAL - IN CONFIDENCE

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We collect **EVENT** data

An **EVENT** is any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, any alteration of clinical importance in laboratory values or any other complaint which was considered of sufficient importance to enter in the patient's notes.
Example: A broken leg is an **EVENT.**

Please indicate if you suspect an **EVENT** to be an adverse reaction to a drug.

These studies are conducted in accordance with the results of authorative discussions and the International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva 1993. The method of study also complies with the Guidelines on the practice of Ethics Committees in Medical Research Involving Human Subjects, as issued by the Royal College of Physicians of London (August 1996)

Ref:

PLEASE RETURN THIS HALF OF THE FORM

Ref:

Sex: Date of birth: ___/___/___	Was the drug effective? Yes ☐ No ☐ Don't Know ☐
Indication for prescribing	Has the drug been stopped? Yes ☐ No ☐ Don't Know ☐
	If 'YES' reason for stopping
Start Of Treatment	Date of stopping if known ___/___/___ Or
Date ___/___/___ Dose mg/day	Date of last prescription ___/___/___

Event Date	Dose mg/day	**Events while taking this drug** If none, please tick box ☐	Event Date	**Events after stopping this drug** If none, please tick box ☐

IMPORTANT: PLEASE INDICATE ANY EVENTS REPORTED TO CSM OR MANUFACTURER

Thus, in PEM the exposure data are derived from the original prescriptions for the drug being monitored and the outcome data are the events recorded by the original prescribers on the green forms.

Materials and Methods

Collection and analysis of data obtained from Mirtazapine and Paroxetine PEM Studies

The data collection and analysis for the Mirtazapine PEM study was undertaken solely by me, including designing of follow up questionnaires; developing special questionnaires for specific events e.g. of abnormal liver function test questionnaires; and the follow-up of pregnancies and deaths. Data collection for the Paroxetine study was originally undertaken by Dr Kiyoshi Kubota between March 1991 to March 1992. The data collected by Dr Kubota was through the technique of Prescription Event Monitoring, however, the methodology used for determining possible signals in the original evaluation carried out by Dr Kubota was by the use of Rate Ratios (RR) for the events during the first month of treatment and the subsequent 6 months. For the paroxetine data analysis, described within chapter 4 of this thesis, I have used the method of calculating Incidence Densities (ID) in place of Rate Ratios, for determining possible signals, to better compare the findings with those of mirtazapine.

For PEM, the exposure is the drug under investigation (in this case mirtazapine and paroxetine), and outcome data is provided by event collection. In the first study, the exposed are those receiving mirtazapine, and in the second the exposed are those receiving the SSRI paroxetine. The patients were identified by means of events coded from data held for mirtazapine and paroxetine. This helps to ensure that the control population will have similar characteristics by means of

prescribing indication to that of the exposed, but where the drugs used have a different mechanism of action.

For each drug only those events reported within the first six months whilst on treatment were included. Any events reported without an event date specified were excluded. Events occurring after 30 days from the start date, and where no stopping date was given were also excluded, as were events occurring more than 30 days after stopping the drug.

Exposure data

The DSRU is provided with electronic copies of the dispensed prescriptions for selected newly marketed drugs intended for general widespread, long-term use. Special emphasis is given to drugs likely to be initiated and continued in primary care. For each patient the DSRU prepares a computerised longitudinal record comprising, in date order, all prescriptions dispensed for the monitored drug. Further details of data coding and computerisation have been provided in recent publications[32].

Outcome data

After an interval of six to twelve months from the first prescription for each patient, the DSRU sends to the prescriber a 'green form' questionnaire seeking information on any events which may have occurred since the drug was first prescribed. For each drug, an interval is chosen for the period of time between the date of the first prescription issued to an individual and the date when the first green form is sent. On average, 58% of the green forms sent out are returned.

The study starts as soon as possible after the new drug has been marketed in England. Each study aims to collect exposure and outcome data on a minimum of 10,000 patients.

Green forms request specific information on patients' date of birth, indication for treatment, dates of starting and stopping treatment, reason for stopping the drug, every significant event and its date of occurrence and any relevant additional information. The definition of an "event" is given as any significant occurrence in the patients medical history since the day the drug was started including any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction or any complaint considered of sufficient importance to enter into the patient's notes.

Coding

All events reported on green forms were coded onto a computer using a dictionary which is arranged in a system-organ classification. This dictionary is maintained within the DSRU. The data were assembled in such a way as to show the number of reports for each event in each of the first six months of the observation period. Certain coding conventions have been adopted in order to facilitate the processing and retrieval of the massive quantities of data involved in PEM. These conventions include the following:-

i. Pre-existing diseases are not coded unless an exacerbation occurs.

ii. Where the same event was reported more than once, only the first episode is included in the appendices to this report.

iii. If an event is part of a diagnosis or syndrome which is coded, then it and any related individual signs, symptoms or laboratory test results which are part of the syndrome are not coded.

iv. Where linked events are coincidental in time, only the more serious is coded, signs taking precedence over symptoms.

v. A patient may experience more than one event from the same patho-physiological system-organ class and this is recognised during the coding process. For example if a patient developed eczema and urticaria, two events would be recorded. A full list of coding conventions is maintained within the DSRU.

Events

Incidence densities

Analysis of PEM data involved calculation of rates for particular events reported during the observation period following the start of treatment. Apparent associations were assessed using information provided on the green forms. For each of the event terms included in the DSRU dictionary the PEM data provide a numerator (the number of reports of the event), a denominator (the number of patient-months of exposure) and a known time frame (the time between the start and stop dates of mirtazapine in individual patients). Incidence densities (IDs) are then calculated for all the events occurring during treatment with the study drug during a specified time period (**t**). The figures are expressed as ID per 1000 patient-months of treatment.

$$ID_t = \frac{\text{Number of reports of an event } \textit{during treatment} \text{ for period t}}{\text{Number of patient-months of treatment for period t}} \times 1000$$

Thus,

$$ID_t = \frac{N_t}{D_t} \times 1000$$

Where: N_t = Number of reports of an event during treatment for period **t,**

And $D_t = \frac{\text{Number of patients-days of treatment for period } \mathbf{t}}{30}$

IDs for events occurring in the first month of treatment (ID_1), during the second to sixth months of treatment (ID_2) and for events occurring during the overall treatment period (ID_A) were calculated. The difference between the IDs in the first month of treatment and IDs for month's two to six (ID_1 - ID_2) are calculated. The difference between the two IDs (ID_2 - ID_1) is calculated in order to test the null hypothesis that the rate for the event is not increasing or decreasing over time. This figure is important for it may signal the event is associated with the drug based on the considerations of the typical time distribution of ADRs.

The Incidence Densities in the treatment groups (mirtazapine and paroxetine), were also calculated for the adverse events. Separate denominators are shown in the appendices for males and females.

Signals are generated by the report of a typically iatrogenic reaction or by an event having an unusually high ID. Alternatively it may be noticed that the pattern of the number of reports from week to week, or month to month suggests a relationship to exposure or to drug treatment being

terminated. Comparing the time specific or age and sex adjusted relative risks of the drug being monitored, and a group of drugs already studied by PEM, strengthens such a signal.

Sample size

The ability to detect an ADR is dependent upon the expected incidence rate of that ADR for those exposed, the background rate in those unexposed, and the number of patients available. As a rule, a sample size of 10,000 patients should allow for the detection of at least three cases of an ADR if it occurred with an incident rate of between 1 in 1000 and 1 in 2000 patients assuming the event was very rare as a background event.

Validity of study design

This form of investigation produces generalisable findings because study subjects are chosen from a UK-wide population based database. However, there are several important limitations in the investigations described in this thesis, as in all other observational cohort designs.

Information bias (information being missed due to treatment having been started in hospital; patients being treated as temporary residents so that only part of their treatment period is known; migration at any stage of treatment) was reduced by limiting the study to incident cases, and obtaining copies of the hospital discharge letters.

Not all potential confounding factors would have had data on the PEM database e.g. family history, concomitant medications, concurrent illnesses, etc. which are important confounding factors that are not always recorded on the green forms by the GPs.

Medical review of selected events

The data in Appendix 3a were examined to detect events of possible interest such as iatrogenic diseases; possible serious unlabelled adverse drug reactions (i.e. events not already mentioned in the data sheet or Summary of Product Characteristics); or events that are reported more often than documented in the data sheet or events of unknown aetiology (e.g. jaundice reported on the green form). The green forms for these selected events were scrutinised by a medical officer and further letters were sent to the patients' GPs or hospital consultants as appropriate. When GPs were sent letters requesting additional information they were offered £10 reimbursement for secretarial expenses. The green forms for the events coded as 'unspecified' were also scrutinised to identify any serious adverse events.

Medically qualified staff assessed the causal relationship between exposure and selected events using the following categories: possible, unlikely, or not assessable. The assessments took into account the temporal relation; past medical history; concurrent illnesses; concomitant medication use; whether the event was the reason for stopping therapy; and if yes, the resolution of the event (with or without specific treatment); whether the symptoms returned on re-challenge; whether it was pharmacologically plausible; or whether there was an alternative cause specified. If the event occurred after mirtazapine was taken and there were no

alternative reasonable explanations or rechallenge, the event was considered as possibly related to mirtazapine. The event was assessed as unlikely if the clinical event, including a laboratory test abnormality, had a temporal relationship to drug administration which made a causal relationship improbable, or if other drugs or underlying or concurrent diseases provided a more plausible explanation. An event was assessed as 'unassessable' if it was not possible to obtain the additional information necessary for an appropriate evaluation.

Specific supplementary questionnaires were sent to determine the outcomes of pregnancies. Further information was obtained regarding the cause of death for deaths for which the cause was not specified by obtaining death certificates from the Office for National Statistics.

Pregnancies

The use of mirtazapine during pregnancy is not recommended[17]. The patients who were identified as having taken mirtazapine within three months of pregnancy or during pregnancy were followed up. Each GP was sent a detailed questionnaire with questions regarding drug history and dosage during pregnancy and eventual outcome (Figure 2). When GPs were sent a pregnancy questionnaire they were offered £10 reimbursement for secretarial expenses.

Deaths

If no clear cause of death could be established from the green form, the death certificate was requested from the Office for National Statistics. If any cause of death remained uncertain or the death was possibly drug related, the GP was asked to give permission for the DSRU to retrieve the patients' notes from the Health Authority. These notes were used to identify the cause of death and obtain further information regarding patients' medical history.

Ethical considerations

The study was conducted in accordance with the International Ethical Guidelines for Biomedical Research prepared by the Council for International Organisations of Medical Sciences in collaboration with the World Health Organization[33]. The method also complied with the guidelines on the Practice of Ethics Committees in Medical Research involving Human Subjects, as issued by the Royal College of Physicians of London[34].

Figure 2. Pregnancy questionnaire (side one)

Date: _____ Ref number: _____

CONFIDENTIAL PREGNANCY REPORT

Please complete the following form in as much detail as possible.

Patient Details

DOB: _____ LMP date: _____ EDD: _____

Patients smoking status: (*please tick appropriate box*)

Current smoker ☐ Ex-smoker ☐ Non-smoker ☐ Not known ☐

Details of Drug Exposure during Pregnancy (please tick appropriate box)

Date treatment with mirtazapine started ___/___/___

Date treatment with mirtazapine stopped: ___/___/___

Was treatment continuous between these dates? YES NO

Was this drug given at any other time during this pregnancy? YES ☐ NO ☐

If **YES** please specify: Start date: ___/___/___ Stop date: ___/___/___

Was this pregnancy planned? YES ☐ NO ☐ Not Known ☐

If **NO** was the patient taking an OCP? YES ☐ NO ☐

Please give details of any other known drugs taken during this pregnancy:

Drug	Date Started	Date Stopped
.....	___/___/___	___/___/___
.....	___/___/___	___/___/___
.....	___/___/___	___/___/___
.....	___/___/___	___/___/___

Please turn to back:

Figure 2. Pregnancy questionnaire (side two)

Details of Adverse Outcome *(please tick appropriate box)*

Ectopic ☐ Spontaneous abortion ☐

Therapeutic termination ☐

Other (please specify) .....

In the case of spontaneous abortion or therapeutic termination was there any foetal abnormality or medical reason?

YES ☐ NO ☐

If **YES** please give brief details: .....

Live Birth:Details of Delivery *(please tick appropriate box)*

Normal vaginal delivery ☐ Caesarean section ☐

Date of delivery ____/____/____ Weeks gestation.....

Details of Baby *(please tick appropriate box)*

Liveborn ☐ Stillborn ☐ Neonatal death ☐

Number born: ..... Birthweight(s) ..... Sex Male ☐ Female ☐

..... Male ☐ Female ☐

Details of Abnormalities *(please tick appropriate box)*

Were there any abnormalities? YES ☐ NO ☐

If **YES** please give details: .....

.....

If there was an abnormality, would you please give details of any other relevant treatment or exposure to hazardous chemicals:

.....

.....

Please specify any problems with previous pregnancies and/or any family congenital abnormalities, if known:

.....

Thank you for your help and assistance in completing this questionnaire.
Please return in the **"FREEPOST"** envelope provided.

CHAPTER 3: RESULTS OF THE MIRTAZAPINE PRESCRIPTION EVENT MONITORING STUDY

RESULTS OF MIRTAZAPINE PEM STUDY

Study sample

65 095 prescriptions were collected which were used to identify 28 016 patients who had commenced treatment between September 1997 and February 1999. 28 016 green forms were posted to 11 008 doctors and 15 684 (56.0%) were returned. As can be seen in Table 3.1, the response varied according to the number of forms posted to individual doctors. 3518 (32.0%) of the 11 008 general practitioners who were sent a total of 8043 green forms failed to return any of them.

Table 3.1. Green forms returned according to the number originally posted to individual doctors.

Number of Patients per doctor	Number of doctors	Number of patients (forms sent)	Number of forms returned	Percentage of forms returned
1	5807	5807	3704	63.8
2	2262	4524	2754	60.9
3	1097	3291	1907	57.9
4	507	2028	1156	57.0
5	333	1665	916	55.0
6	216	1296	713	55.0
7	165	1155	593	51.3
8	140	1120	561	50.1
9	99	891	498	55.9
10	54	540	314	58.1
11-20	248	3463	1607	46.4
21-30	58	1397	712	51.0
31-40	15	532	112	21.1
41-50	7	307	137	44.6
Total	**11008**	**28016**	**15684**	**56.0**

*NOTE: 3518 of these GPs who had treated 8043 patients did not return any forms.

2130 (13.6%) of the 15 684 returned forms were classified as void (patient no longer registered with doctor, 1269; blank forms, 338; no record of treatment in notes, 306; mirtazapine

prescribed but not taken, 191; patient's doctor moved or retired, 18; duplicate green form for patient, 8). Useful information was thus available for 13 554 patients.

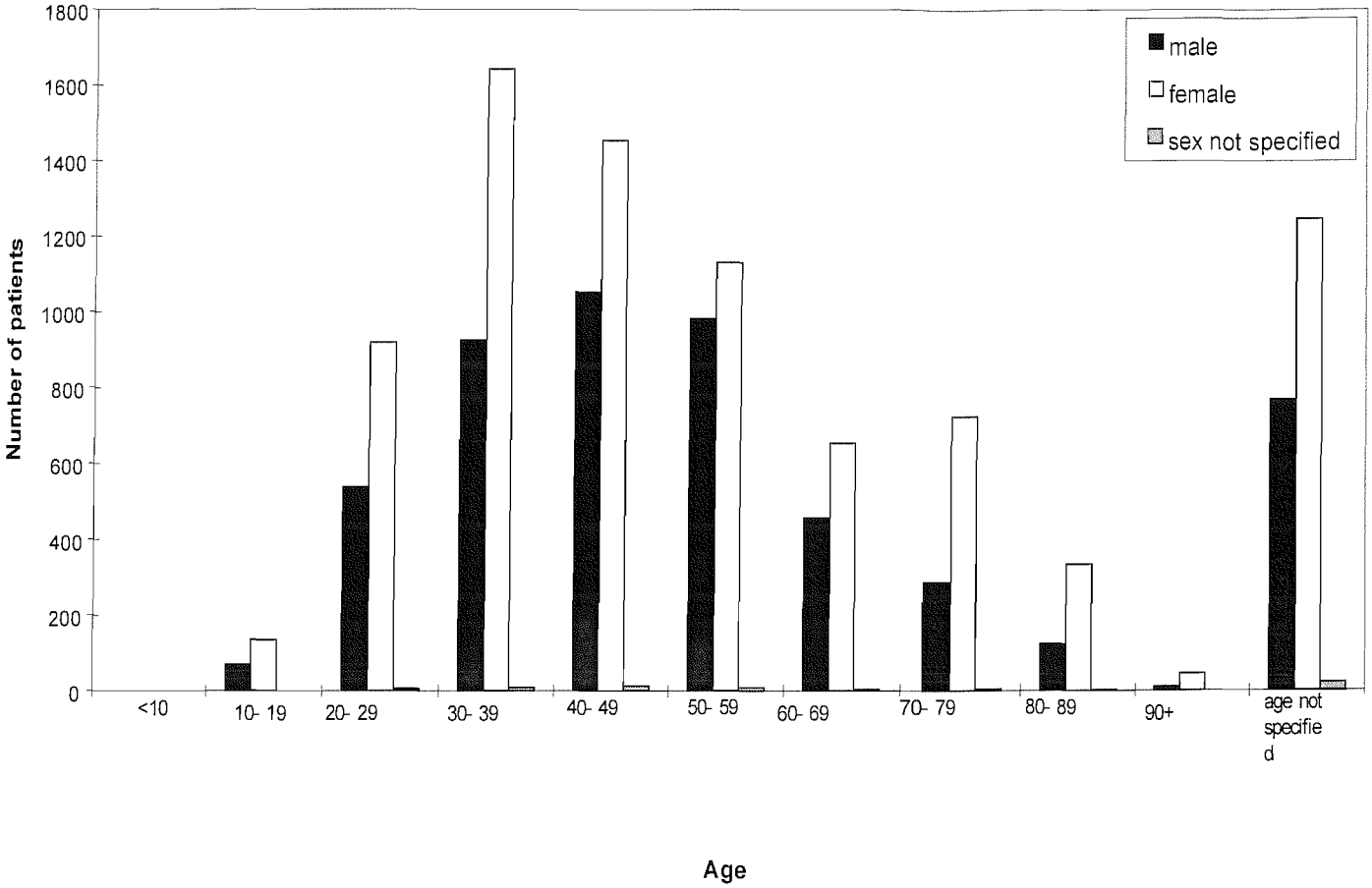
Age and sex

The age distribution and sex of the cohort is shown in Table 3.2 and Figure 3. The age had not been recorded for 2035 patients (15.0%). Of the 13 554 patients, 5210 (38.4%) were males and 8280 (61.1%) were recorded as females. The sex was not recorded in 64 (0.5%). The mean age for males was 46.9 ± 15.5 years (range 14-99 years), and the mean age for females was 47.7 ± 17.7 years (range13-97 years). Overall the mean age of the cohort was 47.4 ± 16.9 years (range 13-99 years).

Table 3.2. Age and sex of patients

Age	Male		Female		Sex not specified		All patients	
	Number	%	Number	%	Number	%	Number	%
10-19	70	1.3	135	1.6	0	-	205	1.5
20-29	537	10.3	919	11.1	6	9.4	1462	10.8
30-39	925	17.8	1642	19.8	8	12.5	2575	19.0
40-49	1052	20.2	1454	17.6	12	18.8	2518	18.6
50-59	982	18.8	1131	13.7	9	14.1	2122	15.7
60-69	457	8.8	653	7.9	3	4.7	1113	8.2
70-79	286	5.5	723	8.7	4	6.3	1013	7.5
80-89	123	2.4	333	4.0	1	1.6	457	3.4
90+	10	0.2	44	0.5	0	-	54	0.4
Age not specified	768	14.7	1246	15.0	21	32.8	2035	15.0
Total	**5210**	100.0	**8280**	100.0	**64**	100.0	**13554**	100.0
Average	46.9 ± 15.5		47.7 ± 17.7				47.4 ± 16.9	

Figure 3. Age distribution and sex of patients for mirtazapine.



Mirtazapine use in children

The SPC mentions that since safety and efficacy of mirtazapine has not been established in children, it is not recommended to treat children with mirtazapine. In this study, there were 71 children less than 18 years. Of these 71 children, 15 were boys and the remaining 56 were girls. The major indication for prescribing mirtazapine in this age group were: depression (total 42 depression; male nine and female 33), followed by indication not specified 26 (male five, female 21). There were two suspected ADRs reported in this group. Both of these suspected ADRs were in two children of 16 years of age, one was dizziness and tremor and the other was unspecified side effect, which resolved on stopping mirtazapine.

Indications

The major indication for patients treated with mirtazapine was depression (57.6%). The indication was not specified for 4167 (30.7%) of the patients. (Table 3.3).

Table 3.3. Indications analysed by sex

Indication	Male		Female		Sex not known		All patients	
	Number	%*	Number	%*	Number	%*	Number	%*
Depression	2955	56.7	4811	58.1	35	54.7	7801	57.6
Anxiety/depression	376	7.2	557	6.7	3	4.7	936	6.9
Anxiety	76	1.5	75	0.9	0	-	151	1.1
Depression manic	23	0.4	47	0.6	0	-	70	0.5
Psychosis	30	0.6	32	0.4	1	1.6	63	0.5
Depression postnatal	0	-	38	0.5	0	-	38	0.3
Schizophrenia	23	0.4	13	0.2	0	-	36	0.3
Insomnia	9	0.2	23	0.3	1	1.6	33	0.2
Personality disorder	11	0.2	8	0.1	0	-	19	0.1
Obsession/compulsive	10	0.2	8	0.1	0	-	18	0.1
Dementia	6	0.1	8	0.1	0	-	14	0.1
Agitation	6	0.1	7	0.1	0	-	13	0.1
Mood swings	9	0.2	3	-	0	-	12	0.1
Post viral syndrome	6	0.1	6	0.1	0	-	12	0.1
Panic attack	4	0.1	7	0.1	0	-	11	0.1
Psychiatric unspecified	4	0.1	7	0.1	0	-	11	0.1
Drug abuse	8	0.2	1	-	0	-	9	0.1
Phobia	7	0.1	2	-	0	-	9	0.1
Anorexia nervosa	0	-	7	0.1	0	-	7	0.1
Alcoholism chronic	4	0.1	1	-	0	-	5	-
Bereavement	3	0.1	2	-	0	-	5	-
Dependence	5	0.1	0	-	0	-	5	-
Hypomania	2	-	3	-	0	-	5	-
Myalgia	2	-	3	-	0	-	5	-
Pain	1	-	4	-	0	-	5	-
Paranoia	3	0.1	2	-	0	-	5	-
Grief reaction	0	-	4	-	0	-	4	-
Libido decreased	1	-	3	-	0	-	4	-
Psychosomatic unspecified	0	-	4	-	0	-	4	-
Agoraphobia	2	-	1	-	0	-	3	-
Premenstrual tension	0	-	3	-	0	-	3	-
Alzheimer's disease	1	-	1	-	0	-	2	-
Domestic	1	-	1	-	0	-	2	-
Emotional disturbance	1	-	1	-	0	-	2	-
Headache	1	-	1	-	0	-	2	-
Hypertension	1	-	1	-	0	-	2	-
Irritable bowel syndrome	1	-	1	-	0	-	2	-
Impotence	2	-	0	-	0	-	2	-
Male reproductive unspecified	2	-	0	-	0	-	2	-

Table 3.3. Indications analysed by sex (continued)

Indication	Male		Female		Sex not known		All patients	
	Number	%*	Number	%*	Number	%*	Number	%*
Marital	0	-	2	-	0	-	2	-
Migraine	0	-	2	-	0	-	2	-
Nausea	1	-	1	-	0	-	2	-
Neurosis	1	-	1	-	0	-	2	-
Pain back	1	-	1	-	0	-	2	-
Parkinson's disease	1	-	1	-	0	-	2	-
Self injury	0	-	2	-	0	-	2	-
Suicidal thoughts	2	-	0	-	0	-	2	-
Thought disorder	2	-	0	-	0	-	2	-
Urticaria	0	-	2	-	0	-	2	-
Akathisia	0	-	1	-	0	-	1	-
Alcoholism acute	1	-	0	-	0	-	1	-
Amnesia	0	-	1	-	0	-	1	-
Arthritis osteo	1	-	0	-	0	-	1	-
Asthenia	0	-	1	-	0	-	1	-
Atrophy brain	1	-	0	-	0	-	1	-
Behaviour abnormal	0	-	1	-	0	-	1	-
Bulimia nervosa	0	-	1	-	0	-	1	-
Cancer phobia	0	-	1	-	0	-	1	-
Central nervous system unspecified	1	-	0	-	0	-	1	-
Crohn's disease	0	-	1	-	0	-	1	-
Dementia presenile	1	-	0	-	0	-	1	-
Eating disorder	0	-	1	-	0	-	1	-
Eczema	1	-	0	-	0	-	1	-
Epilepsy	1	-	0	-	0	-	1	-
Flushing	0	-	1	-	0	-	1	-
Gout	1	-	0	-	0	-	1	-
Hyperactive	1	-	0	-	0	-	1	-
Hypochondriasis	0	-	1	-	0	-	1	-
Illegible	0	-	1	-	0	-	1	-
Irritability	1	-	0	-	0	-	1	-
Lassitude	0	-	1	-	0	-	1	-
Malaise	1	-	0	-	0	-	1	-
Mania	0	-	1	-	0	-	1	-
Mood change	1	-	0	-	0	-	1	-
Myasthenia gravis	1	-	0	-	0	-	1	-
Neuralgia	0	-	1	-	0	-	1	-
Overdose	0	-	1	-	0	-	1	-
Pain abdomen	1	-	0	-	0	-	1	-
Rash	1	-	0	-	0	-	1	-
Restless legs	0	-	1	-	0	-	1	-
Rhinitis allergic	0	-	1	-	0	-	1	-
Somnambulism	1	-	0	-	0	-	1	-
Suicide attempt	0	-	1		0	-	1	-
Suicide threat	1	-	0	-	0	-	1	-
Indication not specified	1589	30.5	2554	30.8	24	37.5	4167	30.7
Total	**5210**	100.0	**8280**	100.0	**64**	100.0	**13554**	100.0

* Percentages less than 0.1% are not shown.

Use of mirtazapine

Duration of treatment

After six months, 4940 (40.0%) of the 12 345 patients for whom it was recorded that treatment was continuing or that the date of stopping medication was given, were still being prescribed mirtazapine (Table 3.4).

It was not possible to record when the patient stopped the drug in 1209 cases (8.9% of total cohort of 13 554). Only 245 patients (1.8%, of the total cohort) were known to have taken the drug intermittently (more than one stop and start date) but it was not known whether 1312 (9.6%, of the total cohort) patients took the drug continuously or not.

Table 3.4. Number still using mirtazapine at the end of each month

Month		Number still taking mirtazapine	Percentage of patients
Baseline	0	12345	100.0
End of month	1	9073	73.5
End of month	2	7677	62.2
End of month	3	6737	54.6
End of month	4	5999	48.6
End of month	5	5438	44.1
End of month	6	4940	40.0

Dose

The PPA provided data on the number of tablets of mirtazapine dispensed for each prescription, but no direct information on dosage.

Effectiveness

9756 (72.0%) of 13 554 reports included an opinion about the effectiveness of mirtazapine (Table 3.5). Mirtazapine was reported by the GP to have been effective in 5423 (55.6%) of these. In 28.0% of the total cohort the effectiveness of mirtazapine was not specified in response to the question on the green form.

Table 3.5. Effectiveness of mirtazapine - total cohort

Effective	Number	Percentage
Yes	5423	55.6
No	4333	44.4
Total	**9756**	**100.0**
(Not specified)	(3798)	(28.0)

Adverse reactions

An event was coded as an adverse drug reaction (ADR) if the general practitioner specified on the green form that the event was attributable to a drug. 807 events in 573 patients were reported by the general practitioners as ADRs to mirtazapine (Table 3.6). Twenty-eight of these 807 events were documented on the green form as having been reported to the Committee on Safety of Medicines (CSM). The most frequently reported adverse reactions to mirtazapine were unspecified side effects in 177 patients and drowsiness/sedation in 116 patients.

Table 3.6. Adverse reactions (ADRs) to mirtazapine

ADR	Total	Number reported to CSM
Unspecified side effects	177	1
Drowsiness	83	-
Dizziness	57	1
Malaise	36	1
Lassitude	35	-
Sedation	33	2
Weight gain	31	2
Nausea	27	-
Headache	21	1
Dreams abnormal	15	-
Agitation	14	2
Intolerance	12	-
Irritability	12	2
Aggression	11	2
Appetite increased	11	-
Tremor	11	-
Confusion	10	-
Insomnia	10	1
Dry mouth	9	-
Anxiety	7	-
Gastro-intestinal unspecified	7	-
Rash	7	-
Oedema	6	1
Vomiting	6	-
Diarrhoea	5	-
Dyspepsia	5	1
Myalgia	5	-
Pruritus	5	1
Withdrawal symptoms	5	1
Liver function test abnormal	4	-
Palpitations	4	-
Panic attack	4	-
Pharyngitis	4	-
Sweating	4	-
Faintness	3	-
Muscle weakness	3	-
Pain abdomen	3	-
Pain joint	3	1
Pain limb	3	-
Paraesthesia	3	-
Restless legs	3	1
Syncope	3	1
Thought disorder	3	-
Unsteadiness	3	-
Visual disturbance	3	-
Behaviour abnormal	2	-
Central nervous system unspecified	2	-
Depression	2	-
Disorientation	2	-
Distension abdomen	2	-
Dyspnoea	2	-
Eczema	2	1
Excessive thirst	2	-
Hair loss	2	1

ADR	Total	Number reported to CSM
Hallucinations	2	1
Impotence	2	-
Lost consciousness	2	-
Mood change	2	-
Sensation abnormal	2	-
Slurred speech	2	-
Spasm muscular	2	-
Vertigo	2	-
Amnesia	1	-
Angina	1	-
Anorexia	1	-
Arthritis	1	-
Ataxia	1	-
Burning sensation	1	-
Candidiasis oral	1	-
Constipation	1	-
Coryza	1	-
Diabetes worse	1	-
Dysarthria	1	-
Dysphasia	1	-
Emotional disturbance	1	-
Epilepsy	1	1
Feeling hot	1	-
Flatulence	1	-
Flushing	1	-
Frequency	1	-
Haemorrhage oral	1	-
Haemorrhage rectal	1	-
Hemianopia	1	-
Hypoaesthesia	1	-
Hypomania	1	-
Hypotension	1	-
Libido decreased	1	-
Mania	1	-
Metabolic unspecified	1	-
Migraine	1	-
Mood swings	1	-
Movement involuntary	1	
Musculoskeletal unspecified	1	-
Obesity	1	-
Oesophageal reflux	1	1
Pain bone	1	1
Paranoia	1	-
Photosensitivity	1	-
Premenstrual tension	1	-
Psychiatric unspecified	1	-
Retention	1	-
Sore mouth	1	-
Swollen ankles	1	-
Tachycardia	1	-
Taste abnormal	1	-
Tinnitus	1	-
Toothache	1	-
Ulcer mouth	1	-
Vision deteriorated	1	-
Total	**807**	**28**

Adverse reactions to other drugs

Events attributed to other medication were examined in order to detect possible interactions between mirtazapine and specific drugs. Eighty-one adverse reactions were reported to other drugs in 66 patients as shown in Table 3.7.

Table 3.7. Adverse reactions (ADRs) to other drugs

Drug	Adverse reaction	Concurrent treatment with mirtazapine	Number of ADR's reported
Amitriptyline	sedation	no	1
	tremor	yes	1
Amlodipine	malaise	yes	1
Antidepressant unspecified	ADR*	no	1
Aspirin	allergy	no	1
Atorvastatin	intolerance	no	1
Beclomethasone	candidiasis oral	no	1
Bendrofluazide	angioneurotic oedema	yes	1
Ciprofloxacin	rash	not known	1
Citalopram	ADR*	yes	1
	haemorrhage cerebral	no	1
Clomipramine	ADR*	yes	1
Diazepam	withdrawal symptoms	yes	1
Diclofenac	nausea	yes	1
	oesophageal reflux	yes	1
Dihydrocodeine	ADR*	yes	1
Diltiazem	hypotension	no	1
	nausea	no	1
Dothiepin	ADR*	no	2
Erythromycin	pain abdomen	no	1
Flunitrazepam	withdrawal symptoms	yes	1
Fluoxetine	nausea	yes	1
	rash	no	1
	withdrawal symptoms	yes	1
Flupenthixol	lassitude	yes	1
Frusemide	constipation	yes	1
	nausea	yes	1
	sedation	yes	1
Haloperidol	tremor	no	1
Hormone replacement therapy	ADR*	no	1
	anxiety	yes	1
Ibuprofen	dyspepsia	yes	1
Lansoprazole	headache	no	1

	nausea	no	1
	oedema	no	1
Laxative unspecified	diarrhoea	yes	1
Lithium	ADR*	yes	2
	renal failure chronic	yes	1
	tremor	yes	1
Lofepramine	agitation	yes	1
Metformin	diarrhoea	yes	1
Metronidazole	vomiting	not known	1
Nifedipine	hypotension	yes	1
	oedema	yes	1
Norethisterone	premenstrual tension	yes	1
NSAID unspecified	anaemia iron deficiency	no	1
	vision deteriorated	no	1
Olanzapine	ADR*	no	1
	weight gain	no	1
Paroxetine	ADR*	no	1
	headache	no	1
	nausea	no	1
	rash	no	1
Penicillin	allergy	yes	1
Pipothiazine	saliva increased	yes	1
Prednisolone	weight gain	no	1
Procyclidine	frequency	yes	1
	micturition abnormal	yes	1
Reboxetine	intolerance	no	1
Risperidone	convulsion	no	1
Steroid unspecified	ADR*	yes	1
Sulphasalazine	globulin abnormal	yes	1
	laboratory test abnormal	yes	1
Sulpiride	pain joint	yes	1
Thioridazine	drowsiness	yes	1
	lassitude	no	1
Trazodone	dizziness	no	1
	headache	no	1
	hypertension	no	1
Trifluoperazine	dyskinesia	yes	1
Trimethoprim	intolerance	yes	1
Venlafaxine	hyperactive	no	1
	insomnia	no	1
	nausea	no	1
	tremor	no	1
	withdrawal symptoms	yes	2
Dianette	vomiting	yes	1
Madopar	hallucinations	yes	1
Total			**81**

* Adverse drug reaction, otherwise unspecified e.g. "side effects from atenolol"

The Summary of Product Characteristics provides a comprehensive list of potential drug interactions (Appendix 1). There were no drug interactions reported in this study.

Reasons for stopping mirtazapine

GPs recorded 8634 reasons for stopping mirtazapine, for 7122 patients (Table 3.8). The most frequently reported event given as the reason for stopping mirtazapine was not effective (2432 cases, 17.9% of the total cohort). The most frequently reported clinical adverse events given as the reason for stopping mirtazapine were drowsiness/sedation 800 cases (5.9 % of the total cohort), followed by weight gain (362 cases,2.6% of the cohort).

Table 3.8. Reasons for stopping mirtazapine

Reason	Number
Not effective	2432
Condition improved	1117
Patient request	483
Drowsiness	424
Sedation	376
Weight gain	362
Non compliance	266
Intolerance	228
Malaise	178
Unspecified side effects	175
Dizziness	165
Lassitude	160
Depression	154
Anxiety	107
Hospital referral psychiatric	106
Nausea	98
Headache	94
Hospital admission non-surgical	93
Insomnia	84
Agitation	73
Appetite increased	71
Dreams abnormal	56
Aggression	55
Irritability	47
Hospital referral unspecified	43
Diarrhoea	42

Confusion	39
Oedema	39
Rash	34
Pregnancy	33
Tremor	28
Dry mouth	25
Vomiting	24
Myalgia	23
Indication for mirtazapine changed	22
Pruritus	22
Pharyngitis	20
Swollen ankles	20
Panic attack	19
Restless legs	19
Distension abdomen	17
Dyspepsia	17
Mood swings	17
Pain abdomen	17
Pain joint	17
Constipation	16
Overdose	15
Psychiatric unspecified	15
Pain limb	14
Effective	13
Impotence	13
Libido decreased	13
Sweating	13
Liver function test abnormal	12
Mood change	12
Palpitations	12
Paraesthesia	11
Spasm muscular	11
Unsteadiness	11
Amnesia	10
Drug information	10
Syncope	10
Visual disturbance	10
Alcoholism	9
Gastro-intestinal unspecified	9
Hallucinations	9
Hypotension	9
Mania	9
Anorexia	8
Domestic	8
Sensation abnormal	8
Vertigo	8
Dyspnoea	7
Hospital referral paramedical	7
Mental state worse	7
Overdose unknown drug	7
Pain chest	7
Retention	7
Convulsion	6
Depersonalization	6
Faintness	6
Fluid retention	6

Frequency	6
Heartburn	6
Mental state improved	6
Muscle weakness	6
Psychosis	6
Suicidal thoughts	6
Ulcer mouth	6
Behaviour abnormal	5
Cramp	5
Disorientation	5
Electroconvulsive therapy	5
Non formulary	5
Paranoia	5
Slurred speech	5
Tachycardia	5
Taste abnormal	5
Thought disorder	5
Alcoholism chronic	4
Drug abuse	4
Eating disorder	4
Flushing	4
Hypomania	4
Movement involuntary	4
Oedema face	4
Overdose other drug	4
Sore mouth	4
Allergy	3
Angina	3
Dementia	3
Dependence	3
Eczema	3
Emotional disturbance	3
Excessive thirst	3
Fall	3
Hyperactive	3
Immobility	3
Leucopenia	3
Lost consciousness	3
Micturition abnormal	3
Migraine	3
Personality disorder	3
Sciatica	3
Akathisia	2
Anaemia	2
Asthma	2
Ataxia	2
Bone marrow abnormal	2
Central nervous unspecified	2
Cerebrovascular accident	2
Dysphasia	2
Event not coded	2
Gynaelogical unspecified	2
Haemorrhage rectal	2
Hair loss	2
Hyperventilation	2

Hypoaesthesia	2
Hypothyroidism	2
Illegible	2
Incontinence	2
Infection chest	2
Marital	2
Musculoskeletal unspecified	2
Neutropenia	2
Pain unspecified	2
Parkinson's disease	2
Polysymptomatic	2
Pyrexia	2
Somnambulism	2
Stomatitis	2
Suicide threat	2
Swelling joint	2
Tinnitus	2
Urinary unspecified	2
Urticaria	2
Vision deteriorated	2
Abscess	1
Acne	1
Adenoma endocrine	1
Amputation	1
Anaemia iron deficiency	1
Aneurysm aortic	1
Angioneurotic oedema	1
Arthritis	1
Arthritis rheumatoid	1
Breast disorder	1
Bulimia	1
Burning sensation	1
Candidiasis	1
Candidiasis oral	1
Carcinoma lung fatal	1
Carcinoma ovary fatal	1
Cardiomyopathy	1
Euphoria	1
Carpal tunnel syndrome	1
Congestive cardiac failure	1
Coryza	1
Cough	1
Depression manic	1
Diabetes mellitus	1
Diabetes worse	1
Dry eye	1
Dry skin	1
Dysarthria	1
Dystonia	1
Dysuria	1
Ejaculation premature	1
Epilepsy	1
Feeling hot	1
Flatulence	1
Flu like symptoms	1

Fracture	1
Galactorrhoea	1
Gastritis	1
Gingivitis	1
Glands swollen	1
Gynaecomastia	1
Haemorrhage oral	1
Haemorrhage subarachnoid	1
Haematological tests	1
Haematuria	1
Haemoptysis	1
Hemianopia	1
Hepatic unspecified	1
Hepatitis	1
Irritable bowel syndrome	1
Infection viral	1
Jaundice	1
Jaundice obstructive	1
Left ventricular failure	1
Male reproductive unspecified	1
Metabolic unspecified	1
Metrorrhagia	1
Myocardial infraction	1
Myelodysplasia	1
Neuralgia	1
Neuropathy peripheral	1
Nystagmus	1
Obsession/compulsive	1
Pain back	1
Pain bone	1
Pain hand	1
Pancytopenia	1
Photosensitivity	1
Premenstrual tension	1
Pneumonia	1
Prison admission	1
Prostatism	1
Purpura	1
Renal failure chronic	1
Renal transplant	1
Respiratory unspecified	1
Schizophrenia	1
Scleritis	1
Self injury	1
Shivering	1
Stiffness	1
Tics	1
Toothache	1
Tumour	1
Vascular surgery	1
Weight loss	1
Wheezing	1
Total	**8634**

Treatment after stopping mirtazapine

Forty-one drugs were substituted for the monitored drug in 451 of the patients in whom mirtazapine was withdrawn (Appendix 2). The medication most frequently substituted was fluoxetine in 111 (24.6%) patients, then paroxetine in 75 patients (16.6%). The total number of substituted drugs was 468, indicating that 17 patients received two drugs after stopping treatment with mirtazapine.

The Events

A list of all events recorded during the PEM study is shown in Appendix 3a. The DSRU dictionary groups together related events (lower level terms) under a broader term (higher level term), e.g. the lower level terms 'glands swollen', 'lymphadenitis' and 'lymphadenopathy' are grouped under the higher level term 'lymphadenopathy'. In Appendices 3a, 3b, 3c, column A contains higher and lower level coding terms, the lower level terms being indented.

The total for all the events reported at any time after the first prescription is listed in column B, irrespective of whether or not the patient was still taking the drug. This total in column B includes events which occurred within six months of the first prescription for mirtazapine, more than six months after the first prescription and those events for which the date of occurrence has not been reported. The events in each of the first six months are listed separately (columns C to H) and the total number of events during the first six months is shown in column I. If the date of the event is not known or it is only an approximate date then the event is included in the total number of events but not in columns C to I. Although these

events are not included in the statistical analyses they are examined during the follow-up procedure. The number of events in which the date of occurrence is not known is given in column J.

In Appendix 3a the total number of patient-months of observation is given in column B. The monthly denominators represent the number of patient-months of observation in each month. The figures diminish slightly throughout the period due to date errors or patients lost to surveillance. In Appendix 3a, separate denominators are shown for males and females.

Appendix 3b gives a list of events reported for all patients during treatment with mirtazapine. Each term reported in Appendix 3a is also given in this appendix even if there were no occurrences of this event during treatment with mirtazapine. Events for those patients for whom the date of stopping therapy with the drug under surveillance is not known are not included in Appendices 3b unless reported by the GP on the green form as occurring during treatment and recorded as during treatment by the coding clerk. Also if the date of the event is not known or it is coded as an approximate date then the event is not included in Appendix 3b unless it is clear that the event occurred during treatment with the drug. For this latter case the event will be included in the total for that event but will not be included in the numbers for the first six months.

The total number of patient-months of treatment is given in column B. The monthly denominators (columns C-H) are the number of patient-months of treatment for each month. These are calculated from the total number of days of treatment in each month for those patients who continued to take the drug throughout the month, who will each contribute 30

treatment days and for those patients who stopped treatment during that month who will each contribute the number of days of treatment they received during the month. The total number of days of treatment is divided by 30 to determine the number of patient months of treatment.

Incidence densities

Table 3.9 gives the denominators in patient-months for each time period. The time period, D_1, relates to the first month of treatment for individual patients and not merely to the first month of the entire study. Patients who stop treatment before the end of their first month of therapy will contribute to the denominator, D_1, only the number of days for which they were treated. Similarly, the sum of the number of months of treatment for individual patients was used to calculate the denominators D_2, D_3 and D_A.

Table 3.9.

Denominators (patient-months of treatment) used to calculate incidence densities for mirtazapine

	Denominators (patient-months of treatment)			
	D_1	D_2	D_3	D_A
Male	4376	13473	6835	24684
Female	6822	19149	9130	35101
Sex not specified	49	129	60	238
Total	**11247**	**32751**	**16024**	**60022**

D_1 = Total number of patient-months of exposure during the first month of treatment

D_2 = Total number of patient-months of exposure during treatment months 2-6 inclusive

D_3 = Total number of patient-months of exposure during treatment after month 6

D_A = Total number of patient-months exposure during the whole treatment period

Thus, $D_A = D_1 + D_2 + D_3$

Table 3.10 gives the number of events reported during treatment and the ID for the first month of treatment, the second to sixth months inclusive and the overall time period. Only the first report of an event in an individual patient is used in the calculation. The events given in this table are the higher level terms.

Column A shows the rank of each event. Column B lists the higher term event. Columns C to K provide the following:-

N_1 = Total number of reports of each event during the first month of treatment

N_2 = Total number of reports of each event during treatment in months 2-6

ID_1 = Incidence density for each event during the first month of treatment

ID_2 = Incidence density for each event during treatment months 2-6

ID_1-ID_2 = Arithmetic difference between ID_1 and ID_2

99% CI = 99% confidence intervals for ID_1-ID_2

N_A = Total number of reports of each event during the total treatment period

ID_A = Incidence density for each event for the total treatment period.

The ranking order given in column A is that of ID_1. Thus, the values for ID_2 and ID_A are not ranked. The difference between ID_1 and ID_2 (column G) and the 99% confidence intervals for this difference (columns H and I) are given to examine the null hypothesis that the rate for the event is not increasing or decreasing between the two time periods.

Table 3.10. Incidence densities (ID) ranked for mirtazapine in order of ID_1 per 1000 patient-months

A	B EVENT	C N_1	D N_2	E ID_1	F ID_2	G ID_1-ID_2	H 99% min	I CI* max	J N_A	K ID_A
1	Drowsiness, sedation	654	278	58.1	8.5	49.7	43.6	55.7	985	16.4
2	Dose increased	408	421	36.3	12.9	23.4	18.5	28.3	953	15.9
3	Malaise, lassitude	313	155	27.8	4.7	23.1	18.9	27.3	509	8.5
4	Condition improved	256	774	22.8	23.6	-0.9	-5.1	3.4	1278	21.3
5	Patient request	199	220	17.7	6.7	11.0	7.5	14.4	488	8.1
6	Dizziness	175	58	15.6	1.8	13.8	10.7	16.9	241	4.0
7	Weight gain	175	281	15.6	8.6	7.0	3.7	10.3	523	8.7
8	Intolerance	165	64	14.7	2.0	12.7	9.7	15.7	238	4.0
9	Non compliance	152	120	13.5	3.7	9.9	6.9	12.8	302	5.0
10	Depression	145	257	12.9	7.8	5.0	2.0	8.1	493	8.2
11	Nausea, vomiting	134	64	11.9	2.0	10.0	7.2	12.7	215	3.6
12	Anxiety	131	100	11.6	3.1	8.6	5.9	11.3	280	4.7
13	Headache, migraine	119	79	10.6	2.4	8.2	5.6	10.8	227	3.8
14	Respiratory tract infection	113	240	10.0	7.3	2.7	0.0	5.4	440	7.3
15	Unspecified side effects	110	53	9.8	1.6	8.2	5.7	10.6	176	2.9
16	Insomnia	80	84	7.1	2.6	4.5	2.4	6.7	194	3.2
17	Non-surgical admissions	80	136	7.1	4.2	3.0	0.7	5.2	267	4.4
18	Appetite increased	77	45	6.8	1.4	5.5	3.4	7.6	125	2.1
19	Oedema	75	93	6.7	2.8	3.8	1.7	6.0	196	3.3
20	Hospital referrals no admission	73	163	6.5	5.0	1.5	-0.7	3.7	311	5.2
21	Dose reduced	68	151	6.0	4.6	1.4	-0.7	3.6	288	4.8
22	Agitation	60	51	5.3	1.6	3.8	1.9	5.6	126	2.1
23	Dreams abnormal	56	32	5.0	1.0	4.0	2.2	5.8	91	1.5
24	Aggression	51	31	4.5	0.9	3.6	1.9	5.3	88	1.5
25	Diarrhoea	43	75	3.8	2.3	1.5	-0.1	3.2	134	2.2
26	Confusion	41	26	3.6	0.8	2.9	1.3	4.4	75	1.2
27	Suicide attempt, drug overdose	38	80	3.4	2.4	0.9	-0.6	2.5	142	2.4
28	Pain abdomen	36	65	3.2	2.0	1.2	-0.3	2.7	116	1.9
29	Irritability	33	26	2.9	0.8	2.1	0.8	3.5	61	1.0
30	Tremor	33	22	2.9	0.7	2.3	0.9	3.6	63	1.0
31	Dyspepsia	32	60	2.8	1.8	1.0	-0.4	2.4	114	1.9
32	Constipation	31	47	2.8	1.4	1.3	-0.1	2.7	85	1.4
33	Dry mouth	31	11	2.8	0.3	2.4	1.1	3.7	45	0.7
34	Pain joint	30	78	2.7	2.4	0.3	-1.2	1.7	139	2.3
35	Rash	29	39	2.6	1.2	1.4	0.1	2.7	84	1.3
36	Impotence, ejaculation failure	10	13	2.3	1.0	1.3	-0.7	3.3	29	1.2
37	Sensation abnormal	22	35	2.0	1.1	0.9	-0.3	2.1	66	1.1
38	Hypertension	21	27	1.9	0.8	1.0	-0.1	2.2	56	0.9
39	Myalgia	21	30	1.9	0.9	1.0	-0.2	2.1	62	1.0
40	Unsteadiness	21	6	1.9	0.2	1.7	0.6	2.8	28	0.5
41	Mood change	20	19	1.8	0.6	1.2	0.1	2.3	42	0.7
42	Panic attack	20	42	1.8	1.3	0.5	-0.7	1.6	73	1.2
43	Pregnancy	12	26	1.8	1.4	0.4	-1.1	1.9	57	1.6
44	Fall	19	34	1.7	1.0	0.7	-0.4	1.8	66	1.1
45	Pain back	19	75	1.7	2.3	-0.6	-1.8	0.6	113	1.9
46	Pain chest, tight chest	19	45	1.7	1.4	0.3	-0.8	1.4	76	1.3
47	Pruritus	19	28	1.7	0.9	0.8	-0.2	1.9	60	1.0

Table 3.10. Incidence densities (ID) ranked for mirtazapine in order of ID_1 per 1000 patient-months (continued)

A	B EVENT	C N_1	D N_2	E ID_1	F ID_2	G ID_1-ID_2	H 99% min	I CI* max	J N_A	K ID_A
48	Urinary tract infection	19	46	1.7	1.4	0.3	-0.8	1.4	80	1.3
49	Haematological tests	18	42	1.6	1.3	0.3	-0.8	1.4	74	1.2
50	Alcoholism	17	28	1.5	0.9	0.7	-0.4	1.7	55	0.9
51	Malignancies	17	20	1.5	0.6	0.9	-0.1	1.9	46	0.8
52	Sweating	17	15	1.5	0.5	1.1	0.1	2.0	40	0.7
53	Asthma, wheezing	16	36	1.4	1.1	0.3	-0.7	1.4	65	1.1
54	Cough	15	21	1.3	0.6	0.7	-0.3	1.7	49	0.8
55	Hallucination	15	7	1.3	0.2	1.1	0.2	2.0	30	0.5
56	Micturition disorder	15	37	1.3	1.1	0.2	-0.8	1.2	65	1.1
57	Restless legs	15	14	1.3	0.4	0.9	0.0	1.8	29	0.5
58	Syncope	15	16	1.3	0.5	0.8	-0.1	1.8	44	0.7
59	Vertigo	15	8	1.3	0.2	1.1	0.2	2.0	26	0.4
60	Visual defect	15	14	1.3	0.4	0.9	0.0	1.8	35	0.6
61	Palpitation	14	10	1.2	0.3	0.9	0.0	1.8	32	0.5
62	Injury	13	37	1.2	1.1	0.0	-0.9	1.0	66	1.1
63	Pain limb	13	24	1.2	0.7	0.4	-0.5	1.3	42	0.7
64	Dyspnoea	12	31	1.1	0.9	0.1	-0.8	1.0	53	0.9
65	Infection skin, unspecified	12	25	1.1	0.8	0.3	-0.6	1.2	54	0.9
66	Psychiatric unspecified	12	33	1.1	1.0	0.1	-0.9	1.0	60	1.0
67	Menstrual disorder	7	19	1.0	1.0	0.0	-1.1	1.2	37	1.1
68	Vaginitis, vulvitis	7	27	1.0	1.4	-0.4	-1.6	0.8	39	1.1
69	Cardiovascular tests	11	18	1.0	0.5	0.4	-0.4	1.3	40	0.7
70	Distension abdominal	11	24	1.0	0.7	0.2	-0.6	1.1	39	0.6
71	Faintness	11	1	1.0	0.0	0.9	0.2	1.7	12	0.2

Drowsiness/sedation was the adverse event with the highest incidence density in month one (58.1 per 1000 patient-months of exposure). The difference between the rate of events in month one and months 2-6 was examined. Where the 99% confidence limits around the point estimate of the difference did not include the null value, this suggested that the rate of events in month one was significantly greater than the rate of events in months 2-6. This result can be considered to be a signal of a possible adverse event associated with starting the drug.

The following clinical adverse events occurred significantly more commonly in month 1 compared to months 2-6, when the 99% confidence limits of the differences were calculated: drowsiness/sedation, malaise/lassitude, dizziness, weight gain, intolerance, depression,

nausea/vomiting, anxiety, headache/migraine, respiratory tract infection, unspecified side effects, insomnia, increased appetite, oedema, agitation, dreams abnormal, aggression, confusion, irritability, tremor, and dry mouth. These results can be considered to be a signal of a possible adverse event associated with starting the drug. However, anxiety and depression is more likely to be associated with the indication for treatment with mirtazapine than with adverse events to the drug itself.

Events after stopping mirtazapine

There were 833 events recorded in the first 30 days after stopping mirtazapine. Table 3.11 displays the 25 most frequent events reported within this period. Only first occurrences of events for each particular patient are included in Table 3.11. Events that have already occurred during treatment were therefore not included in the analysis.

Table 3. 11. Ranked rates for events during first 30 days after stopping treatment with mirtazapine

Total number of patient-months for first 30 days after stopping the drug		8138
EVENT	**Number in first month after stopping**	**Rate per 1000 patient months**
Depression	50	6.1
Anxiety	27	3.3
Condition improved	24	2.9
Hospital admission, non-surgical	19	2.3
Diarrhoea	16	2.0
Insomnia	14	1.7
Nausea	14	1.7

Table 3.11 (continued). Ranked rates for events during first 30 days after stopping treatment with mirtazapine

EVENT	Number in first month after stopping	Rate per 1000 patient months
Pain abdomen	14	1.7
Headache	13	1.6
Hospital referral unspecified	13	1.6
Pain back	13	1.6
Panic attack	12	1.5
Vomiting	12	1.5
Infection chest	11	1.4
Pain joint	11	1.4
Upper respiratory tract infection	11	1.4
Dizziness	10	1.2
Lassitude	10	1.2
Agitation	9	1.1
Pain neck	9	1.1
Pharyngitis	9	1.1
Constipation	8	1.0
Cardiovascular tests	8	1.0
Pain chest	8	1.0
Weight gain	8	1.0

Selected Events

The data in Appendix 3a were examined to detect uncommon events of medical interest and serious events. Serious events were defined as those that were fatal, life threatening, disabling, incapacitating or which resulted in prolonged hospitalisation. The green forms for the events were reviewed. Those events thought to require further investigations were followed up with the reporting GP. Follow up was deemed unnecessary for cases where:

1. Events occurred many weeks/months after the treatment and therefore were considered unlikely to be associated with the use of mirtazapine, or
2. An alternative cause was reported, or
3. The reporting doctor had already provided all the information available.

The events of specific interest which were specifically followed up by examination of the green forms and/or writing to the GP are listed below.

SKIN

There were 84 reports of rash during treatment with mirtazapine, of which 29 were reported in the first month. In 34 cases it was the reason for stopping treatment, 11 of which were within the first month of use.

PSYCHIATRIC

Aggression

There were 88 reports of aggression during treatment with mirtazapine, of which 51 (62.5%) were reported in the first month. All of the reports of aggression were reviewed: in 73 cases it was considered that the event was possibly due to mirtazapine, in 13 cases it was unlikely to be due to mirtazapine, while in the remaining 11 cases it was difficult to assess the causality due to limited information. Overall, in 55 cases it was the reason for stopping treatment, 32 of which were within the first month of use. Eleven cases were coded as suspected ADRs, of which only two cases were reported to the CSM.

Agitation

There were 126 reports of agitation during treatment with mirtazapine, of which 60 were reported in the first month. All of the 126 reports of agitation were reviewed: in 70 cases it was considered that the event was possibly due to mirtazapine, in 40 cases it was considered

unlikely to be due to mirtazapine, while in the remaining 16 cases it was difficult to assess the causality due to limited information. Overall, in 73 cases it was the reason for stopping treatment, 38 of which were within the first month of use. Fourteen cases were coded as suspected ADRs, of which only two were reported to the CSM.

Abnormal behaviour

There were 16 reports of abnormal behaviour during treatment with mirtazapine, of which five were reported in the first month. In five cases it was the reason for stopping treatment, one of which was within the first month of use. Two of these five cases were coded as suspected ADRs. In the first case, the patient was prescribed mirtazapine for depression, previously treated with paroxetine. A month after starting the medication the patient complained of disturbed behaviour and mirtazapine was stopped. Once mirtazapine was stopped the event resolved completely. In the second case, the patient was prescribed mirtazapine for depression. Two weeks after starting the medication, the patient was reported to have abnormal bizzare behaviour, and the drug was withdrawn. On stopping the medication the event gradually resolved.

Dreams abnormal

There were 91 reports of abnormal dreams during treatment with mirtazapine, of which 56 were reported in the first month. All of the 91 reports were reviewed: 31 cases were considered to be possibly due to mirtazapine, 42 cases were considered unlikely to be due to mirtazapine and in the remaining 18 cases it was difficult to assess the causality due to limited

information. In 56 cases it was the reason for stopping treatment, 36 of which were in the first month of use. Fifteen cases were coded as suspected ADRs.

Hallucinations

There were 30 reports of hallucinations during treatment with mirtazapine, of which 15 were reported in the first month of use. All of these 30 cases were reviewed: 13 were considered to be possibly due to mirtazapine, while in the remaining 17 cases it was unlikely to be due to mirtazapine. In nine cases it was the reason for stopping the drug, and two cases were reported as possible suspected ADRs, of which one was reported to the CSM.

In the first case, the patient was prescribed 30mg of mirtazapine. Two days after starting the medication the patient complained of hallucinations and the drug was stopped. The event resolved on stopping mirtazapine. In the second case, the patient was prescribed 15mg of mirtazapine for depression. A week after starting the medication the patient complained of sleep disturbance and hallucinations, and the medication was stopped. The event resolved on stopping the mirtazapine. The GP has also sent a yellow card to the CSM, describing the event as possibly related to mirtazapine.

Libido decreased

There were 26 reports of libido decreased during treatment with mirtazapine; eight were reported in the first month of use. In 13 cases it was the reason for stopping treatment, two of which were in the first month of use. Only one of these 13 cases was coded as suspected ADRs. In this case the patient was prescribed mirtazapine for depression. Three weeks after

starting the medication the patient complained of decreased libido and the drug was withdrawn. The event gradually resolved on stopping mirtazapine.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

Dizziness

There were 241 reports of dizziness during treatment with mirtazapine, of which 175 were reported in the first month of use. Of these 175 reports, 122 cases were considered to be possibly due to mirtazapine, 45 cases were considered unlikely to be due to mirtazapine, while in the remaining eight cases it was difficult to assess the causality due to limited information. In nine cases it was the reason for stopping mirtazapine, and 57 cases were reported as possible suspected ADRs, only one being reported to the CSM.

Syncope

There were 44 reports of syncope during treatment with mirtazapine, of which 15 were reported during the first month. All of these 15 reports were reviewed: eight were considered to be possibly due to mirtazapine, while the rest were unlikely to be due to mirtazapine. There were 10 cases in which it was the reason for stopping the drug and three cases were reported as possible suspected ADRs.

Tremor

There were 63 reports of tremor during treatment with mirtazapine, of which 33 were reported in the first month of use. All of these 33 reports were reviewed: in 14 cases it was considered to be possibly due to mirtazapine, in 11 cases it was unlikely to be due to mirtazapine, while in

the remaining eight cases it was difficult to assess due to limited information. In 28 cases it was the reason for stopping the drug and 11 cases were reported as possible suspected ADRs.

EYE

Visual disturbance

There were 111 reports of visual disturbance during treatment with mirtazapine, of which 32 were reported in the first month of treatment. All of these 32 cases were reviewed: in nine cases it was the reason for stopping the drug, and three cases were reported as possible ADRs. In all of these three cases the event resolved on stopping mirtazapine, and the event was therefore considered possibly due to mirtazapine.

CARDIOVASCULAR

Palpitations

There were 32 reports of palpitations during treatment with mirtazapine, of which 14 were reported in the first month of use. All of these 32 cases were reviewed: in 10 cases it was considered to be possibly due to mirtazapine, while in the remaining 22 cases it was considered unlikely to be due to mirtazapine. There were 12 cases of stopping the drug and four cases were reported as possible ADRs.

Atrial Fibrillation

There were six reports of atrial fibrillation during treatment with mirtazapine, two of which were in the first month. All of these six reports were reviewed, none of which were considered to be due to mirtazapine.

Hypertension

There were 56 reports of hypertension during treatment with mirtazapine, of which 21 were in the first month of use. All of these 21 reports were reviewed, none of which were considered to be due to mirtazapine use.

Hypotension

There were 26 reports of hypotension during treatment with mirtazapine, of which nine were in the first month of use. In nine cases it was the reason for stopping the treatment, four of which were in the first month of use. Only one of these nine cases was coded as a suspected ADR. In this case the patient was prescribed mirtazapine for depression. A day after starting the medication the patient complained of hypotension and the drug was withdrawn. The event resolved completely once the drug was stopped. The GP considered the event to be due to mirtazapine.

All of the 26 reports of hypotension were reviewed: nine cases were considered to be possibly due to mirtazapine, 12 cases were unlikely to be due to mirtazapine while in the remaining five cases it was difficult to assess the causality due to limited information.

Oedema

There were 116 reports of oedema during treatment with mirtazapine, of which 40 were in the first month of use. All of the 40 reports of oedema were reviewed: 30 cases were considered to

be possibly due to mirtazapine, four cases were unlikely to be due to mirtazapine, while in the remaining six cases it was difficult to assess the causality due to limited information. Overall in 39 cases it was the reason for stopping the treatment, 19 of which were in the first month of use. Only seven of these 39 cases were coded as suspected ADRs.

Fluid retention

There were 17 reports of fluid retention during treatment with mirtazapine, of which 10 were in the first month of use. In six cases it was the reason for stopping the treatment, five of which were in the first month of use. All of these 17 cases were reviewed, of which five cases were considered possibly related to mirtazapine and in the remaining 12 cases it was considered unlikely to be due to mirtazapine.

Facial oedema

There were 12 reports of facial oedema during treatment with mirtazapine, of which six were in the first month of use. In four cases it was the reason for stopping the treatment. All of these 12 reports were reviewed: five cases were considered to be possibly due to mirtazapine, four cases were unlikely to be due to mirtazapine, while in the remaining three cases it was unassessable, due to limited information.

Swollen ankles

There were 42 reports of swollen ankles during treatment with mirtazapine, of which 16 were in the first month of use. All of these 42 cases were reviewed: in 20 cases it was considered to be possibly due to mirtazapine. The remaining 22 cases were unlikely to be due to mirtazapine. In 16 cases it was the reason for stopping the drug.

ALIMENTARY

Hepatic Failure

There were two reports of hepatic failure during treatment with mirtazapine, of which one was in the first month of use. Both the cases were reviewed and neither was considered to be due to mirtazapine. In the first case the patient was prescribed 30 mg of mirtazapine. Five months after starting the medication the patient was reported to have liver failure. The GP wrote that the patient had pre-existing primary biliary cirrhosis, and the patient was on multiple medications with azothiaprine, prednisolone and ranitidine. In the second case, the patient was prescribed mirtazapine for depression. Six months after starting the medication, the patient was reported to have hepatic failure. The patient had a previous history of Hepatitis B.

Jaundice

There were two reports of jaundice reported during treatment with mirtazapine. In the first case, the patient had two brief episodes of jaundice. Blood tests done during the first episode were normal. The second episode of jaundice was not witnessed by a doctor, and it settled spontaneously. Both episodes of jaundice resolved before stopping mirtazapine. There were no further episodes after stopping mirtazapine. It was difficult to assess the presumed causality, as pharmacologically it may be plausible for jaundice to occur with mirtazapine. In the second case, the jaundice occurred six months after starting mirtazapine. On further follow up it was revealed that the jaundice was probably due to alcohol abuse.

Abnormal liver function test (LFT)

There were 40 reports of abnormal LFTs during treatment with mirtazapine, of which 10 were in the first month of use. Overall in12 cases it was the reason for stopping the drug, of which four cases were reported as suspected ADRs. All of these 40 cases were reviewed: 12 cases were considered to be due to mirtazapine, two cases were unassessable due to limited information, while the remaining 26 cases had alternative explanations.

Pancreatitis

There were three reports of pancreatitis during treatment with mirtazapine. All three cases were reviewed and none were considered to be due to mirtazapine. In two of the three cases, the patient had history of increased alcohol intake, and in the third case the patient developed acute cholecystitis, with a pre-existing history of gallstones.

MALE REPRODUCTIVE AND GYNAECOMASTIA

Impotence

There were 28 reports of impotence during treatment with mirtazapine, of which nine were in the first month of use. All of these nine reports were reviewed: two cases were considered possibly due to mirtazapine, which were also reported as suspected ADRs. The remaining seven cases were considered unlikely to be due to mirtazapine.

BREAST DISORDER

Galactorrhea

There were two reports of galactorrhea during treatment with mirtazapine, both of which occurred in the first month of use. Both these cases were reviewed: in one it was also the reason for stopping mirtazapine.

In the first case the patient was prescribed 15mg of mirtazapine for depression. Three weeks after starting the medication the patient was reported to have galactorrhoea of the left breast and irritability and the drug was stopped. Nothing was found on examination and prolaction levels were also normal. The GP thought that the event was related to mirtazapine. At the time of the event the patient was also on ibuprofen. The event resolved once mirtazapine was stopped.

In the second case, the patient was prescribed 30mg of mirtazapine for depression and anxiety. Two weeks after starting the patient developed galactorrhoea and the medication was stopped. At the time of the event the patient was also taking diazepam 2mg. On stopping mirtazapine the event resolved. The GP considered the event to be due to mirtazapine.

HAEMOPOEITIC

Bone marrow abnormal

There were three reports of 'bone marrow abnormal' during treatment with mirtazapine of which one report was in the first month of use. All of these three cases were reviewed. In the first case the patient was prescribed 30mg of mirtazapine for obsessive-compulsive disorder.

Three months after starting treatment the patient was found to have agranulocytosis and the drug was stopped immediately. The GP wrote that the patient was also taking trifluoperazine and procyclidine and the consultant thought that the side effect was due to trifluoperazine rather than mirtazapine.

In the second case, the patient was prescribed 60mg of mirtazapine for depression. Five months after starting mirtazapine the patient presented with a history of sore throat, and a blood test revealed a low neutrophil count, and mirtazapine was stopped. The GP considered the event to be drug related as on stopping mirtazapine the neutrophil count improved. In the third case the patient was admitted to the hospital with *Klebsiella* right lower lobe pneumonia and discharged on 30mg of mirtazapine. Two months after starting mirtazapine the patient was reported to have disturbed liver function tests and agranulocytosis, and mirtazapine was stopped, after which the patient's blood count was back to normal. The GP considered the event to be a possible bone marrow toxicity due to mirtazapine.

Leucopenia

There were 12 reports of leucopenia during treatment with mirtazapine, of which four were reported in the first month of use. All 12 cases were reviewed: in three cases it was the reason for stopping treatment. In the first case, the patient was prescribed 30mg of mirtazapine. Two weeks after starting medication, the patient was reported to have anaemia and a low white cell count, and mirtazapine was stopped. In the second case, the patient was prescribed 30mg of mirtazapine for depression. A week after starting the medication the patient was reported to have intolerance and on routine blood tests it was found that the patient had eosinopenia, and

mirtazapine was stopped. In the third case, the patient was prescribed 30mg mirtazapine for anxiety and depression. A month after starting mirtazapine the patient was reported to have a low white cell count and the drug was discontinued. The GP wrote that the patient was also having salazopyrine at the time of the event, and considered it to be due to salazopyrine.

Neutropenia

There were seven reports of neutropenia during treatment with mirtazapine, of which only one was reported during the first month of use. All seven cases were reviewed: only one was considered to be possibly due to mirtazapine. In this case, the patient was prescribed 30mg of mirtazapine. Five months after starting the medication the patient complained of myalgia and stomatitis. A blood test done at that time showed neutrophil shift to the left, and mirtazapine was stopped. Four weeks after stopping mirtazapine the neutrophil count came back to normal. The GP considered it to be possibly due to mirtazapine.

Myelodysplastic syndrome

There were three reports of myelodysplastic syndrome during treatment with mirtazapine: in one case it was the reason for stopping the drug. In this case, the patient was prescribed 30mg of mirtazapine for depression. Five months after starting the medication the patient developed myelodysplasia, and mirtazapine was stopped. On stopping mirtazapine the event resolved. The remaining two cases were unlikely to be due to mirtazapine, as in both the cases the patients were on chemotherapy.

Pancytopenia

There was one case of pancytopenia during treatment with mirtazapine, in a patient prescribed 45mg of mirtazapine. A month after starting the medication the patient was reported to have developed pancytopenia, and the medication was stopped. The GP wrote that the patient was also taking methotrexate and prednisolone at the time of the event.

IMMUNOLOGICAL

Allergy

There were six reports of allergy during treatment with mirtazapine of which four were reported to be in the first month of use. All of these six cases were reviewed: in three it was the reason for stopping treatment and also considered to be possibly due to mirtazapine. In the first case, the patient was prescribed mirtazapine for hypomania. Soon after starting the medication the patient developed an allergic reaction (details not mentioned) and mirtazapine was stopped. The event resolved on stopping mirtazapine.

In the second case, the patient was prescribed 15mg mirtazapine for 'flat affect and retarded behaviour'. Two weeks after starting the medication the patient developed rash and vulvodynia, and the drug was discontinued. The GP considered it to be an allergic reaction, which resolved on stopping mirtazapine.In the third case, the patient was prescribed 30mg of mirtazapine for depression. Three weeks after starting medication the patient developed itchy rash all over, which resolved on stopping mirtazapine. The remaining three cases were considered unlikely to be due to mirtazapine.

Angioneurotic oedema

There were three cases of angioneurotic oedema during treatment with mirtazapine. All three cases were reviewed, and none of the cases were considered to be due to mirtazapine. In the first case the GP considered the angioneurotic oedema to be due bendrofluazide, in a second case the oedema occurred six months after stopping mirtazapine. In the remaining case the patient developed angioneurotic oedema seven months after starting mirtazapine: considering the time of occurrence of the event it is unlikely to be due to mirtazapine.

ADVERSE REACTION TO SPECIFIC DRUGS

Withdrawal symptoms

There were eight reports of withdrawal symptoms during treatment with mirtazapine, of which four were reported in the first month of use. All eight cases were reviewed: five were considered to be possibly due to mirtazapine, while the remaining three were due to other drugs. All five cases were also reported as possible suspected ADRs, of which one was also reported to the CSM. The remaining three cases of withdrawal symptoms were due to diazepam, flunitrazepam and sudden withdrawal of venlafaxine.

In the first case, the patient was prescribed mirtazapine for depression, and remained on treatment for seven months, after which the drug was stopped as it was ineffective. Soon after stopping the patient complained of severe anxiety, sleep disturbance, agitation and nausea. The GP considered it to be withdrawal symptoms due to stopping medication. In the second case,

the patient was prescribed 15mg of mirtazapine for depression and continued on the treatment for seven months, after which it was stopped by the GP as the patient was planning to get pregnant. After stopping mirtazapine, the patient complained of a severe withdrawal reaction, feeling very unwell and nausea. The GP reported this to the CSM.

In the third case the patient was prescribed 15mg mirtazapine and remained on treatment for 5 months, after which it was stopped as it was ineffective. After stopping the patient was reported to have very unpleasant symptoms which the GP attributed as withdrawal symptoms due to mirtazapine. In the fourth case the patient was prescribed 30mg mirtazapine, and continued treatment for four months. On stopping mirtazapine the patient complained of severe headaches, unable to sleep, and aching legs. The GP considered it to be withdrawal symptoms attributed to stopping mirtazapine.

In the fifth case, the patient was prescribed 30mg mirtazapine for depression, and remained on treatment for four months. Mirtazapine was stopped as it was ineffective. Soon after stopping mirtazapine the patient complained of panic attacks and extreme anxiety, which the GP attributed it to be withdrawal symptoms due to mirtazapine.

Pregnancies

There were 68 pregnancies reported as an event during this study (Table 3.12), of which eight were classified as 'void' (five patients were actually not pregnant, one patient stopped taking drug four months before last menstrual period, and one patient became pregnant five months

after last treatment). Forty one (41) patients took mirtazapine during the first trimester of pregnancy. The outcomes of these 41 pregnancies were as follows: eight spontaneous abortions (one patient had a miscarriage at seven weeks in a previous pregnancy and endometriosis was diagnosed at laparoscopy); eight therapeutic terminations of pregnancy (one patient had history of two premature stillbirths, and a third baby had died of meningococal disease at about 4 months); 24 live births; and one outcome not known. Of the 24 live births, there were four premature births (two premature live births at 36 weeks gestation, and the other two at 26 weeks and 29 weeks gestation). The baby born at 29 weeks had a patent ductus arteriosus.

Fifteen patients had stopped taking mirtazapine before becoming pregnant. The outcomes were as follows: six live births, two spontaneous abortions, six therapeutic termination of pregnancy, and one unknown outcome.

Table 3.12. Outcomes of pregnancies

Exposure to Mirtazapine	Total	Live Birth	Spontaneous abortion	TOP	Outcome unknown
Drug stopped before getting pregnant	15	6	2	6	1
Drug taken in 1st trimester	41	24	8	8	1
Exposure uncertain	4	0	1	1	2
TOTAL	**60**	**30**	**11**	**15**	**4**

Deaths

There were 258 deaths reported during the total period of observation for mirtazapine. (Table 3.13). At follow up there were 257 confirmed deaths, as one patient was found to be still alive. Three patients could not be traced. There were 13 suicides; eight fatal overdoses; and in eight the cause of death could not be ascertained. Of the 13 deaths due to suicide, eight patients were still taking mirtazapine at the time of death.

Table 3.13. Causes of death

Cause of death	Total	Months from first prescription							
		1	2	3	4	5	6	>6	Not known
Alcoholism	1	0	0	0	0	1	0	0	0
Alpha antitrypsin deficiency	1	0	1	0	0	0	0	0	0
Alzheimer's disease	1	0	0	1	0	0	0	0	0
Anaemia	1	0	1	0	0	0	0	0	0
Aneurysm aortic	3	0	1	0	0	1	1	0	0
Anorexia	1	0	0	1	0	0	0	0	0
Anorexia nervosa	1	0	0	0	0	0	0	1	0
Asphyxia	2	0	0	0	1	0	0	1	0
Astrocytoma	1	0	0	0	0	0	0	1	0
Bronchiectasis	1	0	0	0	1	0	0	0	0
Bronchitis acute	1	0	0	1	0	0	0	0	0
Bronchopneumonia	19	3	3	0	0	6	2	5	0
Cancer	3	1	0	0	1	0	0	1	0
Carcinoma bladder	1	1	0	0	0	0	0	0	0
Carcinoma brain	2	0	0	1	0	1	0	0	0
Carcinoma breast	3	0	0	1	1	0	1	0	0
Carcinoma bronchus	1	0	0	1	0	0	0	0	0
Carcinoma colon	7	0	3	0	2	0	1	1	0
Carcinoma kidney	2	0	1	0	0	0	1	0	0
Carcinoma liver	1	0	0	1	0	0	0	0	0
Carcinoma lung	7	1	2	2	0	1	0	1	0
Carcinoma oesophagus	1	0	0	1	0	0	0	0	0
Carcinoma ovary	4	0	2	1	1	0	0	0	0
Carcinoma pancreas	2	0	1	1	0	0	0	0	0
Carcinoma prostate	3	0	1	1	0	1	0	0	0

Table 3.13 Causes of death (continued)

Cause of death	Total	Months from first prescription							
		1	2	3	4	5	6	>6	Not known
Carcinoma stomach	4	0	0	2	0	0	0	2	0
Carcinoma thyroid	1	0	0	1	0	0	0	0	0
Carcinomatosis	10	0	4	1	2	1	1	1	0
Cardiac arrest	1	0	0	0	0	0	0	1	0
Cardiac failure	3	1	1	0	0	0	0	1	0
Cardiomyopathy	1	1	0	0	0	0	0	0	0
Cardiovascular unspecified	1	0	0	1	0	0	0	0	0
Cerebrovascular accident	24	2	2	6	3	2	2	7	0
Choking	1	0	0	0	0	1	0	0	0
Cirrhosis	3	0	0	0	1	1	0	1	0
COAD*	8	2	2	1	0	1	2	0	0
Colitis pseudomembranous	1	0	0	1	0	0	0	0	0
Congestive cardiac failure	3	1	0	1	1	0	0	0	0
Death cause not ascertained	8	1	1	2	2	0	1	1	0
Deep vein thrombosis	4	1	1	0	1	0	0	1	0
Dementia	1	0	1	0	0	0	0	0	0
Dementia senile	1	0	1	0	0	0	0	0	0
Depression	1	0	0	0	0	0	0	1	0
Diabetes mellitus	1	0	1	0	0	0	0	0	0
Embolus pulmonary	2	1	1	0	0	0	0	0	0
Fall	1	0	0	0	0	0	0	1	0
Glioma	1	0	0	0	0	1	0	0	0
Haematemesis	1	0	0	0	0	1	0	0	0
Haemorrhage gastrointestinal	2	0	1	1	0	0	0	0	0
Haemorrhage subarachnoid	1	0	1	0	0	0	0	0	0
Hepatic failure	1	0	0	0	0	0	0	1	0
Hepatitis	1	0	0	0	0	0	1	0	0
Hypertension	2	1	0	0	0	1	0	0	0
Hypoglaecaemia	1	0	0	0	1	0	0	0	0
Infection chest	5	1	0	0	1	3	0	0	0
Injury	2	1	1	0	0	0	0	0	0
Ischaemic heart disease	14	1	3	1	1	1	2	5	0
Left ventricular failure	1	0	0	0	0	1	0	0	0
Leukaemia	1	0	0	1	0	0	0	0	0
Leukaemia lymphocytic chronic	1	0	1	0	0	0	0	0	0
Leukaemia myeloid acute	1	0	0	0	0	1	0	0	0
Lymphoma malignant	1	0	0	0	0	1	0	0	0
Mesothelioma	1	0	0	1	0	0	0	0	0
Multiple sclerosis	1	0	0	0	0	0	0	1	0
Myeloma	1	0	0	0	0	1	0	0	0
Myocardial infarction	21	2	2	6	5	1	2	3	0

Cause of death	Total	Months from first prescription							
		1	2	3	4	5	6	>6	Not known
Oesophageal haemorrhage	1	0	0	0	0	1	0	0	0
Orthopaedic surgery	1	0	0	1	0	0	0	0	0
Overdose other drug	7	0	0	0	3	0	1	3	0
Overdose unknown drug	1	0	1	0	0	0	0	0	0
Pancreatitis	1	1	0	0	0	0	0	0	0
Parkinson's disease	2	0	0	1	0	1	0	0	0
Patient not traced	3	0	0	0	0	0	0	0	3
Pneumonia	4	0	0	0	0	1	1	2	0
Renal failure	2	1	0	0	0	0	0	1	0
Renal failure chronic	1	0	0	0	1	0	0	0	0
Senility	7	0	1	1	1	0	1	3	0
Septicaemia	2	0	1	0	1	0	0	0	0
Suicide	13	0	2	1	3	0	2	5	0
Thrombosis mesenteric	1	0	1	0	0	0	0	0	0
Total hip replacement	1	1	0	0	0	0	0	0	0
Total	**257**	**25**	**46**	**43**	**34**	**32**	**22**	**52**	**3**

*COAD - Chronic obstructive airways disease

CHAPTER 4: RESULTS OF THE PAROXETINE PRESCRIPTION EVENT MONITORING STUDY

METHOD

The methods used in the analysis of data obtained during PEM in the paroxetine study are similar to those used for the mirtazapine study. The original PEM study for paroxetine was undertaken between March 1991 to March 1992[25]. The methodology used for determining possible signals in the original investigation was to use Rate Ratios (RR) for the events during the first month of treatment and the subsequent 6 months. Having undertaken the evaluation of mirtazapine, I calculated Incidence Densities in place of Rate Ratios in a further analysis of the paroxetine database, to determining possible signals, and to allow a comparison with the findings from the mirtazapine study.

Study sample

Approximately 50,000 prescriptions were collected which were used to identify 26,194 patients who had commenced treatment in general practice between March 1991 and March 1992. Green forms were posted to 9026 doctors regarding 26194 patients, and 15 907 (61.0%) were returned. 72% of the doctors returned at least one green form, while 2557 doctors failed to return any. As can be seen in Table 4,1, the response varied according to the number of forms posted to individual doctors. The range extended from nearly 67% for those who were posted only a single form, to less than 50% in those sent more than 30 forms.

Table 4.1. Green forms returned according to the number originally posted to individual doctors.

Number of Patients per doctor	Number of doctors	Number of patients (forms sent)	Number of forms returned	Percentage of forms returned
1	4425	4425	2963	67.0
2	1753	3506	2340	67.0
3	910	2730	1756	64.0
4	541	2164	1313	61.0
5	322	1610	1034	64.0
6	211	1266	722	61.0
7	204	1428	847	59.0
8	118	944	602	64.0
9	106	954	457	58.0
10	79	790	314	58.0
11-20	273	3886	2116	55.0
21-30	60	1468	738	50.0
31-40	12	419	15	36.0
41-50	8	362	176	49.0
50+	4	242	93	38.0
Total	**9026**	**26194**	**15907**	**61.0**

*NOTE: 3518 of these GPs who had treated 8043 patients did not return any forms.

A total of 2166 of the returned forms were void for the following reasons: in 1046 the patient was no longer registered with the doctor; in 642 the forms were blank; in 244 paroxetine was prescribed but not taken; in 199 there was no record of treatment in the notes; and in 35 the doctor had moved or retired.

Useful information was thus available for 13 741 patients (52% of the patients identified). Most patients were studied for seven to nine months after the first prescription regardless of when treatment was stopped.

Age and sex

The age distribution and sex of the cohort is shown in Table 4.2. The age had not been recorded for 1150 patients (%). Of the 13,741 patients, 5,015 (36.4%) were male and 8576 (62.4%) female. The mean age for males was 48.6 years (range 14-93 years), the mean age for females was 48.8 years (range13-99 years).

Table 4. 2. Age and sex distribution in the paroxetine cohort

Age	Male	Female	Not Specified	All Patients
010-019	68	145	0	213
020-029	464	1193	12	1669
030-039	755	1692	15	2462
040-049	950	1808	11	2769
050-059	729	1210	6	1945
060-069	539	1078	8	1625
070-079	367	1004	5	1376
080-089	144	425	2	571
090+	10	23	1	34
Negative	0	12	0	12
NS	347	690	28	1065
TOTAL	**4373**	**9280**	**88**	**13741**

NS, not specified.

Indications

The major indication for patients treated with paroxetine was depression (82%). The indication was not specified for 1519 (11%) of the patients. (Table 4.3). There was no difference in the distribution of indications between men and women: a small proportion of the indications were conditions such as bereavement, obesity or "post viral syndrome" which may have been the cause of depression rather than the primary indication.

Table 4.3. Indications for paroxetine analysed by sex

Indications for paroxetine

Indication	Male	%	Female	%	Sex not specified	%	Total	%
Depression	3610	83	7662	83	59	67	11331	82
Not specified	513	12	982	11	24	27	1519	11
Anxiety	163	4	289	3	1	1	453	3
Depression Postnatal	0	0	143	2	1	1	144	1
Depression Manic	17	0	46	0	1	1	64	0
Insomnia	5	0	18	0	0	0	23	0
Post Viral Syndrome	8	0	13	0	0	0	21	0
Panic Attack	4	0	15	0	0	0	19	0
Obsession/compulsive	8	0	10	0	0	0	18	0
Bereavement	2	0	14	0	1	1	17	0
Neurosis	7	0	9	0	0	0	16	0
Pain	3	0	7	0	0	0	10	0
Schizophrenia	5	0	4	0	0	0	9	0
Grief Reaction	2	0	6	0	0	0	8	0
Lassitude	3	0	4	0	1	1	8	0
Mood Swings	4	0	4	0	0	0	8	0
Premenstrual Tension	0	0	8	0	0	0	8	0
Agitation	2	0	5	0	0	0	7	0
Bulimia	0	0	6	0	0	0	6	0
Phobia	2	0	4	0	0	0	6	0
Psychosis	3	0	3	0	0	0	6	0
Suicidal Thoughts	2	0	4	0	0	0	6	0
Headache	2	0	3	0	0	0	5	0
Agoraphobia	0	0	4	0	0	0	4	0
Neuralgia	2	0	2	0	0	0	4	0
Dementia	0	0	3	0	0	0	3	0
Malaise	0	0	3	0	0	0	3	0
Neuralgia Postherpetic	2	0	1	0	0	0	3	0
Depression Menopausal	0	0	2	0	0	0	2	0
Pain Back	0	0	2	0	0	0	2	0
Alzheimer's Disease	1	0	0	0	0	0	1	0
Dementia senile	0	0	1	0	0	0	1	0
Hypochondriasis	0	0	1	0	0	0	1	0
Marital	0	0	1	0	0	0	1	0
Narcolepsy	1	0	0	0	0	0	1	0
Pain Abdomen	1	0	0	0	0	0	1	0
Paranoia	0	0	1	0	0	0	1	0
Suicide Attempt	1	0	0	0	0	0	1	0
Total	**4373**	100	**9280**	100	**88**	100	**13741**	100

Duration and dosage of paroxetine

After six months, 4547 (33.0%) of the original cohort of 13741 patients were still being prescribed paroxetine. Table 4.4 shows the pattern of dose prescribed in paroxetine to patients. The dose distribution shown in Table 4 was based on a sample of the first prescriptions for 4394 patients. 93% were using 20 mg. Where an opinion about effectiveness was given, 62% of GPs reported that the drug had been effective.

Table 4.4. Dose of paroxetine

Initial daily dose (mg)	Percentage
10	1
20	93
30	3
>30	3
Total	**100**

Adverse reactions

An event was coded as an adverse drug reaction if the general practitioner specified on the green form that the event was attributable to a drug. 119 events were reported by the general practitioners as ADRs to paroxetine (Table 4.5). Ninety six of these 119 events were documented on the green form as having been reported to the Committee on Safety of Medicines. The most frequently reported adverse reactions to paroxetine were withdrawal symptoms in 15 patients, followed by tremor in 13 patients and nausea/vomiting in 11 patients (nausea 7 patients, vomiting 4 patients).

Table 4.5: Adverse reactions (ADRs) to paroxetine

ADRs to paroxetine

Event	ADR	Total	Reported to CSM	Reported to manufacturer
Withdrawal symptoms	Withdrawal Symptoms	15	1	0
Tremor	Tremor	13	12	0
Sweating	Sweating	8	8	0
Nausea, vomiting	Nausea	7	6	0
Insomnia	Insomnia	5	5	0
Rash	Rash	5	4	0
Dizziness	Dizziness	4	2	0
Drowsiness, sedation	Drowsiness	4	4	0
Nausea, vomiting	Vomiting	4	4	0
Agitation	Agitation	3	3	0
Diarrhoea	Diarrhoea	3	3	0
Dry mouth	Dry Mouth	3	2	0
Headache, migraine	Headache	3	3	0
Dreams abnormal	Dreams Abnormal	2	2	0
Impotence, ejaculation failure	Ejaculation Failure	2	2	0
Convulsion, epilepsy	Epilepsy Grand Mal	2	2	0
Irritability	Irritability	2	2	0
Sensation abnormal	Paraesthesia	2	2	0
Spasm muscular	Spasm Muscular	2	2	0
Vertigo	Vertigo	2	2	0
Aggression	Aggression	1	1	0
Alcoholism	Alcoholism	1	1	0
Anorexia	Anorexia	1	1	0
Anxiety	Anxiety	1	0	0
Ataxia	Ataxia	1	1	0
Confusion	Confusion	1	1	0
Cough	Cough	1	1	0
Dependence	Dependence	1	0	0
Drug interaction	Drug Interaction	1	1	0
Dyspepsia	Dyspepsia	1	1	0
Epistaxis	Epistaxis	1	1	0
Faintness	Faintness	1	1	0
Flushing	Flushing	1	1	0
Glossitis	Glossitis	1	1	0
Dyspepsia	Heartburn	1	1	0
Sensation abnormal	Hypoaesthesia	1	1	0

Hypomania	Hypomania	1	1	0
Labyrinthitis	Labyrinthitis	1	0	0
Malaise, lassitude	Lassitude	1	1	0
Headache, migraine	Migraine	1	1	0
Pain abdomen	Pain Abdomen	1	1	0
Palpitation	Palpitation	1	1	0
Panic attack	Panic Attack	1	1	0
Pruritus	Pruritus	1	1	0
Pyrexia of unknown origin	Pyrexia Of Unknown Origin	1	1	0
Drowsiness, sedation	Sedation	1	1	0
Unspecified side effects	Unspecified Side Effects	1	1	0
Visual defect	Visual Disturbance	1	1	0
Total		**119**	**96**	**0**

Treatment after stopping paroxetine

The majority of drugs used after stopping paroxetine were other antidepressants (tricyclic and related antidepressants 67%; other SSRIs 14%; MAOIs and combined preparations 4%). The ndividual drugs that were most frequently used after paroxetine were dothiepin (470 reports), lofepramine (240), amitryptiline (227) and fluoxetine (174). Other drugs included antipsychotics (11%), and anxiolytics and hypnotics (5%).

Reasons for stopping paroxetine

The GPs recorded 4434 reasons for stopping paroxetine in patients (Table 4.6). The most frequently reported event given as the reason for stopping paroxetine was not effective 1391 cases (10.1% of the total cohort). The most frequently reported clinical adverse events given as the reason for stopping paroxetine were nausea/vomiting 459 cases (3.3% of the total cohort) followed by drowsiness/sedation 171 cases (1.2% of the cohort).

Table 4.6: Reasons for stopping paroxetine

Reason	Number
Not effective	1391
Effective	944
Nausea	376
Drowsiness	137
Malaise	120
Dizziness	107
Tremor	104
Insomnia	102
Headache	91
Vomiting	83
Hospital Admissions	63
Diarrhoea	53
Lassitude	51
Sweating	51
Sedation	46
Agitation	44
Unspecified Side Effects	31
Anxiety	28
Dyspepsia	25
Pregnancy	25
Changed indication	24
Dry Mouth	22
Pain Abdomen	20
Rash	19
Ataxia	15
Dreams Abnormal	15
Constipation	14
Palpitation	14
Weight Gain	14
Impotence	13
Libido Decreased	13
Hospital Referrals: Psychiatry	12
Confusion	11
Depression	11
Flushing	11
Visual Disturbance	11
Anorexia	10
Panic Attack	10
Paraesthesia	10
Ejaculation Failure	9
Hypomania	9
Pruritus	9
Irritability	8
Aggression	7
Euphoria	7

Table 4.6: Reasons for stopping Paroxetine

Faintness	6
Hyperactive	6
Migraine	6
Myalgia	6
Burning Sensation	5
Flatulence	5
Spasm Muscular	5
Suicidal Thoughts	5
Syncope	5
Tinnitus	5
Distension Abdominal	4
Epilepsy	4
Frequency	4
Paranoia	4
Parkinson's Disease	4
Vertigo	4
Amenorrhoea	3
Central nervous System Unspecified	3
Cerebrovascular accident	3
Cramp	3
Dyspnoea	3
Epilepsy Grand Mal	3
Feeling Cold	3
Feeling Hot	3
Heartburn	3
Mania	3
Movement Involuntary	3
Oedema Face	3
Pain Chest	3
Pyrexia Of Unknown Origin	3
Behaviour Abnormal	2
Bulimia	2
Catarrh	2
Convulsion	2
Dementia	2
Diplopia	2
Disorientation	2
Dysphagia	2
Dysuria	2
Electroconvulsive Therapy	2
Excessive Thirst	2
Fluid Retention	2
Galactorrhoea	2
Hallucination	2
Hypothyroidism	2
Irritable Bowel Syndrome	2
Mood Swings	2
Neuralgia	2
Obsession/compulsive	2

Pain Joint	2
Premenstrual Tension	2
Restless Legs	2
Retention	2
Sore Mouth	2
Suicide Attempt	2
Suicide Threat	2
Taste Abnormal	2
Vaginal Soreness	2
Abscess Breast	1
Aneurysm Aortic	1
Angina	1
Cardiogenic Shock	1
COAD (Chronic Obstructive Airways Disease)	1
Deep vein thrombosis	1
Delusion	1
Depression Manic	1
Dermatitis	1
Diabetes mellitus	1
Disc Prolapsed	1
Dysphasia	1
Earache	1
Embolus pulmonary	1
Epistaxis	1
Erythema	1
Fall	1
Fibrillation Atrial	1
Fixed Eruption	1
Gastritis	1
Gynaecological Surgery	1
Hepatic Failure	1
Hepatitis Infectious A	1
Hoarseness	1
Hypertension	1
Hyperthyroidism	1
Hyperventilation	1
Hypoaesthesia	1
Hyponatraemia	1
Hypotension	1
Infection Chest	1
Irregular Periods	1
Labyrinthitis	1
Laryngitis	1
Left Ventricular Failure	1
Lymphadenitis	1
Marital	1
Menopausal Symptoms	1
Mood Change	1
Muscle Weakness	1
Myocardial Infarction	1
Nystagmus	1
Oesophageal Reflux	1
Overdose Other Drug	1

Overdose Unknown Drug	1
Pain	1
Pain Limb	1
Prostatism	1
Psychiatric Unspecified	1
Psychosis	1
Rhinitis	1
Schizophrenia	1
Self Injury	1
Somnambulism	1
Sore Eye	1
Sore Skin	1
Swollen Tongue	1
Tachycardia	1
Thrombocytosis	1
Toothache	1
Transient Ischaemic Attack	1
Ulcer Mouth	1
Ulcer Peptic	1
Vascular Surgery	1
Vision Deteriorated	1
Vision Field Defect	1
Weight Loss	1
Wheezing	1
Total	**4434**

Recorded events

A list of all events recorded during this PEM study is shown in Appendix 3a. As described in the previous chapter, the DSRU dictionary groups related events (lower level terms) under a broader term (higher level term), e.g. the lower level terms 'glands swollen', 'lymphadenitis' and 'lymphadenopathy' are grouped under the higher level term 'lymphadenopathy'. In Appendices 3a, 3b, 3c, column A contains higher and lower level coding terms, the lower level terms being indented.

The total for all the events reported at any time after the first prescription is listed in column B, irrespective of whether or not the patient was still taking the drug. This total in column B includes events which occurred within six months of the first prescription for paroxetine, more

than six months after the first prescription and those events for which the date of occurrence has not been reported. The events in each of the first six months are listed separately (columns C to H) and the total number of events during the first six months is shown in column I. If the date of the event is not known or it is only an approximate date then the event is included in the total number of events but not in columns C to I. Although these events are not included in the statistical analyses they are examined during the follow-up procedure. The number of events in which the date of occurrence is not known is given in column J.

In Appendix 3a the total number of patient-months of observation is given in column B. The monthly denominators represent the number of patient-months of observation in each month. The figures diminish slightly throughout the period due to date errors or patients lost to surveillance. In Appendix 3a, separate denominators are shown for males and females.

Appendix 3b gives a list of events reported for all patients during treatment with paroxetine. Each term reported in Appendix 3a is also given in this appendix even if there were no occurrences of this event during treatment with paroxetine. Events for those patients for whom the date of stopping therapy with the drug under surveillance is not known are not included in Appendix 3b unless reported by the GP on the green form as occurring during treatment and recorded as during treatment by the coding clerk. Also if the date of the event is not known or it is coded as an approximate date then the event is not included in Appendix 3b unless it is clear that the event occurred during treatment with the drug. For this latter case the event was included in the total for that event but was not included in the numbers for the first six months.

The total number of patient-months of treatment is given in column B. The monthly denominators (columns C-H) are the number of patient-months of treatment for each month. These are calculated from the total number of days of treatment in each month for those patients who continued to take the drug throughout the month, who will each contribute 30 treatment days and for those patients who stopped treatment during that month who will each contribute the number of days of treatment they received during the month. The total number of days of treatment is divided by 30 to determine the number of patient months of treatment.

Incidence densities

Table 4.7 gives the denominators in patient-months for each time period. The time period, D_1, relates to the first month of treatment for individual patients and not merely the first month of the entire study. Patients who stop treatment before the end of their first month of therapy will contribute to the denominator, D_1, only the number of days for which they were treated. Similarly, the sum of the number of months of treatment for individual patients was used to calculate the denominators D_2, D_3 and D_A.

Table 4.7. Denominators (patient-months of treatment) used to calculate incidence densities (IDs) for paroxetine

	Denominators (patient-months of treatment)			
	D_1	D_2	D_3	D_A
Male	3605.80	10207.60	8522.90	22336.30
Female	7390.70	20111.30	15337.00	42839.00
Sex not specified	62.20	127.10	84.40	273.80
Total	**11058.70**	**30446.00**	**23944.30**	**65449.10**

D_1 = Total number of patient-months of exposure during the first month of treatment

D_2 = Total number of patient-months of exposure during treatment months 2-6 inclusive

D_3 = Total number of patient-months of exposure during treatment after month 6

D_A = Total number of patient-months exposure during the whole treatment period

Thus, $D_A = D_1 + D_2 + D_3$

Table 4.8 gives the number of events reported during treatment and the ID for the first month of treatment, the second to sixth months inclusive and the overall time period. Only the first report of an event in an individual patient is used in the calculation. The events given in this table are the higher level terms.

Column A shows the rank of each event. Column B lists the higher term event. Columns C to K provide the following:-

N_1 = Total number of reports of each event during the first month of treatment

N_2 = Total number of reports of each event during treatment in months 2-6

ID_1 = Incidence density for each event during the first month of treatment

ID_2 = Incidence density for each event during treatment months 2-6

ID_1-ID_2 = Arithmetic difference between ID_1 and ID_2

99% CI = 99% confidence intervals for ID_1-ID_2

N_A = Total number of reports of each event during the total treatment period

ID_A = Incidence density for each event for the total treatment period.

The ranking order given in column A is that of ID_1. Thus, the values for ID_2 and ID_A are not ranked. The difference between ID_1 and ID_2 (column G) and the 99% confidence intervals for

this difference (columns H and I) are given to examine the null hypothesis that the rate for the event is not increasing or decreasing between the two time periods.

Table 4. 8. Incidence densities (ID) ranked for paroxetine in order of ID_1 per 1000 patient-months

	Incidence densities for paroxetine									
	HigherTermDescription	**N1**	**N2**	**ID1**	**ID2**	**ID1_Id2**	**CI_MIN**	**CI_MAX**	**Na**	**IDa**
1	Nausea, vomiting	592	155	53.50	5.10	48.40	42.70	54.20	850	13.00
2	Substitute	546	573	49.40	18.80	30.60	24.70	36.40	1448	22.10
3	Not effective	528	645	47.80	21.20	26.60	20.80	32.30	1391	21.30
4	Drowsiness, sedation	232	66	21.00	2.20	18.80	15.20	22.40	327	5.00
5	Malaise, lassitude	200	88	18.10	2.90	15.20	11.80	18.60	342	5.20
6	Headache, migraine	147	102	13.30	3.40	9.90	7.00	12.90	312	4.80
7	Insomnia	145	79	13.10	2.60	10.50	7.60	13.40	269	4.10
8	Effective	138	560	12.50	18.40	-5.90	-9.30	-2.50	944	14.40
9	Tremor	137	37	12.40	1.20	11.20	8.40	13.90	194	3.00
10	Dizziness	131	73	11.90	2.40	9.50	6.70	12.20	259	4.00
11	Impotence, ejaculation failure	32	23	8.90	2.30	6.60	2.40	10.80	71	3.20
12	Non-surgical admissions	89	114	8.10	3.70	4.30	1.90	6.70	289	4.40
13	Diarrhoea	86	85	7.80	2.80	5.00	2.70	7.30	218	3.30
14	Respiratory tract infection higher	80	198	7.20	6.50	0.70	-1.70	3.10	435	6.60
15	Sweating	72	44	6.50	1.50	5.10	3.00	7.10	146	2.20
16	Agitation	57	28	5.20	0.90	4.20	2.40	6.00	107	1.60
17	Dyspepsia	53	74	4.80	2.40	2.40	0.50	4.20	165	2.50
18	Pain abdomen	51	56	4.60	1.80	2.80	1.00	4.50	146	2.20
19	Respiratory tract infection lower	50	139	4.50	4.60	-0.10	-2.00	1.90	298	4.60
20	Anxiety	48	46	4.30	1.50	2.80	1.10	4.50	116	1.80
21	Dry mouth	47	12	4.30	0.40	3.90	2.20	5.50	63	1.00
22	Suicide attempt, drug overdose	35	48	3.20	1.60	1.60	0.10	3.10	119	1.80
23	Constipation	34	44	3.10	1.50	1.60	0.20	3.10	103	1.60
24	Hospital referrals no admission	33	61	3.00	2.00	1.00	-0.50	2.50	175	2.70
25	Unspecified side effects	29	8	2.60	0.30	2.40	1.10	3.60	44	0.70
26	Pain back	27	58	2.40	1.90	0.50	-0.80	1.90	135	2.10
27	Panic attack	27	14	2.40	0.50	2.00	0.70	3.20	52	0.80
28	Palpitation	24	17	2.20	0.60	1.60	0.40	2.80	53	0.80
29	Injury	23	51	2.10	1.70	0.40	-0.90	1.70	111	1.70
30	Anorexia	22	6	2.00	0.20	1.80	0.70	2.90	36	0.60
31	Micturition disorder	22	28	2.00	0.90	1.10	-0.10	2.30	85	1.30
32	Rash	22	41	2.00	1.40	0.60	-0.60	1.90	84	1.30
33	Urinary tract infection	22	46	2.00	1.50	0.50	-0.80	1.70	110	1.70
34	Pain joint	21	62	1.90	2.00	-0.10	-1.40	1.10	124	1.90
35	Vaginitis, vulvitis	13	43	1.80	2.10	-0.40	-1.90	1.10	78	1.80
36	Visual defect	20	15	1.80	0.50	1.30	0.20	2.40	45	0.70
37	Fall	16	59	1.50	1.90	-0.50	-1.60	0.60	115	1.80

38	Flushing	17	10	1.50	0.30	1.20	0.20	2.20	31	0.50
39	Pain chest, tight chest	17	28	1.50	0.90	0.60	-0.40	1.70	64	1.00
40	Pregnancy	10	27	1.40	1.30	0.00	-1.30	1.30	60	1.40
41	Dreams abnormal	13	25	1.20	0.80	0.40	-0.60	1.30	50	0.80
42	Menstrual disorder	9	27	1.20	1.30	-0.10	-1.40	1.10	66	1.50
43	Sensation abnormal	13	22	1.20	0.70	0.50	-0.50	1.40	48	0.70
44	Syncope	13	13	1.20	0.40	0.80	-0.10	1.60	39	0.60
45	Changed indication	12	7	1.10	0.20	0.90	0.00	1.70	24	0.40
46	Fatal outcome	12	20	1.10	0.70	0.40	-0.50	1.30	49	0.70
47	Premenstrual tension	8	9	1.10	0.50	0.60	-0.40	1.70	25	0.60
48	Confusion	11	13	1.00	0.40	0.60	-0.30	1.40	32	0.50
49	Depression	11	13	1.00	0.40	0.60	-0.30	1.40	33	0.50
50	Dyspnoea	11	11	1.00	0.40	0.60	-0.20	1.50	34	0.50
51	Menopausal symptoms	7	18	1.00	0.90	0.10	-1.00	1.10	30	0.70
52	Metrorrhagia	7	7	1.00	0.40	0.60	-0.40	1.60	22	0.50
53	Pain neck	11	24	1.00	0.80	0.20	-0.70	1.10	52	0.80
54	Pruritus	11	20	1.00	0.70	0.30	-0.50	1.20	46	0.70
55	Ataxia	10	9	0.90	0.30	0.60	-0.20	1.40	23	0.40
56	Faintness	10	2	0.90	0.10	0.80	0.10	1.60	13	0.20
57	Hypertension	10	13	0.90	0.40	0.50	-0.30	1.30	38	0.60
58	Infection skin, unspecified/local bacterial	10	33	0.90	1.10	-0.20	-1.10	0.70	70	1.10
59	Asthma, wheezing	9	36	0.80	1.20	-0.40	-1.20	0.50	74	1.10
60	Cough	9	50	0.80	1.60	-0.80	-1.70	0.10	104	1.60
61	Eczema	9	25	0.80	0.80	0.00	-0.80	0.80	50	0.80
62	Oedema	9	25	0.80	0.80	0.00	-0.80	0.80	55	0.80
63	Pain limb	9	17	0.80	0.60	0.30	-0.50	1.00	39	0.60
64	Prostatism	3	3	0.80	0.30	0.50	-0.80	1.90	10	0.40
65	Extrapyramidal disease	8	9	0.70	0.30	0.40	-0.30	1.10	29	0.40
66	Fracture	8	24	0.70	0.80	-0.10	-0.80	0.70	59	0.90
67	Libido decreased	8	18	0.70	0.60	0.10	-0.60	0.90	40	0.60
68	Suicidal thoughts	8	12	0.70	0.40	0.30	-0.40	1.10	29	0.40
69	Flatulence	7	6	0.60	0.20	0.40	-0.20	1.10	15	0.20
70	Malignancies	7	12	0.60	0.40	0.20	-0.40	0.90	35	0.50
71	Myalgia	7	26	0.60	0.90	-0.20	-1.00	0.50	47	0.70
72	Orchitis	2	2	0.60	0.20	0.40	-0.70	1.40	4	0.20
73	Otitis externa	7	14	0.60	0.50	0.20	-0.50	0.90	32	0.50
74	Sciatica	7	17	0.60	0.60	0.10	-0.60	0.80	37	0.60
75	Smell, taste abnormal	7	0	0.60	0.00	0.60	0.00	0.00	9	0.10
76	Vertigo	7	17	0.60	0.60	0.10	-0.60	0.80	33	0.50
77	Cardiac failure	6	12	0.50	0.40	0.20	-0.50	0.80	24	0.40
78	Convulsion, epilepsy	6	8	0.50	0.30	0.30	-0.30	0.90	24	0.40
79	Earache	6	7	0.50	0.20	0.30	-0.30	0.90	18	0.30
80	Electroconvulsive therapy	5	10	0.50	0.30	0.10	-0.50	0.70	30	0.50
81	Epistaxis	5	8	0.50	0.30	0.20	-0.40	0.80	15	0.20
82	Euphoria	6	5	0.50	0.20	0.40	-0.20	1.00	14	0.20
83	Feeling cold	5	1	0.50	0.00	0.40	-0.10	0.90	7	0.10
84	Feeling hot	6	1	0.50	0.00	0.50	-0.10	1.10	7	0.10
85	Gastroenteritis	6	6	0.50	0.20	0.30	-0.30	0.90	21	0.30
86	Hallucination	6	4	0.50	0.10	0.40	-0.20	1.00	16	0.20
87	Herpes	5	4	0.50	0.10	0.30	-0.20	0.90	13	0.20
88	Hyperactive	5	1	0.50	0.00	0.40	-0.10	0.90	7	0.10

89	Hypotension	6	6	0.50	0.20	0.30	-0.30	0.90	13	0.20
90	Irritability	6	9	0.50	0.30	0.20	-0.40	0.90	17	0.30
91	Ischaemic heart disease	6	23	0.50	0.80	-0.20	-0.90	0.50	40	0.60
92	Non-malignant tumours	5	12	0.50	0.40	0.10	-0.50	0.70	31	0.50
93	Spasm muscular	5	3	0.50	0.10	0.40	-0.20	0.90	11	0.20
94	Transient ischaemic attack	5	7	0.50	0.20	0.20	-0.30	0.80	16	0.20
95	Burning sensation	4	3	0.40	0.10	0.30	-0.20	0.70	10	0.20
96	Candidiasis	4	6	0.40	0.20	0.20	-0.30	0.70	18	0.30
97	Colic renal	4	2	0.40	0.10	0.30	-0.20	0.80	6	0.10
98	Conjunctivitis	4	24	0.40	0.80	-0.40	-1.10	0.20	40	0.60
99	Cramp	4	3	0.40	0.10	0.30	-0.20	0.70	11	0.20
100	Dermatitis	4	9	0.40	0.30	0.10	-0.50	0.60	20	0.30
101	Diabetes mellitus, hyperglycaemia	4	9	0.40	0.30	0.10	-0.50	0.60	25	0.40
102	Disorders of heart rate	4	4	0.40	0.10	0.20	-0.30	0.70	10	0.20
103	Frozen shoulder	4	3	0.40	0.10	0.30	-0.20	0.70	12	0.20
104	Labyrinthitis	4	10	0.40	0.30	0.00	-0.50	0.60	16	0.20
105	Lymphadenopathy	4	3	0.40	0.10	0.30	-0.20	0.70	14	0.20
106	Mastalgia	4	8	0.40	0.30	0.10	-0.40	0.60	17	0.30
107	Neuralgia	4	5	0.40	0.20	0.20	-0.30	0.70	11	0.20
108	Psoriasis	4	2	0.40	0.10	0.30	-0.20	0.80	7	0.10
109	Sore mouth	4	2	0.40	0.10	0.30	-0.20	0.80	9	0.10
110	Tinnitus	4	13	0.40	0.40	-0.10	-0.60	0.50	27	0.40
111	Ulcer mouth	4	16	0.40	0.50	-0.20	-0.70	0.40	26	0.40
112	Adverse reaction to other drug	3	5	0.30	0.20	0.10	-0.30	0.60	12	0.20
113	Alcoholism	3	6	0.30	0.20	0.10	-0.40	0.50	16	0.20
114	Anaemia	3	2	0.30	0.10	0.20	-0.20	0.60	7	0.10
115	Balanitis	1	0	0.30	0.00	0.30	0.00	0.00	1	0.00
116	Bereavement	3	9	0.30	0.30	0.00	-0.50	0.40	17	0.30
117	Central nervous system unspecified	3	1	0.30	0.00	0.20	-0.20	0.70	6	0.10
118	Deep vein thrombosis	3	1	0.30	0.00	0.20	-0.20	0.70	9	0.10
119	Disorientation	3	0	0.30	0.00	0.30	0.00	0.00	3	0.00
120	Distension abdominal	3	10	0.30	0.30	-0.10	-0.50	0.40	20	0.30
121	Dysphagia	3	2	0.30	0.10	0.20	-0.20	0.60	7	0.10
122	Earwax	3	10	0.30	0.30	-0.10	-0.50	0.40	28	0.40
123	Genitourinary Surgery	3	3	0.30	0.10	0.20	-0.30	0.60	10	0.20
124	Glossitis	3	1	0.30	0.00	0.20	-0.20	0.70	5	0.10
125	Haematoma	3	6	0.30	0.20	0.10	-0.40	0.50	12	0.20
126	Haemorrhage postmenopausal	2	0	0.30	0.00	0.30	0.00	0.00	4	0.10
127	Haemorrhoids	3	13	0.30	0.40	-0.20	-0.70	0.30	29	0.40
128	Hyperventilation	3	2	0.30	0.10	0.20	-0.20	0.60	6	0.10
129	Hypothyroidism	3	4	0.30	0.10	0.10	-0.30	0.60	10	0.20
130	Infection viral	3	17	0.30	0.60	-0.30	-0.80	0.20	22	0.30
131	Mania	3	1	0.30	0.00	0.20	-0.20	0.70	4	0.10
132	Mood change	3	3	0.30	0.10	0.20	-0.30	0.60	13	0.20
133	Pain	3	3	0.30	0.10	0.20	-0.30	0.60	8	0.10
134	Paranoia	3	6	0.30	0.20	0.10	-0.40	0.50	14	0.20
135	Phlebitis	3	1	0.30	0.00	0.20	-0.20	0.70	7	0.10
136	Psychosis	3	4	0.30	0.10	0.10	-0.30	0.60	8	0.10
137	Retention	3	4	0.30	0.10	0.10	-0.30	0.60	8	0.10
138	Rhinitis allergic	3	13	0.30	0.40	-0.20	-0.70	0.30	28	0.40
139	Self injury	3	3	0.30	0.10	0.20	-0.30	0.60	10	0.20

140	Sore skin	3	5	0.30	0.20	0.10	-0.30	0.60	11	0.20
141	Surgery	3	2	0.30	0.10	0.20	-0.20	0.60	10	0.20
142	Tennis elbow	3	10	0.30	0.30	-0.10	-0.50	0.40	22	0.30
143	Weight gain	3	25	0.30	0.80	-0.60	-1.10	0.00	61	0.90
144	Abdominal surgery	2	7	0.20	0.20	-0.10	-0.40	0.30	17	0.30
145	Abscess dental	2	6	0.20	0.20	0.00	-0.40	0.40	8	0.10
146	Anaemia iron deficiency	2	3	0.20	0.10	0.10	-0.30	0.40	12	0.20
147	Arthritis	2	9	0.20	0.30	-0.10	-0.50	0.30	19	0.30
148	Behaviour abnormal	2	4	0.20	0.10	0.10	-0.30	0.40	8	0.10
149	Capsulitis	2	2	0.20	0.10	0.10	-0.20	0.50	7	0.10
150	Cerebrovascular accident	2	12	0.20	0.40	-0.20	-0.70	0.20	25	0.40
151	COAD (Chronic Obstructive Airways Disease)	2	9	0.20	0.30	-0.10	-0.50	0.30	18	0.30
152	Cold extremities	2	0	0.20	0.00	0.20	0.00	0.00	2	0.00
153	Death cause uncertain	2	3	0.20	0.10	0.10	-0.30	0.40	10	0.20
154	Dementia	2	1	0.20	0.00	0.20	-0.20	0.50	6	0.10
155	Dermatitis contact	2	1	0.20	0.00	0.20	-0.20	0.50	6	0.10
156	Disc prolapsed	2	3	0.20	0.10	0.10	-0.30	0.40	10	0.20
157	Electrolyte abnormal	2	2	0.20	0.10	0.10	-0.20	0.50	4	0.10
158	Excessive thirst	2	5	0.20	0.20	0.00	-0.40	0.40	8	0.10
159	Galactorrhoea	2	1	0.20	0.00	0.20	-0.20	0.50	6	0.10
160	Haemoptysis	2	0	0.20	0.00	0.20	0.00	0.00	2	0.00
161	Haemorrhage gastrointestinal	2	1	0.20	0.00	0.20	-0.20	0.50	4	0.10
162	Haemorrhage gastrointestinal upper	2	1	0.20	0.00	0.20	-0.20	0.50	8	0.10
163	Hepatitis, jaundice	2	3	0.20	0.10	0.10	-0.30	0.40	7	0.10
164	Hoarseness	2	2	0.20	0.10	0.10	-0.20	0.50	5	0.10
165	Hyperthyroidism	2	1	0.20	0.00	0.20	-0.20	0.50	5	0.10
166	Hypomania	2	8	0.20	0.30	-0.10	-0.50	0.30	17	0.30
167	Inflammatory disease colon	2	5	0.20	0.20	0.00	-0.40	0.40	14	0.20
168	Irritable bowel syndrome	2	11	0.20	0.40	-0.20	-0.60	0.30	17	0.30
169	Marital	2	5	0.20	0.20	0.00	-0.40	0.40	10	0.20
170	Muscle weakness	2	1	0.20	0.00	0.20	-0.20	0.50	4	0.10
171	Obsession/compulsive	2	3	0.20	0.10	0.10	-0.30	0.40	5	0.10
172	Osteoarthritis	2	16	0.20	0.50	-0.40	-0.80	0.10	32	0.50
173	Pain eye	2	2	0.20	0.10	0.10	-0.20	0.50	6	0.10
174	Phobia	2	2	0.20	0.10	0.10	-0.20	0.50	8	0.10
175	Pyrexia of unknown origin	2	2	0.20	0.10	0.10	-0.20	0.50	8	0.10
176	Redundancy	2	1	0.20	0.00	0.20	-0.20	0.50	4	0.10
177	Road traffic accident	2	12	0.20	0.40	-0.20	-0.70	0.20	22	0.30
178	Spondylosis cervical	2	7	0.20	0.20	-0.10	-0.40	0.30	13	0.20
179	Swollen tongue	2	0	0.20	0.00	0.20	0.00	0.00	2	0.00
180	Tinea	2	12	0.20	0.40	-0.20	-0.70	0.20	17	0.30
181	Ulcer peptic	2	1	0.20	0.00	0.20	-0.20	0.50	5	0.10
182	Abscess anorectal	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
183	Acne	1	12	0.10	0.40	-0.30	-0.70	0.10	21	0.30
184	Aggression	1	11	0.10	0.40	-0.30	-0.60	0.10	22	0.30
185	Alopecia	1	0	0.10	0.00	0.10	0.00	0.00	4	0.10
186	Arthritis rheumatoid	1	0	0.10	0.00	0.10	0.00	0.00	4	0.10
187	Assault	1	5	0.10	0.20	-0.10	-0.40	0.20	13	0.20
188	Bell's palsy	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
189	Blepharitis	1	2	0.10	0.10	0.00	-0.20	0.30	4	0.10

190	Breast discharge	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
191	Breast disorder	1	2	0.10	0.10	0.00	-0.20	0.30	5	0.10
192	Bulimia	1	4	0.10	0.10	0.00	-0.30	0.20	6	0.10
193	Burn	1	2	0.10	0.10	0.00	-0.20	0.30	5	0.10
194	Bursitis	1	5	0.10	0.20	-0.10	-0.40	0.20	9	0.10
195	Calculus renal	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
196	Calculus salivary	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
197	Candidiasis oral	1	5	0.10	0.20	-0.10	-0.40	0.20	13	0.20
198	Cardiac arrest	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
199	Cervical erosion	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
200	Choking sensation	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
201	Cholelithiasis, cholecystitis	1	2	0.10	0.10	0.00	-0.20	0.30	4	0.10
202	Chondromalacia	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
203	Cyst Bartholin's	1	0	0.10	0.00	0.10	0.00	0.00	3	0.10
204	Deafness	1	4	0.10	0.10	0.00	-0.30	0.20	6	0.10
205	Dental surgery	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
206	Domestic	1	3	0.10	0.10	0.00	-0.30	0.30	9	0.10
207	Effusion pleural	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
208	Embolus pulmonary	1	0	0.10	0.00	0.10	0.00	0.00	3	0.00
209	Enuresis	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
210	Erythema	1	2	0.10	0.10	0.00	-0.20	0.30	4	0.10
211	Fissure anorectal	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
212	Floaters	1	0	0.10	0.00	0.10	0.00	0.00	3	0.00
213	Ganglion	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
214	Gardnerella infection	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
215	Gastroscopy	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
216	Globus hystericus	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
217	Goitre	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
218	Gout	1	3	0.10	0.10	0.00	-0.30	0.30	5	0.10
219	Granuloma pyogenic	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
220	Gynaecological surgery	1	7	0.10	0.20	-0.10	-0.50	0.20	21	0.30
221	Gynaecology unspecified	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
222	Haematuria	1	3	0.10	0.10	0.00	-0.30	0.30	6	0.10
223	Haemorrhage rectal	1	4	0.10	0.10	0.00	-0.30	0.20	15	0.20
224	Hair change	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
225	Hair loss	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
226	Hemiparesis	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
227	Hernia	1	3	0.10	0.10	0.00	-0.30	0.30	5	0.10
228	Hernia hiatus	1	5	0.10	0.20	-0.10	-0.40	0.20	11	0.20
229	Herpes simplex, skin	1	8	0.10	0.30	-0.20	-0.50	0.20	12	0.20
230	Herpes zoster	1	8	0.10	0.30	-0.20	-0.50	0.20	14	0.20
231	Hyperkeratosis	1	0	0.10	0.00	0.10	0.00	0.00	4	0.10
232	Infection	1	2	0.10	0.10	0.00	-0.20	0.30	5	0.10
233	Infection postoperative	1	2	0.10	0.10	0.00	-0.20	0.30	6	0.10
234	Irritation eye	1	1	0.10	0.00	0.10	-0.20	0.30	7	0.10
235	Ischaemia peripheral	1	6	0.10	0.20	-0.10	-0.40	0.20	11	0.20
236	Laboratory test abnormal	1	0	0.10	0.00	0.10	0.00	0.00	5	0.10
237	Leucocytosis	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
238	Liver function test abnormal	1	0	0.10	0.00	0.10	0.00	0.00	4	0.10
239	Lost consciousness	1	7	0.10	0.20	-0.10	-0.50	0.20	14	0.20
240	Mastectomy	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
241	Mastitis	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00

242	Meniere's disease	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
243	Meningitis	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
244	Neurosis	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
245	Nystagmus	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
246	Obesity	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
247	Oesophageal spasm	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
248	Onychomycosis	1	2	0.10	0.10	0.00	-0.20	0.30	3	0.00
249	Ophthalmic surgery	1	3	0.10	0.10	0.00	-0.30	0.30	8	0.10
250	Orthopaedic surgery	1	7	0.10	0.20	-0.10	-0.50	0.20	18	0.30
251	Osteochondritis	1	1	0.10	0.00	0.10	-0.20	0.30	5	0.10
252	Otitis media	1	17	0.10	0.60	-0.50	-0.90	-0.10	23	0.40
253	Pain groin	1	3	0.10	0.10	0.00	-0.30	0.30	4	0.10
254	Pelvic inflammatory disease	1	3	0.10	0.20	0.00	-0.40	0.40	4	0.10
255	Pharynx irritation	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
256	Photophobia	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
257	Photosensitivity	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
258	Polyuria	1	2	0.10	0.10	0.00	-0.20	0.30	3	0.00
259	Pressure sore	1	2	0.10	0.10	0.00	-0.20	0.30	3	0.00
260	Prolapse rectal	1	2	0.10	0.10	0.00	-0.20	0.30	3	0.00
261	Prolapse uterine	1	2	0.10	0.10	0.00	-0.40	0.40	5	0.10
262	Psychiatric unspecified	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
263	Raynaud's phenomenon	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
264	Renal failure	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
265	Restless legs	1	4	0.10	0.10	0.00	-0.30	0.20	6	0.10
266	Retinal thrombosis vein	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
267	Sore eye	1	4	0.10	0.10	0.00	-0.30	0.20	6	0.10
268	Stomatitis	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
269	Sunburn	1	1	0.10	0.00	0.10	-0.20	0.30	3	0.00
270	Swelling joint	1	5	0.10	0.20	-0.10	-0.40	0.20	10	0.20
271	Tenosynovitis	1	3	0.10	0.10	0.00	-0.30	0.30	5	0.10
272	Thoracic surgery	1	2	0.10	0.10	0.00	-0.20	0.30	6	0.10
273	Threadworms	1	1	0.10	0.00	0.10	-0.20	0.30	4	0.10
274	Toothache	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
275	Torticollis	1	1	0.10	0.00	0.10	-0.20	0.30	2	0.00
276	Ulcer skin	1	7	0.10	0.20	-0.10	-0.50	0.20	12	0.20
277	Ulcer varicose	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
278	Urticaria	1	6	0.10	0.20	-0.10	-0.40	0.20	10	0.20
279	Vaginal soreness	1	4	0.10	0.20	-0.10	-0.50	0.40	5	0.10
280	Valvular disease	1	0	0.10	0.00	0.10	0.00	0.00	1	0.00
281	Varicella	1	5	0.10	0.20	-0.10	-0.40	0.20	8	0.10
282	Veins varicose	1	0	0.10	0.00	0.10	0.00	0.00	2	0.00
283	Weight loss	1	15	0.10	0.50	-0.40	-0.80	0.00	21	0.30
284	Abortion spontaneous	0	1	0.00	0.10	-0.10	0.00	0.00	2	0.00
285	Abscess breast	0	3	0.00	0.10	-0.10	0.00	0.00	5	0.10
286	Acupuncture	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
287	Allergy	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
288	Amaurosis	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
289	Amnesia	0	4	0.00	0.10	-0.10	0.00	0.00	4	0.10
290	Anaemia macrocytic	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
291	Anaphylaxis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
292	Aneurysm	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
293	Animal bite	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00

294	Aphasia, dysphasia	0	1	0.00	0.00	0.00	0.00	0.00	3	0.00
295	Arteriosclerosis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
296	Arteriosclerosis cerebral	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
297	Arteritis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
298	Birth normal	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
299	Bladder irritability	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
300	Bowel obstruction	0	2	0.00	0.10	-0.10	0.00	0.00	4	0.10
301	Burgled	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
302	Campylobacter	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
303	Cardiogenic shock	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
304	Cataract	0	3	0.00	0.10	-0.10	0.00	0.00	7	0.10
305	Chemotherapy	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
306	Choking	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
307	Cyst Baker's	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
308	Cyst Meibomian	0	1	0.00	0.00	0.00	0.00	0.00	3	0.00
309	Cyst ovarian	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
310	Cyst sebaceous	0	3	0.00	0.10	-0.10	0.00	0.00	7	0.10
311	Dacryocystitis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
312	Dehydration	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
313	Delusion	0	2	0.00	0.10	-0.10	0.00	0.00	4	0.10
314	Dependence	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
315	Depersonalization	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
316	Dermatitis artefacta	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
317	Disorders of rhythm	0	6	0.00	0.20	-0.20	0.00	0.00	10	0.20
318	Dry eye	0	1	0.00	0.00	0.00	0.00	0.00	4	0.10
319	Dry skin	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
320	Dupuytren's contracture	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
321	Dyspareunia	0	1	0.00	0.10	-0.10	0.00	0.00	1	0.00
322	Ear nose and throat surgery	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
323	Eardrum perforation	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
324	Eating disorder	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
325	Eczema varicose	0	3	0.00	0.10	-0.10	0.00	0.00	4	0.10
326	Effusion joint	0	2	0.00	0.10	-0.10	0.00	0.00	5	0.10
327	Ejaculation premature	0	1	0.00	0.10	-0.10	0.00	0.00	1	0.00
328	Endometriosis	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.10
329	Endoscopy	0	0	0.00	0.00	0.00	0.00	0.00	3	0.00
330	Epididymitis	0	2	0.00	0.20	-0.20	0.00	0.00	2	0.10
331	Episcleritis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
332	Eruption bullous	0	1	0.00	0.00	0.00	0.00	0.00	6	0.10
333	Erythrocyte sedimentation rate raised	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
334	Exophthalmos	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
335	Faecal impaction	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
336	Faecal incontinence	0	1	0.00	0.00	0.00	0.00	0.00	4	0.10
337	Fistula colo-vaginal	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
338	Fixed eruption	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
339	Folliculitis	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
340	Foot drop	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
341	Formication	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
342	Gingivitis	0	4	0.00	0.10	-0.10	0.00	0.00	7	0.10
343	Glandular fever	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
344	Glaucoma	0	4	0.00	0.10	-0.10	0.00	0.00	4	0.10

345	Haematoma spontaneous	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
346	Haemorrhage postcoital	0	1	0.00	0.10	-0.10	0.00	0.00	2	0.00
347	Haemorrhage subconjunctival	0	4	0.00	0.10	-0.10	0.00	0.00	7	0.10
348	Haemorrhage vaginal	0	2	0.00	0.10	-0.10	0.00	0.00	4	0.10
349	Haemorrhage vitreous	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
350	Haemorrhagic diarrhoea	0	1	0.00	0.00	0.00	0.00	0.00	3	0.00
351	Haemospermia	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
352	Heart block	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
353	Hepatic failure	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
354	Herpes ophthalmic	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
355	Herpes zoster oticus	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
356	Hydrocele	0	1	0.00	0.10	-0.10	0.00	0.00	1	0.00
357	Hydrocephalus	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
358	Hyperlipidaemia	0	4	0.00	0.10	-0.10	0.00	0.00	5	0.10
359	Hyperuricaemia	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
360	Hypoglycaemia	0	2	0.00	0.10	-0.10	0.00	0.00	2	0.00
361	Hysteria	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
362	Infection bone	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
363	Insect bite & sting	0	0	0.00	0.00	0.00	0.00	0.00	3	0.00
364	Iritis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
365	Ischaemia mesenteric	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
366	Keratitis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
367	Lacrimal block	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
368	Lacrimation	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
369	Lichen planus	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
370	Lumbago	0	2	0.00	0.10	-0.10	0.00	0.00	4	0.10
371	Macular degeneration	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
372	Male reproductive system unspecified	0	1	0.00	0.10	-0.10	0.00	0.00	1	0.00
373	Metabolic unspecified	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
374	Minor surgery	0	5	0.00	0.20	-0.20	0.00	0.00	7	0.10
375	Motor neurone disease	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
376	Multiple sclerosis	0	3	0.00	0.10	-0.10	0.00	0.00	3	0.00
377	Myopathy	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
378	Nail change	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
379	Nerve entrapment	0	2	0.00	0.10	-0.10	0.00	0.00	8	0.10
380	Neuralgia postherpetic	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
381	Neuritis optic	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
382	Neurological surgery	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
383	Neuropathy	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
384	Oesophageal stricture	0	1	0.00	0.00	0.00	0.00	0.00	3	0.00
385	Optic atrophy	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
386	Osteoporosis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
387	Other tumours	0	1	0.00	0.00	0.00	0.00	0.00	5	0.10
388	Otorrhoea	0	2	0.00	0.10	-0.10	0.00	0.00	3	0.00
389	Pain bone	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
390	Paraplegia	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
391	Paresis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
392	Parotitis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
393	Plantar fasciitis	0	3	0.00	0.10	-0.10	0.00	0.00	3	0.00
394	Pleurisy	0	3	0.00	0.10	-0.10	0.00	0.00	5	0.10
395	Poisoning nonmedicinal	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00

396	Polymyalgia rheumatica	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
397	Post viral syndrome	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
398	Proctalgia	0	2	0.00	0.10	-0.10	0.00	0.00	2	0.00
399	Proctitis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
400	Raped	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
401	Rectal discharge	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
402	Rectocele	0	1	0.00	0.10	-0.10	0.00	0.00	1	0.00
403	Red cell abnormal	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
404	Respiratory failure	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
405	Retinal detachment	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
406	Rotator cuff	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
407	Saliva increased	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
408	Scabies	0	2	0.00	0.10	-0.10	0.00	0.00	5	0.10
409	Schizophrenia	0	0	0.00	0.00	0.00	0.00	0.00	2	0.00
410	Scoliosis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
411	Seborrhoea	0	2	0.00	0.10	-0.10	0.00	0.00	5	0.10
412	Senility	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
413	Septicaemia	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
414	Shop lifting	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
415	Sialadenitis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
416	Sinus pilonidal	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
417	Somnambulism	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
418	Spondylitis cervical	0	2	0.00	0.10	-0.10	0.00	0.00	2	0.00
419	Spondylosis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
420	Stye	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
421	Superficial venous thrombosis	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
422	Tendinitis	0	6	0.00	0.20	-0.20	0.00	0.00	7	0.10
423	Tenesmus	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
424	Thrombocytosis	0	2	0.00	0.10	-0.10	0.00	0.00	2	0.00
425	Thrombophlebitis	0	4	0.00	0.10	-0.10	0.00	0.00	4	0.10
426	Thyroid surgery	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00
427	Thyroiditis	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
428	Tietze's syndrome	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
429	Trigger finger	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
430	Ulcer corneal	0	1	0.00	0.00	0.00	0.00	0.00	2	0.00
431	Ulcer pharynx	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
432	Vaccination reaction	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
433	Vascular surgery	0	3	0.00	0.10	-0.10	0.00	0.00	5	0.10
434	Volvulus colon	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
435	Wart	0	3	0.00	0.10	-0.10	0.00	0.00	6	0.10
436	Wart genital	0	1	0.00	0.00	0.00	0.00	0.00	1	0.00
437	Xanthelasma	0	0	0.00	0.00	0.00	0.00	0.00	1	0.00

Nausea/Vomiting was the adverse event with the highest incidence density in month one (53.5 per 1000 patient-months of exposure). The difference between the rate of events in month one and months 2-6 was examined. As in the mirtazapine analysis, where the 99% confidence

limits around the point estimate of the difference did not include the null value, this suggests that the rate of events in month one was significantly greater than the rate of events in months 2-6. This result can be considered to be a signal of a possible adverse event associated with starting the drug.

The following clinical adverse events occurred significantly more commonly in month 1 compared to months 2-6, when the 99% confidence limits of the differences were calculated: drowsiness/sedation, malaise/lassitude, headache/migraine, insomnia, tremor, dizziness, impotence/ejaculation failure, diarrhoea, sweating, dyspepsia, pain abdomen, anxiety and suicide attempt/overdose. These results can be considered to be a signal of a possible adverse event associated with starting the drug. However, anxiety and depression is more likely to be associated with the indication for treatment with paroxetine than with adverse events to the drug itself.

Pregnancies

137 pregnancies were recorded at any time during the study (Table 4.9). Sixty three (63) babies may have been exposed to paroxetine during the first trimester. There were 36 single deliveries and three sets of twins in this group. One twin was stillborn. There were no congenital abnormalities in any of the live births.

Table 4.9. Outcomes of pregnancies

Exposure to paroxetine	Total	Live Birth	Spontaneous abortion	TOP	Outcome unknown
Drug stopped before getting pregnant	66	12	9	5	40
Drug taken in 1st trimester	63	39*	8	11	5
Exposure uncertain	8	2	1	1	4
TOTAL	**137**	**53**	**18**	**17**	**49**

* Three sets of twins (one twin stillborn)

Deaths

The causes of death in this study were established for 350 of the 416 patients who died. There were a wide variety of causes (Table 4.10). Two hundred twenty four (224) occurred during the sixth month study period. The majority of deaths were due to natural causes including cardiovascular, cancer and respiratory.

Twenty five patients were reported to have committed suicide during the six-month period, eight of whom were known to have taken overdoses. Paroxetine had not been taken by any of these patients. Twelve patients had committed suicide by violent means (nine hanging, one jumped from a tall building, one from carbon mono-oxide poisoning and one by suffocation with a plastic bag). In the other five cases the manner of death was not established. No deaths were attributed to paroxetine.

Table 4.10: Causes of death

Causes of death for paroxetine

	Total	Mth 1	Mth 2	Mth 3	Mth 4	Mth 5	Mth 6	>6	Not Known
Anaemia	1	0	0	0	0	0	0	1	0
Aneurysm Aortic	1	0	0	0	0	1	0	0	0
Atherosclerosis Cerebral	1	0	0	0	0	0	0	1	0
Bronchopneumonia	5	0	0	2	0	0	0	3	0
Cancer	1	1	0	0	0	0	0	0	0
Carcinoma Breast	1	0	0	0	0	0	0	1	0
Carcinoma Colon	1	0	0	0	0	0	0	1	0
Carcinoma Lung	1	0	0	1	0	0	0	0	0
Carcinoma Parotid	1	0	0	1	0	0	0	0	0
Cerebrovascular accident	5	1	1	0	2	0	0	1	0
Cirrhosis	1	1	0	0	0	0	0	0	0
COAD (Chronic Obstructive Airways Disease)	3	0	1	0	0	1	0	1	0
Congestive cardiac failure	1	1	0	0	0	0	0	0	0
Death Cause Uncertain	147	6	4	7	5	6	3	21	95
Diabetes mellitus	1	0	1	0	0	0	0	0	0
Eosinophilia	1	0	0	0	0	0	0	1	0
Fibrillation Atrial	1	1	0	0	0	0	0	0	0
Fracture	1	0	0	0	0	0	0	1	0
Gall Bladder Perforated	1	0	0	0	0	1	0	0	0
Infection Chest	1	0	1	0	0	0	0	0	0
Ischaemic Heart Disease	7	0	2	3	0	0	1	1	0
Murdered	1	0	0	0	0	1	0	0	0
Myocardial Infarction	11	2	0	2	1	2	2	2	0
Overdose	1	0	0	1	0	0	0	0	0
Overdose Other Drug	5	3	0	0	1	0	0	1	0
Parkinson's Disease	1	0	0	0	0	0	0	1	0
Senility	3	2	0	0	1	0	0	0	0
Stenosis Aortic	1	0	0	0	0	1	0	0	0
Suicide Attempt	1	0	1	0	0	0	0	0	0
Suicide	25	9	4	5	5	1	1	0	0
Valve Incompetence	1	0	0	0	0	1	0	0	0
Total	**233**	**18**	**11**	**17**	**10**	**14**	**6**	**37**	**95**

CHAPTER 5: DISCUSSION

PRINCIPAL FINDINGS OF THE MIRTAZAPINE AND PAROXETINE PEM STUDY

Summary of Mirtazapine study results

The safety of mirtazapine was studied by using the technique of Prescription Event Monitoring in England between September 1997 and February 1999. Drowsiness/sedation and malaise lassitude were the most frequent reported events and had the highest incidence density (per 1000 patient-months) in the first month of treatment. Agitation, aggression, rash, hallucinations and abnormal dreams were unlabelled adverse events (AEs), while abnormal liver function test, syncope, abnormal behaviour and visual disturbances were labelled AEs possibly due to mirtazapine use. Serious suspected adverse drug reactions (ADRs) reported were facial oedema, allergy, bone marrow toxicity and myelodysplasia.

Summary of Paroxetine study results

The safety of paroxetine, the third of six SSRIs launched in the UK was studied by using the technique of Prescription Event Monitoring in England between March 1991 and March 1992. Withdrawal symptoms and tremor were the most frequently reported ADRs, while nausea/vomiting was the event with highest incidence density (per 1000 patient-months) in the first month of treatment. Withdrawal symptoms, tremor, blurring of vision and hyponatraemia were the unabelled adverse events. Male sexual dysfunction was the only adverse event which appeared to be almost specific to paroxetine. The incidence rate during the first month was 7.1 per 1000 patient-months exposure, compared with 0.3 and 0.5 for fluvoxamine and fluoxetine respectively.

Table 5.1. Summary of Mirtazapine and Paroxetine Study Findings

	Mirtazapine	**Paroxetine**
Total Cohort	13 554	13741
Response Rate	56%	61%
Voids	13.6%	14%
Age	Male: 46.9 years Female: 47.7 years	Male: 48.6 years Female: 48.8 years
Sex:	Male: 38.4% Female: 61.1%	Male: 36.4% Female: 62.4%
Indications	Depression: 57.6% Not specified: 30.7%	Depression: 82% Not specified: 11
Duration of treatment	End of 6 months on mirtazapine: 40%	End of 6 months on paroxetine: 33%
ADRs	807 events (5.9% of total cohort) (0.2% reported to CSM)	119 events (0.8% of total cohort) (0.7% reported to CSM)
Most frequently reported ADRs	Unspecified side effects: 177 Drowsiness/sedation: 116 Malaise/Lasitude: 71	Withdrawal symptoms: 15 Tremor: 13 Sweating: 8
Reasons for stopping treatment	8634 (63.7% of total cohort)	4434 (32.2% of total cohort)
Most frequent reasons for stopping treatment	Not effective: 2432 (17.9%) Drowsiness/sedation: 800 (5.9%) Weight gain: 362 (2.6%)	Not effective: 1391 (10.1%) Nausea/vomiting: 459 (3.3%) Drowsiness/sedation: 183 (1.2%)
Incidence Densities in 1st month of treatment	Drowsiness/sedation: 58.1 Malaise/Lassitude: 27.8 Dizziness: 15.6	Nausea/Vomiting: 53.5 Drowsiness/sedation: 20.5 Maliase/Lassitude: 18.1
Pregnancies	Total: 60 Live births: 41 (one Patent	Total: 137 Live births: 57 (3 sets of twins)

	Ductus aretiosus at 29 weeks)	
Deaths	Total: 257 Suicides: 13 (all violent; 8 patients on mirtazapine at time of death, 5 patients stopped mirtazapine one month before death)	Total: 416 Suicides: 25 (8 overdoses, 12 sucides by violent means, 5 manner of death unknown)

Strengths of the Mirtazapine and Paroxetine studies

The investigations of mirtazapine and paroxetine were both observational cohort studies in which there was no interference with the decision of the general practitioners regarding which drug to prescribe for their individual patients. These studies was, therefore, free of the kind of selection biases which are unavoidable if there was interference with the prescribing decision or if there is a formal process by which patients are either included or excluded from the study. In addition, both these studies provided information on the 'real-world' use of mirtazapine and paroxetine. The patients included in this investigation were those who would, in everyday clinical practice, be prescribed these drugs. They were likely to cover a greater range of ages, to include patients exposed to mirtazapine and paroxetine during pregnancy, children, and to have included more patients in need of polypharmacy than the highly selected patients normally included in the clinical studies undertaken for the marketing authorisation application.

For mirtazapine, the study included over 13000 patients (60 022 patient-months of exposure to mirtazapine) and for paroxetine the study included over 15000 patients (65 449 patient-months

of exposure to paroxetine) and was likely, therefore to have substantially increased previous experience compared with the clinical data available at the licensing stage. Both these studies were of national proportions and were systematic, in the sense that the entire cohort for whom prescriptions were available represented the first group of patients prescribed mirtazapine or paroxetine following their introduction into clinical practice in England.

The studies were based upon 'event' monitoring and was therefore also capable of identifying signals which none of the participating general practitioners might have suspected to have been due to an adverse drug reaction.

Limitations of the Mirtazapine and Paroxetine study

In the mirtazapine study, only 15, 684 (56%) of the 28,016 green forms that were posted were returned, whereas only 15, 907 (61%) of the green forms that were posted were returned in the paroxetine study. One similarity is that, even though these two studies were undertaken in different time frames (the paroxetine study was conducted between March 1991 to March 1992, the mirtazapine study between September 1997 and February 1999), the response rate in both the studies was similar. This is a rather low response rate which could conceal non-response biases. The degree to which non-response bias has affected these results was not assessed, because the population of patients whose doctors did return the green forms was not compared with the population of patients whose doctors did not return these questionnaires. The response rate is, nevertheless, substantial compared with the proportion describing suspected adverse drug reactions in spontaneous ADR reporting schemes[35,36]. It is also a good response rate compared with general practitioner postal surveys in general[37].

The response rate was lowest amongst those doctors who had prescribed mirtazapine and paroxetine to the greatest number of patients. However, the response rate for mirtazapine is slightly lower than those for five other antidepressants studied in the immediate post-marketing periods by means of PEM studies conducted at the DSRU (fluvoxamine 59.9%, fluoxetine 58.4%, sertraline 60.2%, paroxetine 60.7% and moclobemide 58.8%)[38]. In only two of the other antidepressants studied by PEM were the response rates lower than with mirtazapine (venlafaxine 54.6% and nefazodone 54.9%).

In both the studies, a high proportion of green forms that were returned were classified as voids (mirtazapine study - 2130 of the 15,684 green forms, 14 %; paroxetine study - 2166 of the 15, 907 green forms, 14 %). However, the number of patients no longer egistered with the GPs (included within the void green forms) was greater in the mirtazapine cohort (1269, 59.5%) when compared with the paroxetine cohort (1046, 48.2%). Migration of the patient population in these studies may produce its own bias, as patients with mental health problems may be treated more often as temporary residents than other members of the general population. They may have difficulty in maintaining regular jobs and steady relationships and in securing accommodation[39].

The data are limited to experience in general practice and therefore do not include information on patients initially prescribed mirtazapine and paroxetine in secondary care settings, unless treatment was continued by their general practitioner. In addition, as this was an observational study of patients identified from dispensed prescriptions of mirtazapine and paroxetine, it was not possible to estimate the degree of compliance with the prescribed medication.

Finally, the methods used in the analysis of data obtained during PEM in the paroxetine study are similar to those used for the mirtazapine study. However, PEM for paroxetine was undertaken between March 1991 to March 1992[40] and data for paroxetine had been transferred between computer systems, which may have resulted in some loss of data. The methodology used for determining possible signals in the original evaluation was by use of Rate Ratios (RR) for the events during the first month of treatment and the subsequent 6 months. For the paroxetine data analysis, described within chapter 4 of this thesis, I used Incidence Densities (ID) in place of Rate Ratios, for determining possible signals, and to better compare the findings with those for mirtazapine. During this analysis, there have been instances when few green forms were lost from the archived data set and this may have caused some bias of missed data in the analysis.

Implications of the study findings

Discontinuing treatment

Recommendations for the drug treatment of depression include four to six months of therapy after the initial treatment phase to prevent relapse[41]. For the mirtazapine study only 48.6% of patients were being prescribed mirtazapine at the end of four months, and only 40.0% at the end of six months, whereas in the paroxetine study, only 33.0% of patients were still being prescribed paroxetine at the end of six months. There is therefore a clear need for further educational and training efforts stressing the importance of continuing treatment beyond symptomatic recovery, to reduce the chance of early relapse of depression.

The most frequently reported reasons for the discontinuation of therapy in the mirtazapine study were: not effective (2432 cases; 17.9% of total cohort), condition improved (1117 cases; 8.2% of total cohort) and patient request (483 cases; 3.5% of total cohort), while in the paroxetine study the most frequently reported reasons for the discontinuation of therapy were: not effective (1391 cases; 10.1% of total cohort) and effective (944 cases; 6.8% of total cohort). There are multiple reasons for discontinuing antidepressant treatment[42], but the most important factor is the development of side effects and intolerance of drug therapy. The most frequently reported symptoms resulting in withdrawal of mirtazapine included drowsiness (424 cases) /sedation (376 cases) (800 cases; 5.9% of total cohort), weight gain (362 cases; 2.6% of total cohort), and intolerance (228 cases; 1.6% of total cohort); while in the paroxetine study they included nausea (376 cases) / vomiting (83 cases) - 459 cases; 3.3% of total cohort, drowsiness (137 cases) / sedation (46 cases) – 183 cases; 1.3% of total cohort and malaise (120 cases) / lassitude (51 cases) – 171 cases; 1.2% of total cohort. These side effects reduce the possibility of offering long term mirtazapine and paroxetine treatment, in some patients.

Drowsiness/sedation

There were 985 (7.2% of total cohort) cases of drowsiness/sedation reported in the mirtazapine study of which 654 cases (66.3%) were reported in the first month. A substantial proportion (81.2%) of the 985 cases of drowsiness/sedation discontinued treatment because of the event. Drowsiness/sedation was also amongst the most frequently reported suspected ADRs to the MCA for mirtazapine. When compared to paroxetine, there were 327 cases (2.3% of total cohort) of drowsiness/sedation reported in the study, which is considerably less than that of mirtazapine, but 232 cases (70.9%) were reported in the first month of treatment which is

proportionally high when compared with mirtazapine cohort (66.3%). Also, when compared to mirtazapine (81.2% discontinued treatment due to the event), the proportion of cases which had discontinued treatment due to the event was significantly lower in the paroxetine cohort (55.9% of the 327 cases of drowsiness/sedation).

It is well known that sleep disturbances are considered characteristic of mood disorders including unipolar depression. At least 80% of depressed people either experience insomnia -- difficulty falling asleep or, most often, staying asleep, while another 15% of the depressed sleep excessively[43]. Although the precise pathogenesis of sleep disturbances in major depression is unknown, researchers note that the same neurotransmitter systems that regulate mood, motivation, energy, and other functions may be abnormal in depression and contribute to sleep disturbance. Serotonergic neurons play a vital part in the modulation of the onset and maintenance of sleep, and sleep disturbances in depression have been linked to disturbances of serotonergic pathways.

Clinical trials have reported significantly higher incidences of sedation with mirtazapine when compared with placebo. The adverse effects of sedation may be attributed to the antagonistic action of mirtazapine at histamine H_1 receptors. Sedation often seems to be present to a greater extent at lower doses, as the alertness of patients taking 15 and 30mg/day doses has found to be comparable even in the early days of treatment[44,45]. One of the most common side effects seen in clinical trials of mirtazapine is dose-dependent drowsiness (54%)[45], which occurred in the first four weeks of treatment, while in this study drowsiness/sedation for mirtazapine was reported in 654 cases (66.3%) in the first month of treatment.

The side effect profile of paroxetine is similar to that of the other SSRIs, except that paroxetine tends to be more sedating and constipating, probably because of its anticholinergic activity[46]. A PEM study comparing the safety profile of four SSRIs showed that drowsiness/sedation was reported more often with fluvoxamine and paroxetine (IDs 22.6 and 20.5 per 1000 patient-months) in the first month of treatment than with fluoxetine and sertraline (IDs 8.2 and 7.3 per 1000 patient-months). However, when compared to mirtazapine the IDs for drowsiness/sedation was significantly less in the paroxetine cohort (IDs for mirtazapine 58.1 and for paroxetine 20.5 per 1000 patient-months).

There are a number of clinical implications regarding the development of drowsiness/sedation with antidepressant treatment. In the clinical setting, patients may experience morning sedation and daytime drowsiness or fatigue. Drowsiness/sedation as an adverse effect of mirtazapine and paroxetine may impair judgement, thinking, and particularly, motor skills. The drowsiness associated with the use of these drugs may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that these therapies do not adversely affect their ability to perform these activities satisfactorily. Secondly, sedation is also one of the most common causes of drug-induced falls and fractures, especially in older people due to confusion and slowing of reaction time. Thirdly, the patients experiencing drowsiness/sedation need to be prescribed other drugs carefully, as combination treatments may further worsen drowsiness. Also, patients must be cautioned about the intake of alcohol, as antidpressants can potentiate the effect of alcohol, with an increase in drowsiness and sedation.

Weight gain

Weight gain during antidepressant treatment can be a sign of improvement in patients who have weight loss as a symptom of depression, or a residual symptom in patients who overeat when depressed. However, significant weight gain during the acute phase of treatment or weight gain that continues despite achieving full remission of depressive symptoms is likely to be a side effect of antidepressant treatment. Weight gain is a relatively common problem during both acute and long-term treatment with antidepressants, and it is an important contributing factor to non-compliance[47]. It appears that tricyclic antidepressants (TCAs) and perhaps monoamine oxidase inhibitors (MAOIs) may be more likely to cause weight gain than the selective serotonin reuptake inhibitors (SSRIs) or other newer antidepressants, with the exception of mirtazapine, which may be placed between the SSRIs and the TCAs in terms of relative risk for weight gain. Paroxetine may be more likely to cause weight gain than the other SSRIs during long-term treatment[48], although more studies are necessary to confirm these impressions.

In the mirtazapine cohort there were 523 (3.8% of total cohort) cases of weight gain reported of which 175 cases (33.4%) were reported in the first month. 362 (69.2%) of the 523 cases of weight gain discontinued treatment because of the event; while in the paroxetine cohort there were 84 (0.6% of total cohort) cases of weight gain, of which 14 (16.6%) cases of weight gain discontinued treatment because of the event.

Apart from the high rates of treatment discontinuation and non-compliance as a result of weight gain during antidepressant therapy, there are other clinical implications as well. In this study nearly 70% of patients discontinued mirtazapine as a result of weight gain. Firstly,

weight gain associated with antidepressant medication affects general health and quality of life and can be difficult to manage. Secondly, weight gain associated with some psychotropic drugs (e.g. mirtazapine, olanzapine) has emerged as a major clinical problem during the treatment of some patients, as weight gain may lead to medical problems such as type 2 diabetes mellitus, coronary artery disease including hypertension, sleep apnea, certain cancers, low back pain and arthritis[49]. Some studies have suggested that mirtazapine treatment may lead to increases in blood lipids[50,51]. Weight gain has particular implications for women in terms of hormonal changes associated with menstrual irregularity, early menopause, sexual dysfunction and infertility. There are also negative impacts on self-esteem, stigma, quality of life, treatment adherence, and health care use. The above clinical implications should be taken into account when prescribing antidepressants to patients with depression.

Sexual dysfunction

Sexual dysfunction is common among individuals with major depressive disorder. For instance, a study by Kennedy and colleagues[52], revealed that of 134 patients with major depression surveyed, 40% of men and 50% of women reported decreased sexual interest; 40% to 50% of the sample also reported reduced levels of arousal. Sexual dysfunction is also a common side effect of antidepressant treatment, particularly with SSRIs, and it has been estimated that treatment-emergent SSRI-induced sexual dysfunction ranges from approximately 30% to 70% of patients treated for depression[53,54,55].

Antidepressant-induced sexual dysfunction becomes an important issue in the context of treatment effectiveness, as antidepressant medications are helpful only insofar as patients take them. Intolerable side effects may be one reason that patients are non-compliant with

antidepressant treatment. Given the important clinical implications of premature discontinuation -- for example, higher rates of relapse and recurrence -- increasing attention is currently being devoted to the management of antidepressant-induced sexual dysfunction and other unwanted side effects of pharmacotherapy for depression.

The SSRIs have the highest incidence of sexual dysfunction, close to 40% to 50%[54]. The incidence of sexual dysfunction associated with bupropion, mirtazapine and nefazodone is fairly low, usually less than 10%. In this study, the were a total of 71 (0.5% of total cohort) cases of sexual dysfunction (ID of 8.9 per 1000 patient-months), of which 32 (45%) cases were reported in the first month of treatment, and 22 (30.9%) cases discontinued treatment due to the adverse event in the paroxetine cohort. In the mirtazapine cohort there were a total of 29 (0.2% of total cohort) cases of sexual dysfunction of which 10 (34.4%) cases were reported in the first month of treatment and 13 (44.8%) cases were reported to have discontinued treatment.

Need for Continuous Postmarketing Surveillance

The side effect profile of a licensed medication is not fully identified during the clinical trial programme conducted prior to its launch[19]. With mirtazapine, the adverse events, not confounded by indication, that were reported significantly more frequently in the first month of treatment compared to the second to sixth months were drowsiness/sedation, malaise/lassitude, dizziness, weight gain, intolerance, nausea/vomiting, anxiety, headache/migraine, respiratory tract infection, unspecified side effects, insomnia, appetite increased, oedema, agitation, dreams abnormal, aggression, tremor and confusion. Of these only drowsiness/sedation, weight gain, malaise/lassitude, nausea/vomiting were described in the SPC for mirtazapine[17], at the

time of its launch. However, other events (anxiety, insomnia, oedema, agitation, aggression, abnormal dreams, aggression and tremor) are unlabelled adverse events, not included in the SPC. Similarly with paroxetine the adverse events not confounded by indication and that were reported significantly more frequently in the first month of treatment were nausea/vomiting, drowsiness/sedation, malaise/lassitude, headache/migraine, insomnia, tremor, dizziness, impotence/ejaculation failure, diarrhoea, sweating, dyspepsia, pain abdomen, anxiety and suicide attempt/overdose. These events in both the mirtazapine and paroxetine studies can be considered to be signals of a possible adverse event associated with starting the drug. However, anxiety and depression is more likely to be associated with the indication for treatment with paroxetine and mirtazapine than with adverse events to the drug itself. This demonstrates the need for systematic post-marketing surveillance, at least in the period that follows the launch of a new medication.

Adequate systems for spontaneous monitoring of adverse drug reactions

Headache, abnormal dreams, agitation, intolerance, irritability, aggression, tremor, withdrawal symptom and oedema were also the events most commonly reported as suspected ADRs, excluding unspecified side effects, and the reason for stopping treatment with mirtazapine. These events are also amongst those reported most frequently as suspected ADRs to the Medicines Control Agency (MCA_ (ADROIT DAP- listing 6/12/99; lower leg oedema 44, oedema NOS 43, abnormal dreams eight, insomnia 22, irritability 22, aggression 15, agitation 17, withdrawal reactions nine, hallucinations 17 and rash 25). Only a proportion of adverse events described on green forms were reported to the regulatory authorities, suggesting that

comprehensive assessment of the profile of medications is not possible through current systems for spontaneous monitoring of adverse drug reactions.

Consideration of specific adverse events in Mirtazapine & Paroxetine cohort

A substantial proportion (40.4%) of the 84 cases of rash discontinued treatment because of the event. Rash was also amongst the most frequently reported suspected ADRs to the MCA but rash was not included in the SPC. Of the reports of cardiovascular events, the possibility that mirtazapine was associated with the event could not be excluded for four cases of palpitations ,which resolved on discontinuing mirtazapine treatment.

There were nine possible cases of hypotension of which only one was reported as possible suspected ADR. There were 116 reports of oedema, of which 33.6% discontinued the drug due to the event. Oedema has been listed as one of the rare undesirable side effects in the SPC. The other cardiovascular events possibly related to mirtazapine in this study were dizziness, described in 122 reports (57 reported as possible suspected ADRs), and oedema, described in 30 reports (7 reported as possible suspected ADRs). Dizziness in particular has important clinical implications, especially in the elderly as it is known to cause increased falls and fractures in that population.

In the observational study for mirtazapine there were a total of 126 (1% of total cohort; ID 5.3 per 1000 patient-months) reported cases of agitation, of which nearly 60 (48%) cases were

reported in the first month of treatment and in 73 (58%) cases it was the reason for stopping treatment. Also, of the 73 possible cases of agitation 11 reported as possible suspected ADR. Aggression was reported in a total of 88 (0.6% of total cohort) cases, of which 51 (63.7%) cases were reported in the first month and 55 (62.5%) stopped mirtazapine. Also of the 70 possible cases of aggression 14 reported as possible suspected ADR. There were 31 possible reports of abnormal dreams (15 reported as possible suspected ADR); 13 reports of hallucinations (two reported as suspected ADR); 14 possible cases of tremor (11 reported as suspected ADR); and five possible cases of withdrawal symptoms which were also reported as possible suspected ADRs. It is often difficult to distinguish adverse drug reactions manifest through changes in mental state or behaviour, from the underlying disorder being treated with psychotropic drugs, and particular vigilance may therefore be required in patients with mental health problems and with adverse events that appear similar to psychological symptoms. In this patient group, problems such as apathy, cognitive impairment and lack of insight may also lead to difficulties in the reporting of adverse effects.

There were two cases of hepatic failure in this study, but these were not attributed to mirtazapine. There were 12 cases of abnormal liver function tests considered possibly related to mirtazapine use, four of which were also reported as possible suspected ADRs by the GPs. There were few serious events reported in this study. There were five reports of facial oedema, three cases of allergy, two cases of bone marrow toxicity and one case of myelodysplasia possibly associated with mirtazapine use.

One of the current concerns regarding paroxetine treatment is the potential for development of dependence.. In the paroxetine cohort there were a total of 15 reports of adverse reactions due to withdrawal reactions, while in the mirtazapine cohort there were 5 cases reported.

In recent years, the CSM has drawn attention to a possible increase in the frequency of 'withdrawal' symptoms with SSRIs. During this study there was a greater tendency over time among GPs to use the word "withdrawal" when recording events occurring after discontinuation of antidepressant drugs, hypnotics and tranquillisers. The reports with events as "withdrawal symptoms" were analysed in detail, but they did not appear to provide any clear evidence of dependence. Many events were spontaneous, others merely represented a recurrence of symptoms present before the drug was stopped. There were certainly no reports such as tolerance, craving, drug-seeking behaviour or self-neglect which would support the diagnosis of physical or psychological dependence upon SSRIs.

The assessments of reports of epilepsy reported for paroxetine were inconclusive. There were some suggestions, that in five known epileptic patients, the fits might have been rather more frequent while using paroxetine, but no objective data - such as diaries recording the frequency of fits - were available. The reports of extra-pyramidal symptoms were also examined, and it was concluded that if they were drug-induced, this was more a class effect of SSRIs and not one which is specific to paroxetine, having been seen in previous PEM studies with other SSRIs. Tremor also appeared to be a class effect of all other SSRIs studied by PEM.

There were two published literature reports of hyponatraemia with SSRI treatment, and therefore the reports of the seven patients in this study were reviewed. All but one were elderly and it was concluded that one of the seven probably developed hyponatraemia after paroxetine had caused vomiting.

The only noteworthy difference between paroxetine and other two SSRIs studied by PEM was the higher incidence of male sexual dysfunction. The incidence rate during the first month was 7.1 per 1000 patient-months exposure, compared with 0.3 and 0.5 for fluvoxamine and fluoxetine respectively[31].

Pregnancies

It is well known that a substantial number of women of child-bearing age suffer from depression. A recent prevalence study was published in which 3472 pregnant women were screened for depressive symptoms, in which the authors found that 20% of the women surveyed scored above the cut-off score for depressive symptoms[56]. This statistic coupled with the fact that at least 50% of pregnancies are unplanned means that a relatively large number of women may use an antidepressant in pregnancy, especially in the early stages.

The safety of medication during pregnancy is always a concern particularly for newly marketed drugs, because of the limited experience of a drug during human pregnancy before marketing. However, severe depression and psychiatric problems may complicate pregnancy and it is recommended that minimal therapy should be used to treat psychiatric problems and depression because of the potential risks to mother and foetus. Few studies exist in the

literature on pregnancy outcomes following exposure to antidepressants. Those that have been published are comprised of sample sizes of 150 or less, which allow the detection of only a fourfold increase in risk for major malformations above the baseline of 1-3%.

A meta analysis of the prospective cohort studies that compared outcomes from exposed women with those from non-exposed women for the currently available SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) SNRI (venlafaxine), dual action drugs (nefazodone, trazodone and mirtazapine) and bupropion[57], showed that malformations detected from the individuals studies did not consistently present any one malformation or cluster of malformations, and that the observed anomalies (e.g. ventricular septal defect, hypospadius and cleft palate) were amongst the mostly commonly reported problems. In the PEM studies for mirtazapine and paroxetine, 41 women were known to have taken mirtazapine during the first trimester of pregnancy, of which there were four premature births and the baby born at 29 weeks had patent ductus arteriousus; while in the paroxetine study 63 women were known to have taken the drug in the first trimester of pregnancy, and there were no reports of congenital abnormalities. However, it may be helpful for physicians to question women of reproductive age whether they are intending to become pregnant, prior to starting treatment with newly licensed drugs of uncertain safety in pregnancy.

Deaths

There has been concern over a possible relationship between the use of antidepressants and deaths due to suicides and debate persists on whether the selective serotonin reuptake inhibitors might cause the emergence or worsening of suicidal ideas in vulnerable patients. All seriously

depressed patients are at potential risk of suicide and up to 15% of patients with unipolar depression eventually commit suicide and many patients will make suicide attempts[58].

Fergusson et al[59], conducted a systematic review of published randomised controlled trials comparing SSRIs with either placebo or other active treatments in patients with depression and other clinical conditions and found an almost twofold increase in the odds of fatal and non-fatal suicidal attempts in users of SSRIs compared with users of placebo or other therapeutic interventions (excluding tricyclics). No increase in risk was seen, however, when only fatal suicidal attempts were compared between SSRIs and placebo, and also no differences were observed when overall suicide attempts were compared between users of SSRIs and tricyclic andidepressants. The systematic review reported by Gunnell et al[60], included published and unpublished randomised controlled trials submitted by pharmaceutical companies to the safety review of the Medicine and Healthcare products Regulatory Agency (MHRA). These trials compared SSRIs with placebo in adults with depression and other clinical conditions. The researchers found no evidence for an increased risk of completed suicide, only weak evidence of an increased risk of non-fatal self-harm, and inconclusive evidence of an increased risk of suicidal thoughts. A nested case-control study reported by Martinez et al[61], based on information extracted from the General Practice Research Database, analysed the risk of non-fatal self harm and suicide in patients with a new diagnosis of depression who were prescribed SSRIs or tricyclics. The cohort included 146 095 patients. In comparison with users of tricyclics, users of SSRIs were not at increased risk of suicide or non-fatal self harm. However, in patients aged 18 years or less, weak evidence indicated a higher risk of non-fatal self harm in those prescribed SSRIs.

In the mirtazapine study there were 13 deaths due to suicides (of which eight patients were still taking mirtazapine at the time of death), and eight deaths were as a result of overdose. After follow up none of the deaths due to suicide or overdose were considered related to mirtazapine. There were eight deaths for which the cause of death could not be ascertained. However, in the paroxetine study, 25 patients were reported to have committed suicide during the six month period, eight of whom were known to have taken overdoses. Paroxetine had not been taken by any of these patients; 12 patients committed suicide by violent means (9 hanging, one from tall building, one carbon monoxide poisoning, one plastic bag). In the remaining five cases the manner of death was not established. No deaths were attributed to paroxetine.

CHAPTER 6: CONCLUSION

Mirtazapine is the first of a new class of antidepressants, the noradrenaline and serotonin specific antidepressants (NaSSA). It is indicated for the treatment of all types of depressive illness and was first marketed in the UK in 1997. The main study described within this thesis was a large, non-interventional observational cohort study started immediately after mirtazapine was introduced into the UK market. The study was undertaken as an exercise in pharmacovigilance and adds to the data provided by the UK spontaneous adverse drug reaction reporting scheme. The study included 13 554 patients (60 022 patient-months of exposure to mirtazapine). Thus, the data are likely to have substantially increased the recorded safety database of the drug used in the kinds of patients who receive the medication in "real world" clinical practice.

The study was of national proportions and systematic in that the entire cohort for whom prescriptions were available represented the first group of patients given mirtazapine after its introduction into clinical practice in England. The analysis was based upon Prescription Event Monitoring (PEM) and was capable of identifying signals that none of the participating doctors suspected to be caused by the drug. The PEM methodology used in this study also readily permits contact between the medical and scientific staff at the DSRU and the prescribing GPs, allowing for extensive follow-up and collection of additional data for patients of special interest, or in those who died.

A possible weakness of this study was the response rate. Only 15 684 (56%) of the 28,016 green forms that were posted were returned, which could conceal biases. If the patients whose GPs failed to return the green forms were different from the patients whose GPs responded,

then this difference may have remained undetected. Nevertheless, the response rate was substantial compared to the rate of reporting in spontaneous adverse-reaction reporting schemes. It is also satisfactory compared to the response rate in GP postal surveys in general[28]. In the mirtazapine PEM study the response rate was slightly lower than in the paroxetine PEM study (60.7%).

Drowsiness/sedation was the most frequent reason for stopping mirtazapine and the event with the highest ID in the first month of treatment (58.1 reports per 1000 patient-months of therapy). The incidence rate for drowsiness/sedation was significantly higher with mirtazapine when compared to paroxetine (ID_1 20.5) and also to the other three SSRIs studied by PEM (fluvoxamine: drowsiness/sedation ID_1 22.6; fluoxetine 8.2; sertraline 7.3)[29]. There were 985 (7.3% of total cohort) cases of drowsiness/sedation in this study, of which 654 cases (66.3%) were reported in the first month. A substantial proportion (81.2%) of the 985 cases of drowsiness/sedation discontinued treatment because of the event. It has been reported that there is a lower incidence of drowsiness/sedation after the first week of starting mirtazapine (SmPC Organon Laboratories, 1997)[17].

The incidence of some events in this study is lower than that reported in published trials, but, for others the event rate was within the proportion given in the SmPC for mirtazapine. There are several factors that might explain this difference. Clinical trial subjects are followed up regularly and frequently, whereas in clinical practice patients may not report minor complaints to their GPs. When patients are monitored by psychiatrists or community psychiatric nurses, events may not be recorded in the GP records. Finally, GPs may fail to report events on the

green forms. However, PEM reflects the "real world" of general medical practice in England, and therefore is more likely to be "generalisable" or representative of the use of mirtazapine in the population of patients who will receive this drug for depression than those receiving drugs in clinical trials represent a carefully selected group.

Weight gain was another common adverse event in this study. Weight gain during antidepressant treatment can either be a sign of improvement in patients who have lost weight due to the illness, or a side-effect of the treatment. In the mirtazapine PEM study, weight gain was reported as an adverse event with an ID_1 of 15.6 per 1000 patient-months of exposure. There were 523 cases of weight gain reported in this study, of which 175 cases (33.4%) were reported in the first month itself. Three hundred and sixty two (362) (69.2%) of the 523 cases with weight gain discontinued treatment due to the event. It was also one of the most frequently reported reasons for stopping mirtazapine in 362 patients (2.6% of total cohort). By contrast, in the paroxetine PEM study, there were only 84 (0.6% of total cohort) cases of weight gain, of which only 38 cases were reported in the first month of treatment.

Agitation and aggression are side-effects sometimes associated with the use of antidepressants. In the mirtazapine study, during the first month of treatment, the ID for agitation (ID_1 5.3) and aggression (ID_1 4.7) was similar to paroxetine (agitation ID_1 5.0); and similar to that seen with two other SSRIs: sertraline, agitation ID_1 4.9; fluoxetine, agitation ID_1 5.9. With another SSRI, fluvoxamine, the ID_1 9.3, was notably higher[29].

Events which are not listed in the SmPC for mirtazapine or paroxetine (unlabelled adverse events) could be confounded by indication. However, further studies and lager databases would be needed to allow further possible evaluation of these events as potential confounders. Rash, an unlabelled adverse event, was also amongst the most frequently reported reasons for stopping treatment, but rash was not included in the SmPC[17]. A substantial proportion (40.4%) of the 84 cases of rash discontinued treatment because of the event.

Of the reports of cardiovascular events, the possibility that mirtazapine was associated with the event could not be excluded for four cases of palpitations which resolved on discontinuing mirtazapine. The other event possibly related to mirtazapine was dizziness in 122 patients (57 reported as a possible suspected ADR), which again was not included in the SmPC[17]. Oedema was another event (196 reports), where more than one third (33.6%) discontinued the drug due to the event, though oedema has been listed as a rare undesireable side-effect in the SmPC.

There were a number of serious suspected ADRs reported in this study. There were five reports of facial oedema, three reports of allergy, two cases of bone marrow toxicity and one case of myelodysplasia possibly associated with mirtazapine use and this illustrated the use of this form of post-marketing surveillance studies in large cohort of patients.

Possibilities for improved pharmacovigilance

Within the last decade, there has been a growing awareness that the scope of pharmacovigilance should be extended beyond the strict confines of detecting new signals of

safety concerns. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. Recently, its remit has been widened to include herbal, traditional and complementary medicines, blood products, biological products, medical devices and vaccines.. Many other issues are relevant to pharmacovigilance, namely the production of substandard medicines: medication errors: lack of efficacy in reports of the use of medicines for unapproved indications; assessment of drug-related mortality; abuse and misuse of medicines; and adverse interactions of medicines with chemicals, other medicines, and food.

The specific aims of pharmacovigilance are to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions; to improve public health and safety in relation to the use of medicines: to contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use; and to promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

For these reasons, it is imperative that pharmacovigilance and post-marketing surveillance should be mandatory, so that more complete information on any new medication is available to clinicians, to optimise the treatment of patients in routine medical practice. Suggestions to improve pharmacovigilance could include mandatory ADR reporting by all health care professionals via the Yellow Card Scheme for all new drugs on market; improved quality of monitoring through the use of a control group of patients with the same condition, but who have not been exposed to the study drug, and perhaps through the use of automatically updated pharmacovigilance information, available through the Internet.

But the onus on spontaneous reporting the detection of unexpected ADRs will continue to rely on the awareness and co-operation of sensitive clinicians. Improvements in this area are only likely to be accomplished through the provision of increased resources and more effective collaboration between practitioners, national monitoring centres, regulatory authorities, university institutions and pharmaceutical manufacturers.

REFERENCES

1. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu H-G, Joyce PR, Karem EG, Lee C-K, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H-U, Yeh E-K. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996; 276: 293-299

2. Jenkins R, Lewis G, Bebbington P, Brugha T, Farrell M, Gill B, Meltzer H. The National Psychiatric Morbidity Surveys of Great Britain - initial findings from the household surveys. Psychol Med 1997; 27: 775-789.

3. Bebbington P, Dunn G, Jenkins R, Lewis G, Brugha T, Farrell, Meltzer H. The influence of age and sex on the prevalence of depressive conditions: report from the National Survey of Psychiatric Morbidity. Psychol Med 1998; 28: 9-19.

4. Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997; 349: 1436-1442

5. Barrett JE, Barrett JA, Oxman TE, Gerber PD. The prevalence of psychiatric disorders in a primary care practice. Arch Gen Psychiatry 1988; 45: 1100 - 1106.

6. Tiemens BG, Ormel J, Simon GE. Occurrence, recognition, and outcome of psychological disorders in primary care. Am J Psychiatry 1996; 153: 636 - 644.

7. Andrews G, Slade T, Peters L. Classification in psychiatry: ICD 10 Vs DSM IV. Br J Psych 1999; 174: 3-5.

8. Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD et al. Association of anxiety related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 1996; 274: (5292): 1527-31.

9. Drevets Wc. Neuroimaging studies of mood disorders. Biol Psych 2000; 48(8): 813-29.

10. The Medical Letter, Inc. (1998), Drugs that cause psychiatric symptoms. Med Lett Drugs Ther 35:65-70.

11. Freeling P, Rao BM, Paykel ES, Sireling LI, Burton RH. Unrecognised depression in general practice. BMJ 1985, 290: 1880-1883

12. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther* 2001; **26:** 331–342.
13. Nelson JC, Kennedy JS, Pollock BG et al. Treatment of major depression with nortriptyline and paroxetine in patients with Ischaemic Heart Disease. Am J Psych 1999; 156: 1024-1028.

14. R. Hubbard et al. Exposure to Commonly Prescribed Drugs and the Etiology of Crytogenic Fibrosing Alveolitis". Am J Respir Crit Care Med 1998;157:743-747.

15. Frederick W. R, Jay D. Amsterdam M.D, Frederic M et al. Optimal Length of Continuation Therapy in Depression: A Prospective Assessment During Long-Term Fluoxetine Treatment. Am J Psychiatry 1998; 155:1247-1253

16. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996;57(Suppl 4):19-25.

17. Organon Laboratories (1997). Mirtazapine Summary of Product Characteristics. The Netherlands:Organon Laboratories.

18. Anderson IM, Nutt DJ, Deakin JFW. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. J Psychopharmacol 2000; 14: 3–20

19. Rawlins MD, Jefferys DB. United Kingdom Product License applications involving new active substances, 1987-1989: their fate after appeals. Br J Clin Pharmacol 1993;35:599-602.

20. J Lazarou, BM Pomeranz, PN Corey. Incidence of Adverse Drug Reactions in hospitalized patients: A Meta-Analysis of prospective studies. JAMA 1998 279: 1200-5.

21. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329: 15-9.

22. Biswas PN, Wilton LV, Shakir SAW. Pharmacovigilance study of alendronate in England. Osteoporosis International, 2003;**14:**507-514.

23. Biswas PN, Wilton LV, Shakir SAW. The Pharmacovigilance of Mirtazapine: results of a prescription event monitoring study on 13554 patients in England. Journal of Psychopharmacology 2003;**17(1):**121-126.

24. Biswas PN, Wilton LV, Shakir SAW. Pharmacovigilance of Valsartan: Results of a Post-Marketing Surveillance Study on 12 881 Patients in England. Journal of Human Hypertension 2002;**16:**795-803.

25. Biswas PN, Wilton LV, Shakir SAW. Troglitazone and Liver Function Abnormalities. *Drug Safety*, 2001;**24:**(2).149-154.

26. Marin RM, Biswas PN, Wilton LV, Mann RD. The incidence of adverse events and risk factors for upper gastro-intestinal disorders associated with meloxicam use amongst 19 087 patients in general practice in England: cohort study. British Journal of Clinical Pharmacology, 2000;50:35-42

27. Biswas PN, Wilton LV, Shakir SAW Montelukast and improvement of eczema: observations from a prescription event monitoring study in England. International Journal of Clinical Pharmacology and Therapeutics, 2001;**39:**529-533.

28. Biswas PN, Wilton LV, Shakir SAW The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. Journal of Psychopharmacology, 2001;15:(4).265-271).

29. Biswas PN, Wilton LV, Mann RD The pharmacovigilance of tamsulosin: event data on 12,484 patients. British Journal of Urology International 2000;**85:**446-450).

30. Marin RM, Biswas PN, Wilton LV, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. British Journal of Clinical Pharmacology, 1998;**46:**505-551).

31. Mann RD. Prescription Event Monitoring - recent progress and future horizons. Br J Clin Pharmacol 1998; *46*: 195-201.

32. Freemantle SN, Pearce GL, Wilton LV, Mann RD. The incidence of the most commonly reported events with 40 newly marketed drugs – a study by prescription event monitoring. Pharmacoepidemiol Drug Safety 1996, 6 (Suppl 1):1-8.

33. International Ethical Guidelines for Biomedical Research Involving Human Subjects. CIOMS/WHO, Geneva 1993.

34. Guidelines on the practice of Ethical Committees in Medical Research involving Human Subjects. Royal College of Physicians of London. August 1996.

35. Templeton L, Deeham A, Taylor c, Drummond C, Strang J. Surveying general practitioners: does a low response rate matter? Br J Gen Pract 47: 91-94, 1997.

36. Heely E, Riley J, Layton D, Wilton LV, Shakir SAW. Presription Event Monitoring and reporting of adverse drug reactions. Lancet 358: 1872-1873, 2001.

37. McAvoy BR, Kramer EFS. General practice postal surveys: a questionnaire too far? BMJ 313: 732-733, 1996.

38. Mackay FJ, Dunn NR, Wilton LV, Pearce GL, Freemantle SN, Mann RD. A comparison of fluvoxamine, fluoxetine, sertraline and paroxetine examined by observational cohort studies. Pharmacoepidemiol Drug Safety 6: 235-246, 1997.

39. Goldberg D, Tantam D. The public health impact of mental disorders. In Holland WW, Detels R, Knox G (eds), Oxford text book of public health, vol. 3, application in public health, 2nd edn, pp 268-269. Oxford: Oxford University Press.

40. Paroxetine PEM Report No. 6. August 1993.

41. I.M. Anderson, D.J. Nutt and J.F.W. Deakin (2000) Journal of Psychopharmacology 14: 3-20

42. Compliance to antidepressant drug therapy for treatment of premenstrual syndrome. Sundstrom-Poromaa I, Bixo M, Bjorn I, Nordh O. J Psychosom Obstet Gynaecol. 2000 Dec;21(4):205-11.

43. Thase ME. Depression, sleep and antidepressants. J Clin Psychiatry 1998;59 (suppl 4):55-65

44. Nutt D. Mirtazapine: pharmacology in relation to adverse effects. Acta Psychiatr Scand 1997; 391(Suppl):31-7.

45. Preskorn SH. Selection of an antidepressant: mirtazapine. J Clin Psychiatry 1997;58(Suppl 6):3-8.

46. Claghorn JL. The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients. J Clin Psychiatry 53 (Suppl):33-5, 1992 Feb

47. Richard Balon. Managing Compliance. *Psychiatric Times* •May 2002 •Vol. XIX •Issue 5

48. Fava M, Judge R, Hoog SL et al. (2000), Fluoxetine versus sertraline and paroxetine in major depressive disorder: changes in weight with long-term treatment. J Clin Psychiatry 61(11):863-867.

49. Ness-Abramof R, Apovian CM. Drug-induced weight gain. Timely Top Med Cardiovasc Dis. 2005 Oct 28

50. Nicholas LM, Ford AL, Esposito SM, Ekstrom RD, Golden RN. The effects of mirtazapine on plasma lipid profiles in healthy subjects. J Clin Psychiatry. 2004 Jul;65(7):1017-8

51. Himmerich H, Fulda S, Schaaf L, Beitinger PA, Schuld A, Pollmächer T. Changes in weight and glucose tolerance during treatment with mirtazapine. Diabetes Care. 2006 Jan;29(1):170-1

52. Kennedy SH, Dickens SE, Eisfeld BS, Bagby RM. Sexual dysfunction before antidepressant therapy in major depression. J Affect Disord. 1999;56:201-208.

53. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. J Clin Psychiatry. 2002;63:357-366.

54. Ferguson JM. The effects of antidepressants on sexual functioning in depressed patients: a review. J Clin Psychiatry. 2001;62(suppl 3):22-34.

55. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19:67-85.

56. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetric settings. J Womens Health 2003; 12: 373-380.

57. Begg CB, Mazumdar M. Operationg characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.

58. Davies S, Naik PC, Lee AS. Depression, suicide, and the national service framework. *BMJ* 2001;322: 1501-2.

59. Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005;330: 396-9.

60. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330: 385-8.

61. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ* 2005;330: 389-93

Appendix 1: Summary of Product Characteristics

SUMMARY OF PRODUCT CHARACTERISTICS Ra M1060.050.103

1. Name of the medicinal product

Zispin 30 mg ▼

2. Qualitative and quantitative composition

Each tablet contains 30 mg of mirtazapine.

3. Pharmaceutical form

Tablet

4. Clinical particulars

4.1 Therapeutic Indications

Treatment of depressive illness

4.2 Posology and method of administration

The tablets should be taken orally, if necessary with fluid, and swallowed without chewing.

Adults : 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

Elderly : The recommended dose is the same as that for adults. In elderly patients an increase in dosing should be done under close supervision to elicit a satisfactory and safe response.

Children : Since safety and efficacy of Zispin has not been established in children, it is not recommended to treat children with Zispin.

The clearance of mirtazapine may be decreased in patients with renal or hepatic insufficiency. This should be taken into account when prescribing Zispin to this category of patients. Mirtazapine has a half-life of 20-40 hours and therefore Zispin is suitable for once-a-day administration. It should be taken preferably as a single night-time dose before going to bed. Zispin may also be given in sub-doses equally divided over the day (once in the morning and once at night-time).

Treatment should preferably be continued until the patient has been completely symptom-free for 4-6 months. After this, treatment can be gradually discontinued. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased up to the maximum dose. If there is no response within a further 2-4 weeks, then treatment should be stopped.

4.3 Contraindications

Hypersensitivity to mirtazapine or any of the other ingredients of Zispin.

4.4 Special warnings and special precautions for use

Reversible white blood cell disorders including agranulocytosis, leukopenia and granulocytopenia have been reported with Zispin. With respect to agranulocytosis the physician should be alert to symptoms such as fever, sore throat, stomatitis or other signs of infection; when such symptoms occur, treatment should be stopped and blood counts taken. Patients should also be advised of the importance of these symptoms.

Careful dosing as well as regular and close monitoring is necessary in patients with:

- epilepsy and organic brain syndrome: from clinical experience it appears that insults occur rarely in patients treated with Zispin
- hepatic or renal insufficiency
- cardiac diseases like conduction disturbances, angina pectoris and recent myocardial infarct, where normal precautions should be taken and concomitant medicines carefully administered
- low blood pressure.

As with other antidepressants care should be taken in patients with:

- micturition disturbances like prostate hypertrophy (although problems are not to be expected because Zispin possesses only very weak anticholinergic activity)
- acute narrow-angle glaucoma and increased intra-ocular pressure (also here little chance of problems with Zispin because of its very weak anticholinergic activity)
- diabetes mellitus.

Treatment should be discontinued if jaundice occurs.

Moreover, as with other antidepressants, the following should be taken into account:

- worsening of psychotic symptoms can occur when antidepressants are administered to patients with schizophrenia or other psychotic disturbances: paranoid thoughts can be intensified
- when the depressive phase of manic-depressive psychosis is being treated, it can transform into the manic phase
- with regard to the chance of suicide, in particular at the beginning of treatment, only a limited number of Zispin tablets should be given to the patient
- although antidepressants are not addictive, the abrupt termination of treatment after long-term administration may result in nausea, headache and malaise
- elderly patients are often more sensitive, especially with regard to the side-effects of antidepressants. During clinical research with Zispin, side-effects have not been reported more often in elderly patients than in other age groups: however experience until now is limited.

4.5 Interaction with other medicaments and other forms of interaction

- Mirtazapine may potentiate the central nervous dampening action of alcohol: patients should therefore be advised to avoid alcohol during treatment with Zispin.
- Zispin should not be administered concomitantly with MAO inhibitors or within two weeks of cessation of therapy with these agents.
- Mirtazapine may potentiate the sedative effects of benzodiazepines; caution should be taken when these drugs are prescribed together with Zispin.
- No data are available from formal clinical studies on interactions with neuroleptics.
- In vitro data suggest that mirtazapine is a very weak competitive inhibitor of the cytochrome P450 enzymes CYP1A2, CYP2D6 and CYP3A and clinically significant interactions are unlikely with mirtazapine.

4.6 Pregnancy and lactation

The safety of Zispin in human pregnancy has not been established.

Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg (approx. 3 and 5 times respectively the maximum recommended human dose on the basis of exposure) have revealed no evidence of teratogenic effects. There was, however, in rats an increase in post-implantation loss; there was also an increase in pup deaths during the first three days of lactation (cause of death unknown) and a decrease in pup birth weights. These findings are common with CNS-active drugs at high dose levels in animals.

As the relevance of these findings to humans is not certain the use of Zispin during pregnancy is not recommended. Women of child bearing potential should employ an adequate method of contraception if taking Zispin.

Although animal experiments show that mirtazapine is excreted only in very small amounts in the milk, the use of Zispin in nursing mothers is not recommended since no human data in breast milk are available.

4.7 Effects on ability to drive and use machines

Zispin has sedative properties and may impair concentration and alertness. Patients treated with Zispin should avoid the performance of potentially dangerous tasks, which require alertness and good concentration, such as driving a motor vehicle or operating machinery.

4.8 Undesirable effects

Depressed patients display a number of symptoms that are associated with the illness itself. It is therefore sometimes difficult to ascertain which symptoms are a result of the illness itself and which are a result of treatment with Zispin.

The following adverse effects have been reported:

Common (>1/100): Increase in appetite and weight gain. Drowsiness/sedation, generally occurring during the first few weeks of treatment. (N.B. dose reduction generally does not lead to less sedation but can jeopardize antidepressant efficacy).

Less common: Increases in liver enzyme levels.

Rare (<1/1000): Oedema and accompanying weight gain. Reversible agranulocytosis has been reported as a rare occurrence with Zispin. (See also section 4.4 'Special warnings and special precautions for use'). (Orthostatic) hypotension. Exanthema. Mania, convulsions (insults), tremor, myoclonus.

4.9 Overdose

Toxicity studies in animals suggest that clinically relevant cardiotoxic effects will not occur after overdosing with Zispin. Experience in clinical trials and from the market has shown that no serious adverse effects have been associated with Zispin in overdose. Symptoms of acute overdosage are confined to prolonged sedation.

Cases of overdose should be treated by gastric lavage with appropriate symptomatic and supportive therapy for vital functions.

5. Pharmacological properties

Zispin (mirtazapine) is an antidepressant, which can be given as treatment for episodes of major depression. The presence of symptoms such as anhedonia, psychomotor inhibition, sleep disturbances (early wakening) and weight loss, increase the chance of a positive response. Other symptoms are: loss of interest, suicidal thoughts and changes in mood (better in the evening than in the morning). Zispin begins to exert its effect in general after 1-2 weeks of treatment.

5.1 Pharmacodynamic properties

Mirtazapine is a centrally active presynaptic α_2-antagonist, which increases central noradrenergic and serotonergic neurotransmission. The enhancement of serotonergic neurotransmission is specifically mediated via 5-HT_1 receptors, because 5-HT_2 and 5-HT_3 receptors are blocked by mirtazapine. Both enantiomers of mirtazapine are presumed to contribute to the antidepressant activity; the S(+) enantiomer by blocking α_2 and 5-HT_2 receptors and the R(-) enantiomer by blocking 5-HT_3 receptors. The histamine H_1-antagonistic activity of mirtazapine is responsible for its sedative properties. Mirtazapine is generally well tolerated. It has practically no anticholinergic activity and, at therapeutic doses, has practically no effect on the cardiovascular system.

5.2 Pharmacokinetic properties

After oral administration of Zispin tablets, the active constituent mirtazapine is rapidly and well absorbed (bioavailability ≈ 50%), reaching peak plasma levels after about 2 hours. Binding of mirtazapine to plasma proteins is approx. 85%. The mean half-life of elimination is 20-40 hours; longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young men. The half-life of elimination is sufficient to justify once-a-day dosing. Steady state is reached after 3-4 days, after which there is no further accumulation. Mirtazapine displays linear pharmacokinetics within the recommended dose range. Food intake has no influence on the

pharmacokinetics of mirtazapine. Mirtazapine is extensively metabolized and eliminated via the urine and faeces within a few days. Major pathways of biotransformation are demethylation and oxidation, followed by conjugation. In vitro data from human liver microsomes indicate that cytochrome P450 enzymes CYP2D6 and CYP1A2 are involved in the formation of the 8-hydroxy metabolite of mirtazapine, whereas CYP3A4 is considered to be responsible for the formation of the N-demethyl and N-oxide metabolites.The demethyl metabolite is pharmacologically active and appears to have the same pharmacokinetic profile as the parent compound. There are no differences in the pharmacokinetic parameters of racemic mirtazapine or its demethyl metabolite in extensive and poor metabolisers. Plasma metabolite profiles for the individual enantiomers are qualitatively similar in extensive and poor metabolisers.
The clearance of mirtazapine may be decreased as a result of renal or hepatic insufficiency.

5.3 Preclinical safety data
No special particulars

6. Pharmaceutical particulars
6.1 List of excipients
Zispin 30 mg tablets contain:

Core	: maize starch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose
Coating layer	: hydroxypropyl methylcellulose, polyethylene glycol 8000, titanium dioxide (E171), yellow iron oxide (E172) and red iron oxide (E172).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
The shelf life for Zispin tablets is 3 years, if stored in the dark and dry at 2-30° C. Zispin tablets should not be used after the expiry date on the package.

6.4 Special precautions for storage
Zispin should be stored in the dark and dry.

6.5 Nature and contents of containers
Zispin tablets are oval, biconvex, scored and marked with 'Organon' on one side and a code on the other side.
Zispin tablets are packed in child-safe, push-through strips made of opaque white polyvinyl chloride film and aluminium foil containing a heat-seal coating on the side in contact with the tablets.
Pack size: 4 push-through strips with 7 red-brown tablets each containing 30 mg mirtazapine (code TZ/5).

6.6 Instructions for use/handling
Not applicable

7. Marketing authorization holder
Organon Laboratories Limited, Cambridge Science Park, Milton Road, Cambridge, CB4 4FL

8. Marketing authorization number:
PL 0065/0145

9. Date of first authorization/renewal of authorization
July 1997

10. DATE OF (PARTIAL) REVISION OF THE TEXT
July 1997

Ref: USZISP1A

Appendix 2: Treatment after stopping mirtazapine

Forty one drugs were substituted for the monitored drug in 451 of the patients in whom mirtazapine was withdrawn. The medication most frequently substituted was fluoxetine in 111 (24.6%) patients and paroxetine in 75 patients (16.6%). The total number of substituted drugs was 468 indicating that 17 patients received two drugs after stopping treatment with mirtazapine.

Drug	Number
fluoxetine	111
paroxetine	75
venlafaxine	45
dothiepin	44
citalopram	33
lofepramine	22
antidepressant unspecified	21
sertraline	18
amitriptyline	16
trazodone	15
reboxetine	10
lithium	7
nefazodone	7
clomipramine	5
flupenthixol	4
carbamazepine	2
diazepam	2
haloperidol	2
imipramine	2
moclobemide	2
other substances	2
sulpiride	2
trimipramine	2
zopiclone	2
chlorpromazine	1
cisapride	1
Dianette	1
fluvoxamine	1
mianserin	1
mirtazapine	1
Motival	1
olanzapine	1
Optimax	1
oxazepam	1
phenelzine	1

Appendix 2: Treatment after stopping mirtazapine (continued)

Drug	Number
promazine	1
risperidone	1
thioridazine	1
tranylcypromine	1
trifluoperazine	1
Triptafen	1
Total	**468**

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
5	**Skin**									
6	Acne	29	3	6	3	5	4	2	23	-
7	Acne	18	2	3	1	4	3	1	14	-
8	Acne rosacea	11	1	3	2	1	1	1	9	-
9	Alopecia	3	1	-	-	1	-	-	2	-
10	Cyst sebaceous	18	-	2	4	2	5	2	15	-
11	Dermatitis	23	2	3	5	3	1	2	16	-
12	Dermatitis contact	2	-	1	-	-	1	-	2	-
13	Dry skin	13	2	2	2	3	2	2	13	-
14	Eczema	73	7	10	10	10	7	9	53	1
15	Eczema	63	6	9	9	8	6	7	45	1
16	Intertrigo	8	1	1	1	1	-	2	6	-
17	Pompholyx	2	-	-	-	1	1	-	2	-
18	Eczema varicose	3	1	1	-	-	-	-	2	-
19	Eruption bullous	3	-	-	-	-	1	-	1	1
20	Blister	2	-	-	-	-	1	-	1	-
21	Dermatitis herpetiformis	1	-	-	-	-	-	-	-	1
22	Erythema	4	1	2	-	-	1	-	4	-
23	Erythema nodosum	1	1	-	-	-	-	-	1	-
24	Erythroderma	1	-	-	-	-	-	-	-	-
25	Dermatitis exfoliative	1	-	-	-	-	-	-	-	-
26	Folliculitis	10	1	-	1	1	1	-	4	-
27	Hair ingrown	1	-	-	-	-	1	-	1	-
28	Hair loss	7	3	1	1	1	-	-	6	-
29	Herpes simplex, skin	6	1	2	-	-	-	1	4	-
30	Herpes zoster	15	3	-	-	3	2	2	10	-
31	Hirsutism	1	-	-	-	-	-	-	-	-
32	Hyperkeratosis	3	-	-	-	-	2	-	2	-
33	Hyperkeratosis	1	-	-	-	-	1	-	1	-
34	Pityriasis	2	-	-	-	-	1	-	1	-
35	Infection skin, unspecified/local bacterial	88	12	8	15	8	11	4	58	-
36	Abscess skin	19	3	2	5	-	2	1	13	-
37	Cellulitis	27	1	2	6	5	3	-	17	-
38	Impetigo	7	2	1	-	-	2	-	5	-
39	Infection skin	32	6	2	4	2	4	3	21	-
40	Paronychia	3	-	1	-	1	-	-	2	-
41	Lice	5	-	-	-	1	-	2	3	-
42	Lichen sclerosus	2	-	-	1	-	-	-	1	-
43	Lupus discoid	2	-	-	1	-	-	1	2	-
44	Nail change	6	2	1	1	1	-	1	6	-
45	Nail change	1	-	-	-	-	-	1	1	-
46	Nail ingrown	5	2	1	1	1	-	-	5	-
47	Onychomycosis	9	-	1	-	4	-	-	5	-
48	Photosensitivity	4	-	1	-	-	1	1	3	-
49	Pigmentation	1	-	-	-	-	1	-	1	-
50	Pressure sore	1	-	-	-	-	-	1	1	-
51	Pruritus	91	19	12	12	12	6	7	68	-
52	Pruritus	80	18	9	9	10	5	7	58	-
53	Pruritus ani	5	-	3	-	1	-	-	4	-
54	Pruritus vulvae	6	1	-	3	1	1	-	6	-
55	Psoriasis	9	3	1	1	1	1	1	8	-
56	Purpura	3	-	1	-	1	-	1	3	-
57	Rash	112	31	16	11	15	9	9	91	1
58	Scabies	6	-	-	1	2	2	1	6	-
59	Seborrhoea	4	-	1	1	-	1	1	4	-
60	Dandruff	1	-	-	-	-	1	-	1	-
61	Seborrhoea	3	-	1	1	-	-	1	3	-
62	Sinus pilonidal	1	-	-	1	-	-	-	1	-
63	Sore skin	7	2	-	1	-	-	-	3	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
64	Tinea	18	-	3	5	1	1	3	13	1
65	Ulcer skin	14	-	3	3	1	1	2	10	-
66	Urticaria	18	3	1	-	4	2	4	14	-
67	Vitiligo	1	-	-	-	1	-	-	1	-
68	TOTAL	618	98	79	80	81	64	59	461	4
69	**Musculoskeletal**									
70	Arthritis	18	1	3	2	2	1	3	12	1
71	Arthritis psoriatic	1	-	-	-	1	-	-	1	-
72	Arthritis rheumatoid	6	3	2	-	-	1	-	6	-
73	Arthritis rheumatoid*	6	3	2	-	-	1	-	6	-
74	Bone abnormal	1	-	-	-	-	-	-	-	-
75	Bursitis	15	-	4	2	-	5	1	12	-
76	Bursitis	7	-	2	-	-	4	-	6	-
77	Bursitis knee	2	-	-	-	-	1	1	2	-
78	Bursitis olecranon	4	-	1	2	-	-	-	3	-
79	Bursitis toe	2	-	1	-	-	-	-	1	-
80	Capsulitis	3	1	1	-	-	-	1	3	-
81	Chondromalacia	1	-	-	-	-	1	-	1	-
82	Cramp	21	6	3	2	2	2	3	18	-
83	Cyst Baker's	1	-	-	-	-	-	-	-	-
84	Disc prolapsed	1	-	-	1	-	-	-	1	-
85	Dupuytren's contracture	1	1	-	-	-	-	-	1	-
86	Effusion joint	6	-	1	1	1	2	-	5	-
87	Frozen shoulder	16	2	3	2	1	2	4	14	-
88	Ganglion	3	-	-	1	-	-	1	2	-
89	Lumbago	1	-	-	-	-	-	-	-	-
90	Muscle weakness	21	10	2	1	-	-	2	15	1
91	Myalgia	78	21	14	8	6	7	7	63	-
92	Nerve entrapment	14	4	-	2	3	-	1	10	-
93	Carpal tunnel syndrome	11	4	-	2	2	-	1	9	-
94	Nerve entrapment	3	-	-	-	1	-	-	1	-
95	Osteoarthritis	39	7	2	2	5	5	2	23	1
96	Osteochondritis	8	3	-	-	-	1	3	7	-
97	Osteomyelitis	1	-	-	-	-	-	-	-	1
98	Osteoporosis	1	-	-	-	-	-	1	1	-
99	Pain back	183	22	30	23	21	24	19	139	1
100	Pain bone	2	-	-	1	-	1	-	2	-
101	Pain groin	4	1	-	1	-	-	-	2	-
102	Pain joint	205	31	32	23	22	16	24	148	2
103	Pain joint	203	31	32	22	22	16	24	147	2
104	Rheumatism	2	-	-	1	-	-	-	1	-
105	Pain limb	62	14	10	7	5	9	5	50	-
106	Pain neck	52	2	9	9	9	5	7	41	-
107	Plantar fasciitis	11	1	1	1	-	1	3	7	-
108	Polymyalgia rheumatica	7	1	1	1	1	-	1	5	1
109	Rotator cuff	4	-	1	-	1	-	2	4	-
110	Sciatica	39	8	5	4	6	3	4	30	1
111	Scoliosis	2	-	1	-	1	-	-	2	-
112	Spasm muscular	28	10	6	6	2	1	1	26	-
113	Spondylosis	2	-	-	-	-	1	-	1	-
114	Spondylosis cervical	7	-	-	1	2	-	2	5	-
115	Swelling joint	18	3	5	1	1	2	2	14	-
116	Synovitis	1	-	-	-	-	-	-	-	-
117	Tendinitis	15	2	2	1	-	3	3	11	-
118	Tennis elbow	22	3	2	3	2	2	1	13	-
119	Tenosynovitis	4	1	-	-	-	-	-	1	-
120	Torticollis	6	1	-	2	-	1	1	5	-
121	Trigger finger	5	-	-	3	-	1	-	4	-
122	TOTAL	936	159	140	111	94	97	104	705	9

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
123	**Psychiatric**									
124	Aggression	96	51	14	8	5	6	2	86	1
125	Agitation	146	62	24	15	8	6	6	121	2
126	Alcoholism	79	18	10	7	5	12	8	60	1
127	Alcohol withdrawal	6	1	-	-	1	2	2	6	-
128	Alcoholism *	35	10	5	4	2	2	1	24	-
129	Alcoholism acute	4	1	-	-	-	-	2	3	-
130	Alcoholism chronic*	34	6	5	3	2	8	3	27	1
131	Anxiety	388	138	39	38	26	27	23	291	13
132	Anxiety	388	138	39	38	26	27	23	291	13
133	Behaviour abnormal	18	5	1	-	2	6	-	14	-
134	Confusion	85	42	10	6	7	5	3	73	-
135	Delusion	8	2	1	1	-	1	-	5	-
136	Dementia	10	2	1	-	2	1	2	8	-
137	Alzheimer's disease*	3	-	-	-	-	1	-	1	-
138	Dementia	6	2	-	-	2	-	2	6	-
139	Dementia senile*	1	-	1	-	-	-	-	1	-
140	Depersonalization	9	6	2	-	-	-	-	8	-
141	Depression	772	159	101	84	71	66	65	546	40
142	Depression	765	156	100	83	71	66	64	540	40
143	Depression manic	6	3	1	1	-	-	1	6	-
144	Depression postnatal	1	-	-	-	-	-	-	-	-
145	Dreams abnormal	94	56	17	6	5	5	1	90	-
146	Euphoria	3	2	-	-	1	-	-	3	-
147	Formication	2	-	1	-	-	-	-	1	-
148	Globus hystericus	2	-	-	-	-	-	-	-	-
149	Grief reaction	7	-	1	-	-	-	1	2	-
150	Hallucination	32	16	2	-	1	3	1	23	-
151	Hyperactive	6	3	2	1	-	-	-	6	-
152	Hypochondriasis	2	-	-	1	-	1	-	2	-
153	Hypomania	7	1	3	1	-	-	-	5	-
154	Insomnia	257	81	45	21	19	19	12	197	3
155	Irritability	71	35	13	11	2	5	2	68	-
156	Libido decreased	33	8	6	5	2	-	3	24	-
157	Malaise, lassitude	587	317	75	43	37	22	24	518	4
158	Lassitude	326	144	47	32	23	16	17	279	3
159	Malaise	261	173	28	11	14	6	7	239	1
160	Mania	14	5	1	1	2	3	1	13	-
161	Mood change	50	20	10	8	2	2	1	43	1
162	Mood change	15	8	3	1	-	-	-	12	-
163	Mood swings	35	12	7	7	2	2	1	31	1
164	Neurosis	2	1	-	-	-	-	-	1	-
165	Obsession/compulsive	11	3	1	1	-	1	3	9	1
166	Panic attack	101	23	17	13	8	10	7	78	3
167	Paranoia	14	6	2	2	-	1	1	12	-
168	Phobia	18	2	1	3	1	2	2	11	1
169	Agoraphobia	12	1	1	1	-	2	2	7	1
170	Cancer phobia	1	-	-	1	-	-	-	1	-
171	Phobia	5	1	-	1	1	-	-	3	-
172	Psychosis	21	4	1	-	3	4	2	14	2
173	Schizophrenia	3	-	1	-	-	1	-	2	-
174	Self injury	24	10	1	2	3	1	1	18	2
175	Senility	4	1	-	-	-	-	-	1	1
176	Somnambulism	3	1	-	1	1	-	-	3	-
177	Suicidal thought	34	6	5	3	3	5	5	27	-
178	Suicide attempt, drug overdose	202	40	22	33	26	22	13	156	5
179	Overdose*	26	10	3	3	3	1	2	22	-
180	Overdose other drug*	68	12	9	14	9	6	3	53	3
181	Overdose unknown drug*	50	9	4	9	7	6	3	38	2

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
182	Suicide attempt*	36	5	3	4	5	3	5	25	-
183	Suicide threat	22	4	3	3	2	6	-	18	-
184	Tics	1	1	-	-	-	-	-	1	-
185	TOTAL	3216	1127	430	315	242	237	189	2540	80
186	**Central and Peripheral Nervous System**									
187	Amnesia	28	10	1	1	2	1	3	18	2
188	Aphasia, dysphasia	4	3	-	-	-	-	-	3	-
189	Dysphasia	4	3	-	-	-	-	-	3	-
190	Ataxia	3	2	1	-	-	-	-	3	-
191	Burning sensation	6	-	1	2	-	1	1	5	-
192	Coma	2	-	-	-	-	-	-	-	-
193	Convulsion, epilepsy	36	8	5	7	5	3	3	31	-
194	Convulsion*	22	3	5	5	4	1	3	21	-
195	Epilepsy *	12	5	-	2	1	1	-	9	-
196	Epilepsy grand mal	2	-	-	-	-	1	-	1	-
197	Disorientation	7	6	-	-	1	-	-	7	-
198	Dizziness	284	180	26	17	15	13	11	262	-
199	Drop attack	1	-	-	-	-	-	-	-	-
200	Drowsiness, sedation	1001	660	135	52	35	38	23	943	2
201	Drowsiness	547	365	69	25	19	25	13	516	1
202	Sedation	454	295	66	27	16	13	10	427	1
203	Dysphonia	1	-	-	-	-	-	-	-	-
204	Extrapyramidal disease	15	2	3	3	2	-	1	11	1
205	Dystonia	2	-	-	1	1	-	-	2	-
206	Extrapyramidal disease	4	1	1	1	-	-	-	3	-
207	Movement involuntary	4	1	2	-	1	-	-	4	-
208	Parkinson's disease*	5	-	-	1	-	-	1	2	1
209	Feeling cold	6	3	1	-	1	-	-	5	-
210	Feeling hot	4	1	-	-	2	-	1	4	-
211	Flushing	31	6	4	5	1	2	3	21	-
212	Headache, migraine	312	123	29	30	21	22	27	252	2
213	Headache	265	113	24	26	16	15	22	216	1
214	Migraine	47	10	5	4	5	7	5	36	1
215	Hemiparesis	4	-	-	2	-	-	1	3	-
216	Lost consciousness	13	5	-	1	2	1	1	10	-
217	Meningitis	1	-	-	-	-	-	-	-	-
218	Meningitis *	1	-	-	-	-	-	-	-	-
219	Multiple sclerosis	3	-	-	1	1	-	-	2	-
220	Myelopathy	2	-	-	-	-	-	1	1	-
221	Neuralgia	18	1	2	2	2	4	1	12	2
222	Neuralgia trigeminal	5	2	1	1	1	-	-	5	-
223	Neuropathy	4	1	1	1	1	-	-	4	-
224	Neuritis*	1	-	1	-	-	-	-	1	-
225	Neuropathy peripheral	1	1	-	-	-	-	-	1	-
226	Neuropathy	2	-	-	1	1	-	-	2	-
227	Paralysis ocular	1	-	-	1	-	-	-	1	-
228	Paresis	1	-	-	-	-	1	-	1	-
229	Post viral syndrome	7	2	-	1	1	1	1	6	1
230	Ptosis	1	-	-	1	-	-	-	1	-
231	Sensation abnormal	81	22	13	10	7	7	6	65	-
232	Hypoaesthesia	25	5	2	3	1	5	2	18	-
233	Paraesthesia	56	17	11	7	6	2	4	47	-
234	Smell, taste abnormal	14	4	2	2	2	-	1	11	-
235	Taste abnormal	14	4	2	2	2	-	1	11	-
236	Syncope	50	15	3	6	3	3	4	34	-
237	Tremor	73	33	9	4	6	5	3	60	1
238	TOTAL	2019	1089	237	150	111	102	92	1781	11
239	**Eye**									
240	Amaurosis	1	-	-	-	1	-	-	1	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
241	Amaurosis fugax	1	-	-	-	1	-	-	1	-
242	Blepharitis	11	1	-	2	2	2	1	8	-
243	Cataract	11	1	1	3	1	1	-	7	-
244	Conjunctivitis	34	7	5	3	6	2	3	26	-
245	Corneal dystrophy	1	-	-	-	-	-	1	1	-
246	Cyst Meibomian	2	1	-	-	-	-	-	1	-
247	Dry eye	5	1	-	1	2	-	-	4	-
248	Episcleritis	2	-	1	-	-	-	1	2	-
249	Floaters	2	-	-	-	-	1	-	1	-
250	Glaucoma	5	-	-	-	-	2	-	2	-
251	Haemorrhage subconjunctival	5	-	1	1	-	-	2	4	-
252	Herpes ophthalmic	2	-	2	-	-	-	-	2	-
253	Irritation eye	4	-	2	1	1	-	-	4	-
254	Lacrimation	1	-	-	-	1	-	-	1	-
255	Macular degeneration	2	-	-	-	1	-	-	1	-
256	Nystagmus	2	1	-	-	-	-	-	1	-
257	Pain eye	1	1	-	-	-	-	-	1	-
258	Retinal detachment	3	-	-	-	1	-	-	1	-
259	Retinopathy	2	-	-	2	-	-	-	2	-
260	Scleritis	2	-	2	-	-	-	-	2	-
261	Sore eye	6	1	-	1	1	1	1	5	-
262	Stye	4	-	-	-	-	-	-	-	-
263	Ulcer corneal	3	1	-	-	2	-	-	3	-
264	Uveitis	3	2	1	-	-	-	-	3	-
265	Visual defect	38	15	4	4	2	3	4	32	-
266	Diplopia	3	-	-	1	-	-	-	1	-
267	Hemianopia	2	1	-	-	-	-	-	1	-
268	Vision deteriorated	3	2	-	-	-	1	-	3	-
269	Vision field defect	1	-	-	-	-	1	-	1	-
270	Visual disturbance	29	12	4	3	2	1	4	26	-
271	TOTAL	152	32	19	18	21	12	13	115	-
272	**Ear**									
273	Deafness	20	2	4	2	1	2	2	13	-
274	Earache	22	1	4	3	5	5	1	19	-
275	Eardrum perforation	1	-	-	-	-	-	-	-	-
276	Earwax	35	5	4	2	3	3	9	26	-
277	Labyrinthitis	10	2	2	2	1	1	1	9	-
278	Otitis externa	36	6	5	4	3	7	5	30	-
279	Otitis media	24	4	4	5	1	3	3	20	-
280	Otorrhoea	1	-	-	-	1	-	-	1	-
281	Tinnitus	21	6	1	3	1	-	5	16	-
282	Vertigo	35	15	4	3	2	1	2	27	-
283	TOTAL	205	41	28	24	18	22	28	161	-
284	**Cardiovascular**									
285	Aneurysm	3	1	-	-	1	-	-	2	-
286	Aneurysm aortic*	3	1	-	-	1	-	-	2	-
287	Cardiac arrest	3	-	1	-	1	-	-	2	-
288	Cardiac failure	28	3	2	2	3	5	3	18	1
289	Cardiac failure*	9	-	1	-	2	2	-	5	1
290	Congestive cardiac failure*	11	1	1	1	1	2	2	8	-
291	Left ventricular failure*	8	2	-	1	-	1	1	5	-
292	Cardiomegaly	3	-	2	-	-	-	-	2	-
293	Cardiomyopathy	2	-	-	-	-	-	-	-	-
294	Cardiomyopathy*	2	-	-	-	-	-	-	-	-
295	Cerebrovascular accident	37	8	1	2	4	3	1	19	3
296	Cerebro-vascular accident*	31	7	1	1	4	2	1	16	3
297	Haemorrhage cerebral*	3	1	-	1	-	-	-	2	-
298	Haemorrhage subarachnoid*	2	-	-	-	-	-	-	-	-
299	Vertebrobasilar syndrome	1	-	-	-	-	1	-	1	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
300	Chilblain	2	-	-	-	-	-	1	1	-
301	Cold extremities	5	2	-	-	-	-	1	3	-
302	Deep vein thrombosis	5	-	-	1	1	-	1	3	-
303	Disorders of heart rate	17	5	2	3	-	2	2	14	-
304	Bradycardia	1	-	-	-	-	1	-	1	-
305	Tachycardia	16	5	2	3	-	1	2	13	-
306	Disorders of rhythm	17	3	1	1	2	1	3	11	-
307	Arrhythmia	5	-	1	-	1	1	1	4	-
308	Extrasystoles	4	1	-	-	-	-	2	3	-
309	Fibrillation atrial*	8	2	-	1	1	-	-	4	-
310	Embolus pulmonary	6	1	-	1	1	-	-	3	-
311	Faintness	13	11	-	1	-	1	-	13	-
312	Hypertension	80	21	10	12	6	7	8	64	-
313	Hypertension*	80	21	10	12	6	7	8	64	-
314	Hypotension	31	9	3	5	3	2	2	24	-
315	Ischaemia mesenteric	1	-	-	-	-	-	-	-	-
316	Infarction gastrointestinal*	1	-	-	-	-	-	-	-	-
317	Ischaemia peripheral	5	-	-	1	-	-	-	1	1
318	Claudication	3	-	-	1	-	-	-	1	-
319	Ischaemia peripheral	2	-	-	-	-	-	-	-	1
320	Ischaemic heart disease	61	7	6	5	7	14	3	42	1
321	Angina	41	6	5	4	5	8	2	30	-
322	Ischaemic heart disease*	6	-	-	1	-	3	1	5	-
323	Myocardial infarction*	14	1	1	-	2	3	-	7	1
324	Oedema	220	75	45	25	12	14	14	185	-
325	Fluid retention	18	10	1	1	1	1	2	16	-
326	Oedema face	16	6	3	3	-	-	2	14	-
327	Oedema	131	40	30	12	9	10	8	109	-
328	Swollen ankles	44	16	8	7	2	3	2	38	-
329	Swollen limb	11	3	3	2	-	-	-	8	-
330	Pain chest, tight chest	110	21	14	15	8	16	14	88	-
331	Pain chest	100	21	13	12	7	15	14	82	-
332	Tight chest	10	-	1	3	1	1	-	6	-
333	Palpitation	40	14	5	5	3	1	2	30	-
334	Pericarditis	1	-	1	-	-	-	-	1	-
335	Phlebitis	2	1	-	-	-	1	-	2	-
336	Raynaud's phenomenon	3	-	-	-	-	1	-	1	-
337	Restless legs	32	16	7	3	2	2	1	31	-
338	Thrombophlebitis	7	2	-	1	1	1	1	6	-
339	Transient ischaemic attack	10	4	-	-	3	-	-	7	-
340	Valvular disease	1	-	-	-	-	-	1	1	-
341	Stenosis aortic*	1	-	-	-	-	-	1	1	-
342	Vasculitis	1	-	-	1	-	-	-	1	-
343	Veins varicose	11	-	1	3	1	1	1	7	-
344	TOTAL	757	204	101	87	59	72	59	582	6
345	**Respiratory**									
346	Asthma, wheezing	99	18	17	16	11	7	7	76	1
347	Asthma*	56	12	8	9	8	2	5	44	-
348	Bronchospasm	2	-	-	-	1	-	-	1	-
349	Wheezing	41	6	9	7	2	5	2	31	1
350	Chronic Obstructive Airways Disease	24	3	3	4	4	5	1	20	1
351	Bronchiectasis*	2	-	-	1	-	1	-	2	-
352	Chronic Obstructive Airways Disease*	21	3	3	3	4	3	1	17	1
353	Emphysema*	1	-	-	-	-	1	-	1	-
354	Cough	85	17	3	17	8	9	6	60	-
355	Dyspnoea	70	12	17	8	5	8	6	56	-
356	Effusion pleural	3	-	-	-	-	-	1	1	-
357	Epistaxis	6	-	-	1	1	1	3	6	-
358	Fibrosis lung	1	1	-	-	-	-	-	1	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
359	Alveolitis fibrosing*	1	1	-	-	-	-	-	1	-
360	Haemoptysis	11	4	1	-	1	1	1	8	-
361	Hoarseness	11	-	2	2	3	2	-	9	-
362	Hyperventilation	11	4	2	2	1	1	-	10	-
363	Pleurisy	6	1	2	-	-	-	1	4	-
364	Pleurodynia	5	-	2	-	2	-	-	4	-
365	Pneumothorax	3	-	-	-	2	-	-	2	-
366	Respiratory Failure	1	-	-	-	-	1	-	1	-
367	Respiratory tract infection	712	119	123	90	85	63	58	538	1
368	Bronchitis acute	18	2	1	2	4	2	1	12	-
369	Bronchitis*	52	5	7	9	9	2	7	39	-
370	Bronchopneumonia*	7	-	1	1	-	1	-	3	1
371	Catarrh	29	7	2	1	7	6	2	25	-
372	Coryza	17	4	2	4	1	2	2	15	-
373	Infection chest*	172	25	24	19	24	16	14	122	-
374	Influenza*	17	1	4	5	2	1	1	14	-
375	Laryngitis	10	2	1	1	1	-	2	7	-
376	Pharyngitis	132	36	23	14	15	11	7	106	-
377	Pneumonia*	14	2	1	1	1	4	-	9	-
378	Rhinitis	10	1	1	2	1	2	-	7	-
379	Rhinorrhea	1	-	1	-	-	-	-	1	-
380	Sinusitis	68	12	16	7	5	7	7	54	-
381	Tonsillitis	30	6	6	2	3	1	4	22	-
382	Tracheitis	6	2	-	-	1	-	1	4	-
383	Upper respiratory tract infection	129	14	33	22	11	8	10	98	-
384	Rhinitis allergic	15	1	1	3	1	4	2	12	-
385	TOTAL	1063	180	173	143	124	102	86	808	3
386	**Alimentary**									
387	Abscess dental	20	-	3	6	1	2	1	13	-
388	Anorexia	43	11	5	6	3	4	6	35	-
389	Appendicitis	1	-	-	-	-	-	-	-	-
390	Appendicitis	1	-	-	-	-	-	-	-	-
391	Ascites	2	-	-	-	-	-	-	-	-
392	Bowel obstruction	6	-	1	1	1	2	-	5	-
393	Bowel obstruction*	6	-	1	1	1	2	-	5	-
394	Bulimia	5	3	1	-	-	-	-	4	-
395	Campylobacter	4	1	-	2	-	-	-	3	-
396	Candidiasis oral	14	4	-	2	-	3	-	9	-
397	Cheilitis	1	-	-	1	-	-	-	1	-
398	Cholelithiasis, cholecystitis	12	-	-	1	2	3	3	9	-
399	Cholecystitis	2	-	-	-	-	1	1	2	-
400	Cholelithiasis*	8	-	-	1	2	2	1	6	-
401	Colic biliary	2	-	-	-	-	-	1	1	-
402	Cirrhosis	9	-	3	-	-	2	-	5	-
403	Cirrhosis*	7	-	2	-	-	2	-	4	-
404	Oesophageal varices	2	-	1	-	-	-	-	1	-
405	Coeliac disease	1	-	-	-	-	-	-	-	-
406	Constipation	109	33	16	13	12	13	6	93	1
407	Diarrhoea	180	45	34	27	14	16	12	148	-
408	Distension abdominal	51	11	14	5	5	1	3	39	1
409	Dry mouth	47	31	4	5	1	2	1	44	-
410	Dyspepsia	175	36	29	20	16	14	19	134	-
411	Duodenitis	1	-	-	-	-	-	-	-	-
412	Dyspepsia	108	24	12	15	10	6	13	80	-
413	Gastritis	14	3	4	1	-	2	1	11	-
414	Heartburn	21	6	4	2	1	2	2	17	-
415	Oesophageal reflux	20	2	5	1	4	1	3	16	-
416	Oesophagitis	11	1	4	1	1	3	-	10	-
417	Dysphagia	12	1	1	-	-	4	2	8	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
418	Faecal incontinence	5	-	3	-	1	-	1	5	-
419	Fissure anorectal	2	-	-	1	-	-	-	1	-
420	Flatulence	8	2	2	2	1	1	-	8	-
421	Gastroenteritis	24	1	5	2	3	3	-	14	-
422	Giardiasis	1	-	-	-	-	-	-	-	-
423	Gingivitis	10	1	1	2	-	-	2	6	-
424	Glossitis	4	1	1	1	1	-	-	4	-
425	Gum hypertrophy	1	-	-	-	-	-	-	-	-
426	Haemorrhage gastrointestinal	4	1	-	-	-	-	1	2	-
427	Haemorrhage gastrointestinal upper	18	2	2	1	2	1	2	10	-
428	Haematemesis*	12	1	1	1	2	1	1	7	-
429	Melena	5	1	-	-	-	-	1	2	-
430	Oesophageal haemorrhage*	1	-	1	-	-	-	-	1	-
431	Haemorrhage oral	1	1	-	-	-	-	-	1	-
432	Haemorrhage rectal	26	8	-	3	2	3	1	17	-
433	Haemorrhagic diarrhoea	2	-	1	-	1	-	-	2	-
434	Haemorrhoids	32	3	5	9	2	3	1	23	-
435	Halitosis	2	1	1	-	-	-	-	2	-
436	Hepatic failure	5	1	-	1	-	-	-	2	-
437	Hepatic failure*	5	1	-	1	-	-	-	2	-
438	Hepatitis, jaundice	5	1	3	-	-	-	-	4	-
439	Hepatitis*	1	-	1	-	-	-	-	1	-
440	Jaundice	3	-	2	-	-	-	-	2	-
441	Jaundice obstructive*	1	1	-	-	-	-	-	1	-
442	Hepatomegaly	2	-	-	-	-	1	-	1	-
443	Hernia	3	1	-	-	1	-	-	2	-
444	Hernia hiatus	4	-	2	2	-	-	-	4	-
445	Hiccough	1	-	1	-	-	-	-	1	-
446	Inflammatory disease colon	24	4	2	2	5	3	1	17	-
447	Colitis	4	-	-	-	1	-	-	1	-
448	Colitis pseudomembranous*	1	-	-	-	1	-	-	1	-
449	Colitis ulcerative	1	1	-	-	-	-	-	1	-
450	Colon perforated*	1	-	-	1	-	-	-	1	-
451	Crohn's disease*	2	-	1	-	-	-	-	1	-
452	Diverticulitis	8	1	1	1	2	-	-	5	-
453	Diverticulosis*	6	2	-	-	1	3	-	6	-
454	Diverticulum perforated*	1	-	-	-	-	-	1	1	-
455	Irritable bowel syndrome	49	5	3	8	10	7	5	38	-
456	Leukoplakia oral	1	-	-	-	-	-	-	-	-
457	Liver function test abnormal	49	11	8	4	7	2	4	36	-
458	Nausea, vomiting	289	137	33	30	20	13	19	252	-
459	Nausea	192	103	19	21	14	7	8	172	-
460	Vomiting	97	34	14	9	6	6	11	80	-
461	Pain abdomen	182	39	26	25	17	17	16	140	1
462	Pancreatitis	4	-	-	-	-	-	2	2	-
463	Pancreatitis*	4	-	-	-	-	-	2	2	-
464	Parotid enlarged	2	-	1	-	1	-	-	2	-
465	Parotitis	1	-	-	-	-	1	-	1	-
466	Pharynx irritation	2	1	-	1	-	-	-	2	-
467	Proctalgia	9	1	1	-	-	-	-	2	-
468	Proctitis	4	1	1	-	-	1	1	4	-
469	Prolapse rectal	1	1	-	-	-	-	-	1	-
470	Rectal discharge	4	-	-	-	1	-	-	1	-
471	Saliva increased	3	1	-	-	1	-	-	2	-
472	Sialadenitis	1	-	-	-	-	-	-	-	-
473	Sore mouth	10	5	2	1	-	1	-	9	-
474	Stomatitis	8	2	1	1	-	2	1	7	-
475	Tenesmus	3	2	-	-	-	-	1	3	-
476	Toothache	8	1	-	2	1	-	2	6	-
477	Ulcer mouth	22	9	5	2	2	3	-	21	-

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	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
478	Ulcer oesophageal	1	-	-	-	-	-	1	1	-
479	Ulcer peptic	5	2	-	-	-	-	-	2	-
480	Ulcer duodenal*	2	-	-	-	-	-	-	-	-
481	Ulcer gastric	1	1	-	-	-	-	-	1	-
482	Ulcer peptic*	2	1	-	-	-	-	-	1	-
483	TOTAL	1534	422	221	189	134	128	114	1208	3
484	**Metabolic and Endocrine**									
485	Acromegaly	1	-	-	-	-	1	-	1	-
486	Dehydration	1	-	-	-	1	-	-	1	-
487	Diabetes mellitus improved	1	-	-	1	-	-	-	1	-
488	Diabetes mellitus, hyperglycaemia	38	5	4	4	3	6	1	23	1
489	Diabetes mellitus worsened	9	1	1	2	-	2	1	7	-
490	Diabetes mellitus*	17	3	1	2	2	1	-	9	1
491	Glycosuria	1	1	-	-	-	-	-	1	-
492	Hyperglycaemia	7	-	2	-	1	-	-	3	-
493	Ketoacidosis diabetic*	2	-	-	-	-	2	-	2	-
494	Retinopathy diabetic	2	-	-	-	-	1	-	1	-
495	Electrolyte abnormal	7	1	1	3	1	-	-	6	-
496	Hyperkalaemia	1	-	-	1	-	-	-	1	-
497	Hypokalaemia	3	1	-	1	-	-	-	2	-
498	Hyponatraemia	3	-	1	1	1	-	-	3	-
499	Excessive thirst	14	5	2	3	-	-	1	11	-
500	Globulin abnormal	3	1	-	-	-	1	-	2	-
501	Gout	15	1	3	1	2	2	2	11	-
502	Hyperlipidaemia	10	2	1	-	1	-	4	8	-
503	Hypercholesterolaemia	7	1	1	-	-	-	4	6	-
504	Hyperlipidaemia	3	1	-	-	1	-	-	2	-
505	Hyperprolactinaemia	1	-	-	-	-	-	-	-	-
506	Hyperthyroidism	3	-	1	-	-	1	-	2	-
507	Hypoglycaemia	2	-	-	-	-	-	1	1	-
508	Hypothyroidism	29	2	2	1	3	4	1	13	-
509	Obesity	14	4	2	1	-	2	-	9	1
510	Obesity	14	4	2	1	-	2	-	9	1
511	Sweating	52	20	4	6	3	4	5	42	-
512	Weight gain	542	176	109	77	47	35	22	466	6
513	Weight loss	30	3	2	2	2	5	2	16	2
514	TOTAL	763	220	131	99	63	61	39	613	10
515	**Urologic**									
516	Albuminuria	5	2	-	-	-	1	1	4	-
517	Bladder irritability	1	1	-	-	-	-	-	1	-
518	Calculus renal	2	-	-	-	1	1	-	2	-
519	Caruncle urethral	1	-	-	-	-	-	1	1	-
520	Colic renal	8	-	-	1	1	2	3	7	-
521	Colic renal	4	-	-	-	-	1	2	3	-
522	Pain renal	4	-	-	1	1	1	1	4	-
523	Enuresis	4	1	-	-	1	-	-	2	-
524	Haematuria	19	3	1	6	2	1	2	15	-
525	Hydronephrosis	1	-	-	-	-	-	-	-	-
526	Micturition disorder	93	15	6	15	14	13	5	68	-
527	Dysuria	19	1	-	2	6	2	-	11	-
528	Frequency	35	9	-	6	4	6	1	26	-
529	Incontinence	29	4	5	6	2	4	2	23	-
530	Nocturia	7	1	1	-	2	-	2	6	-
531	Urgency	3	-	-	1	-	1	-	2	-
532	Polyuria	4	2	-	1	-	-	-	3	-
533	Pyuria	1	-	-	-	-	1	-	1	-
534	Renal failure	9	3	1	-	1	2	-	7	-
535	Renal failure acute	2	1	-	-	-	-	-	1	-
536	Renal failure chronic*	4	1	1	-	1	1	-	4	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
537	Renal failure*	3	1	-	-	-	1	-	2	-
538	Renal function test abnormal	5	1	-	2	2	-	-	5	-
539	Retention	11	3	1	1	2	1	2	10	-
540	Urea raised	2	1	-	1	-	-	-	2	-
541	Urinary tract infection	134	20	17	20	11	14	18	100	1
542	Cystitis	25	4	2	5	2	4	1	18	-
543	Pyelitis	1	-	-	-	-	-	-	-	-
544	Pyelonephritis*	2	-	-	-	-	1	-	1	-
545	Urethritis	5	-	-	-	-	2	2	4	1
546	Urinary tract infection*	101	16	15	15	9	7	15	77	-
547	TOTAL	300	52	26	47	35	36	32	228	1
548	**Male Reproductive and Gynaecomastia**									
549	Balanitis	4	1	-	-	1	1	-	3	-
550	Cyst epididymis	2	-	-	-	-	2	-	2	-
551	Ejaculation premature	1	-	-	-	-	1	-	1	-
552	Epididymitis	4	1	-	1	-	-	-	2	-
553	Gynaecomastia	4	-	1	-	-	-	1	2	-
554	Haemospermia	2	-	1	-	1	-	-	2	-
555	Impotence, ejaculation failure	39	10	6	5	4	3	3	31	1
556	Ejaculation failure	1	1	-	-	-	-	-	1	-
557	Impotence	38	9	6	5	4	3	3	30	1
558	Phimosis	1	1	-	-	-	-	-	1	-
559	Prostatism	12	1	2	-	-	1	4	8	-
560	Prostatitis	4	1	-	-	-	1	1	3	-
561	TOTAL	73	15	10	6	6	9	9	55	1
562	**Female Reproductive**									
563	Abscess Bartholin's gland	1	-	-	-	-	-	-	-	-
564	Bartholinitis	1	-	-	-	-	-	1	1	-
565	Cervical smear abnormal	4	-	1	1	-	-	1	3	-
566	Cyst Bartholin's	2	-	-	-	-	-	-	-	-
567	Cyst ovarian	5	-	2	-	1	1	-	4	-
568	Dyskaryosis	2	-	-	-	2	-	-	2	-
569	Dyspareunia	12	2	2	1	2	2	-	9	-
570	Endometriosis	2	-	-	-	1	-	1	2	-
571	Haemorrhage postcoital	4	1	1	-	-	2	-	4	-
572	Haemorrhage postmenopausal	4	-	1	-	1	1	1	4	-
573	Haemorrhage vaginal	21	7	1	2	-	3	1	14	-
574	Infertility female	1	-	-	-	1	-	-	1	-
575	Menopausal symptoms	11	-	3	1	-	-	1	5	1
576	Menstrual disorder	66	9	4	7	9	6	11	46	1
577	Amenorrhoea	10	4	-	1	1	1	-	7	1
578	Dysmenorrhoea	10	2	1	2	1	1	1	8	-
579	Irregular periods	11	1	2	1	2	-	-	6	-
580	Menorrhagia	34	2	1	3	5	4	10	25	-
581	Polymenorrhoea	1	-	-	-	-	-	-	-	-
582	Metrorrhagia	8	3	-	1	2	1	1	8	-
583	Pelvic inflammatory disease	3	-	1	-	-	-	-	1	-
584	Pelvic inflammatory disease	3	-	1	-	-	-	-	1	-
585	Premenstrual tension	20	1	1	5	2	4	2	15	-
586	Prolapse uterine	6	-	3	-	-	1	1	5	-
587	Vaginal soreness	2	1	-	-	-	-	-	1	-
588	Vaginitis, vulvitis	74	9	12	8	9	12	8	58	2
589	Infection vaginal bacterial	4	1	-	1	1	-	1	4	-
590	Vaginal candidiasis	32	3	6	3	4	5	5	26	1
591	Vaginal discharge	26	4	5	3	1	4	2	19	-
592	Vaginitis	8	-	1	1	3	2	-	7	1
593	Vaginitis trichomonas	1	-	-	-	-	-	-	-	-
594	Vulvitis	3	1	-	-	-	1	-	2	-
595	TOTAL	249	33	32	26	30	33	29	183	4

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
596	**Breast Disorder**									
597	Abscess breast	2	-	1	1	-	-	-	2	-
598	Breast discharge	1	-	1	-	-	-	-	1	-
599	Breast disorder	6	1	-	1	1	1	1	5	-
600	Galactorrhoea	5	2	-	-	-	-	2	4	-
601	Mastalgia	24	6	-	2	4	4	-	16	-
602	Mastitis	3	-	-	-	-	-	1	1	-
603	TOTAL	41	9	2	4	5	5	4	29	-
604	**Obstetric**									
605	Abortion threatened	2	-	1	-	-	-	-	1	-
606	TOTAL	2	-	1	-	-	-	-	1	-
607	**Haemopoietic**									
608	Anaemia	18	4	2	2	1	1	2	12	-
609	Anaemia iron deficiency	10	1	1	-	1	3	1	7	-
610	Anaemia iron deficiency	10	1	1	-	1	3	1	7	-
611	Anaemia macrocytic	2	-	-	-	1	-	-	1	-
612	Anaemia macrocytic	1	-	-	-	1	-	-	1	-
613	Anaemia vitamin B12 deficiency	1	-	-	-	-	-	-	-	-
614	Bone marrow abnormal	3	1	-	1	1	-	-	3	-
615	Eosinophilia	3	-	1	1	-	-	-	2	-
616	Eosinophilia	3	-	1	1	-	-	-	2	-
617	Erythrocyte sedimentation rate raised	4	2	-	1	-	-	-	3	-
618	Haematoma spontaneous	7	1	-	-	1	-	1	3	-
619	Hyperbilirubinaemia	2	-	2	-	-	-	-	2	-
620	Leucocytosis	12	3	1	3	-	1	2	10	-
621	Leucocytosis	5	2	-	2	-	1	-	5	-
622	Neutrophilia	7	1	1	1	-	-	2	5	-
623	Leucopenia	12	4	2	2	-	2	-	10	-
624	Leucopenia	5	3	1	-	-	-	-	4	-
625	Neutropenia	7	1	1	2	-	2	-	6	-
626	Lymphadenopathy	18	3	-	2	2	2	3	12	-
627	Glands swollen	8	1	-	1	1	-	2	5	-
628	Lymphadenitis	4	-	-	-	1	1	-	2	-
629	Lymphadenopathy	6	2	-	1	-	1	1	5	-
630	Myelodysplastic syndrome	3	-	-	1	-	-	1	2	-
631	Pancytopenia	2	-	-	-	1	-	-	1	-
632	Anaemia hypoplastic	1	-	-	-	1	-	-	1	-
633	Pancytopenia	1	-	-	-	-	-	-	-	-
634	Red cell abnormal	7	1	-	2	-	1	1	5	-
635	Thrombocytopenia	3	-	-	2	-	-	-	2	-
636	Thrombocytosis	3	-	-	1	-	1	-	2	-
637	TOTAL	109	20	9	18	8	11	11	77	-
638	**Neoplasm**									
639	Malignancies	79	20	6	8	10	4	8	56	8
640	Cancer*	3	1	-	-	-	-	1	2	1
641	Carcinoma bladder*	1	1	-	-	-	-	-	1	-
642	Carcinoma brain*	1	-	-	-	-	1	-	1	-
643	Carcinoma breast*	5	-	-	1	1	1	-	3	1
644	Carcinoma bronchus*	2	-	-	-	2	-	-	2	-
645	Carcinoma cervix*	2	-	-	-	1	-	-	1	-
646	Carcinoma colon*	10	4	1	-	2	-	-	7	1
647	Carcinoma kidney*	1	-	-	-	1	-	-	1	-
648	Carcinoma larynx*	2	1	-	1	-	-	-	2	-
649	Carcinoma liver*	1	-	-	-	1	-	-	1	-
650	Carcinoma lung*	6	1	1	-	-	-	2	4	-
651	Carcinoma ovary*	2	1	-	-	-	-	1	2	-
652	Carcinoma pancreas*	2	1	-	1	-	-	-	2	-
653	Carcinoma prostate*	4	2	-	-	-	-	-	2	2
654	Carcinoma rectum*	3	-	-	1	-	1	-	2	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
655	Carcinoma skin*	7	2	1	-	-	-	2	5	-
656	Carcinoma stomach*	3	1	1	1	-	-	-	3	-
657	Carcinoma thyroid*	1	-	1	-	-	-	-	1	-
658	Carcinomatosis*	14	1	1	2	2	1	1	8	3
659	Glioma*	1	1	-	-	-	-	-	1	-
660	Leukaemia lymphocytic chronic*	1	-	-	-	-	-	1	1	-
661	Leukaemia myeloid acute*	1	1	-	-	-	-	-	1	-
662	Leukaemia myeloid chronic*	1	1	-	-	-	-	-	1	-
663	Leukaemia*	1	-	-	-	-	-	-	-	-
664	Melanoma*	1	-	-	-	-	-	-	-	-
665	Myeloma*	1	-	-	-	-	-	-	-	-
666	Sarcoma*	2	1	-	1	-	-	-	2	-
667	Non-malignant tumours	31	2	5	5	2	6	3	23	-
668	Adenoma endocrine	1	1	-	-	-	-	-	1	-
669	Fibroids	6	-	2	1	1	-	1	5	-
670	Lymphoma	1	-	-	-	1	-	-	1	-
671	Non-malignant tumour breast	6	-	1	1	-	3	-	5	-
672	Non-malignant tumour skin	10	-	2	2	-	1	1	6	-
673	Polyp gastrointestinal	3	-	-	1	-	1	-	2	-
674	Polyp nasal	1	-	-	-	-	1	-	1	-
675	Polyp uterine	3	1	-	-	-	-	1	2	-
676	TOTAL	110	22	11	13	12	10	11	79	8
677	**Miscellaneous Infection**									
678	Abscess	3	1	1	1	-	-	-	3	-
679	Candidiasis	18	3	3	4	1	1	-	12	-
680	Chlamydial infection	1	-	-	-	-	-	-	-	-
681	Gardnerella infection	1	1	-	-	-	-	-	1	-
682	Herpes	3	-	-	1	-	-	1	2	-
683	Herpes	2	-	-	-	-	-	1	1	-
684	Herpes simplex	1	-	-	1	-	-	-	1	-
685	HIV positive and AIDS	1	-	-	-	-	-	-	-	1
686	HIV (Human immunodeficiency virus) positi	1	-	-	-	-	-	-	-	1
687	Infection	3	-	1	1	-	-	-	2	-
688	Infection postoperative	5	-	3	-	-	-	-	3	-
689	Infection viral	25	2	2	2	3	3	2	14	-
690	Rigor	3	-	-	-	-	1	1	2	-
691	Septicaemia	2	-	-	-	-	2	-	2	-
692	Varicella	1	-	-	-	-	1	-	1	-
693	Wart	5	1	1	-	-	-	-	2	-
694	Wart genital	2	-	1	-	1	-	-	2	-
695	TOTAL	73	8	12	9	5	8	4	46	1
696	**Immunological**									
697	Allergy	10	4	-	-	-	-	1	5	1
698	Angioneurotic oedema	4	-	-	-	-	1	-	1	-
699	Antinuclear antibody positive	1	-	-	-	-	-	-	-	-
700	Unspecified side effects	178	111	23	11	9	4	6	164	1
701	TOTAL	193	115	23	11	9	5	7	170	2
702	**Adverse Reaction to Specific Drug**									
703	Adverse reaction to other drug	14	2	1	2	2	2	-	9	1
704	Dependence	10	3	-	1	-	1	2	7	-
705	Withdrawal symptoms	14	5	2	2	1	1	-	11	1
706	TOTAL	38	10	3	5	3	4	2	27	2
707	**Accident and Injury**									
708	Animal bite	3	1	-	-	1	1	-	3	-
709	Assault	15	4	3	2	1	2	1	13	-
710	Burn	5	3	-	-	-	1	-	4	-
711	Drug overdose accidental	3	1	1	-	-	-	-	2	-
712	Fall	107	21	14	7	19	6	7	74	-
713	Fall*	68	14	8	5	14	4	5	50	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
714	Fall minor injury	38	7	6	2	5	2	2	24	-
715	Fall no injury	1	-	-	-	-	-	-	-	-
716	Fracture	47	8	9	2	6	3	7	35	-
717	Haematoma	14	2	-	2	2	-	3	9	-
718	Hyperkeratosis solar	2	1	-	-	-	-	1	2	-
719	Injury	125	13	15	14	12	13	17	84	-
720	Insect bite & sting	3	-	-	-	-	-	-	-	-
721	Bee sting	1	-	-	-	-	-	-	-	-
722	Insect bite	2	-	-	-	-	-	-	-	-
723	Poisoning nonmedicinal	1	-	-	-	-	-	-	-	-
724	Raped	1	-	-	-	-	-	1	1	-
725	Road traffic accident	30	5	4	5	4	2	4	24	-
726	Sunburn	1	-	-	-	-	-	-	-	-
727	TOTAL	357	59	46	32	45	28	41	251	-
728	**Death**									
729	Death cause uncertain	137	5	12	14	14	10	9	64	57
730	TOTAL	137	5	12	14	14	10	9	64	57
731	**Surgery**									
732	Abdominal surgery	26	2	4	3	-	4	4	17	1
733	Appendicectomy	4	-	1	-	-	1	2	4	-
734	Cholecystectomy	5	-	-	-	-	1	1	2	-
735	Gastrointestinal surgery	11	1	2	3	-	1	-	7	1
736	Hernia surgery	6	1	1	-	-	1	1	4	-
737	Acupuncture	3	-	-	-	-	-	-	-	-
738	Blood transfusion	5	1	1	1	-	-	1	4	-
739	Catheterisation	2	-	-	1	-	1	-	2	-
740	Chemotherapy	2	2	-	-	-	-	-	2	-
741	Dental surgery	7	1	-	-	1	2	-	4	-
742	Dialysis renal	1	-	1	-	-	-	-	1	-
743	Ear nose and throat surgery	3	-	1	1	-	1	-	3	-
744	Electroconvulsive therapy	36	6	5	4	2	2	4	23	6
745	Endoscopy	13	3	2	1	-	1	1	8	-
746	Gastroscopy	4	-	1	1	-	-	1	3	1
747	Genitourinary surgery	6	2	1	-	1	1	1	6	-
748	Cystoscopy	1	1	-	-	-	-	-	1	-
749	Genitourinary surgery	2	-	1	-	-	1	-	2	-
750	Renal transplantation	1	1	-	-	-	-	-	1	-
751	Transurethral resection of prostate	2	-	-	-	1	-	1	2	-
752	Gynaecological surgery	25	1	6	2	2	4	1	16	1
753	Abortion therapeutic	8	-	2	1	1	1	-	5	1
754	Caesarean section	1	-	-	-	-	-	-	-	-
755	Gynaecological surgery	13	1	3	1	-	3	1	9	-
756	Hysterectomy	3	-	1	-	1	-	-	2	-
757	Lumpectomy	1	-	-	-	-	-	-	-	-
758	Mastectomy	1	-	-	-	-	-	1	1	-
759	Minor surgery	34	4	5	5	3	5	3	25	-
760	Ophthalmic surgery	8	-	-	1	-	2	-	3	-
761	Cataract extraction	5	-	-	-	-	1	-	1	-
762	Eye surgery	3	-	-	1	-	1	-	2	-
763	Orthopaedic surgery	20	2	5	2	3	2	3	17	-
764	Amputation	3	-	1	-	-	1	-	2	-
765	Orthopaedic surgery	15	2	4	2	2	1	3	14	-
766	Total hip replacement*	2	-	-	-	1	-	-	1	-
767	Radiotherapy	3	1	1	-	-	-	-	2	-
768	Surgery	10	1	3	1	1	1	-	7	-
769	Thoracic surgery	7	-	-	3	-	-	2	5	-
770	Cardiac catheter	1	-	-	-	-	-	-	-	-
771	Cardiac surgery*	3	-	-	2	-	-	-	2	-
772	Heart-lung transplantation*	1	-	-	1	-	-	-	1	-

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Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
773	Thoracic surgery*	2	-	-	-	-	-	2	2	-
774	Vascular surgery	2	1	-	1	-	-	-	2	-
775	Vascular surgery	2	1	-	1	-	-	-	2	-
776	TOTAL	219	27	36	27	13	26	22	151	9
777	**Referrals**									
778	Hospital referrals no admission	442	75	54	49	43	38	46	305	13
779	Hospital referrals: Cardiology	17	4	2	2	1	-	3	12	-
780	Hospital referrals: Dermatology	5	-	-	-	-	-	2	2	-
781	Hospital referrals: Ear, nose and throat	12	1	-	-	1	2	3	7	-
782	Hospital referrals: Gastroenterology	11	-	1	1	-	-	2	4	-
783	Hospital referrals: General medicine	2	-	-	1	-	-	-	1	1
784	Hospital referrals: Gynaecology	22	3	2	3	2	3	1	14	-
785	Hospital referrals: Haematology	1	-	-	-	-	-	1	1	-
786	Hospital referrals: Neurology	10	1	2	-	1	1	-	5	2
787	Hospital referrals: Ophthalmology	8	3	-	1	-	1	-	5	-
788	Hospital referrals: Orthopaedics	8	1	1	-	1	-	1	4	-
789	Hospital referrals: Psychiatry	196	40	25	22	23	21	16	147	6
790	Hospital referrals: Respiratory	3	-	-	-	-	2	1	3	-
791	Hospital referrals: Rheumatology	3	-	1	-	-	-	1	2	-
792	Hospital referrals: Urology	4	-	1	-	-	1	-	2	-
793	Hospital referrals	140	22	19	19	14	7	15	96	4
794	Non-surgical admissions	356	87	43	42	30	31	36	269	10
795	TOTAL	798	162	97	91	73	69	82	574	23
796	**Social**									
797	Bereavement	24	3	4	4	1	2	2	16	2
798	Domestic	79	11	8	16	7	9	4	55	2
799	Loneliness	1	-	-	-	-	-	1	1	-
800	Marital	14	4	2	1	1	-	4	12	-
801	Prison admission	5	-	-	2	2	-	-	4	-
802	Redundancy	2	-	-	-	1	-	-	1	-
803	TOTAL	125	18	14	23	12	11	11	89	4
804	**Other Events**									
805	Cardiovascular system unspecified	5	1	-	-	-	-	1	2	-
806	Central nervous system unspecified	7	4	-	-	1	1	-	6	-
807	Ear unspecified	2	-	-	1	-	-	-	1	-
808	Event not coded	4	3	-	-	-	-	-	3	-
809	Eye unspecified	3	2	1	-	-	-	-	3	-
810	Gastrointestinal unspecified	23	5	4	3	4	2	-	18	1
811	Gynaecology unspecified	10	1	1	3	2	-	-	7	-
812	Haemorrhage postoperative	2	1	-	-	-	-	-	1	-
813	Laboratory test abnormal	15	3	1	1	2	4	1	12	-
814	Liver unspecified	2	1	-	-	-	-	-	1	-
815	Male reproductive system unspecified	8	4	1	-	1	-	1	7	-
816	Metabolic unspecified	3	2	-	1	-	-	-	3	-
817	Musculoskeletal unspecified	11	2	3	1	-	-	1	7	-
818	Nodule	3	-	-	1	-	-	-	1	-
819	Non-malignant tumour unspecified	2	-	-	-	-	1	-	1	-
820	Pain	12	2	-	2	-	1	4	9	1
821	Pain postoperative	3	-	-	-	-	-	1	1	-
822	Psychiatric unspecified	80	13	10	12	6	5	9	55	1
823	Psychosomatic unspecified	3	1	-	-	-	1	-	2	1
824	Respiratory unspecified	9	-	3	-	-	1	2	6	-
825	Skin unspecified	7	-	1	1	-	2	1	5	-
826	Urinary unspecified	5	1	-	3	-	-	-	4	-
827	Pregnancy	77	12	14	7	5	6	7	51	9
828	Abortion	3	-	1	1	1	-	-	3	-
829	Abortion spontaneous	6	-	-	2	-	1	-	3	-
830	Birth normal	2	-	-	-	-	1	-	1	-
831	Pregnancy	66	12	13	4	4	4	7	44	9

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
832	TOTAL	295	58	39	36	21	23	28	205	13
833	**New Events**									
834	Abortion missed	1	-	-	-	-	1	-	1	-
835	Absence seizure/attack	1	-	-	-	-	-	1	1	-
836	Akathisia	2	2	-	-	-	-	-	2	-
837	Anaemia fatal	1	1	-	-	-	-	-	1	-
838	Angina improved	1	-	-	-	-	1	-	1	-
839	Anorexia nervosa fatal	1	-	-	1	-	-	-	1	-
840	Appetite increased	130	79	23	12	6	3	2	125	1
841	Asthma nocturnal	1	-	-	-	-	-	-	-	-
842	Asthma worse	11	4	2	1	2	-	-	9	-
843	Baldness	1	-	-	-	1	-	-	1	-
844	Bowel habit changed	9	2	3	-	2	-	-	7	-
845	Breast disorder male	2	-	-	-	1	-	-	1	-
846	Breast tests	3	-	-	-	1	-	-	1	-
847	Cardiovascular tests	80	13	10	8	5	13	9	58	-
848	Cardiovascular unspecified fatal	1	-	-	-	-	-	-	-	-
849	Central nervous system tests	9	1	1	2	-	-	2	6	1
850	Chesty	13	-	3	3	1	2	1	10	-
851	Condition improved	1351	262	220	157	163	143	128	1073	22
852	Connective tissue disease	1	-	-	-	-	1	-	1	-
853	Cyst	3	-	1	-	-	1	-	2	-
854	Dementia fatal	1	-	1	-	-	-	-	1	-
855	Dependence other drug	2	-	-	-	-	1	-	1	1
856	Dislocated joint	1	-	-	1	-	-	-	1	-
857	Dose increased	963	409	162	95	64	57	46	833	3
858	Dose reduced	294	69	43	29	27	25	30	223	9
859	Drug abuse	26	10	2	2	1	5	2	22	-
860	Drug information	10	9	1	-	-	-	-	10	-
861	Dysarthria	2	-	1	-	-	-	1	2	-
862	Dyskinesia	2	1	-	-	-	-	-	1	-
863	Ear tests	1	-	-	-	-	-	1	1	-
864	Ear trivial	2	-	-	1	1	-	-	2	-
865	Eating disorder	10	5	1	1	-	1	1	9	1
866	Emotional disturbance	14	5	4	-	-	1	2	12	-
867	Eye tests	2	-	1	-	1	-	-	2	-
868	Flu like symptoms	21	5	2	1	3	-	5	16	-
869	Gastro-intestinal tests	17	3	2	3	2	2	3	15	1
870	Glue ear	3	-	-	-	-	1	-	1	-
871	Gynaecological tests	26	6	2	4	4	4	-	20	-
872	Gynaecological trivial	5	-	-	-	-	2	-	2	1
873	Haematological tests	100	21	14	10	13	7	9	74	2
874	Helicobacter	6	1	-	-	1	-	3	5	-
875	Hepatic tests	20	5	2	3	4	-	3	17	-
876	Herpes genital	2	1	-	-	-	1	-	2	-
877	Hospital referral paramedical	68	12	14	11	5	4	6	52	3
878	Hypoglycaemia fatal	1	-	-	-	-	-	-	-	-
879	Illegible	15	1	1	2	2	3	2	11	-
880	Immobility	6	3	-	1	-	-	-	4	-
881	Immounological tests	1	1	-	-	-	-	-	1	-
882	Inappropriate adh synd	1	-	-	-	-	-	1	1	-
883	Intolerance	241	165	35	13	6	7	4	230	1
884	Lipid tests	7	-	-	2	1	1	-	4	-
885	Male reproductive tests	2	-	-	-	1	-	-	1	-
886	Medical cert	14	4	3	2	1	1	-	11	-
887	Mental state improved	16	4	1	1	1	1	1	9	1
888	Mental state worse	16	4	1	2	-	2	2	11	-
889	Metabolic tests	36	4	1	7	6	6	3	27	-
890	Micturition abnormal	13	2	1	1	2	1	2	9	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3a. All events reported on green forms for mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**112677**	**13535**	**13473**	**13434**	**13392**	**13338**	**13279**		**known**
3	**Denominator male**	**43096**	**5203**	**5178**	**5163**	**5145**	**5126**	**5105**		
4	**Denominator female**	**69094**	**8268**	**8230**	**8206**	**8183**	**8148**	**8111**		
891	Multi system atrophy	1	-	-	-	1	-	-	1	-
892	Musculoskeletal tests	11	2	1	-	1	1	1	6	-
893	Non compliance	314	161	37	32	27	11	14	282	4
894	Non formulary	5	1	-	-	2	-	1	4	-
895	Osteopenia	1	-	-	-	-	-	-	-	-
896	Pain foot	23	4	2	1	-	1	5	13	-
897	Pain hand	15	2	4	1	3	1	1	12	-
898	Pain musculoskeletal	47	5	7	7	5	4	3	31	1
899	Pain pelvis	10	1	1	1	3	1	3	10	-
900	Pallor	2	-	-	-	-	-	-	-	-
901	Patient request	494	202	83	49	38	29	22	423	5
902	Personality disorder	9	3	-	-	1	1	2	7	1
903	Polysymptomatic	6	4	-	-	-	-	-	4	2
904	Post operation unspecified	2	1	1	-	-	-	-	2	-
905	Pyrexia	13	3	-	3	-	-	1	7	-
906	Respiratory tests	27	5	5	4	4	2	2	22	-
907	Respiratory trivial	8	1	1	1	1	1	1	6	-
908	Sensation abnormal	23	10	3	-	1	2	-	16	2
909	Shivering	5	3	1	-	1	-	-	5	-
910	Skin trivial	5	-	-	-	-	2	1	3	-
911	Slapped cheek syndrome	1	-	-	-	-	-	-	-	-
912	Slurred speech	6	5	1	-	-	-	-	6	-
913	Smoker	8	6	-	-	-	1	-	7	-
914	Stammer	1	-	-	-	1	-	-	1	-
915	Stiffness	9	3	-	1	-	1	1	6	-
916	Tardive dyskinesia	1	-	-	-	-	-	-	-	-
917	Teichopsia	1	-	-	-	-	-	-	-	-
918	Tendon rupture	2	-	1	-	-	-	-	1	-
919	Testis pain/discomfort	3	1	-	-	1	-	1	3	-
920	Thought disorder	11	2	4	-	1	-	-	7	1
921	Tumour	19	-	4	1	3	-	2	10	-
922	Unsteadiness	35	21	4	1	2	1	3	32	-
923	Urinary tests	31	5	7	5	3	4	2	26	-
924	Urine outflow obstruction	1	-	-	-	-	-	-	-	-
925	Urology tests	6	1	-	1	-	2	1	5	-
926	Vaccination	26	1	4	2	4	1	3	15	-
927	Whiplash	6	-	-	1	1	1	1	4	-
928	TOTAL	4777	1567	729	487	432	365	341	3921	63

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
5	**Skin**									
6	Acne	16	3	3	2	4	2	1	15	-
7	Acne	10	2	1	1	3	1	1	9	-
8	Acne rosacea	6	1	2	1	1	1	-	6	-
9	Alopecia	1	1	-	-	-	-	-	1	-
10	Cyst sebaceous	11	-	1	2	1	4	1	9	-
11	Dermatitis	17	2	2	5	1	-	2	12	-
12	Dermatitis contact	1	-	1	-	-	-	-	1	-
13	Dry skin	9	2	2	1	2	-	2	9	-
14	Eczema	47	7	9	5	5	1	6	33	-
15	Eczema	41	6	8	5	4	1	5	29	-
16	Intertrigo	5	1	1	-	-	-	1	3	-
17	Pompholyx	1	-	-	-	1	-	-	1	-
18	Eczema varicose	3	1	1	-	-	-	-	2	-
19	Eruption bullous	1	-	-	-	-	1	-	1	-
20	Blister	1	-	-	-	-	1	-	1	-
21	Dermatitis herpetiformis	-	-	-	-	-	-	-	-	-
22	Erythema	3	1	2	-	-	-	-	3	-
23	Erythema nodosum	1	1	-	-	-	-	-	1	-
24	Erythroderma	1	-	-	-	-	-	-	-	-
25	Dermatitis exfoliative	1	-	-	-	-	-	-	-	-
26	Folliculitis	3	1	-	-	-	-	-	1	-
27	Hair ingrown	1	-	-	-	-	1	-	1	-
28	Hair loss	6	3	1	1	1	-	-	6	-
29	Herpes simplex, skin	3	1	1	-	-	-	1	3	-
30	Herpes zoster	8	3	-	-	1	2	1	7	-
31	Hirsutism	-	-	-	-	-	-	-	-	-
32	Hyperkeratosis	2	-	-	-	-	1	-	1	-
33	Hyperkeratosis	-	-	-	-	-	-	-	-	-
34	Pityriasis	2	-	-	-	-	1	-	1	-
35	Infection skin, unspecified/local bacterial	54	12	3	13	2	6	1	37	-
36	Abscess skin	11	3	1	5	-	-	-	9	-
37	Cellulitis	12	1	-	4	2	1	-	8	-
38	Impetigo	7	2	1	-	-	2	-	5	-
39	Infection skin	23	6	-	4	-	3	1	14	-
40	Paronychia	1	-	1	-	-	-	-	1	-
41	Lice	2	-	-	-	1	-	-	1	-
42	Lichen sclerosus	1	-	-	-	-	-	-	-	-
43	Lupus discoid	1	-	-	-	-	-	1	1	-
44	Nail change	3	1	1	1	-	-	-	3	-
45	Nail change	-	-	-	-	-	-	-	-	-
46	Nail ingrown	3	1	1	1	-	-	-	3	-
47	Onychomycosis	6	-	1	-	2	-	-	3	-
48	Photosensitivity	3	-	1	-	-	-	1	2	-
49	Pigmentation	1	-	-	-	-	1	-	1	-
50	Pressure sore	1	-	-	-	-	-	1	1	-
51	Pruritus	60	19	8	4	9	3	4	47	-
52	Pruritus	55	18	6	4	7	3	4	42	-
53	Pruritus ani	3	-	2	-	1	-	-	3	-
54	Pruritus vulvae	2	1	-	-	1	-	-	2	-
55	Psoriasis	8	3	1	1	1	-	1	7	-
56	Purpura	1	-	-	-	-	-	1	1	-
57	Rash	84	29	11	8	12	4	4	68	-
58	Scabies	4	-	-	-	1	2	1	4	-
59	Seborrhoea	2	-	1	-	-	-	1	2	-
60	Dandruff	-	-	-	-	-	-	-	-	-
61	Seborrhoea	2	-	1	-	-	-	1	2	-
62	Sinus pilonidal	1	-	-	1	-	-	-	1	-
63	Sore skin	4	2	-	-	-	-	-	2	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
64	Tinea	10	-	1	4	1	1	1	8	-
65	Ulcer skin	7	-	1	2	-	1	1	5	-
66	Urticaria	9	3	1	-	2	1	-	7	-
67	Vitiligo	-	-	-	-	-	-	-	-	-
68	TOTAL	396	95	53	50	46	31	32	307	-
69	**Musculoskeletal**									
70	Arthritis	13	1	3	1	2	1	2	10	-
71	Arthritis psoriatic	1	-	-	-	1	-	-	1	-
72	Arthritis rheumatoid	5	3	2	-	-	-	-	5	-
73	Arthritis rheumatoid*	5	3	2	-	-	-	-	5	-
74	Bone abnormal	-	-	-	-	-	-	-	-	-
75	Bursitis	7	-	4	-	-	2	-	6	-
76	Bursitis	3	-	2	-	-	1	-	3	-
77	Bursitis knee	1	-	-	-	-	1	-	1	-
78	Bursitis olecranon	1	-	1	-	-	-	-	1	-
79	Bursitis toe	2	-	1	-	-	-	-	1	-
80	Capsulitis	2	1	1	-	-	-	-	2	-
81	Chondromalacia	1	-	-	-	-	1	-	1	-
82	Cramp	13	5	3	1	-	1	-	10	-
83	Cyst Baker's	-	-	-	-	-	-	-	-	-
84	Disc prolapsed	1	-	-	1	-	-	-	1	-
85	Dupuytren's contracture	-	-	-	-	-	-	-	-	-
86	Effusion joint	3	-	1	1	-	1	-	3	-
87	Frozen shoulder	9	2	2	1	-	1	2	8	-
88	Ganglion	1	-	-	1	-	-	-	1	-
89	Lumbago	-	-	-	-	-	-	-	-	-
90	Muscle weakness	17	10	2	-	-	-	2	14	-
91	Myalgia	62	21	11	7	4	4	4	51	-
92	Nerve entrapment	10	4	-	1	2	-	1	8	-
93	Carpal tunnel syndrome	10	4	-	1	2	-	1	8	-
94	Nerve entrapment	-	-	-	-	-	-	-	-	-
95	Osteoarthritis	25	7	2	2	3	2	-	16	-
96	Osteochondritis	5	3	-	-	-	1	-	4	-
97	Osteomyelitis	-	-	-	-	-	-	-	-	-
98	Osteoporosis	1	-	-	-	-	-	1	1	-
99	Pain back	113	19	21	17	16	10	11	94	1
100	Pain bone	2	-	-	1	-	1	-	2	-
101	Pain groin	3	1	-	1	-	-	-	2	-
102	Pain joint	139	30	23	14	19	7	15	108	-
103	Pain joint	138	30	23	13	19	7	15	107	-
104	Rheumatism	1	-	-	1	-	-	-	1	-
105	Pain limb	42	13	9	4	4	4	3	37	-
106	Pain neck	28	1	5	4	6	4	3	23	-
107	Plantar fasciitis	7	1	1	-	-	1	2	5	-
108	Polymyalgia rheumatica	6	1	1	1	1	-	1	5	-
109	Rotator cuff	3	-	1	-	1	-	1	3	-
110	Sciatica	23	8	2	4	5	1	-	20	-
111	Scoliosis	2	-	1	-	1	-	-	2	-
112	Spasm muscular	24	9	6	4	2	1	1	23	-
113	Spondylosis	-	-	-	-	-	-	-	-	-
114	Spondylosis cervical	3	-	-	1	-	-	1	2	-
115	Swelling joint	14	3	4	1	1	1	2	12	-
116	Synovitis	1	-	-	-	-	-	-	-	-
117	Tendinitis	11	2	2	1	-	3	1	9	-
118	Tennis elbow	15	3	2	3	1	1	1	11	-
119	Tenosynovitis	2	1	-	-	-	-	-	1	-
120	Torticollis	3	1	-	-	-	1	-	2	-
121	Trigger finger	3	-	-	2	-	1	-	3	-
122	TOTAL	620	150	109	74	69	50	54	506	1

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
123	**Psychiatric**									
124	Aggression	88	51	14	6	4	5	2	82	1
125	Agitation	126	60	23	13	6	4	5	111	-
126	Alcoholism	55	17	7	6	3	8	4	45	-
127	Alcohol withdrawal	3	1	-	-	1	1	-	3	-
128	Alcoholism *	29	9	5	4	2	2	1	23	-
129	Alcoholism acute	3	1	-	-	-	-	1	2	-
130	Alcoholism chronic*	20	6	2	2	-	5	2	17	-
131	Anxiety	280	131	30	25	20	16	9	231	1
132	Anxiety	280	131	30	25	20	16	9	231	1
133	Behaviour abnormal	16	5	1	-	2	5	-	13	-
134	Confusion	75	41	9	5	7	3	2	67	-
135	Delusion	8	2	1	1	-	1	-	5	-
136	Dementia	7	2	-	-	2	-	2	6	-
137	Alzheimer's disease*	1	-	-	-	-	-	-	-	-
138	Dementia	6	2	-	-	2	-	2	6	-
139	Dementia senile*	-	-	-	-	-	-	-	-	-
140	Depersonalization	9	6	2	-	-	-	-	8	-
141	Depression	493	145	75	63	35	45	39	402	6
142	Depression	487	142	75	62	35	45	38	397	6
143	Depression manic	5	3	-	1	-	-	1	5	-
144	Depression postnatal	1	-	-	-	-	-	-	-	-
145	Dreams abnormal	91	56	16	5	5	5	1	88	-
146	Euphoria	3	2	-	-	1	-	-	3	-
147	Formication	2	-	1	-	-	-	-	1	-
148	Globus hystericus	1	-	-	-	-	-	-	-	-
149	Grief reaction	4	-	1	-	-	-	-	1	-
150	Hallucination	30	15	2	-	1	3	1	22	-
151	Hyperactive	5	3	1	1	-	-	-	5	-
152	Hypochondriasis	2	-	-	1	-	1	-	2	-
153	Hypomania	6	1	3	1	-	-	-	5	-
154	Insomnia	194	80	39	16	9	12	8	164	-
155	Irritability	61	33	12	9	2	3	-	59	-
156	Libido decreased	26	8	6	4	2	-	-	20	-
157	Malaise, lassitude	509	313	69	37	24	14	11	468	-
158	Lassitude	272	141	43	28	14	10	8	244	-
159	Malaise	237	172	26	9	10	4	3	224	-
160	Mania	12	5	1	1	2	2	1	12	-
161	Mood change	42	20	9	7	1	1	1	39	-
162	Mood change	14	8	3	1	-	-	-	12	-
163	Mood swings	28	12	6	6	1	1	1	27	-
164	Neurosis	1	1	-	-	-	-	-	1	-
165	Obsession/compulsive	5	2	1	1	-	1	-	5	-
166	Panic attack	73	20	14	9	7	7	5	62	-
167	Paranoia	14	6	2	2	-	1	1	12	-
168	Phobia	9	2	1	3	-	1	1	8	-
169	Agoraphobia	6	1	1	1	-	1	1	5	-
170	Cancer phobia	1	-	-	1	-	-	-	1	-
171	Phobia	2	1	-	1	-	-	-	2	-
172	Psychosis	18	4	1	-	3	3	2	13	1
173	Schizophrenia	3	-	1	-	-	1	-	2	-
174	Self injury	20	10	1	2	3	-	1	17	1
175	Senility	1	1	-	-	-	-	-	1	-
176	Somnambulism	3	1	-	1	1	-	-	3	-
177	Suicidal thought	21	6	3	2	2	3	2	18	-
178	Suicide attempt, drug overdose	142	38	19	25	16	11	9	118	2
179	Overdose*	25	10	3	3	3	1	2	22	-
180	Overdose other drug*	43	11	7	9	6	3	-	36	1
181	Overdose unknown drug*	35	9	4	7	5	2	3	30	1

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
182	Suicide attempt*	22	5	3	3	1	1	4	17	-
183	Suicide threat	17	3	2	3	1	4	-	13	-
184	Tics	1	1	-	-	-	-	-	1	-
185	TOTAL	2456	1088	365	246	158	156	107	2120	12
186	**Central and Peripheral Nervous System**									
187	Amnesia	20	10	1	1	2	-	1	15	-
188	Aphasia, dysphasia	3	3	-	-	-	-	-	3	-
189	Dysphasia	3	3	-	-	-	-	-	3	-
190	Ataxia	3	2	1	-	-	-	-	3	-
191	Burning sensation	3	-	1	1	-	-	-	2	-
192	Coma	-	-	-	-	-	-	-	-	-
193	Convulsion, epilepsy	27	7	4	7	3	1	2	24	-
194	Convulsion*	17	2	4	5	2	1	2	16	-
195	Epilepsy *	10	5	-	2	1	-	-	8	-
196	Epilepsy grand mal	-	-	-	-	-	-	-	-	-
197	Disorientation	6	6	-	-	-	-	-	6	-
198	Dizziness	241	175	21	12	8	8	9	233	-
199	Drop attack	1	-	-	-	-	-	-	-	-
200	Drowsiness, sedation	985	654	133	52	35	36	22	932	2
201	Drowsiness	539	363	68	25	19	24	13	512	1
202	Sedation	446	291	65	27	16	12	9	420	1
203	Dysphonia	1	-	-	-	-	-	-	-	-
204	Extrapyramidal disease	11	2	2	3	2	-	-	9	1
205	Dystonia	2	-	-	1	1	-	-	2	-
206	Extrapyramidal disease	2	1	-	1	-	-	-	2	-
207	Movement involuntary	4	1	2	-	1	-	-	4	-
208	Parkinson's disease*	3	-	-	1	-	-	-	1	1
209	Feeling cold	5	3	1	-	-	-	-	4	-
210	Feeling hot	3	1	-	-	1	-	1	3	-
211	Flushing	18	6	3	1	1	2	1	14	-
212	Headache, migraine	227	119	22	19	13	14	11	198	-
213	Headache	200	111	18	16	10	8	10	173	-
214	Migraine	27	8	4	3	3	6	1	25	-
215	Hemiparesis	2	-	-	1	-	-	1	2	-
216	Lost consciousness	10	5	-	1	2	1	-	9	-
217	Meningitis	1	-	-	-	-	-	-	-	-
218	Meningitis *	1	-	-	-	-	-	-	-	-
219	Multiple sclerosis	3	-	-	1	1	-	-	2	-
220	Myelopathy	1	-	-	-	-	-	-	-	-
221	Neuralgia	9	1	2	1	2	1	1	8	-
222	Neuralgia trigeminal	5	2	1	1	1	-	-	5	-
223	Neuropathy	2	1	1	-	-	-	-	2	-
224	Neuritis*	1	-	1	-	-	-	-	1	-
225	Neuropathy peripheral	1	1	-	-	-	-	-	1	-
226	Neuropathy	-	-	-	-	-	-	-	-	-
227	Paralysis ocular	1	-	-	1	-	-	-	1	-
228	Paresis	-	-	-	-	-	-	-	-	-
229	Post viral syndrome	5	2	-	1	-	1	1	5	-
230	Ptosis	-	-	-	-	-	-	-	-	-
231	Sensation abnormal	66	22	12	9	6	4	4	57	-
232	Hypoaesthesia	15	5	1	3	1	2	2	14	-
233	Paraesthesia	51	17	11	6	5	2	2	43	-
234	Smell, taste abnormal	11	3	2	1	1	-	1	8	-
235	Taste abnormal	11	3	2	1	1	-	1	8	-
236	Syncope	44	15	3	6	2	3	2	31	-
237	Tremor	63	33	8	4	4	4	2	55	-
238	TOTAL	1777	1072	218	123	84	75	59	1631	3
239	**Eye**									
240	Amaurosis	1	-	-	-	1	-	-	1	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
241	Amaurosis fugax	1	-	-	-	1	-	-	1	-
242	Blepharitis	6	1	-	1	2	-	-	4	-
243	Cataract	9	1	1	1	1	1	-	5	-
244	Conjunctivitis	20	7	2	1	5	1	-	16	-
245	Corneal dystrophy	-	-	-	-	-	-	-	-	-
246	Cyst Meibomian	2	1	-	-	-	-	-	1	-
247	Dry eye	3	1	-	-	2	-	-	3	-
248	Episcleritis	1	-	-	-	-	-	1	1	-
249	Floaters	2	-	-	-	-	1	-	1	-
250	Glaucoma	4	-	-	-	-	1	-	1	-
251	Haemorrhage subconjunctival	3	-	1	-	-	-	2	3	-
252	Herpes ophthalmic	2	-	2	-	-	-	-	2	-
253	Irritation eye	4	-	2	1	1	-	-	4	-
254	Lacrimation	1	-	-	-	1	-	-	1	-
255	Macular degeneration	2	-	-	-	1	-	-	1	-
256	Nystagmus	1	1	-	-	-	-	-	1	-
257	Pain eye	1	1	-	-	-	-	-	1	-
258	Retinal detachment	1	-	-	-	1	-	-	1	-
259	Retinopathy	2	-	-	2	-	-	-	2	-
260	Scleritis	2	-	2	-	-	-	-	2	-
261	Sore eye	2	1	-	-	1	-	-	2	-
262	Stye	2	-	-	-	-	-	-	-	-
263	Ulcer corneal	2	1	-	-	1	-	-	2	-
264	Uveitis	3	2	1	-	-	-	-	3	-
265	Visual defect	35	15	4	4	2	1	3	29	-
266	Diplopia	3	-	-	1	-	-	-	1	-
267	Hemianopia	2	1	-	-	-	-	-	1	-
268	Vision deteriorated	2	2	-	-	-	-	-	2	-
269	Vision field defect	1	-	-	-	-	1	-	1	-
270	Visual disturbance	27	12	4	3	2	-	3	24	-
271	TOTAL	111	32	15	10	19	5	6	87	-
272	**Ear**									
273	Deafness	11	2	4	1	-	1	-	8	-
274	Earache	12	1	3	1	4	1	1	11	-
275	Eardrum perforation	1	-	-	-	-	-	-	-	-
276	Earwax	28	5	3	2	3	3	5	21	-
277	Labyrinthitis	7	2	2	1	1	1	-	7	-
278	Otitis externa	22	6	4	1	-	3	4	18	-
279	Otitis media	15	4	2	4	1	1	2	14	-
280	Otorrhoea	1	-	-	-	1	-	-	1	-
281	Tinnitus	10	6	1	-	1	-	1	9	-
282	Vertigo	26	15	2	2	2	1	1	23	-
283	TOTAL	133	41	21	12	13	11	14	112	-
284	**Cardiovascular**									
285	Aneurysm	2	1	-	-	-	-	-	1	-
286	Aneurysm aortic*	2	1	-	-	-	-	-	1	-
287	Cardiac arrest	-	-	-	-	-	-	-	-	-
288	Cardiac failure	20	3	2	2	3	2	3	15	-
289	Cardiac failure*	4	-	1	-	2	1	-	4	-
290	Congestive cardiac failure*	9	1	1	1	1	1	2	7	-
291	Left ventricular failure*	7	2	-	1	-	-	1	4	-
292	Cardiomegaly	1	-	1	-	-	-	-	1	-
293	Cardiomyopathy	1	-	-	-	-	-	-	-	-
294	Cardiomyopathy*	1	-	-	-	-	-	-	-	-
295	Cerebrovascular accident	22	8	1	1	1	1	1	13	-
296	Cerebro-vascular accident*	20	7	1	1	1	1	1	12	-
297	Haemorrhage cerebral*	1	1	-	-	-	-	-	1	-
298	Haemorrhage subarachnoid*	1	-	-	-	-	-	-	-	-
299	Vertebrobasilar syndrome	-	-	-	-	-	-	-	-	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
300	Chilblain	-	-	-	-	-	-	-	-	-
301	Cold extremities	5	2	-	-	-	-	1	3	-
302	Deep vein thrombosis	4	-	-	1	1	-	-	2	-
303	Disorders of heart rate	14	5	2	2	-	2	1	12	-
304	Bradycardia	1	-	-	-	-	1	-	1	-
305	Tachycardia	13	5	2	2	-	1	1	11	-
306	Disorders of rhythm	12	2	1	1	1	1	1	7	-
307	Arrhythmia	4	-	1	-	-	1	1	3	-
308	Extrasystoles	2	1	-	-	-	-	-	1	-
309	Fibrillation atrial*	6	1	-	1	1	-	-	3	-
310	Embolus pulmonary	4	1	-	1	1	-	-	3	-
311	Faintness	12	11	-	1	-	-	-	12	-
312	Hypertension	56	21	9	9	4	2	3	48	-
313	Hypertension*	56	21	9	9	4	2	3	48	-
314	Hypotension	26	9	3	5	3	1	1	22	-
315	Ischaemia mesenteric	1	-	-	-	-	-	-	-	-
316	Infarction gastrointestinal*	1	-	-	-	-	-	-	-	-
317	Ischaemia peripheral	5	-	-	1	-	-	-	1	1
318	Claudication	3	-	-	1	-	-	-	1	-
319	Ischaemia peripheral	2	-	-	-	-	-	-	-	1
320	Ischaemic heart disease	43	6	4	4	6	8	1	29	-
321	Angina	31	6	4	3	4	6	-	23	-
322	Ischaemic heart disease*	4	-	-	1	-	1	1	3	-
323	Myocardial infarction*	8	-	-	-	2	1	-	3	-
324	Oedema	196	75	42	21	10	9	11	168	-
325	Fluid retention	17	10	1	1	1	1	1	15	-
326	Oedema face	12	6	2	1	-	-	1	10	-
327	Oedema	116	40	30	11	7	5	7	100	-
328	Swollen ankles	42	16	7	7	2	3	2	37	-
329	Swollen limb	9	3	2	1	-	-	-	6	-
330	Pain chest, tight chest	76	19	10	10	8	7	10	64	-
331	Pain chest	71	19	10	8	7	6	10	60	-
332	Tight chest	5	-	-	2	1	1	-	4	-
333	Palpitation	32	14	4	3	1	1	1	24	-
334	Pericarditis	-	-	-	-	-	-	-	-	-
335	Phlebitis	1	1	-	-	-	-	-	1	-
336	Raynaud's phenomenon	1	-	-	-	-	-	-	-	-
337	Restless legs	29	15	7	3	1	2	1	29	-
338	Thrombophlebitis	5	1	-	1	1	-	1	4	-
339	Transient ischaemic attack	8	3	-	-	2	-	-	5	-
340	Valvular disease	-	-	-	-	-	-	-	-	-
341	Stenosis aortic*	-	-	-	-	-	-	-	-	-
342	Vasculitis	-	-	-	-	-	-	-	-	-
343	Veins varicose	4	-	-	3	1	-	-	4	-
344	TOTAL	580	197	86	69	44	36	36	468	1
345	**Respiratory**									
346	Asthma, wheezing	65	16	15	7	5	4	5	52	-
347	Asthma*	38	11	7	5	3	1	3	30	-
348	Bronchospasm	-	-	-	-	-	-	-	-	-
349	Wheezing	27	5	8	2	2	3	2	22	-
350	Chronic Obstructive Airways Disease	14	3	1	4	3	-	1	12	-
351	Bronchiectasis*	1	-	-	1	-	-	-	1	-
352	Chronic Obstructive Airways Disease*	13	3	1	3	3	-	1	11	-
353	Emphysema*	-	-	-	-	-	-	-	-	-
354	Cough	49	15	2	7	3	6	3	36	-
355	Dyspnoea	53	12	10	8	4	5	4	43	-
356	Effusion pleural	-	-	-	-	-	-	-	-	-
357	Epistaxis	3	-	-	-	1	1	1	3	-
358	Fibrosis lung	1	1	-	-	-	-	-	1	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
359	Alveolitis fibrosing*	1	1	-	-	-	-	-	1	-
360	Haemoptysis	10	4	1	-	1	1	1	8	-
361	Hoarseness	4	-	1	-	1	2	-	4	-
362	Hyperventilation	9	4	2	2	1	-	-	9	-
363	Pleurisy	3	1	1	-	-	-	-	2	-
364	Pleurodynia	2	-	1	-	1	-	-	2	-
365	Pneumothorax	-	-	-	-	-	-	-	-	-
366	Respiratory Failure	-	-	-	-	-	-	-	-	-
367	Respiratory tract infection	440	113	94	49	46	28	23	353	-
368	Bronchitis acute	8	2	1	1	1	1	-	6	-
369	Bronchitis*	34	4	7	7	5	1	4	28	-
370	Bronchopneumonia*	5	-	-	1	-	1	-	2	-
371	Catarrh	18	7	1	1	4	2	1	16	-
372	Coryza	12	4	2	3	1	-	1	11	-
373	Infection chest*	108	24	18	9	17	8	5	81	-
374	Influenza*	11	1	3	4	1	-	1	10	-
375	Laryngitis	9	2	1	1	-	-	2	6	-
376	Pharyngitis	89	35	17	5	9	5	3	74	-
377	Pneumonia*	7	2	-	1	-	2	-	5	-
378	Rhinitis	5	1	1	1	-	2	-	5	-
379	Rhinorrhea	1	-	1	-	-	-	-	1	-
380	Sinusitis	40	11	12	4	2	3	2	34	-
381	Tonsillitis	17	5	6	-	-	-	2	13	-
382	Tracheitis	4	2	-	-	1	-	-	3	-
383	Upper respiratory tract infection	72	13	24	11	5	3	2	58	-
384	Rhinitis allergic	7	1	-	2	-	2	1	6	-
385	TOTAL	660	170	128	79	66	49	39	531	-
386	**Alimentary**									
387	Abscess dental	14	-	2	6	-	1	1	10	-
388	Anorexia	30	10	4	4	3	3	2	26	-
389	Appendicitis	-	-	-	-	-	-	-	-	-
390	Appendicitis	-	-	-	-	-	-	-	-	-
391	Ascites	-	-	-	-	-	-	-	-	-
392	Bowel obstruction	2	-	1	-	-	1	-	2	-
393	Bowel obstruction*	2	-	1	-	-	1	-	2	-
394	Bulimia	5	3	1	-	-	-	-	4	-
395	Campylobacter	2	1	-	1	-	-	-	2	-
396	Candidiasis oral	10	3	-	2	-	1	-	6	-
397	Cheilitis	1	-	-	1	-	-	-	1	-
398	Cholelithiasis, cholecystitis	6	-	-	-	2	3	1	6	-
399	Cholecystitis	1	-	-	-	-	1	-	1	-
400	Cholelithiasis*	5	-	-	-	2	2	1	5	-
401	Colic biliary	-	-	-	-	-	-	-	-	-
402	Cirrhosis	2	-	2	-	-	-	-	2	-
403	Cirrhosis*	1	-	1	-	-	-	-	1	-
404	Oesophageal varices	1	-	1	-	-	-	-	1	-
405	Coeliac disease	1	-	-	-	-	-	-	-	-
406	Constipation	85	31	15	8	10	11	3	78	-
407	Diarrhoea	134	43	28	20	11	9	7	118	-
408	Distension abdominal	39	11	13	3	5	-	3	35	-
409	Dry mouth	45	31	4	4	1	2	-	42	-
410	Dyspepsia	114	32	19	15	9	6	11	92	-
411	Duodenitis	1	-	-	-	-	-	-	-	-
412	Dyspepsia	71	23	7	12	4	2	8	56	-
413	Gastritis	10	2	3	1	-	1	-	7	-
414	Heartburn	14	5	3	1	1	1	2	13	-
415	Oesophageal reflux	10	1	3	-	3	-	1	8	-
416	Oesophagitis	8	1	3	1	1	2	-	8	-
417	Dysphagia	9	1	1	-	-	3	1	6	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
418	Faecal incontinence	4	-	3	-	1	-	-	4	-
419	Fissure anorectal	1	-	-	1	-	-	-	1	-
420	Flatulence	7	2	1	2	1	1	-	7	-
421	Gastroenteritis	11	1	4	1	1	2	-	9	-
422	Giardiasis	-	-	-	-	-	-	-	-	-
423	Gingivitis	8	-	1	2	-	-	2	5	-
424	Glossitis	2	1	1	-	-	-	-	2	-
425	Gum hypertrophy	-	-	-	-	-	-	-	-	-
426	Haemorrhage gastrointestinal	2	1	-	-	-	-	1	2	-
427	Haemorrhage gastrointestinal upper	12	2	2	-	2	-	1	7	-
428	Haematemesis*	8	1	1	-	2	-	1	5	-
429	Melena	3	1	-	-	-	-	-	1	-
430	Oesophageal haemorrhage*	1	-	1	-	-	-	-	1	-
431	Haemorrhage oral	1	1	-	-	-	-	-	1	-
432	Haemorrhage rectal	15	8	-	2	1	2	-	13	-
433	Haemorrhagic diarrhoea	2	-	1	-	1	-	-	2	-
434	Haemorrhoids	19	3	4	6	1	1	-	15	-
435	Halitosis	2	1	1	-	-	-	-	2	-
436	Hepatic failure	2	1	-	-	-	-	-	1	-
437	Hepatic failure*	2	1	-	-	-	-	-	1	-
438	Hepatitis, jaundice	4	1	3	-	-	-	-	4	-
439	Hepatitis*	1	-	1	-	-	-	-	1	-
440	Jaundice	2	-	2	-	-	-	-	2	-
441	Jaundice obstructive*	1	1	-	-	-	-	-	1	-
442	Hepatomegaly	1	-	-	-	-	1	-	1	-
443	Hernia	2	1	-	-	-	-	-	1	-
444	Hernia hiatus	3	-	1	2	-	-	-	3	-
445	Hiccough	1	-	1	-	-	-	-	1	-
446	Inflammatory disease colon	18	3	2	1	4	2	1	13	-
447	Colitis	2	-	-	-	1	-	-	1	-
448	Colitis pseudomembranous*	1	-	-	-	1	-	-	1	-
449	Colitis ulcerative	1	1	-	-	-	-	-	1	-
450	Colon perforated*	1	-	-	1	-	-	-	1	-
451	Crohn's disease*	2	-	1	-	-	-	-	1	-
452	Diverticulitis	6	1	1	-	1	-	-	3	-
453	Diverticulosis*	4	1	-	-	1	2	-	4	-
454	Diverticulum perforated*	1	-	-	-	-	-	1	1	-
455	Irritable bowel syndrome	29	4	1	4	9	3	2	23	-
456	Leukoplakia oral	1	-	-	-	-	-	-	-	-
457	Liver function test abnormal	40	10	6	3	7	2	3	31	-
458	Nausea, vomiting	215	134	20	18	13	5	8	198	-
459	Nausea	152	101	13	13	10	3	4	144	-
460	Vomiting	63	33	7	5	3	2	4	54	-
461	Pain abdomen	116	36	20	19	9	10	7	101	-
462	Pancreatitis	3	-	-	-	-	-	2	2	-
463	Pancreatitis*	3	-	-	-	-	-	2	2	-
464	Parotid enlarged	1	-	1	-	-	-	-	1	-
465	Parotitis	1	-	-	-	-	1	-	1	-
466	Pharynx irritation	1	1	-	-	-	-	-	1	-
467	Proctalgia	6	1	-	-	-	-	-	1	-
468	Proctitis	4	1	1	-	-	1	1	4	-
469	Prolapse rectal	-	-	-	-	-	-	-	-	-
470	Rectal discharge	1	-	-	-	1	-	-	1	-
471	Saliva increased	3	1	-	-	1	-	-	2	-
472	Sialadenitis	1	-	-	-	-	-	-	-	-
473	Sore mouth	8	5	2	-	-	1	-	8	-
474	Stomatitis	5	1	1	-	-	2	1	5	-
475	Tenesmus	2	1	-	-	-	-	1	2	-
476	Toothache	6	1	-	2	-	-	2	5	-
477	Ulcer mouth	17	9	5	1	2	-	-	17	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
478	Ulcer oesophageal	1	-	-	-	-	-	1	1	-
479	Ulcer peptic	4	2	-	-	-	-	-	2	-
480	Ulcer duodenal*	2	-	-	-	-	-	-	-	-
481	Ulcer gastric	1	1	-	-	-	-	-	1	-
482	Ulcer peptic*	1	1	-	-	-	-	-	1	-
483	TOTAL	1081	399	172	128	95	74	62	930	-
484	**Metabolic and Endocrine**									
485	Acromegaly	-	-	-	-	-	-	-	-	-
486	Dehydration	1	-	-	-	1	-	-	1	-
487	Diabetes mellitus improved	-	-	-	-	-	-	-	-	-
488	Diabetes mellitus, hyperglycaemia	24	5	3	4	2	1	1	16	-
489	Diabetes mellitus worsened	6	1	1	2	-	-	1	5	-
490	Diabetes mellitus*	13	3	1	2	1	1	-	8	-
491	Glycosuria	1	1	-	-	-	-	-	1	-
492	Hyperglycaemia	3	-	1	-	1	-	-	2	-
493	Ketoacidosis diabetic*	-	-	-	-	-	-	-	-	-
494	Retinopathy diabetic	1	-	-	-	-	-	-	-	-
495	Electrolyte abnormal	4	1	-	2	-	-	-	3	-
496	Hyperkalaemia	1	-	-	1	-	-	-	1	-
497	Hypokalaemia	3	1	-	1	-	-	-	2	-
498	Hyponatraemia	-	-	-	-	-	-	-	-	-
499	Excessive thirst	9	4	2	3	-	-	-	9	-
500	Globulin abnormal	2	1	-	-	-	-	-	1	-
501	Gout	10	-	2	1	2	2	1	8	-
502	Hyperlipidaemia	8	1	1	-	1	-	3	6	-
503	Hypercholesterolaemia	6	1	1	-	-	-	3	5	-
504	Hyperlipidaemia	2	-	-	-	1	-	-	1	-
505	Hyperprolactinaemia	1	-	-	-	-	-	-	-	-
506	Hyperthyroidism	2	-	-	-	-	1	-	1	-
507	Hypoglycaemia	1	-	-	-	-	-	-	-	-
508	Hypothyroidism	25	2	1	1	3	4	-	11	-
509	Obesity	9	3	2	-	-	2	-	7	1
510	Obesity	9	3	2	-	-	2	-	7	1
511	Sweating	40	17	3	5	3	3	1	32	-
512	Weight gain	523	175	108	76	44	32	21	456	4
513	Weight loss	14	2	2	1	1	2	1	9	-
514	TOTAL	673	211	124	93	57	47	28	560	5
515	**Urologic**									
516	Albuminuria	4	2	-	-	-	1	1	4	-
517	Bladder irritability	1	1	-	-	-	-	-	1	-
518	Calculus renal	1	-	-	-	-	1	-	1	-
519	Caruncle urethral	1	-	-	-	-	-	1	1	-
520	Colic renal	2	-	-	1	-	1	-	2	-
521	Colic renal	1	-	-	-	-	1	-	1	-
522	Pain renal	1	-	-	1	-	-	-	1	-
523	Enuresis	2	1	-	-	-	-	-	1	-
524	Haematuria	10	3	-	3	1	-	1	8	-
525	Hydronephrosis	1	-	-	-	-	-	-	-	-
526	Micturition disorder	65	15	5	12	10	8	2	52	-
527	Dysuria	10	1	-	2	4	-	-	7	-
528	Frequency	28	9	-	5	3	5	-	22	-
529	Incontinence	20	4	4	5	2	2	1	18	-
530	Nocturia	5	1	1	-	1	-	1	4	-
531	Urgency	2	-	-	-	-	1	-	1	-
532	Polyuria	4	2	-	1	-	-	-	3	-
533	Pyuria	-	-	-	-	-	-	-	-	-
534	Renal failure	5	3	1	-	-	1	-	5	-
535	Renal failure acute	1	1	-	-	-	-	-	1	-
536	Renal failure chronic*	3	1	1	-	-	1	-	3	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
537	Renal failure*	1	1	-	-	-	-	-	1	-
538	Renal function test abnormal	5	1	-	2	2	-	-	5	-
539	Retention	8	3	1	1	-	1	2	8	-
540	Urea raised	2	1	-	1	-	-	-	2	-
541	Urinary tract infection	80	19	12	11	7	7	9	65	1
542	Cystitis	16	4	2	3	-	3	-	12	-
543	Pyelitis	-	-	-	-	-	-	-	-	-
544	Pyelonephritis*	1	-	-	-	-	-	-	-	-
545	Urethritis	2	-	-	-	-	1	-	1	1
546	Urinary tract infection*	61	15	10	8	7	3	9	52	-
547	TOTAL	191	51	19	32	20	20	16	158	1
548	**Male Reproductive and Gynaecomastia**									
549	Balanitis	3	1	-	-	1	1	-	3	-
550	Cyst epididymis	1	-	-	-	-	1	-	1	-
551	Ejaculation premature	1	-	-	-	-	1	-	1	-
552	Epididymitis	1	1	-	-	-	-	-	1	-
553	Gynaecomastia	1	-	1	-	-	-	-	1	-
554	Haemospermia	1	-	1	-	-	-	-	1	-
555	Impotence, ejaculation failure	29	10	5	4	3	-	1	23	1
556	Ejaculation failure	1	1	-	-	-	-	-	1	-
557	Impotence	28	9	5	4	3	-	1	22	1
558	Phimosis	1	1	-	-	-	-	-	1	-
559	Prostatism	6	1	2	-	-	-	-	3	-
560	Prostatitis	2	1	-	-	-	-	-	1	-
561	TOTAL	46	15	9	4	4	3	1	36	1
562	**Female Reproductive**									
563	Abscess Bartholin's gland	1	-	-	-	-	-	-	-	-
564	Bartholinitis	-	-	-	-	-	-	-	-	-
565	Cervical smear abnormal	2	-	-	1	-	-	-	1	-
566	Cyst Bartholin's	1	-	-	-	-	-	-	-	-
567	Cyst ovarian	3	-	2	-	-	1	-	3	-
568	Dyskaryosis	-	-	-	-	-	-	-	-	-
569	Dyspareunia	8	2	1	1	1	1	-	6	-
570	Endometriosis	1	-	-	-	1	-	-	1	-
571	Haemorrhage postcoital	2	1	-	-	-	1	-	2	-
572	Haemorrhage postmenopausal	3	-	1	-	1	1	-	3	-
573	Haemorrhage vaginal	14	6	1	1	-	2	1	11	-
574	Infertility female	1	-	-	-	1	-	-	1	-
575	Menopausal symptoms	5	-	2	-	-	-	1	3	-
576	Menstrual disorder	37	7	3	3	6	3	4	26	-
577	Amenorrhoea	8	4	-	1	1	1	-	7	-
578	Dysmenorrhoea	3	1	-	-	1	-	-	2	-
579	Irregular periods	8	1	2	-	2	-	-	5	-
580	Menorrhagia	17	1	1	2	2	2	4	12	-
581	Polymenorrhoea	1	-	-	-	-	-	-	-	-
582	Metrorrhagia	2	2	-	-	-	-	-	2	-
583	Pelvic inflammatory disease	1	-	1	-	-	-	-	1	-
584	Pelvic inflammatory disease	1	-	1	-	-	-	-	1	-
585	Premenstrual tension	14	1	-	2	2	3	1	9	-
586	Prolapse uterine	4	-	3	-	-	-	-	3	-
587	Vaginal soreness	-	-	-	-	-	-	-	-	-
588	Vaginitis, vulvitis	39	7	8	2	6	7	4	34	1
589	Infection vaginal bacterial	3	1	-	-	1	-	1	3	-
590	Vaginal candidiasis	15	3	3	-	1	4	2	13	-
591	Vaginal discharge	13	3	4	2	1	1	1	12	-
592	Vaginitis	6	-	1	-	3	1	-	5	1
593	Vaginitis trichomonas	-	-	-	-	-	-	-	-	-
594	Vulvitis	2	-	-	-	-	1	-	1	-
595	TOTAL	138	26	22	10	18	19	11	106	1

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
596	**Breast Disorder**									
597	Abscess breast	2	-	1	1	-	-	-	2	-
598	Breast discharge	1	-	1	-	-	-	-	1	-
599	Breast disorder	2	1	-	-	1	-	-	2	-
600	Galactorrhoea	2	2	-	-	-	-	-	2	-
601	Mastalgia	17	4	-	2	-	4	-	10	-
602	Mastitis	1	-	-	-	-	-	1	1	-
603	TOTAL	25	7	2	3	1	4	1	18	-
604	**Obstetric**									
605	Abortion threatened	-	-	-	-	-	-	-	-	-
606	TOTAL	-	-	-	-	-	-	-	-	-
607	**Haemopoietic**									
608	Anaemia	15	4	2	2	1	1	2	12	-
609	Anaemia iron deficiency	5	-	-	-	1	1	-	2	-
610	Anaemia iron deficiency	5	-	-	-	1	1	-	2	-
611	Anaemia macrocytic	1	-	-	-	1	-	-	1	-
612	Anaemia macrocytic	1	-	-	-	1	-	-	1	-
613	Anaemia vitamin B12 deficiency	-	-	-	-	-	-	-	-	-
614	Bone marrow abnormal	3	1	-	1	1	-	-	3	-
615	Eosinophilia	2	-	1	1	-	-	-	2	-
616	Eosinophilia	2	-	1	1	-	-	-	2	-
617	Erythrocyte sedimentation rate raised	4	2	-	1	-	-	-	3	-
618	Haematoma spontaneous	4	1	-	-	1	-	1	3	-
619	Hyperbilirubinaemia	1	-	1	-	-	-	-	1	-
620	Leucocytosis	6	3	1	1	-	-	-	5	-
621	Leucocytosis	3	2	-	1	-	-	-	3	-
622	Neutrophilia	3	1	1	-	-	-	-	2	-
623	Leucopenia	12	4	2	2	-	2	-	10	-
624	Leucopenia	5	3	1	-	-	-	-	4	-
625	Neutropenia	7	1	1	2	-	2	-	6	-
626	Lymphadenopathy	11	3	-	1	1	-	3	8	-
627	Glands swollen	6	1	-	1	1	-	2	5	-
628	Lymphadenitis	1	-	-	-	-	-	-	-	-
629	Lymphadenopathy	4	2	-	-	-	-	1	3	-
630	Myelodysplastic syndrome	3	-	-	1	-	-	1	2	-
631	Pancytopenia	1	-	-	-	-	-	-	-	-
632	Anaemia hypoplastic	-	-	-	-	-	-	-	-	-
633	Pancytopenia	1	-	-	-	-	-	-	-	-
634	Red cell abnormal	3	1	-	-	-	1	-	2	-
635	Thrombocytopenia	2	-	-	2	-	-	-	2	-
636	Thrombocytosis	2	-	-	1	-	-	-	1	-
637	TOTAL	75	19	7	13	6	5	7	57	-
638	**Neoplasm**									
639	Malignancies	46	17	3	5	3	3	6	37	1
640	Cancer*	1	1	-	-	-	-	-	1	-
641	Carcinoma bladder*	1	1	-	-	-	-	-	1	-
642	Carcinoma brain*	1	-	-	-	-	1	-	1	-
643	Carcinoma breast*	-	-	-	-	-	-	-	-	-
644	Carcinoma bronchus*	2	-	-	-	2	-	-	2	-
645	Carcinoma cervix*	1	-	-	-	-	-	-	-	-
646	Carcinoma colon*	6	4	-	-	1	-	-	5	-
647	Carcinoma kidney*	-	-	-	-	-	-	-	-	-
648	Carcinoma larynx*	2	1	-	1	-	-	-	2	-
649	Carcinoma liver*	-	-	-	-	-	-	-	-	-
650	Carcinoma lung*	5	1	1	-	-	-	2	4	-
651	Carcinoma ovary*	1	1	-	-	-	-	-	1	-
652	Carcinoma pancreas*	2	1	-	1	-	-	-	2	-
653	Carcinoma prostate*	2	2	-	-	-	-	-	2	-
654	Carcinoma rectum*	3	-	-	1	-	1	-	2	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
655	Carcinoma skin*	6	2	-	-	-	-	2	4	-
656	Carcinoma stomach*	1	-	1	-	-	-	-	1	-
657	Carcinoma thyroid*	-	-	-	-	-	-	-	-	-
658	Carcinomatosis*	7	-	1	1	-	1	1	4	1
659	Glioma*	-	-	-	-	-	-	-	-	-
660	Leukaemia lymphocytic chronic*	1	-	-	-	-	-	1	1	-
661	Leukaemia myeloid acute*	1	1	-	-	-	-	-	1	-
662	Leukaemia myeloid chronic*	1	1	-	-	-	-	-	1	-
663	Leukaemia*	-	-	-	-	-	-	-	-	-
664	Melanoma*	-	-	-	-	-	-	-	-	-
665	Myeloma*	-	-	-	-	-	-	-	-	-
666	Sarcoma*	2	1	-	1	-	-	-	2	-
667	Non-malignant tumours	18	2	3	4	-	5	3	17	-
668	Adenoma endocrine	1	1	-	-	-	-	-	1	-
669	Fibroids	2	-	1	-	-	-	1	2	-
670	Lymphoma	-	-	-	-	-	-	-	-	-
671	Non-malignant tumour breast	4	-	1	1	-	2	-	4	-
672	Non-malignant tumour skin	6	-	1	2	-	1	1	5	-
673	Polyp gastrointestinal	2	-	-	1	-	1	-	2	-
674	Polyp nasal	1	-	-	-	-	1	-	1	-
675	Polyp uterine	2	1	-	-	-	-	1	2	-
676	TOTAL	64	19	6	9	3	8	9	54	1
677	**Miscellaneous Infection**									
678	Abscess	1	-	-	1	-	-	-	1	-
679	Candidiasis	11	3	3	3	-	1	-	10	-
680	Chlamydial infection	-	-	-	-	-	-	-	-	-
681	Gardnerella infection	1	1	-	-	-	-	-	1	-
682	Herpes	1	-	-	1	-	-	-	1	-
683	Herpes	-	-	-	-	-	-	-	-	-
684	Herpes simplex	1	-	-	1	-	-	-	1	-
685	HIV positive and AIDS	-	-	-	-	-	-	-	-	-
686	HIV (Human immunodeficiency virus) positi	-	-	-	-	-	-	-	-	-
687	Infection	3	-	1	1	-	-	-	2	-
688	Infection postoperative	3	-	2	-	-	-	-	2	-
689	Infection viral	13	2	1	2	2	1	-	8	-
690	Rigor	2	-	-	-	-	-	1	1	-
691	Septicaemia	1	-	-	-	-	1	-	1	-
692	Varicella	1	-	-	-	-	1	-	1	-
693	Wart	2	-	1	-	-	-	-	1	-
694	Wart genital	2	-	1	-	1	-	-	2	-
695	TOTAL	41	6	9	8	3	4	1	31	-
696	**Immunological**									
697	Allergy	6	4	-	-	-	-	-	4	1
698	Angioneurotic oedema	3	-	-	-	-	1	-	1	-
699	Antinuclear antibody positive	1	-	-	-	-	-	-	-	-
700	Unspecified side effects	176	110	23	11	9	4	6	163	1
701	TOTAL	186	114	23	11	9	5	6	168	2
702	**Adverse Reaction to Specific Drug**									
703	Adverse reaction to other drug	7	2	1	-	-	2	-	5	-
704	Dependence	8	3	-	1	-	1	-	5	-
705	Withdrawal symptoms	8	4	2	-	-	-	-	6	-
706	TOTAL	23	9	3	1	-	3	-	16	-
707	**Accident and Injury**									
708	Animal bite	3	1	-	-	1	1	-	3	-
709	Assault	10	4	2	1	1	1	-	9	-
710	Burn	3	3	-	-	-	-	-	3	-
711	Drug overdose accidental	2	1	1	-	-	-	-	2	-
712	Fall	66	19	10	4	13	4	3	53	-
713	Fall*	45	12	6	3	11	3	1	36	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
714	Fall minor injury	20	7	4	1	2	1	2	17	-
715	Fall no injury	1	-	-	-	-	-	-	-	-
716	Fracture	29	6	5	1	4	2	4	22	-
717	Haematoma	8	2	-	1	1	-	1	5	-
718	Hyperkeratosis solar	1	1	-	-	-	-	-	1	-
719	Injury	66	13	13	6	5	6	7	50	-
720	Insect bite & sting	1	-	-	-	-	-	-	-	-
721	Bee sting	-	-	-	-	-	-	-	-	-
722	Insect bite	1	-	-	-	-	-	-	-	-
723	Poisoning nonmedicinal	1	-	-	-	-	-	-	-	-
724	Raped	1	-	-	-	-	-	1	1	-
725	Road traffic accident	19	4	4	3	4	-	3	18	-
726	Sunburn	1	-	-	-	-	-	-	-	-
727	TOTAL	211	54	35	16	29	14	19	167	-
728	**Death**									
729	Death cause uncertain	39	3	6	7	5	2	5	28	4
730	TOTAL	39	3	6	7	5	2	5	28	4
731	**Surgery**									
732	Abdominal surgery	14	2	3	3	-	3	2	13	-
733	Appendicectomy	1	-	-	-	-	1	-	1	-
734	Cholecystectomy	2	-	-	-	-	1	1	2	-
735	Gastrointestinal surgery	8	1	2	3	-	1	-	7	-
736	Hernia surgery	3	1	1	-	-	-	1	3	-
737	Acupuncture	1	-	-	-	-	-	-	-	-
738	Blood transfusion	4	1	1	1	-	-	1	4	-
739	Catheterisation	1	-	-	1	-	-	-	1	-
740	Chemotherapy	2	2	-	-	-	-	-	2	-
741	Dental surgery	4	1	-	-	1	1	-	3	-
742	Dialysis renal	1	-	1	-	-	-	-	1	-
743	Ear nose and throat surgery	1	-	1	-	-	-	-	1	-
744	Electroconvulsive therapy	22	6	3	2	2	1	2	16	1
745	Endoscopy	9	3	2	1	-	1	-	7	-
746	Gastroscopy	2	-	1	-	-	-	-	1	1
747	Genitourinary surgery	3	2	-	-	-	-	1	3	-
748	Cystoscopy	1	1	-	-	-	-	-	1	-
749	Genitourinary surgery	-	-	-	-	-	-	-	-	-
750	Renal transplantation	1	1	-	-	-	-	-	1	-
751	Transurethral resection of prostate	1	-	-	-	-	-	1	1	-
752	Gynaecological surgery	10	1	2	1	2	1	1	8	-
753	Abortion therapeutic	1	-	-	-	1	-	-	1	-
754	Caesarean section	1	-	-	-	-	-	-	-	-
755	Gynaecological surgery	7	1	2	1	-	1	1	6	-
756	Hysterectomy	1	-	-	-	1	-	-	1	-
757	Lumpectomy	-	-	-	-	-	-	-	-	-
758	Mastectomy	-	-	-	-	-	-	-	-	-
759	Minor surgery	24	4	4	4	3	4	1	20	-
760	Ophthalmic surgery	4	-	-	-	-	2	-	2	-
761	Cataract extraction	2	-	-	-	-	1	-	1	-
762	Eye surgery	2	-	-	-	-	1	-	1	-
763	Orthopaedic surgery	13	2	4	1	2	2	2	13	-
764	Amputation	2	-	1	-	-	1	-	2	-
765	Orthopaedic surgery	11	2	3	1	2	1	2	11	-
766	Total hip replacement*	-	-	-	-	-	-	-	-	-
767	Radiotherapy	3	1	1	-	-	-	-	2	-
768	Surgery	4	1	2	-	-	1	-	4	-
769	Thoracic surgery	4	-	-	2	-	-	2	4	-
770	Cardiac catheter	-	-	-	-	-	-	-	-	-
771	Cardiac surgery*	1	-	-	1	-	-	-	1	-
772	Heart-lung transplantation*	1	-	-	1	-	-	-	1	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
773	Thoracic surgery*	2	-	-	-	-	-	2	2	-
774	Vascular surgery	2	1	-	1	-	-	-	2	-
775	Vascular surgery	2	1	-	1	-	-	-	2	-
776	TOTAL	128	27	25	17	10	16	12	107	2
777	**Referrals**									
778	Hospital referrals no admission	311	73	41	37	31	28	26	236	6
779	Hospital referrals: Cardiology	9	4	-	2	1	-	1	8	-
780	Hospital referrals: Dermatology	2	-	-	-	-	-	-	-	-
781	Hospital referrals: Ear, nose and throat	5	1	-	-	-	1	-	2	-
782	Hospital referrals: Gastroenterology	4	-	1	-	-	-	2	3	-
783	Hospital referrals: General medicine	-	-	-	-	-	-	-	-	-
784	Hospital referrals: Gynaecology	10	3	2	1	1	1	-	8	-
785	Hospital referrals: Haematology	1	-	-	-	-	-	1	1	-
786	Hospital referrals: Neurology	5	1	1	-	-	1	-	3	-
787	Hospital referrals: Ophthalmology	7	3	-	1	-	1	-	5	-
788	Hospital referrals: Orthopaedics	4	1	-	-	1	-	-	2	-
789	Hospital referrals: Psychiatry	167	38	22	20	18	17	14	129	4
790	Hospital referrals: Respiratory	1	-	-	-	-	1	-	1	-
791	Hospital referrals: Rheumatology	1	-	-	-	-	-	-	-	-
792	Hospital referrals: Urology	2	-	-	-	-	1	-	1	-
793	Hospital referrals	93	22	15	13	10	5	8	73	2
794	Non-surgical admissions	267	80	37	34	21	24	20	216	3
795	TOTAL	578	153	78	71	52	52	46	452	9
796	**Social**									
797	Bereavement	12	3	2	3	-	1	-	9	1
798	Domestic	49	11	5	13	4	2	2	37	-
799	Loneliness	-	-	-	-	-	-	-	-	-
800	Marital	8	4	1	-	-	-	2	7	-
801	Prison admission	1	-	-	1	-	-	-	1	-
802	Redundancy	1	-	-	-	1	-	-	1	-
803	TOTAL	71	18	8	17	5	3	4	55	1
804	**Other Events**									
805	Cardiovascular system unspecified	4	1	-	-	-	-	1	2	-
806	Central nervous system unspecified	4	4	-	-	-	-	-	4	-
807	Ear unspecified	1	-	-	-	-	-	-	-	-
808	Event not coded	4	3	-	-	-	-	-	3	-
809	Eye unspecified	1	1	-	-	-	-	-	1	-
810	Gastrointestinal unspecified	17	5	4	2	4	1	-	16	-
811	Gynaecology unspecified	7	1	1	3	2	-	-	7	-
812	Haemorrhage postoperative	1	1	-	-	-	-	-	1	-
813	Laboratory test abnormal	9	3	1	1	1	1	1	8	-
814	Liver unspecified	1	1	-	-	-	-	-	1	-
815	Male reproductive system unspecified	7	4	1	-	-	-	1	6	-
816	Metabolic unspecified	2	2	-	-	-	-	-	2	-
817	Musculoskeletal unspecified	8	2	3	1	-	-	1	7	-
818	Nodule	1	-	-	1	-	-	-	1	-
819	Non-malignant tumour unspecified	-	-	-	-	-	-	-	-	-
820	Pain	5	1	-	1	-	1	2	5	-
821	Pain postoperative	2	-	-	-	-	-	1	1	-
822	Psychiatric unspecified	60	12	8	9	6	5	5	45	-
823	Psychosomatic unspecified	-	-	-	-	-	-	-	-	-
824	Respiratory unspecified	5	-	1	-	-	1	1	3	-
825	Skin unspecified	4	-	1	1	-	1	-	3	-
826	Urinary unspecified	4	1	-	2	-	-	-	3	-
827	Pregnancy	57	12	11	5	4	1	5	38	8
828	Abortion	3	-	1	1	1	-	-	3	-
829	Abortion spontaneous	4	-	-	1	-	-	-	1	-
830	Birth normal	2	-	-	-	-	1	-	1	-
831	Pregnancy	48	12	10	3	3	-	5	33	8

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
832	TOTAL	204	54	31	26	17	11	18	157	8
833	**New Events**									
834	Abortion missed	-	-	-	-	-	-	-	-	-
835	Absence seizure/attack	1	-	-	-	-	-	1	1	-
836	Akathisia	2	2	-	-	-	-	-	2	-
837	Anaemia fatal	1	1	-	-	-	-	-	1	-
838	Angina improved	-	-	-	-	-	-	-	-	-
839	Anorexia nervosa fatal	-	-	-	-	-	-	-	-	-
840	Appetite increased	125	77	23	12	6	2	2	122	-
841	Asthma nocturnal	-	-	-	-	-	-	-	-	-
842	Asthma worse	8	2	2	1	2	-	-	7	-
843	Baldness	1	-	-	-	1	-	-	1	-
844	Bowel habit changed	4	1	1	-	2	-	-	4	-
845	Breast disorder male	1	-	-	-	1	-	-	1	-
846	Breast tests	1	-	-	-	1	-	-	1	-
847	Cardiovascular tests	40	11	6	4	-	5	3	29	-
848	Cardiovascular unspecified fatal	1	-	-	-	-	-	-	-	-
849	Central nervous system tests	6	1	1	1	-	-	1	4	1
850	Chesty	5	-	1	2	-	1	1	5	-
851	Condition improved	1278	256	210	146	154	138	126	1030	8
852	Connective tissue disease	-	-	-	-	-	-	-	-	-
853	Cyst	2	-	1	-	-	-	-	1	-
854	Dementia fatal	-	-	-	-	-	-	-	-	-
855	Dependence other drug	1	-	-	-	-	-	-	-	1
856	Dislocated joint	1	-	-	1	-	-	-	1	-
857	Dose increased	953	408	162	93	64	56	46	829	3
858	Dose reduced	288	68	43	29	27	22	30	219	9
859	Drug abuse	20	10	1	1	1	4	1	18	-
860	Drug information	10	9	1	-	-	-	-	10	-
861	Dysarthria	2	-	1	-	-	-	1	2	-
862	Dyskinesia	2	1	-	-	-	-	-	1	-
863	Ear tests	-	-	-	-	-	-	-	-	-
864	Ear trivial	2	-	-	1	1	-	-	2	-
865	Eating disorder	8	5	1	1	-	1	-	8	-
866	Emotional disturbance	13	5	4	-	-	1	2	12	-
867	Eye tests	1	-	1	-	-	-	-	1	-
868	Flu like symptoms	10	3	2	1	2	-	-	8	-
869	Gastro-intestinal tests	12	2	2	1	1	2	3	11	-
870	Glue ear	1	-	-	-	-	-	-	-	-
871	Gynaecological tests	14	5	2	2	1	2	-	12	-
872	Gynaecological trivial	1	-	-	-	-	1	-	1	-
873	Haematological tests	74	18	11	10	12	4	5	60	-
874	Helicobacter	1	1	-	-	-	-	-	1	-
875	Hepatic tests	12	4	2	1	3	-	-	10	-
876	Herpes genital	1	1	-	-	-	-	-	1	-
877	Hospital referral paramedical	43	10	12	6	1	1	4	34	-
878	Illegible	10	1	1	2	2	1	1	8	-
879	Immobility	5	3	-	1	-	-	-	4	-
880	Immounological tests	-	-	-	-	-	-	-	-	-
881	Inappropriate adh synd	-	-	-	-	-	-	-	-	-
882	Intolerance	238	165	35	13	6	7	3	229	1
883	Lipid tests	1	-	-	1	-	-	-	1	-
884	Male reproductive tests	-	-	-	-	-	-	-	-	-
885	Medical cert	7	4	1	-	1	1	-	7	-
886	Mental state improved	11	3	1	-	-	1	-	5	1
887	Mental state worse	14	4	1	2	-	1	2	10	-
888	Metabolic tests	15	2	1	4	2	1	2	12	-
889	Micturition abnormal	7	2	1	1	2	-	-	6	-
890	Multi system atrophy	-	-	-	-	-	-	-	-	-

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Appendix 3b. Events reported on green forms during treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**60022**	**11247**	**8362**	**7176**	**6347**	**5705**	**5161**		**known**
3	**Denominator male**	**24684**	**4376**	**3390**	**2946**	**2619**	**2361**	**2157**		
4	**Denominator female**	**35101**	**6822**	**4938**	**4201**	**3703**	**3323**	**2984**		
891	Musculoskeletal tests	3	2	1	-	-	-	-	3	-
892	Non compliance	302	152	37	31	27	11	14	272	3
893	Non formulary	5	1	-	-	2	-	1	4	-
894	Osteopenia	-	-	-	-	-	-	-	-	-
895	Pain foot	12	3	2	-	-	-	3	8	-
896	Pain hand	12	2	3	1	2	1	1	10	-
897	Pain musculoskeletal	26	5	4	4	2	4	3	22	-
898	Pain pelvis	5	1	1	1	1	-	1	5	-
899	Pallor	2	-	-	-	-	-	-	-	-
900	Patient request	488	199	83	49	38	28	22	419	4
901	Personality disorder	7	3	-	-	1	1	1	6	-
902	Polysymptomatic	5	4	-	-	-	-	-	4	1
903	Post operation unspecified	2	1	1	-	-	-	-	2	-
904	Pyrexia	8	3	-	2	-	-	-	5	-
905	Respiratory tests	14	5	-	2	3	1	2	13	-
906	Respiratory trivial	1	1	-	-	-	-	-	1	-
907	Sensation abnormal	18	10	2	-	-	2	-	14	1
908	Shivering	3	3	-	-	-	-	-	3	-
909	Skin trivial	2	-	-	-	-	1	-	1	-
910	Slapped cheek syndrome	-	-	-	-	-	-	-	-	-
911	Slurred speech	6	5	1	-	-	-	-	6	-
912	Smoker	7	6	-	-	-	-	-	6	-
913	Stammer	1	-	-	-	1	-	-	1	-
914	Stiffness	8	3	-	1	-	1	1	6	-
915	Tardive dyskinesia	-	-	-	-	-	-	-	-	-
916	Teichopsia	-	-	-	-	-	-	-	-	-
917	Tendon rupture	1	-	1	-	-	-	-	1	-
918	Testis pain/discomfort	-	-	-	-	-	-	-	-	-
919	Thought disorder	9	2	4	-	1	-	-	7	-
920	Tumour	11	-	2	1	3	-	1	7	-
921	Unsteadiness	28	21	2	1	1	-	2	27	-
922	Urinary tests	16	3	5	3	2	2	1	16	-
923	Urine outflow obstruction	1	-	-	-	-	-	-	-	-
924	Urology tests	2	1	-	-	-	-	-	1	-
925	Vaccination	10	1	1	1	3	-	1	7	-
926	Whiplash	2	-	-	1	1	-	-	2	-
927	TOTAL	4271	1522	681	435	381	304	288	3611	33

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
5	**Skin**									
6	Acne	12	4	2	1	-	2	1	10	1
7	Acne	7	3	1	1	-	-	1	6	1
8	Acne rosacea	5	1	1	-	-	2	-	4	-
9	Alopecia	2	-	-	-	1	-	1	2	-
10	Cyst sebaceous	7	1	2	2	1	1	-	7	-
11	Dermatitis	6	-	2	1	1	-	2	6	-
12	Dermatitis contact	1	-	-	-	-	-	-	-	1
13	Dry skin	4	-	3	1	-	-	-	4	-
14	Eczema	24	-	4	5	8	1	4	22	2
15	Eczema	20	-	3	4	6	1	4	18	2
16	Intertrigo	3	-	1	1	1	-	-	3	-
17	Pompholyx	1	-	-	-	1	-	-	1	-
18	Eczema varicose	-	-	-	-	-	-	-	-	-
19	Eruption bullous	2	-	-	-	-	-	1	1	1
20	Blister	1	-	-	-	-	-	1	1	-
21	Dermatitis herpetiformis	1	-	-	-	-	-	-	-	1
22	Erythema	-	-	-	-	-	-	-	-	-
23	Erythema nodosum	-	-	-	-	-	-	-	-	-
24	Erythroderma	-	-	-	-	-	-	-	-	-
25	Dermatitis exfoliative	-	-	-	-	-	-	-	-	-
26	Folliculitis	7	1	1	2	1	-	-	5	-
27	Hair ingrown	-	-	-	-	-	-	-	-	-
28	Hair loss	1	-	1	-	-	-	-	1	-
29	Herpes simplex, skin	3	1	-	1	-	-	1	3	-
30	Herpes zoster	5	1	1	1	-	-	1	4	1
31	Hirsutism	1	-	-	-	-	-	-	-	-
32	Hyperkeratosis	1	-	-	-	-	-	-	-	1
33	Hyperkeratosis	1	-	-	-	-	-	-	-	1
34	Pityriasis	-	-	-	-	-	-	-	-	-
35	Infection skin, unspecified/local bacterial	33	3	5	5	8	2	4	27	2
36	Abscess skin	9	1	-	1	3	1	1	7	1
37	Cellulitis	14	1	2	4	3	-	1	11	1
38	Impetigo	-	-	-	-	-	-	-	-	-
39	Infection skin	8	1	2	-	2	1	2	8	-
40	Paronychia	2	-	1	-	-	-	-	1	-
41	Lice	3	-	1	-	-	1	-	2	-
42	Lichen sclerosus	1	-	1	-	-	-	-	1	-
43	Lupus discoid	1	-	1	-	-	-	-	1	-
44	Nail change	3	1	-	2	-	-	-	3	-
45	Nail change	1	-	-	1	-	-	-	1	-
46	Nail ingrown	2	1	-	1	-	-	-	2	-
47	Onychomycosis	3	-	-	1	1	-	-	2	-
48	Photosensitivity	1	1	-	-	-	-	-	1	-
49	Pigmentation	-	-	-	-	-	-	-	-	-
50	Pressure sore	-	-	-	-	-	-	-	-	-
51	Pruritus	30	7	7	2	5	2	1	24	2
52	Pruritus	24	5	6	2	4	1	1	19	1
53	Pruritus ani	2	-	1	-	-	1	-	2	-
54	Pruritus vulvae	4	2	-	-	1	-	-	3	1
55	Psoriasis	2	-	-	1	-	-	-	1	-
56	Purpura	2	1	1	-	-	-	-	2	-
57	Rash	29	6	6	3	2	3	1	21	3
58	Scabies	2	-	1	-	1	-	-	2	-
59	Seborrhoea	2	-	1	-	1	-	-	2	-
60	Dandruff	1	-	-	-	1	-	-	1	-
61	Seborrhoea	1	-	1	-	-	-	-	1	-
62	Sinus pilonidal	-	-	-	-	-	-	-	-	-
63	Sore skin	3	1	-	1	-	-	1	3	-
64	Tinea	8	1	2	2	-	1	-	6	1

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
65	Ulcer skin	7	1	2	2	1	-	-	6	-
66	Urticaria	9	-	1	1	4	1	1	8	-
67	Vitiligo	1	-	1	-	-	-	-	1	-
68	TOTAL	216	30	46	34	35	14	19	178	15
69	**Musculoskeletal**									
70	Arthritis	6	2	1	-	-	-	1	4	1
71	Arthritis psoriatic	-	-	-	-	-	-	-	-	-
72	Arthritis rheumatoid	2	-	1	-	-	-	-	1	1
73	Arthritis rheumatoid*	2	-	1	-	-	-	-	1	1
74	Bone abnormal	1	-	-	-	-	-	-	-	-
75	Bursitis	8	1	2	-	2	2	-	7	-
76	Bursitis	4	-	1	-	2	1	-	4	-
77	Bursitis knee	1	-	-	-	-	1	-	1	-
78	Bursitis olecranon	3	1	1	-	-	-	-	2	-
79	Bursitis toe	-	-	-	-	-	-	-	-	-
80	Capsulitis	1	-	-	-	-	-	1	1	-
81	Chondromalacia	-	-	-	-	-	-	-	-	-
82	Cramp	8	-	1	-	4	2	-	7	1
83	Cyst Baker's	1	-	-	-	-	-	-	-	-
84	Disc prolapsed	-	-	-	-	-	-	-	-	-
85	Dupuytren's contracture	1	1	-	-	-	-	-	1	-
86	Effusion joint	3	-	-	1	1	-	1	3	-
87	Frozen shoulder	6	1	2	-	1	1	-	5	-
88	Ganglion	2	1	-	-	-	1	-	2	-
89	Lumbago	1	-	-	-	-	-	-	-	-
90	Muscle weakness	4	1	-	2	-	-	-	3	1
91	Myalgia	16	4	3	2	1	3	-	13	1
92	Nerve entrapment	4	-	2	-	-	-	-	2	-
93	Carpal tunnel syndrome	1	-	1	-	-	-	-	1	-
94	Nerve entrapment	3	-	1	-	-	-	-	1	-
95	Osteoarthritis	14	1	1	1	3	2	1	9	3
96	Osteochondritis	3	-	2	1	-	-	-	3	-
97	Osteomyelitis	1	-	-	-	-	-	-	-	1
98	Osteoporosis	-	-	-	-	-	-	-	-	-
99	Pain back	72	13	12	8	13	8	5	59	7
100	Pain bone	-	-	-	-	-	-	-	-	-
101	Pain groin	1	-	-	-	-	1	-	1	-
102	Pain joint	66	10	13	5	11	8	2	49	8
103	Pain joint	65	10	13	5	11	7	2	48	8
104	Rheumatism	1	-	-	-	-	1	-	1	-
105	Pain limb	19	2	4	3	5	4	-	18	-
106	Pain neck	25	9	4	-	3	2	1	19	4
107	Plantar fasciitis	3	-	-	-	-	1	-	1	1
108	Polymyalgia rheumatica	1	-	-	-	-	-	-	-	1
109	Rotator cuff	1	-	-	-	-	-	-	-	1
110	Sciatica	15	1	2	1	2	3	1	10	2
111	Scoliosis	-	-	-	-	-	-	-	-	-
112	Spasm muscular	4	1	1	-	-	-	-	2	1
113	Spondylosis	2	-	-	-	-	2	-	2	-
114	Spondylosis cervical	4	-	1	2	1	-	-	4	-
115	Swelling joint	4	1	-	-	-	1	-	2	-
116	Synovitis	-	-	-	-	-	-	-	-	-
117	Tendinitis	4	1	-	1	-	1	1	4	-
118	Tennis elbow	7	1	-	2	-	1	-	4	-
119	Tenosynovitis	2	-	-	-	-	-	1	1	-
120	Torticollis	3	-	1	1	-	-	1	3	-
121	Trigger finger	2	-	1	1	-	-	-	2	-
122	TOTAL	317	51	54	31	47	43	16	242	34
123	**Psychiatric**									

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
124	Aggression	9	1	2	2	1	-	-	6	2
125	Agitation	22	9	3	1	4	-	-	17	3
126	Alcoholism	23	8	3	4	1	2	1	19	2
127	Alcohol withdrawal	3	1	-	-	-	2	-	3	-
128	Alcoholism *	4	1	1	1	-	-	-	3	-
129	Alcoholism acute	1	-	-	1	-	-	-	1	-
130	Alcoholism chronic*	15	6	2	2	1	-	1	12	2
131	Anxiety	130	27	21	14	11	8	7	88	31
132	Anxiety	130	27	21	14	11	8	7	88	31
133	Behaviour abnormal	3	1	1	-	-	-	1	3	-
134	Confusion	9	1	1	1	2	2	-	7	1
135	Delusion	-	-	-	-	-	-	-	-	-
136	Dementia	3	-	1	-	-	1	-	2	1
137	Alzheimer's disease*	2	-	-	-	-	1	-	1	1
138	Dementia	-	-	-	-	-	-	-	-	-
139	Dementia senile*	1	-	1	-	-	-	-	1	-
140	Depersonalization	-	-	-	-	-	-	-	-	-
141	Depression	308	50	40	34	20	27	15	186	93
142	Depression	306	49	40	34	20	27	15	185	92
143	Depression manic	2	1	-	-	-	-	-	1	1
144	Depression postnatal	-	-	-	-	-	-	-	-	-
145	Dreams abnormal	2	-	2	-	-	-	-	2	-
146	Euphoria	-	-	-	-	-	-	-	-	-
147	Formication	-	-	-	-	-	-	-	-	-
148	Globus hystericus	1	-	1	-	-	-	-	1	-
149	Grief reaction	3	-	1	-	1	1	-	3	-
150	Hallucination	2	1	-	-	-	-	-	1	-
151	Hyperactive	1	-	-	-	-	-	-	-	1
152	Hypochondriasis	-	-	-	-	-	-	-	-	-
153	Hypomania	3	-	1	-	-	-	1	2	-
154	Insomnia	70	14	9	8	5	5	6	47	15
155	Irritability	9	1	1	1	3	1	1	8	1
156	Libido decreased	6	-	2	-	-	1	-	3	1
157	Malaise, lassitude	77	15	12	10	4	6	5	52	13
158	Lassitude	54	10	11	4	4	4	4	37	8
159	Malaise	23	5	1	6	-	2	1	15	5
160	Mania	3	-	1	2	-	-	-	3	-
161	Mood change	7	1	-	-	-	1	-	2	2
162	Mood change	1	-	-	-	-	-	-	-	-
163	Mood swings	6	1	-	-	-	1	-	2	2
164	Neurosis	2	-	-	-	-	-	-	-	1
165	Obsession/compulsive	5	-	-	-	1	2	-	3	2
166	Panic attack	30	12	3	3	1	1	2	22	4
167	Paranoia	-	-	-	-	-	-	-	-	-
168	Phobia	9	2	-	1	1	1	1	6	1
169	Agoraphobia	6	-	-	-	1	1	1	3	1
170	Cancer phobia	-	-	-	-	-	-	-	-	-
171	Phobia	3	2	-	1	-	-	-	3	-
172	Psychosis	5	1	1	-	1	-	-	3	2
173	Schizophrenia	-	-	-	-	-	-	-	-	-
174	Self injury	7	1	-	1	-	-	-	2	4
175	Senility	2	-	2	-	-	-	-	2	-
176	Somnambulism	-	-	-	-	-	-	-	-	-
177	Suicidal thought	13	3	1	3	2	1	1	11	1
178	Suicide attempt, drug overdose	59	7	18	8	9	1	2	45	9
179	Overdose*	3	-	-	-	-	-	1	1	2
180	Overdose other drug*	26	3	8	4	5	1	-	21	5
181	Overdose unknown drug*	12	-	5	1	3	-	-	9	1
182	Suicide attempt*	13	2	4	1	1	-	1	9	1
183	Suicide threat	5	2	1	2	-	-	-	5	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
184	Tics	-	-	-	-	-	-	-	-	-
185	TOTAL	823	155	127	93	67	61	43	546	190
186	**Central and Peripheral Nervous System**									
187	Amnesia	9	2	-	-	1	1	1	5	2
188	Aphasia, dysphasia	1	-	-	-	-	-	1	1	-
189	Dysphasia	1	-	-	-	-	-	1	1	-
190	Ataxia	-	-	-	-	-	-	-	-	-
191	Burning sensation	2	-	-	1	-	1	-	2	-
192	Coma	2	1	-	-	-	-	-	1	1
193	Convulsion, epilepsy	9	2	1	-	1	3	-	7	-
194	Convulsion*	5	2	1	-	-	1	-	4	-
195	Epilepsy *	2	-	-	-	1	-	-	1	-
196	Epilepsy grand mal	2	-	-	-	-	2	-	2	-
197	Disorientation	1	-	-	1	-	-	-	1	-
198	Dizziness	42	10	7	5	3	3	4	32	5
199	Drop attack	-	-	-	-	-	-	-	-	-
200	Drowsiness, sedation	15	9	1	1	1	1	-	13	-
201	Drowsiness	7	3	-	-	1	1	-	5	-
202	Sedation	8	6	1	1	-	-	-	8	-
203	Dysphonia	-	-	-	-	-	-	-	-	-
204	Extrapyramidal disease	5	-	1	2	1	-	-	4	1
205	Dystonia	-	-	-	-	-	-	-	-	-
206	Extrapyramidal disease	2	-	1	1	-	-	-	2	-
207	Movement involuntary	1	-	-	-	-	-	-	-	1
208	Parkinson's disease*	2	-	-	1	1	-	-	2	-
209	Feeling cold	1	1	-	-	-	-	-	1	-
210	Feeling hot	1	1	-	-	-	-	-	1	-
211	Flushing	11	2	1	2	2	1	1	9	1
212	Headache, migraine	86	18	17	11	12	6	4	68	9
213	Headache	63	13	15	8	8	5	2	51	6
214	Migraine	23	5	2	3	4	1	2	17	3
215	Hemiparesis	1	-	-	-	-	-	1	1	-
216	Lost consciousness	4	-	-	-	-	1	2	3	-
217	Meningitis	-	-	-	-	-	-	-	-	-
218	Meningitis *	-	-	-	-	-	-	-	-	-
219	Multiple sclerosis	-	-	-	-	-	-	-	-	-
220	Myelopathy	1	-	-	-	-	1	-	1	-
221	Neuralgia	7	1	-	1	3	-	-	5	1
222	Neuralgia trigeminal	-	-	-	-	-	-	-	-	-
223	Neuropathy	2	-	2	-	-	-	-	2	-
224	Neuritis*	-	-	-	-	-	-	-	-	-
225	Neuropathy peripheral	-	-	-	-	-	-	-	-	-
226	Neuropathy	2	-	2	-	-	-	-	2	-
227	Paralysis ocular	-	-	-	-	-	-	-	-	-
228	Paresis	1	-	-	-	1	-	-	1	-
229	Post viral syndrome	2	-	-	1	-	-	-	1	1
230	Ptosis	1	1	-	-	-	-	-	1	-
231	Sensation abnormal	14	1	2	3	2	3	1	12	-
232	Hypoaesthesia	10	1	-	3	1	2	1	8	-
233	Paraesthesia	4	-	2	-	1	1	-	4	-
234	Smell, taste abnormal	3	2	1	-	-	-	-	3	-
235	Taste abnormal	3	2	1	-	-	-	-	3	-
236	Syncope	6	-	2	-	1	-	2	5	-
237	Tremor	11	1	2	1	2	-	1	7	3
238	TOTAL	238	52	37	29	30	21	18	187	24
239	**Eye**									
240	Amaurosis	-	-	-	-	-	-	-	-	-
241	Amaurosis fugax	-	-	-	-	-	-	-	-	-
242	Blepharitis	5	-	1	-	2	1	-	4	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
243	Cataract	2	1	1	-	-	-	-	2	-
244	Conjunctivitis	14	3	3	3	-	-	1	10	1
245	Corneal dystrophy	1	-	-	-	-	1	-	1	-
246	Cyst Meibomian	-	-	-	-	-	-	-	-	-
247	Dry eye	2	-	1	1	-	-	-	2	-
248	Episcleritis	1	1	-	-	-	-	-	1	-
249	Floaters	-	-	-	-	-	-	-	-	-
250	Glaucoma	1	-	-	1	-	-	-	1	-
251	Haemorrhage subconjunctival	2	-	-	1	-	1	-	2	-
252	Herpes ophthalmic	-	-	-	-	-	-	-	-	-
253	Irritation eye	-	-	-	-	-	-	-	-	-
254	Lacrimation	-	-	-	-	-	-	-	-	-
255	Macular degeneration	-	-	-	-	-	-	-	-	-
256	Nystagmus	1	-	-	1	-	-	-	1	-
257	Pain eye	-	-	-	-	-	-	-	-	-
258	Retinal detachment	2	-	-	-	-	-	2	2	-
259	Retinopathy	-	-	-	-	-	-	-	-	-
260	Scleritis	-	-	-	-	-	-	-	-	-
261	Sore eye	3	-	1	1	1	-	-	3	-
262	Stye	2	1	1	-	-	-	-	2	-
263	Ulcer corneal	1	-	-	1	-	-	-	1	-
264	Uveitis	-	-	-	-	-	-	-	-	-
265	Visual defect	3	-	-	-	2	-	-	2	1
266	Diplopia	-	-	-	-	-	-	-	-	-
267	Hemianopia	-	-	-	-	-	-	-	-	-
268	Vision deteriorated	1	-	-	-	1	-	-	1	-
269	Vision field defect	-	-	-	-	-	-	-	-	-
270	Visual disturbance	2	-	-	-	1	-	-	1	1
271	TOTAL	40	6	8	9	5	3	3	34	2
272	**Ear**									
273	Deafness	9	1	-	1	2	1	2	7	1
274	Earache	10	1	2	2	2	2	-	9	-
275	Eardrum perforation	-	-	-	-	-	-	-	-	-
276	Earwax	7	1	2	-	-	2	1	6	-
277	Labyrinthitis	3	1	-	1	1	-	-	3	-
278	Otitis externa	15	3	3	4	1	1	1	13	-
279	Otitis media	9	2	2	-	3	-	1	8	-
280	Otorrhoea	-	-	-	-	-	-	-	-	-
281	Tinnitus	12	1	3	2	1	3	2	12	-
282	Vertigo	11	5	1	-	1	1	2	10	-
283	TOTAL	76	15	13	10	11	10	9	68	1
284	**Cardiovascular**									
285	Aneurysm	1	-	-	-	1	-	-	1	-
286	Aneurysm aortic*	1	-	-	-	1	-	-	1	-
287	Cardiac arrest	3	1	-	-	2	-	-	3	-
288	Cardiac failure	7	-	-	1	3	-	-	4	1
289	Cardiac failure*	4	-	-	-	2	-	-	2	1
290	Congestive cardiac failure*	2	-	-	1	-	-	-	1	-
291	Left ventricular failure*	1	-	-	-	1	-	-	1	-
292	Cardiomegaly	2	1	-	-	-	-	1	2	-
293	Cardiomyopathy	1	-	-	-	1	-	-	1	-
294	Cardiomyopathy*	1	-	-	-	1	-	-	1	-
295	Cerebrovascular accident	11	-	1	4	2	1	1	9	1
296	Cerebro-vascular accident*	8	-	-	3	1	1	1	6	1
297	Haemorrhage cerebral*	2	-	1	1	-	-	-	2	-
298	Haemorrhage subarachnoid*	-	-	-	-	-	-	-	-	-
299	Vertebrobasilar syndrome	1	-	-	-	1	-	-	1	-
300	Chilblain	2	-	-	-	1	-	-	1	-
301	Cold extremities	-	-	-	-	-	-	-	-	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
302	Deep vein thrombosis	1	-	-	-	1	-	-	1	-
303	Disorders of heart rate	2	-	1	-	-	-	-	1	-
304	Bradycardia	-	-	-	-	-	-	-	-	-
305	Tachycardia	2	-	1	-	-	-	-	1	-
306	Disorders of rhythm	5	-	2	-	1	-	-	3	1
307	Arrhythmia	1	-	-	-	1	-	-	1	-
308	Extrasystoles	2	-	2	-	-	-	-	2	-
309	Fibrillation atrial*	2	-	-	-	-	-	-	-	1
310	Embolus pulmonary	1	-	-	-	-	-	-	-	-
311	Faintness	1	-	-	-	1	-	-	1	-
312	Hypertension	23	2	2	4	3	3	3	17	4
313	Hypertension*	23	2	2	4	3	3	3	17	4
314	Hypotension	5	-	-	2	1	-	-	3	-
315	Ischaemia mesenteric	-	-	-	-	-	-	-	-	-
316	Infarction gastrointestinal*	-	-	-	-	-	-	-	-	-
317	Ischaemia peripheral	-	-	-	-	-	-	-	-	-
318	Claudication	-	-	-	-	-	-	-	-	-
319	Ischaemia peripheral	-	-	-	-	-	-	-	-	-
320	Ischaemic heart disease	16	2	2	1	5	2	-	12	2
321	Angina	10	1	2	-	3	2	-	8	1
322	Ischaemic heart disease*	2	-	-	1	1	-	-	2	-
323	Myocardial infarction*	4	1	-	-	1	-	-	2	1
324	Oedema	23	5	5	3	3	3	2	21	1
325	Fluid retention	1	1	-	-	-	-	-	1	-
326	Oedema face	4	1	3	-	-	-	-	4	-
327	Oedema	15	2	1	3	3	3	1	13	1
328	Swollen ankles	2	1	-	-	-	-	1	2	-
329	Swollen limb	1	-	1	-	-	-	-	1	-
330	Pain chest, tight chest	39	9	9	5	4	2	4	33	1
331	Pain chest	34	8	8	5	4	2	4	31	1
332	Tight chest	5	1	1	-	-	-	-	2	-
333	Palpitation	10	3	2	1	2	1	-	9	1
334	Pericarditis	1	1	-	-	-	-	-	1	-
335	Phlebitis	1	1	-	-	-	-	-	1	-
336	Raynaud's phenomenon	2	1	-	-	1	-	-	2	-
337	Restless legs	4	1	-	1	-	1	-	3	1
338	Thrombophlebitis	2	1	-	-	1	-	-	2	-
339	Transient ischaemic attack	2	-	-	1	-	-	-	1	1
340	Valvular disease	1	-	1	-	-	-	-	1	-
341	Stenosis aortic*	1	-	1	-	-	-	-	1	-
342	Vasculitis	1	-	1	-	-	-	-	1	-
343	Veins varicose	6	1	-	-	-	-	2	3	1
344	TOTAL	173	29	26	23	33	13	13	137	15
345	**Respiratory**									
346	Asthma, wheezing	33	6	9	8	2	2	2	29	1
347	Asthma*	20	2	8	5	2	1	1	19	-
348	Bronchospasm	2	-	-	1	-	-	1	2	-
349	Wheezing	11	4	1	2	-	1	-	8	1
350	Chronic Obstructive Airways Disease	12	5	1	2	2	1	-	11	-
351	Bronchiectasis*	1	-	-	-	-	1	-	1	-
352	Chronic Obstructive Airways Disease*	10	4	1	2	2	-	-	9	-
353	Emphysema*	1	1	-	-	-	-	-	1	-
354	Cough	35	5	12	3	3	5	3	31	1
355	Dyspnoea	14	6	1	2	1	1	1	12	-
356	Effusion pleural	3	-	-	-	2	-	1	3	-
357	Epistaxis	2	-	1	-	-	1	-	2	-
358	Fibrosis lung	-	-	-	-	-	-	-	-	-
359	Alveolitis fibrosing*	-	-	-	-	-	-	-	-	-
360	Haemoptysis	1	-	-	-	-	-	-	-	-
361	Hoarseness	7	-	2	2	-	1	-	5	2

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
362	Hyperventilation	2	1	-	-	-	1	-	2	-
363	Pleurisy	3	2	-	-	-	-	1	3	-
364	Pleurodynia	3	1	-	1	-	-	1	3	-
365	Pneumothorax	3	-	1	2	-	-	-	3	-
366	Respiratory Failure	-	-	-	-	-	-	-	-	-
367	Respiratory tract infection	261	43	49	38	32	33	23	218	15
368	Bronchitis acute	10	-	1	2	2	1	2	8	2
369	Bronchitis*	17	2	1	5	2	1	2	13	3
370	Bronchopneumonia*	1	-	1	-	-	-	-	1	-
371	Catarrh	10	1	-	5	3	1	-	10	-
372	Coryza	4	-	1	-	-	2	1	4	-
373	Infection chest*	63	11	13	4	8	7	5	48	5
374	Influenza*	6	1	1	-	1	-	2	5	1
375	Laryngitis	1	-	-	1	-	-	-	1	-
376	Pharyngitis	43	9	6	5	4	8	5	37	2
377	Pneumonia*	5	1	1	1	-	-	1	4	-
378	Rhinitis	5	1	2	-	1	1	-	5	-
379	Rhinorrhea	-	-	-	-	-	-	-	-	-
380	Sinusitis	28	3	5	5	4	2	2	21	2
381	Tonsillitis	13	2	2	3	1	4	1	13	-
382	Tracheitis	2	1	-	-	-	-	1	2	-
383	Upper respiratory tract infection	53	11	15	7	6	6	1	46	-
384	Rhinitis allergic	8	1	-	4	-	2	-	7	1
385	TOTAL	387	70	76	62	42	47	32	329	20
386	**Alimentary**									
387	Abscess dental	6	1	-	1	1	1	-	4	-
388	Anorexia	12	5	2	-	1	3	-	11	-
389	Appendicitis	1	-	-	-	-	-	-	-	-
390	Appendicitis	1	-	-	-	-	-	-	-	-
391	Ascites	2	-	-	1	-	1	-	2	-
392	Bowel obstruction	3	-	-	1	1	-	1	3	-
393	Bowel obstruction*	3	-	-	1	1	-	1	3	-
394	Bulimia	1	-	-	-	-	-	-	-	1
395	Campylobacter	2	1	-	-	-	-	-	1	-
396	Candidiasis oral	4	1	2	1	-	-	-	4	-
397	Cheilitis	-	-	-	-	-	-	-	-	-
398	Cholelithiasis, cholecystitis	6	-	-	1	1	2	-	4	-
399	Cholecystitis	1	-	-	-	-	1	-	1	-
400	Cholelithiasis*	3	-	-	1	1	-	-	2	-
401	Colic biliary	2	-	-	-	-	1	-	1	-
402	Cirrhosis	3	1	-	-	-	-	1	2	-
403	Cirrhosis*	3	1	-	-	-	-	1	2	-
404	Oesophageal varices	-	-	-	-	-	-	-	-	-
405	Coeliac disease	-	-	-	-	-	-	-	-	-
406	Constipation	26	8	4	6	1	-	3	22	1
407	Diarrhoea	46	15	4	9	6	2	1	37	5
408	Distension abdominal	11	2	1	-	2	-	-	5	1
409	Dry mouth	2	1	-	-	-	-	-	1	1
410	Dyspepsia	57	12	7	10	7	5	4	45	6
411	Duodenitis	-	-	-	-	-	-	-	-	-
412	Dyspepsia	36	6	4	7	4	4	2	27	4
413	Gastritis	4	1	1	-	-	1	-	3	1
414	Heartburn	7	4	-	1	1	-	1	7	-
415	Oesophageal reflux	7	-	2	-	2	-	1	5	1
416	Oesophagitis	3	1	-	2	-	-	-	3	-
417	Dysphagia	3	1	-	1	-	1	-	3	-
418	Faecal incontinence	1	-	-	1	-	-	-	1	-
419	Fissure anorectal	1	-	-	-	-	-	1	1	-
420	Flatulence	1	1	-	-	-	-	-	1	-
421	Gastroenteritis	13	4	3	1	2	1	1	12	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
422	Giardiasis	-	-	-	-	-	-	-	-	-
423	Gingivitis	2	1	-	-	-	-	-	1	-
424	Glossitis	1	-	-	-	1	-	-	1	-
425	Gum hypertrophy	1	-	-	-	-	-	1	1	-
426	Haemorrhage gastrointestinal	1	-	-	-	-	-	-	-	-
427	Haemorrhage gastrointestinal upper	4	2	-	-	1	-	1	4	-
428	Haematemesis*	2	1	-	-	1	-	-	2	-
429	Melena	2	1	-	-	-	-	1	2	-
430	Oesophageal haemorrhage*	-	-	-	-	-	-	-	-	-
431	Haemorrhage oral	-	-	-	-	-	-	-	-	-
432	Haemorrhage rectal	10	2	3	-	1	1	1	8	-
433	Haemorrhagic diarrhoea	-	-	-	-	-	-	-	-	-
434	Haemorrhoids	12	1	4	-	3	2	1	11	1
435	Halitosis	-	-	-	-	-	-	-	-	-
436	Hepatic failure	2	-	-	1	-	1	-	2	-
437	Hepatic failure*	2	-	-	1	-	1	-	2	-
438	Hepatitis, jaundice	1	-	-	-	-	-	-	-	-
439	Hepatitis*	-	-	-	-	-	-	-	-	-
440	Jaundice	1	-	-	-	-	-	-	-	-
441	Jaundice obstructive*	-	-	-	-	-	-	-	-	-
442	Hepatomegaly	1	-	-	-	1	-	-	1	-
443	Hernia	1	-	-	-	1	-	-	1	-
444	Hernia hiatus	1	1	-	-	-	-	-	1	-
445	Hiccough	-	-	-	-	-	-	-	-	-
446	Inflammatory disease colon	6	2	2	-	-	1	1	6	-
447	Colitis	2	-	-	-	-	1	1	2	-
448	Colitis pseudomembranous*	-	-	-	-	-	-	-	-	-
449	Colitis ulcerative	-	-	-	-	-	-	-	-	-
450	Colon perforated*	-	-	-	-	-	-	-	-	-
451	Crohn's disease*	-	-	-	-	-	-	-	-	-
452	Diverticulitis	2	1	1	-	-	-	-	2	-
453	Diverticulosis*	2	1	1	-	-	-	-	2	-
454	Diverticulum perforated*	-	-	-	-	-	-	-	-	-
455	Irritable bowel syndrome	22	4	6	3	4	3	1	21	-
456	Leukoplakia oral	-	-	-	-	-	-	-	-	-
457	Liver function test abnormal	10	6	1	-	2	-	-	9	1
458	Nausea, vomiting	78	26	10	7	8	5	3	59	10
459	Nausea	43	14	6	3	5	1	2	31	5
460	Vomiting	35	12	4	4	3	4	1	28	5
461	Pain abdomen	68	14	9	13	9	6	2	53	5
462	Pancreatitis	1	-	-	-	-	-	-	-	-
463	Pancreatitis*	1	-	-	-	-	-	-	-	-
464	Parotid enlarged	1	-	-	1	-	-	-	1	-
465	Parotitis	-	-	-	-	-	-	-	-	-
466	Pharynx irritation	1	-	1	-	-	-	-	1	-
467	Proctalgia	2	-	-	-	-	-	-	-	-
468	Proctitis	-	-	-	-	-	-	-	-	-
469	Prolapse rectal	-	-	-	-	-	-	-	-	-
470	Rectal discharge	3	-	1	-	-	-	2	3	-
471	Saliva increased	-	-	-	-	-	-	-	-	-
472	Sialadenitis	-	-	-	-	-	-	-	-	-
473	Sore mouth	2	1	-	-	-	-	-	1	1
474	Stomatitis	3	1	1	-	-	-	1	3	-
475	Tenesmus	-	-	-	-	-	-	-	-	-
476	Toothache	1	-	-	-	1	-	-	1	-
477	Ulcer mouth	4	-	-	-	1	1	-	2	1
478	Ulcer oesophageal	-	-	-	-	-	-	-	-	-
479	Ulcer peptic	1	-	-	-	-	-	-	-	-
480	Ulcer duodenal*	-	-	-	-	-	-	-	-	-
481	Ulcer gastric	-	-	-	-	-	-	-	-	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
482	Ulcer peptic*	1	-	-	-	-	-	-	-	-
483	TOTAL	441	114	61	58	55	36	26	350	34
484	**Metabolic and Endocrine**									
485	Acromegaly	1	-	-	-	1	-	-	1	-
486	Dehydration	-	-	-	-	-	-	-	-	-
487	Diabetes mellitus improved	1	-	-	1	-	-	-	1	-
488	Diabetes mellitus, hyperglycaemia	14	3	1	2	3	-	-	9	1
489	Diabetes mellitus worsened	3	-	-	-	2	-	-	2	-
490	Diabetes mellitus*	4	-	1	1	-	-	-	2	1
491	Glycosuria	-	-	-	-	-	-	-	-	-
492	Hyperglycaemia	5	3	-	-	-	-	-	3	-
493	Ketoacidosis diabetic*	1	-	-	1	-	-	-	1	-
494	Retinopathy diabetic	1	-	-	-	1	-	-	1	-
495	Electrolyte abnormal	3	3	-	-	-	-	-	3	-
496	Hyperkalaemia	-	-	-	-	-	-	-	-	-
497	Hypokalaemia	-	-	-	-	-	-	-	-	-
498	Hyponatraemia	3	3	-	-	-	-	-	3	-
499	Excessive thirst	5	-	1	2	-	-	-	3	1
500	Globulin abnormal	-	-	-	-	-	-	-	-	-
501	Gout	5	3	-	-	-	-	1	4	1
502	Hyperlipidaemia	2	1	-	-	1	-	-	2	-
503	Hypercholesterolaemia	1	-	-	-	1	-	-	1	-
504	Hyperlipidaemia	1	1	-	-	-	-	-	1	-
505	Hyperprolactinaemia	-	-	-	-	-	-	-	-	-
506	Hyperthyroidism	1	1	-	-	-	-	-	1	-
507	Hypoglycaemia	1	-	-	-	1	-	-	1	-
508	Hypothyroidism	4	2	1	-	-	1	-	4	-
509	Obesity	4	1	-	-	-	1	-	2	1
510	Obesity	4	1	-	-	-	1	-	2	1
511	Sweating	12	3	4	1	1	1	2	12	-
512	Weight gain	23	8	2	2	2	2	1	17	3
513	Weight loss	14	4	3	3	-	-	-	10	2
514	TOTAL	90	29	12	11	9	5	4	70	9
515	**Urologic**									
516	Albuminuria	1	-	1	-	-	-	-	1	-
517	Bladder irritability	-	-	-	-	-	-	-	-	-
518	Calculus renal	1	-	-	1	-	-	-	1	-
519	Caruncle urethral	-	-	-	-	-	-	-	-	-
520	Colic renal	6	-	-	1	1	2	-	4	1
521	Colic renal	3	-	-	-	-	2	-	2	-
522	Pain renal	3	-	-	1	1	-	-	2	1
523	Enuresis	2	-	1	1	-	-	-	2	-
524	Haematuria	8	3	-	1	-	1	1	6	2
525	Hydronephrosis	-	-	-	-	-	-	-	-	-
526	Micturition disorder	29	7	1	4	4	3	6	25	1
527	Dysuria	9	-	1	2	1	1	1	6	1
528	Frequency	8	4	-	1	-	1	1	7	-
529	Incontinence	9	2	-	-	2	1	4	9	-
530	Nocturia	2	-	-	1	1	-	-	2	-
531	Urgency	1	1	-	-	-	-	-	1	-
532	Polyuria	-	-	-	-	-	-	-	-	-
533	Pyuria	-	-	-	-	-	-	-	-	-
534	Renal failure	3	-	-	-	1	-	-	1	-
535	Renal failure acute	1	-	-	-	-	-	-	-	-
536	Renal failure chronic*	1	-	-	-	1	-	-	1	-
537	Renal failure*	1	-	-	-	-	-	-	-	-
538	Renal function test abnormal	-	-	-	-	-	-	-	-	-
539	Retention	3	1	-	1	1	-	-	3	-
540	Urea raised	-	-	-	-	-	-	-	-	-

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1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
541	Urinary tract infection	53	9	9	9	7	4	5	43	2
542	Cystitis	9	2	1	1	1	-	1	6	-
543	Pyelitis	1	-	-	-	1	-	-	1	-
544	Pyelonephritis*	1	-	-	-	1	-	-	1	-
545	Urethritis	3	-	1	1	-	1	-	3	-
546	Urinary tract infection*	39	7	7	7	4	3	4	32	2
547	TOTAL	106	20	12	18	14	10	12	86	6
548	**Male Reproductive and Gynaecomastia**									
549	Balanitis	1	-	-	-	-	1	-	1	-
550	Cyst epididymis	1	-	-	-	-	-	-	-	1
551	Ejaculation premature	-	-	-	-	-	-	-	-	-
552	Epididymitis	3	-	-	2	-	-	-	2	-
553	Gynaecomastia	3	-	-	-	1	1	-	2	-
554	Haemospermia	1	-	-	1	-	-	-	1	-
555	Impotence, ejaculation failure	10	2	1	3	1	2	-	9	1
556	Ejaculation failure	-	-	-	-	-	-	-	-	-
557	Impotence	10	2	1	3	1	2	-	9	1
558	Phimosis	-	-	-	-	-	-	-	-	-
559	Prostatism	6	-	1	1	2	1	-	5	-
560	Prostatitis	2	-	1	1	-	-	-	2	-
561	TOTAL	27	2	3	8	4	5	-	22	2
562	**Female Reproductive**									
563	Abscess Bartholin's gland	-	-	-	-	-	-	-	-	-
564	Bartholinitis	1	-	-	-	1	-	-	1	-
565	Cervical smear abnormal	1	-	-	-	-	1	-	1	-
566	Cyst Bartholin's	1	-	-	1	-	-	-	1	-
567	Cyst ovarian	2	-	1	-	-	-	1	2	-
568	Dyskaryosis	2	-	-	1	-	-	-	1	1
569	Dyspareunia	4	1	-	-	2	-	-	3	-
570	Endometriosis	1	-	1	-	-	-	-	1	-
571	Haemorrhage postcoital	2	1	-	-	-	1	-	2	-
572	Haemorrhage postmenopausal	1	-	-	1	-	-	-	1	-
573	Haemorrhage vaginal	8	2	2	-	-	-	2	6	1
574	Infertility female	-	-	-	-	-	-	-	-	-
575	Menopausal symptoms	6	2	1	-	-	-	1	4	1
576	Menstrual disorder	31	3	6	4	5	6	4	28	1
577	Amenorrhoea	2	-	-	-	-	-	1	1	1
578	Dysmenorrhoea	7	2	2	-	2	-	1	7	-
579	Irregular periods	3	-	-	1	-	-	2	3	-
580	Menorrhagia	19	1	4	3	3	6	-	17	-
581	Polymenorrhoea	-	-	-	-	-	-	-	-	-
582	Metrorrhagia	5	1	2	-	1	1	-	5	-
583	Pelvic inflammatory disease	2	-	-	-	-	1	-	1	1
584	Pelvic inflammatory disease	2	-	-	-	-	1	-	1	1
585	Premenstrual tension	7	1	2	1	2	-	-	6	-
586	Prolapse uterine	2	-	-	-	1	1	-	2	-
587	Vaginal soreness	2	1	-	-	-	-	-	1	-
588	Vaginitis, vulvitis	36	8	9	2	5	4	3	31	3
589	Infection vaginal bacterial	1	1	-	-	-	-	-	1	-
590	Vaginal candidiasis	18	2	6	2	2	1	2	15	3
591	Vaginal discharge	13	4	1	-	3	2	1	11	-
592	Vaginitis	2	-	1	-	-	1	-	2	-
593	Vaginitis trichomonas	1	-	1	-	-	-	-	1	-
594	Vulvitis	1	1	-	-	-	-	-	1	-
595	TOTAL	114	20	24	10	17	15	11	97	8
596	**Breast Disorder**									
597	Abscess breast	1	-	-	-	1	-	-	1	-
598	Breast discharge	-	-	-	-	-	-	-	-	-
599	Breast disorder	4	-	1	1	-	1	-	3	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
600	Galactorrhoea	3	-	-	-	1	1	1	3	-
601	Mastalgia	6	1	1	2	1	1	-	6	-
602	Mastitis	2	-	-	-	-	-	2	2	-
603	TOTAL	16	1	2	3	3	3	3	15	-
604	**Obstetric**									
605	Abortion threatened	1	-	-	-	-	-	-	-	1
606	TOTAL	1	-	-	-	-	-	-	-	1
607	**Haemopoietic**									
608	Anaemia	4	-	-	-	-	-	2	2	-
609	Anaemia iron deficiency	4	2	1	1	-	-	-	4	-
610	Anaemia iron deficiency	4	2	1	1	-	-	-	4	-
611	Anaemia macrocytic	1	-	-	-	1	-	-	1	-
612	Anaemia macrocytic	-	-	-	-	-	-	-	-	-
613	Anaemia vitamin B12 deficiency	1	-	-	-	1	-	-	1	-
614	Bone marrow abnormal	-	-	-	-	-	-	-	-	-
615	Eosinophilia	1	-	-	-	-	-	1	1	-
616	Eosinophilia	1	-	-	-	-	-	1	1	-
617	Erythrocyte sedimentation rate raised	-	-	-	-	-	-	-	-	-
618	Haematoma spontaneous	2	-	-	-	-	1	1	2	-
619	Hyperbilirubinaemia	-	-	-	-	-	-	-	-	-
620	Leucocytosis	6	-	3	-	1	1	1	6	-
621	Leucocytosis	2	-	1	-	1	-	-	2	-
622	Neutrophilia	4	-	2	-	-	1	1	4	-
623	Leucopenia	-	-	-	-	-	-	-	-	-
624	Leucopenia	-	-	-	-	-	-	-	-	-
625	Neutropenia	-	-	-	-	-	-	-	-	-
626	Lymphadenopathy	6	-	-	2	2	-	-	4	1
627	Glands swollen	1	-	-	-	-	-	-	-	1
628	Lymphadenitis	3	-	-	1	1	-	-	2	-
629	Lymphadenopathy	2	-	-	1	1	-	-	2	-
630	Myelodysplastic syndrome	-	-	-	-	-	-	-	-	-
631	Pancytopenia	1	-	1	-	-	-	-	1	-
632	Anaemia hypoplastic	1	-	1	-	-	-	-	1	-
633	Pancytopenia	-	-	-	-	-	-	-	-	-
634	Red cell abnormal	3	-	1	-	-	1	-	2	1
635	Thrombocytopenia	-	-	-	-	-	-	-	-	-
636	Thrombocytosis	1	-	-	-	1	-	-	1	-
637	TOTAL	29	2	6	3	5	3	5	24	2
638	**Neoplasm**									
639	Malignancies	18	3	3	2	4	1	2	15	-
640	Cancer*	1	-	-	-	-	1	-	1	-
641	Carcinoma bladder*	-	-	-	-	-	-	-	-	-
642	Carcinoma brain*	-	-	-	-	-	-	-	-	-
643	Carcinoma breast*	4	-	1	1	1	-	1	4	-
644	Carcinoma bronchus*	-	-	-	-	-	-	-	-	-
645	Carcinoma cervix*	1	-	1	-	-	-	-	1	-
646	Carcinoma colon*	1	-	-	-	-	-	-	-	-
647	Carcinoma kidney*	1	-	-	-	1	-	-	1	-
648	Carcinoma larynx*	-	-	-	-	-	-	-	-	-
649	Carcinoma liver*	-	-	-	-	-	-	-	-	-
650	Carcinoma lung*	1	-	-	-	-	-	-	-	-
651	Carcinoma ovary*	1	-	-	-	1	-	-	1	-
652	Carcinoma pancreas*	-	-	-	-	-	-	-	-	-
653	Carcinoma prostate*	-	-	-	-	-	-	-	-	-
654	Carcinoma rectum*	-	-	-	-	-	-	-	-	-
655	Carcinoma skin*	1	-	1	-	-	-	-	1	-
656	Carcinoma stomach*	-	-	-	-	-	-	-	-	-
657	Carcinoma thyroid*	-	-	-	-	-	-	-	-	-
658	Carcinomatosis*	4	1	-	1	1	-	-	3	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
659	Glioma*	1	1	-	-	-	-	-	1	-
660	Leukaemia lymphocytic chronic*	-	-	-	-	-	-	-	-	-
661	Leukaemia myeloid acute*	-	-	-	-	-	-	-	-	-
662	Leukaemia myeloid chronic*	-	-	-	-	-	-	-	-	-
663	Leukaemia*	1	-	-	-	-	-	1	1	-
664	Melanoma*	1	1	-	-	-	-	-	1	-
665	Myeloma*	-	-	-	-	-	-	-	-	-
666	Sarcoma*	-	-	-	-	-	-	-	-	-
667	Non-malignant tumours	12	2	2	-	1	2	1	8	2
668	Adenoma endocrine	-	-	-	-	-	-	-	-	-
669	Fibroids	4	2	-	-	-	-	1	3	1
670	Lymphoma	1	-	-	-	-	-	-	-	1
671	Non-malignant tumour breast	2	-	-	-	1	1	-	2	-
672	Non-malignant tumour skin	4	-	2	-	-	-	-	2	-
673	Polyp gastrointestinal	-	-	-	-	-	-	-	-	-
674	Polyp nasal	-	-	-	-	-	-	-	-	-
675	Polyp uterine	1	-	-	-	-	1	-	1	-
676	TOTAL	30	5	5	2	5	3	3	23	2
677	**Miscellaneous Infection**									
678	Abscess	2	1	1	-	-	-	-	2	-
679	Candidiasis	6	-	1	2	-	-	-	3	2
680	Chlamydial infection	1	-	1	-	-	-	-	1	-
681	Gardnerella infection	-	-	-	-	-	-	-	-	-
682	Herpes	2	-	-	-	-	1	-	1	1
683	Herpes	2	-	-	-	-	1	-	1	1
684	Herpes simplex	-	-	-	-	-	-	-	-	-
685	HIV positive and AIDS	1	-	-	-	-	-	-	-	1
686	HIV (Human immunodeficiency virus) positi	1	-	-	-	-	-	-	-	1
687	Infection	-	-	-	-	-	-	-	-	-
688	Infection postoperative	2	-	1	-	-	1	-	2	-
689	Infection viral	12	3	-	-	2	2	2	9	-
690	Rigor	1	-	-	-	-	-	-	-	1
691	Septicaemia	1	1	-	-	-	-	-	1	-
692	Varicella	-	-	-	-	-	-	-	-	-
693	Wart	3	1	-	-	-	1	1	3	-
694	Wart genital	-	-	-	-	-	-	-	-	-
695	TOTAL	31	6	4	2	2	5	3	22	5
696	**Immunological**									
697	Allergy	4	-	-	1	-	-	3	4	-
698	Angioneurotic oedema	2	1	-	-	-	-	1	2	-
699	Antinuclear antibody positive	-	-	-	-	-	-	-	-	-
700	Unspecified side effects	1	-	-	-	-	-	-	-	1
701	TOTAL	7	1	-	1	-	-	4	6	1
702	**Adverse Reaction to Specific Drug**									
703	Adverse reaction to other drug	7	1	2	1	-	-	-	4	3
704	Dependence	3	1	-	-	-	2	-	3	-
705	Withdrawal symptoms	5	3	-	-	-	-	-	3	2
706	TOTAL	15	5	2	1	-	2	-	10	5
707	**Accident and Injury**									
708	Animal bite	-	-	-	-	-	-	-	-	-
709	Assault	4	1	1	-	-	1	-	3	1
710	Burn	1	-	-	-	1	-	-	1	-
711	Drug overdose accidental	1	-	-	-	-	-	-	-	-
712	Fall	37	7	5	6	5	4	3	30	-
713	Fall*	20	5	1	2	5	3	1	17	-
714	Fall minor injury	17	2	4	4	-	1	2	13	-
715	Fall no injury	-	-	-	-	-	-	-	-	-
716	Fracture	17	5	2	2	1	1	2	13	2
717	Haematoma	5	1	1	2	1	-	-	5	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
718	Hyperkeratosis solar	-	-	-	-	-	-	-	-	-
719	Injury	54	6	10	7	7	5	7	42	2
720	Insect bite & sting	2	-	1	-	-	-	-	1	1
721	Bee sting	1	-	1	-	-	-	-	1	-
722	Insect bite	1	-	-	-	-	-	-	-	1
723	Poisoning nonmedicinal	-	-	-	-	-	-	-	-	-
724	Raped	-	-	-	-	-	-	-	-	-
725	Road traffic accident	10	1	2	1	1	-	2	7	-
726	Sunburn	-	-	-	-	-	-	-	-	-
727	TOTAL	131	21	22	18	16	11	14	102	6
728	**Death**									
729	Death cause uncertain	14	1	2	2	4	1	1	11	1
730	TOTAL	14	1	2	2	4	1	1	11	1
731	**Surgery**									
732	Abdominal surgery	13	-	1	1	3	2	2	9	1
733	Appendicectomy	3	-	1	-	1	1	-	3	-
734	Cholecystectomy	3	-	-	-	1	-	-	1	-
735	Gastrointestinal surgery	4	-	-	1	-	-	1	2	1
736	Hernia surgery	3	-	-	-	1	1	1	3	-
737	Acupuncture	2	1	-	-	-	-	1	2	-
738	Blood transfusion	1	-	-	-	-	-	1	1	-
739	Catheterisation	2	1	-	-	1	-	-	2	-
740	Chemotherapy	-	-	-	-	-	-	-	-	-
741	Dental surgery	3	-	-	-	1	1	-	2	1
742	Dialysis renal	-	-	-	-	-	-	-	-	-
743	Ear nose and throat surgery	1	-	-	-	1	-	-	1	-
744	Electroconvulsive therapy	14	2	2	1	-	2	1	8	6
745	Endoscopy	4	-	-	2	-	1	-	3	-
746	Gastroscopy	2	-	2	-	-	-	-	2	-
747	Genitourinary surgery	3	1	-	1	1	-	-	3	-
748	Cystoscopy	-	-	-	-	-	-	-	-	-
749	Genitourinary surgery	2	1	-	-	1	-	-	2	-
750	Renal transplantation	-	-	-	-	-	-	-	-	-
751	Transurethral resection of prostate	1	-	-	1	-	-	-	1	-
752	Gynaecological surgery	16	2	3	1	3	2	-	11	2
753	Abortion therapeutic	7	1	1	-	-	1	-	3	2
754	Caesarean section	-	-	-	-	-	-	-	-	-
755	Gynaecological surgery	7	-	2	1	3	1	-	7	-
756	Hysterectomy	2	1	-	-	-	-	-	1	-
757	Lumpectomy	1	-	-	-	1	-	-	1	-
758	Mastectomy	1	-	-	-	-	1	-	1	-
759	Minor surgery	9	2	2	-	-	2	1	7	1
760	Ophthalmic surgery	4	-	1	-	-	2	1	4	-
761	Cataract extraction	3	-	-	-	-	2	1	3	-
762	Eye surgery	1	-	1	-	-	-	-	1	-
763	Orthopaedic surgery	6	1	2	1	-	1	-	5	-
764	Amputation	1	-	-	-	-	1	-	1	-
765	Orthopaedic surgery	3	-	1	1	-	-	-	2	-
766	Total hip replacement*	2	1	1	-	-	-	-	2	-
767	Radiotherapy	-	-	-	-	-	-	-	-	-
768	Surgery	5	1	-	2	1	1	-	5	-
769	Thoracic surgery	3	1	-	-	-	-	-	1	1
770	Cardiac catheter	1	-	-	-	-	-	-	-	-
771	Cardiac surgery*	2	1	-	-	-	-	-	1	1
772	Heart-lung transplantation*	-	-	-	-	-	-	-	-	-
773	Thoracic surgery*	-	-	-	-	-	-	-	-	-
774	Vascular surgery	-	-	-	-	-	-	-	-	-
775	Vascular surgery	-	-	-	-	-	-	-	-	-
776	TOTAL	90	12	13	9	12	15	7	68	12

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
777	**Referrals**									
778	Hospital referrals no admission	117	25	19	12	10	15	7	88	13
779	Hospital referrals: Cardiology	7	2	1	-	-	-	1	4	-
780	Hospital referrals: Dermatology	3	-	-	1	-	-	1	2	-
781	Hospital referrals: Ear, nose and throat	6	-	-	-	2	1	2	5	1
782	Hospital referrals: Gastroenterology	6	-	1	1	2	-	-	4	-
783	Hospital referrals: General medicine	1	-	-	-	-	-	-	-	1
784	Hospital referrals: Gynaecology	12	3	4	-	2	3	-	12	-
785	Hospital referrals: Haematology	-	-	-	-	-	-	-	-	-
786	Hospital referrals: Neurology	5	1	1	-	-	1	-	3	2
787	Hospital referrals: Ophthalmology	1	-	1	-	-	-	-	1	-
788	Hospital referrals: Orthopaedics	4	1	-	1	1	-	-	3	-
789	Hospital referrals: Psychiatry	26	4	8	6	2	-	2	22	2
790	Hospital referrals: Respiratory	1	-	-	-	-	1	-	1	-
791	Hospital referrals: Rheumatology	2	1	-	-	-	1	-	2	-
792	Hospital referrals: Urology	2	-	-	-	-	-	-	-	2
793	Hospital referrals	41	13	3	3	1	8	1	29	5
794	Non-surgical admissions	92	19	15	13	8	10	4	69	12
795	TOTAL	209	44	34	25	18	25	11	157	25
796	**Social**									
797	Bereavement	10	-	2	2	-	1	3	8	1
798	Domestic	28	7	3	-	5	2	2	19	4
799	Loneliness	1	-	-	1	-	-	-	1	-
800	Marital	6	2	1	2	-	1	-	6	-
801	Prison admission	4	1	1	1	-	-	-	3	1
802	Redundancy	1	-	-	-	-	-	-	-	-
803	TOTAL	50	10	7	6	5	4	5	37	6
804	**Other Events**									
805	Cardiovascular system unspecified	1	-	-	-	1	-	-	1	-
806	Central nervous system unspecified	3	-	-	1	1	1	-	3	-
807	Ear unspecified	1	1	-	-	-	-	-	1	-
808	Event not coded	-	-	-	-	-	-	-	-	-
809	Eye unspecified	1	1	-	-	-	-	-	1	-
810	Gastrointestinal unspecified	7	1	-	-	-	-	-	1	3
811	Gynaecology unspecified	3	-	-	-	1	-	-	1	-
812	Haemorrhage postoperative	1	-	-	-	-	-	1	1	-
813	Laboratory test abnormal	5	-	-	-	2	-	-	2	1
814	Liver unspecified	1	-	-	-	-	-	-	-	-
815	Male reproductive system unspecified	1	-	-	1	-	-	-	1	-
816	Metabolic unspecified	1	-	1	-	-	-	-	1	-
817	Musculoskeletal unspecified	3	-	-	1	-	-	1	2	-
818	Nodule	2	-	-	-	-	-	-	-	-
819	Non-malignant tumour unspecified	2	-	-	-	-	1	-	1	-
820	Pain	7	3	1	-	-	2	-	6	1
821	Pain postoperative	1	-	-	-	-	-	-	-	-
822	Psychiatric unspecified	24	6	3	3	1	2	1	16	5
823	Psychosomatic unspecified	3	1	-	1	-	-	-	2	1
824	Respiratory unspecified	3	2	1	-	-	-	-	3	-
825	Skin unspecified	3	-	-	1	2	-	-	3	-
826	Urinary unspecified	1	-	-	-	-	-	-	-	1
827	Pregnancy	18	1	1	6	1	2	2	13	2
828	Abortion	-	-	-	-	-	-	-	-	-
829	Abortion spontaneous	1	-	-	1	-	-	-	1	-
830	Birth normal	-	-	-	-	-	-	-	-	-
831	Pregnancy	17	1	1	5	1	2	2	12	2
832	TOTAL	92	16	7	14	9	8	5	59	14
833	**New Events**									
834	Abortion missed	1	-	1	-	-	-	-	1	-
835	Absence seizure/attack	-	-	-	-	-	-	-	-	-

* Shows terms for which the total in column B could include one or more deaths reported on a green form

Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
836	Akathisia	-	-	-	-	-	-	-	-	-
837	Anaemia fatal	-	-	-	-	-	-	-	-	-
838	Angina improved	1	1	-	-	-	-	-	1	-
839	Appetite increased	3	1	-	-	1	-	-	2	-
840	Anorexia nervosa fatal	1	-	1	-	-	-	-	1	-
841	Asthma nocturnal	-	-	-	-	-	-	-	-	-
842	Asthma worse	4	2	1	-	-	-	-	3	-
843	Baldness	-	-	-	-	-	-	-	-	-
844	Bowel habit changed	4	2	1	-	1	-	-	4	-
845	Breast disorder male	1	-	-	1	-	-	-	1	-
846	Breast tests	2	-	-	-	-	-	-	-	-
847	Cardiovascular tests	38	8	4	7	5	5	2	31	1
848	Cardiovascular unspecified fatal	-	-	-	-	-	-	-	-	-
849	Central nervous system tests	2	-	1	-	-	1	-	2	-
850	Chesty	8	2	2	2	-	-	-	6	1
851	Condition improved	64	24	11	3	3	3	2	46	14
852	Connective tissue disease	1	-	-	-	1	-	-	1	-
853	Cyst	1	-	-	-	-	-	-	-	1
854	Dementia fatal	1	-	-	-	-	-	-	-	1
855	Dependence other drug	1	-	1	-	-	-	-	1	-
856	Dislocated joint	-	-	-	-	-	-	-	-	-
857	Dose increased	6	2	-	-	-	1	-	3	1
858	Dose reduced	4	1	-	-	-	1	1	3	1
859	Drug abuse	5	2	1	-	1	-	-	4	1
860	Drug information	-	-	-	-	-	-	-	-	-
861	Dysarthria	-	-	-	-	-	-	-	-	-
862	Dyskinesia	-	-	-	-	-	-	-	-	-
863	Ear tests	1	-	-	-	-	1	-	1	-
864	Ear trivial	-	-	-	-	-	-	-	-	-
865	Eating disorder	3	-	-	-	-	1	-	1	2
866	Emotional disturbance	-	-	-	-	-	-	-	-	-
867	Eye tests	1	-	-	-	1	-	-	1	-
868	Flu like symptoms	9	2	1	-	2	2	-	7	1
869	Gastro-intestinal tests	5	1	2	-	1	-	-	4	1
870	Glue ear	2	-	-	-	-	1	1	2	-
871	Gynaecological tests	10	2	1	2	2	1	1	9	-
872	Gynaecological trivial	3	-	-	-	1	-	-	1	1
873	Haematological tests	24	7	2	-	2	-	3	14	4
874	Helicobacter	5	-	2	1	-	-	1	4	-
875	Hepatic tests	8	3	3	-	-	1	-	7	-
876	Herpes gential	1	-	-	-	1	-	-	1	-
877	Hospital referral paramedical	24	5	6	3	3	2	-	19	3
878	Hypoglycaemia fatal	1	-	-	-	-	-	-	-	-
879	Illegible	6	1	1	1	1	1	-	5	1
880	Immobility	1	-	-	-	-	1	-	1	-
881	Immounological tests	1	1	-	-	-	-	-	1	-
882	Inappropriate adh synd	1	-	-	1	-	-	-	1	-
883	Intolerance	3	-	-	-	-	-	1	1	1
884	Lipid tests	6	1	-	2	-	-	-	3	1
885	Male reproductive tests	2	-	-	1	-	-	1	2	-
886	Medical cert	5	1	2	1	-	-	1	5	-
887	Mental state improved	5	1	1	2	1	-	-	5	-
888	Mental state worse	1	-	1	-	-	-	-	1	-
889	Metabolic tests	19	2	4	2	4	1	-	13	2
890	Micturition abnormal	6	2	-	1	2	-	1	6	-
891	Multi system atrophy	1	-	1	-	-	-	-	1	-
892	Musculoskeletal tests	7	-	3	-	1	-	-	4	-
893	Non compliance	1	-	-	-	-	-	-	-	1
894	Non formulary	-	-	-	-	-	-	-	-	-
895	Osteopenia	1	-	-	-	-	-	-	-	-

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Appendix 3c. Events reported on green forms after stopping treatment with mirtazapine

	A	B	C	D	E	F	G	H	I	J
1	**EVENT**	**Total**	**Mth1**	**Mth2**	**Mth3**	**Mth4**	**Mth5**	**Mth6**	**Mths1-6**	**Not**
2	**Denominator total**	**52654**	**8138**	**7869**	**7520**	**7077**	**6563**	**5899**		**known**
3	**Denominator male**	**18412**	**2922**	**2810**	**2680**	**2508**	**2308**	**2052**		
4	**Denominator female**	**33993**	**5181**	**5024**	**4805**	**4536**	**4224**	**3819**		
896	Pain foot	8	3	1	-	1	1	1	7	-
897	Pain hand	3	-	1	1	-	-	1	3	-
898	Pain musculoskeletal	21	2	6	2	2	1	2	15	3
899	Pain pelvis	3	1	-	2	-	-	-	3	-
900	Pallor	-	-	-	-	-	-	-	-	-
901	Patient request	2	-	-	1	1	-	-	2	-
902	Personality disorder	3	1	-	1	-	-	-	2	1
903	Polysymptomatic	1	-	-	-	-	-	-	-	1
904	Post operation unspecified	-	-	-	-	-	-	-	-	-
905	Pyrexia	4	-	2	-	-	-	1	3	-
906	Respiratory tests	10	4	4	-	-	-	-	8	-
907	Respiratory trivial	6	1	3	-	1	-	1	6	-
908	Sensation abnormal	5	1	1	-	1	1	-	4	1
909	Shivering	2	2	-	-	-	-	-	2	-
910	Skin trivial	3	-	-	1	-	1	-	2	-
911	Slapped cheek syndrome	1	-	-	1	-	-	-	1	-
912	Slurred speech	-	-	-	-	-	-	-	-	-
913	Smoker	1	-	-	-	1	-	-	1	-
914	Stammer	-	-	-	-	-	-	-	-	-
915	Stiffness	1	-	-	-	-	-	-	-	-
916	Tardive dyskinesia	1	-	-	-	-	-	1	1	-
917	Teichopsia	1	-	-	-	-	-	-	-	-
918	Tendon rupture	1	-	-	1	-	-	-	1	-
919	Testis pain/discomfort	3	1	-	2	-	-	-	3	-
920	Thought disorder	2	1	-	-	-	-	-	1	1
921	Tumour	8	2	1	-	1	2	-	6	-
922	Unsteadiness	7	1	1	1	3	-	1	7	-
923	Urinary tests	12	3	1	2	1	1	1	9	-
924	Urine outflow obstruction	-	-	-	-	-	-	-	-	-
925	Urology tests	4	1	1	1	-	1	-	4	-
926	Vaccination	15	3	1	-	-	4	2	10	1
927	Whiplash	4	-	-	-	1	1	-	2	-
928	TOTAL	443	101	77	46	47	36	26	333	47

* Shows terms for which the total in column B could include one or more deaths reported on a green form

INDIVIDUAL CASE HISTORIES OF INTEREST

SKIN

Rash

41 years old male patient prescribed 15mg of mirtazapine for depression. Two days after starting the medication the patient developed a very itchy rash on his hands, that resolved when mirtazapine was stopped. Possibly related to mirtazapine.
38005/140

This 55 years old female patient was prescribed 30mg of mirtazapine for depression. A week after starting the medication the patient complained of facial rash and swelling and headache, dizziness and weak legs, and mirtazapine was stopped. At the time of the event the patient was also taking paroxetine on a reducing dose. The events resolved on stopping mirtazapine. Possibly related to mirtazapine.
16005/33

This 73 years old male patient was prescribed mirtazapine for chronic anxiety and depression. A month after starting mirtazapine the patient presented with eczematous rash between the scapula and mirtazapine was stopped. The GP wrote that this was a pre-existing condition and that the patient is also prone to frequent psychosomatic symptoms. At the time of the event the patient was also on tramadol, lactulose and diazepam. Unlikely to be related to mirtazapine.
47056/499

This 48 years old female patient was prescribed 15mg of mirtazapine. Three weeks after starting mirtazapine the patient developed a rash and vulvodynia and mirtazapine was stopped. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
58029/277

This 62 years old male patient was prescribed 30mg of mirtazapine. Two months after starting mirtazapine the patient developed wide spread purpuric rash and the drug was stopped. At the time of the event the patient was also taking flixotide and serevent. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
59102/337

Skin exfoliation

This 43 years old male patient was prescribed 30mg of mirtazapine for chronic intractable depression. Seven months after starting mirtazapine the patient complained of exfoliation of the skin. On follow up the GP wrote that the skin exfoliation predated use of mirtazapine and was also related to poor diet and malabsorption and intake of alcohol. Continues to be on mirtazapine. Unlikely to be related to mirtazapine.
52012/428

Pomphylox eczema

This 44 years old female patient was prescribed 30mg mirtazapine. Few days after starting mirtazapine the dose was increased to 45mg, after which the patient complained of increase in the eczematous rashes, regular bouts of thrush, reduced white blood cell counts and platelets and negative aggressive thoughts. At the time of the event the patient was also on diclofenac and sulphasalazine. On stopping mirtazapine the events resolved. Possibly related to mirtazapine.
62082/148

PSYCHIATRIC

Agitation

This 59 years old male patient was prescribed 30mg of mirtazapine. Forty days after starting the medication the patient developed agitation which started to worsen with increased appetite and mood swings and the drug was stopped. There was no pre-existing condition and the patient did not have any risk factors. The event resolved on stopping mirtazapine. The GP thought that the event was considered to be possibly due to mirtazapine.
7016/453

This 68 years old female patient was prescribed 30mg of mirtazapine for her depression. Three weeks after starting the medication the patient developed increased agitation, and the dose was increased to 45mg for further two months. The GP writes that mirtazapine was not stopped due to the event but the dose was increased without increasing any symptoms, but eventually mirtazapine had to be stopped as it was felt to be ineffective. Possibly related to mirtazapine.
10124/249

This 45 years old male patient was prescribed 30mg of mirtazapine. Two days after starting the medication the patient became increasingly agitated which upset his body clock, and the drug was stopped. The event resolved on stopping mirtazapine and the GP thinks that the event was related to mirtazapine.
17098/280

This 53 years old male patient was prescribed 30mg of mirtazapine. Few days after starting the medication the patient developed agitation an d high levels of expressed anxiety which settled immeadiately once mirtazapine was stopped. The GP thinks the event was possibly related to mirtazapine.
23029/226

This 53 years old male patient was prescribed mirtazapine for depression. Two months after starting the medication the patient presented with agitation and the medication was stopped. The GP wrote that the the agitation was just a part of highly agitated depression and no medication helped, and the aptient required a 10 weeks hospital stay. The patient had a past medical history of anxiety depression. The event did not resolve even after stopping mirtazapine. Unlikely to related to mirtazapine.
23029/227

This 39 years old female patient was prescribed 30mg of mirtazapine. Soon after starting mirtazapine the patient complained of agitation and the drug was stopped. The GP wrote that the patient had swapped herself from mirtazapine to a friends fluoxetine and later came to see a doctor to ask for paroxetine. The patient had a pre-existing condition and also a past medical history, and even after stopping mirtazapine the event did not resolve. Unlikely to be related to mirtazapine.
25005/191

This 31 years old female patient was prescribed 30mg of mirtazapine for her depression. Two weeks after starting mirtazapine the patient presented with severe agitation - not eating, not sleeping biting herself and low mood. The GP writes that the patient was previously depressed but not at all agitated. The agitation resolved once mirtazapine was stopped. Possibly related to mirtazapine.
26049/221

This 64 years old female patient was prescribed 30mg of mirtazapine for unresponsive depression. A week after starting mirtazapine the patient developed agitation, and mirtazapine was stopped. The patient did not have any such problems prior to starting mirtazapine. At the time of the event the patient was also taking bisacodyl and cimetidine. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
48030/222

This 53 years old female patient was prescribed mirtazapine for depression. A month after starting mirtazapine the patient complained of agitation and mirtazapine was stopped. The GP wrote that this patient is generally a very anxious lady and had pre-existing worries and past medical history of anxiety disorder. Unlikey to be related to mirtazapine.
53015/172

This 31 years old male patient was prescribed 15mg of mirtazapine. Three months after starting mirtazapine the patient complained of increased agitation and mirtazapine was stopped. The patient was irritable and aggressive before starting mirtazapine but this became worse with mirtazapine. On stopping mirtazapine aggression improved. Possibly related to mirtazapine.
56066/291

This 41 years old male patient was prescribed 30mg of mirtazapine for depression. Two months after starting mirtazapine the patient complained of agitation, and mirtazapine was stopped. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
59124/140

This 61 years old female patient was prescribed 30mg mirtazapine. Two months after starting mirtazapine the patient complained of agitation, and mirtazapine was stopped. There were no previous episodes of agitation prior to starting mirtazapine. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
75036/121

This 63 years old female patient was prescribed 30mg mirtazapine for depression. Eight months after starting mirtazapine the patient complained of agitation, which resolved on stopping mirtazapine. The patient also had a history of alcohol abuse and has Korsakoff's syndrome. Possibly related to mirtazapine.
80150/94

This 31 years old female patient was prescribed 30mg mirtazapine. Soon after taking mirtazapine the patient complained of being agitated and feeling shakey, which settled when mirtazapine was stopped. Possibly related to mirtazpine.
85023/686

This 54 years old female patient was prescribed mirtazapine. Two months after starting mirtazapine the patient reported of nocturnal agitation and sleep disturbance, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
86061/595

Aggression

This 41 years old female patient was prescribed 15mg of mirtazapine for her depression. Three days after starting the medication the patient developed aggressive behaviour and the drug was stopped. On stopping the drug the event resolved. The GP thinks that the event was possibly related to mirtazapine.
24030/108

45 years old male patient was prescribed 30mg of mirtazapine. Patient reported feeling very aggressive 8 days after starting mirtazapine, and discontinued the drug himself. There was no pre-existing condition and the event resolved once mirtazapine was stopped. Possibly related to mirtazapine.
42017/263

43 years old female patient was prescribed 30mg of mirtazapine. A week after starting the medication the patient complained of developing a short temper with aggressiveness and "felt like killing someone". She also developed an increase in appetitie. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
46131/290

This 60 years old female patient was prescribed 30mg of mirtazapine for depression. Soon after starting mirtazapine the patient developed oedema and aggression and mirtazapine was stopped. At the time of the event the patient was also taking lithium, lactulose and domperidone. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
52076/183

This 55 years old female patient was prescribed 30mg of mirtazapine. Two weeks after starting mirtazapine the patient became aggressive and very argumentative and mirtazapine was stopped. The patient had a previous history of anxiety depression, and was also on chlorpromazine and lorazepam. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.

78044/384

This 36 years old male patient was prescribed 30mg mirtazapine. One month after starting mirtazapine the patient complained of aggression and loss of libido, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
86061/594

Hallucination

This female patient was prescibed 30mg of mirtazapine. Three days after starting the drug the patient complained of hallucinations and the medication was stopped as the GP thought that it was a side effect of mirtazapine. On further follow up it was revealed that the patient had visual hallucination prior to commencing mirtazapine. Therefore it was thought that the event was unlikely to be due to mirtazapine.
10080/371

51 years old male patient prescribed 30mg of mirtazapine for his depression. Two days after starting the medication the patient complained of hallucinations and the drug was stopped. The patient had no pre-existing condition and the event resolved once mirtazapine was stopped. Possibly related to mirtazapine.
27079/295

This 48 years old male patient was prescribed 30mg mirtazapine. Two months after starting mirtazapine the patient complained of becoming more irritable and having hallucinations. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
26046/147

This 38 years old male patient was prescribed 15mg mirtazapine for paranoid ideas. Patient complained of visual hallucinations after taking one dose of mirtazapine, and the medication was stopped. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
39128/57

This 58 years old male patient was prescribed 7.5mg mirtazapine for depression. Two months after starting mirtazapine the patient complained of hallucinations, and mirtazapine was stopped. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
64006/214

This 24 years old female patient was prescribed 30mg mirtazapine for depression. Few days after starting mirtazapine the patient complained of deteriorating mood, auditory hallucinations and suicidal ideation, and mirtazapine was stopped. The events resolved on stopping mirtazapine.
Possibly related to mirtazapine.
68102/636

In the first case, the patient was prescribed 30mg of mirtazapine. Two days after starting the medication the patient complained of hallucinations and the drug was

stopped. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
10080/371

In the second case, the patient was prescribed 15mg of mirtazapine for depression. A week after starting the medication the patient complained of sleep disturbance and hallucinations, and the medication was stopped. The event resolved on stopping the mirtazapine. The GP has also sent a yellow card to the CSM. Possibly related to mirtazapine
63059/317

Restless legs

This 23 years old female patient was prescribed with 30mg of mirtazapine. Two days after starting the drug the patient complained of restless legs and the drug was stopped. The GP wrote that the event was likely to have occurred due to stopping procyclidine and starting mirtazapine. But the GP added that the event worsened on mirtazapine, which resolved on stopping the medication. Possibly related to mirtazapine.
20043/230

76 years old male patient developed restless legs a month after starting mirtazapine. Due to the feeling of restlessness, the patient tends to spend much of the night wandering around. The consultant psychiatrist thought that it was a side effect of mirtazapine. Once the drug was stopped the event resolved. The GP has sent an yellow card to the CSM.
47050/217

Loss of libido

37 years old male patient prescribed 30mg of mirtazapine. A month after starting the medication the patient complained of loss of libido which was previously not a problem. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
25003/166

This 36 years old male patient was prescribed 30mg mirtazapine. One month after starting mirtazapine the patient complained of aggression and loss of libido, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
86061/594

Trance like state

This 45 years old male patient was prescribed 30mg of mirtazapine for his depression. A month after starting the medication the patient complained of three episodes of trance like state before passing out, lasting for 2 minutes each time. The event resolved once mirtazapine was stopped. Possibly related to mirtazapine.

32225/24

Morbid dreams

60 years old female patient was prescribed 30mg of mirtazapine for her depression. Four months after starting the drug the patient started to complain of experiencing morbid dreams and poor sleep pattern, and mirtazapine was stopped. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
42157/461

Aggressive nightmares

This 35 years old male patient was prescribed 30mg mirtazapine. A week after starting mirtazapine the patient complained of being restless and getting aggressive nightmares and mirtazapine was stopped. On stopping mirtazapine the events resolved. Possibly related to mirtazapine.
53087/117

This 23 years old female patient was prescribed 30mg mirtazapine for depression. Two months after starting mirtazapine the patient complained of nightmares, and mirtazapine was stopped. Nightmares resolved on stopping mirtazapine. Possibly related to mirtazapine.
61187/115

This 82 years old male patient was prescribed 30mg mirtazapine for depression. Few days after starting the medication the patient reported of having nightmares and the drug was stopped. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
62019/214

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

Light headedness

This female patient was prescribed 30mg of mirtazapine for her depression. Three months after starting the medication the patient complained of light headedness and the medication was stopped as the GP thought that the signs and symptoms were due to the side effect of mirtazapine. The patient had a previous history of agitated depression. The patient was on propranalol and HRT at the time of the event. On stopping mirtazapine the light headedness resolved but a month after the patient had developed an withdrawal reaction to mirtazapine and complained of strange feelings. The GP wrote that it was a withdrawal reaction to mirtazapine.
10007/208

Female patient prescribed 30mg of mirtazapine. Immidiately after starting the medication the patient complained of light headedness, which resolved on stopping the drug. Possibly related to mirtazapine.
25099/93

Myoclonus - leg spasms

This 52 years old female patient was prescribed 15mg of mirtazapine for agitated depression with insomnia. Two weeks after starting mirtazapine the patient complained of leg spasms at sleep and rest, which resolved once mirtazapine was stopped. At the time of the event the patient was also on microval (HRT), and codydramol. Possibly related to mirtazapine.
59101/308

Leg cramps

This 55 years old female patient was prescribed 15mg of mirtazapine for depression. Soon after starting the medication the patient developed leg cramps in the night, which cleared on stopping mirtazapine. Possibly related to mirtazapine.
60060/236

Lost conciousness

This 34 years old female patient was prescribed 15mg mirtazapine for panic attacks. The patient reported to have been unconcious 10 minutes after taking mirtazapine. The patient has a previous history of alcohol abuse and panic attacks. There have been no further episodes of unconciousness after stopping mirtazapine. Possibly related to mirtazapine.
62023/239

This 71 years old female patient was prescribed mirtazapine. Few days after starting mirtazapine the patient was admitted with collapse to the hospital. The patient had a history of hypertension, COAD and IHD and was taking bricanyl, plumicort, serevent, amlodepine and enalapril at the time of the event. No further episodes occurred on stoping mirtazapine. Possibly related to mirtazapine.
85023/677

Dizziness

This 69 years old female patient was prescribed 30mg mirtazapine. Four months after starting the medication the patient complained of dizziness. The patient was also taking amiadarone, tramadol and aspirin at the time of the eventand has a past history of heart disease. The patient continues to take mirtazapine. Unlikely to be related to mirtazapine.
62030/289

This 77 years old female patient was prescribed 7.5mg mirtazapine. One day after starting the medication the patient complained of dizziness, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
62086/211

This 56 years old female patient was prescribed 45mg mirtazapine for anxiety depression. Two months after starting mirtazapine the patient complained of dizziness, which resolved on stopping mirtazapine.
78029/205

Convulsion

This 55 years old male patient was prescribed 30mg mirtazapine. The patient already had a past history of fits and convulsions, which increased on taking mirtazapine. At the time of the event the patient was also taking carbamazepine and omeprazole. On stopping mirtazapine the fits decreased in frequency. Possibly related to mirtazapine.
83079/355

CARDIOVASCULAR

Arrhythmia

This 54 years old male patient was prescribed 30mg of mirtazapine for depression. Five months after starting the drug the patient was detected to have ventricular tachycardia on the ECG. The patient has a past history of inferior myocardial infarction. Event unlikely to be due to mirtazapine.
18008/241

This 57 years old male patient was prescribed 30mg of mirtazapine for depression. A month after starting the medication the patient complained of feeling ill and was detected to have a tachycardia, and the drug was stopped. The patient then retried mirtazapine after a few days with the development of the same side effects. The event resolved each time after stopping mirtazapine. Possibly related to mirtazapine.
44027/150

Oedema - facial swelling

This 29 years old female patient was prescribed 30mg of mirtazapine for her depression. Two weeks after starting the medication the patient complained of facial swelling as part of generalised fluid retension/oedema, that resolved once mirtazapine was stopped. Possibly related to mirtazapine.
26025/594

Oedema

This 32 years old female patient developed generalised swelling of the fingers and ankles after two months of starting mirtazapnie, which resolved once mirtazapine was stopped. Possibly related to mirtazapine.
46053/429

This female patient was prescribed 30mg of mirtazapine. Two weeks after starting mirtazapine the patient developed pitting oedema to the knees and allergic looking rash on the forearms and mirtazapine was stopped. The patient did not have a pre-existing condition and past medical history of allergy. On stopping mirtazapine the event resolved. Possibly related to mirtazapine. The GP has also sent an yellow card to the CSM.
47056/471

This 60 years old female patient was prescribed 30mg of mirtazapine for depression. Soon after starting mirtazapine the patient developed oedema and aggression and

mirtazapine was stopped. At the time of the event the patient was also taking lithium, lactulose and domperidone. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
52076/183

This 80 years old female patient was prescribed 30mg of mirtazapine. Six days after starting mirtazapine the patient developed swelling of the whole body except the face and mirtazapine was stopped. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
52092/56

This 51 years old female patient was prescribed 30mg of mirtazapine for depression.Two weeks after starting mirtazapine the patient developed mild ankle oedema and mirtazapine was stopped. The patient was also on chemotherapy for breast cancer at the time of the event. The event gradually resolved after some months on stopping mirtazapine. Possibly related to mirtazpine, but chemotherapy and breast cancer should also be taken into consideration.
52176/604

Swollen ankles

This 83 years old female patient was prescribed 15mg of mirtazapine. Three weeks after starting mirtazapine the patient developed swelling of ankles and mirtazapine was stopped. On stopping mirtazapine the swelling gradually resolved. Possibly related to mirtazapine.
52154/160

Palpitations

36 years old male patient was presc4ribed 30mg of mirtazapine for depression. A month after starting mirtazapine patient complained of palpitations, that resolved once mirtazapine was stopped. Possibly related to mirtazapine.
27004/70

Hypotension

29 years old female patient developed sudden hypotension and urinary retention two days after starting mirtazapine. The event resolved once the drug was stopped. Possibly related to mirtazapine.
47049/59

Atrial fibrillation

This 61 years old male patient was prescribed 30mg of mirtazapine for depression. Eight months after taking mirtazapine the patient had atrial fibrillation and chest pains and mirtazapine was stopped. The patient had diabetes mellitus and was on insulin at the time of the event. Even after stopping mirtazapine the event did not resolve. Subsequently a cardioversion was carried out which also failed. Difficult to assesss.
42217/446

Paroxysmal atrial fibrillation

This 58 years old male patient was prescribed 7.5mg mirtazapine for refractory depression. Seven months after starting mirtazapine the patient complained of palpitations and was admitted to the hospital. ECGs done at the time of admission showed atrial flutter with 2:1 block. The patient had a past history of IHD and had also had a CABG. The cardiologists thought that the event was mainly due to his heart problems rather than due to mirtazapine and advised the patient to continue on mirtazapine. Unlikely to be related to mirtazapine.
58053/482

Faintness

This 29 years old female patient was prescribed 30mg of mirtazapine. Few days after starting the medication the patient fainted in the night, and the drug was stopped. There have been no such episodes after stopping mirtazapine. The GP has reported this event to the CSM. Possibly related to mirtazapine.
59013/152

METABOLIC AND ENDOCRINE

Hypothyroidsm

This 29 years old female was prescribed 30mg of mirtazapine for depression. Six months after starting mirtazapine the patient was detected to have hypothyroidism and the medication was stopped. On investigation the patient had positive anti-microsomal antibodies to thyroid and was diagnosed to have autoimmune thyroid disease. At the time of the event the patient was also taking dihidrocodiene. The GP thinks that the event is unlikely to be due to mirtazapine. The event did not resolve after stopping mirtazapine.
1080/229

This 34 years old female patient was prescribed 30mg of mirtazapine for low mood and agarophobia. Three months after starting mirtazapine the patient developed gross primary hypothyroidism and mirtazapine was stopped. The patient did not have any pre-existing disorder and on stopping mirtazapine the event resolved. Possibly related to mirtazapine.
53015/178

ALIMENTARY

Liver failure

This 68 years old female patient was prescribed 30mg of mirtazapine. Five monthas after starting mirtazapine the patient developed liver failure and ulitimately died. On further follow up the patient was diagnosed to have primary biliary cirrhosis and was also taking azathioprine, chlestyramine, ranitidine and prednisolone. Unlikey to be related to mirtazapine.
52253/102

Abnormal liver tests

This 24 years old female patient was prescribed 45mg of mirtazapine for borderline personality disorder and recurrent depression. Three months after starting the medication the patient was detected to have abnormal liver function tests with an ALT of 44 IU/L and γGT of 630 IU/L. The GP wrote that the liver functions were raised after stopping mirtazapine and may have been a possible reaction due to diclofenac. Therefore unlikely to be due to mirtazapine.
04032/102

This 48 years old male patient was prescribed 30 mg of mirtazapine. Two days after starting the medication the patient complained of passing dark coloured urine and pale stools. Abnormal LFTs were detected with an ALT of 59 IU/L and serum albumin of 55g/l and the medication was stopped. Both the GP and the consultant thought that the event was possibly due to mirtazapine. On stopping mirtazapine the ALT levels (25 IU/L) and albumin levels (49g/l) came back to normal within two weeks. Possibly related to mirtazapine.
06017/92

This 28 years old male patient was prescribed 30mg of mirtazapine for his depression. Two and a half months after starting the medication, there was deterioration of depression and the patient was admitted to the hospital. Raised ALT - 60 IU/L was detected on routine blood tests in the hospital, and therefore mirtazapine was stopped. The patient did not have any pre-existing condition and it was not known whether the event resolved on stopping the medication as the patient remained in the hospital. Considered possibly related to mirtazapine.
120641/222

This 49 years old male patient was prescribed mirtazapine for depression. Five weeks after starting the medication the patient was found to have an ALT of 83 IU/L and mirtazapine was stopped. One month after stopping mirtazapine ALT levels came down to 24 IU/L. Considered possibly related to mirtazapine.
12083/177

This 48 years old male patient was prescribed mirtazapine for his depression. A month after starting the medication the patient was detected on routine blood test examination to have increased ALT levels and the medication was stopped. The patient was also on trifluperazine at the time of the event. The GP writes that the patient also took alcohol and had a past history of alcoholism. The event resolved on stopping mirtazapine but the patient had also stopped his alcohol. Difficult to assess causality due to confounding.
12084/82

This 42 years old male patient was prescribed 15mg of mirtazapine for his depression. Four months after starting the medication the patient was detected to have raised ALT levels of 51 IU/L. At the time of the event the patient was also on tramadol, codydramol, and gaviscon. The event may be possibly due to mirtazapine, but the patient continues to be on mirtazapine.
15091/456

This 29 years old female patient was prescribed 30mg of mirtazapine for her depression. Two months after starting the medication the patient was found to have raised alkaline phosphatase and γGT, and the drug was stopped. On stopping the medication the event resolved. The GP thought that the event was due to mirtazapine. Considered possibly related to mirtazapine.
17053/144

This female patient was admitted to the hospital with Klebsilla right lower lobe pneumonia. The patient was discharged from the hospital on 30mg of mirtazapine for her depression. Eight weeks after starting mirtazapine the patient was reported to have agranulocytosis and disturbed LFTs, and mirtazapine was stopped. On stopping mirtazapine, the GP writes that the LFTs and blood counts were back to normal. GP wrote that he suspected it to be a possible bone marrow toxicity. Possibly related to mirtazapine.
24070/171

This 36 years old female patient was prescribed 30mg of mirtazapine for depression. Four weeks after starting the medication the patient's blood tests showed an ALT of 92 IU/L, and mirtazapine was stopped. On stopping mirtazapine the event resolved. Considered to be possibly due to mirtazapine.
29028/234

52 years old female patient was prescribed 15mg of mirtazapine for anxiety and depression. Three months after starting the medication a raised alkaline phosphatase - 102 IU/L was detected, and the medication was stopped. ALP returned to normal on stopping mirtazapine and the GP thinks that the event was possibly related to mirtazapine. The event was considered to be possibly related to mirtazapine.
32221/65

65 years old male patient was prescribed 15mg of mirtazapine for depression. Two weeks after starting the drug the patient was found to have abnormal LFTs with an alkaline phosphatase of 277 IU/L and γGT of 203, and mirtazapine was stopped. The patient did not have any abnormal liver functions previously. On stopping mirtazapine the LFTs improved with an ALP of 19 and γGT of 79 IU/L within a month. Possibly related to mirtazapine.
38013/77

This 40 years old female patient was prescribed 30mg of mirtazapine. Two weeks after starting the medication the patient complained of sore throat, swelling of hands and feet. Blood tests were done which were all normal except an increase in gama GT at 282 IU/L, and mirtazapine was stopped. Two weeks after stopping mirtazapine the blood tests revealed a GGT of 111, AST of 23 and ALP of 94. The GP suspected it to be an adverse drug reaction. Considered possibly related to mirtazapine.
53019/299

This 42 years old male was prescribed 30mg of mirtazapine. A week after taking mirtazapine the blood tests revealed an ALT of 122 IU/L, GGT 1254. Patient had history of alcohol intake. The patient did not attend follow up after drug was stopped. Due to limited information, it was unassessable, though it may be pharmacologically plausible for the event to occur with mirtazapine.

55023/290

This 36 years female patient was prescribed 30mg mirtazapine. Ten days after taking mirtazapine the patient started to feel generally unwell and a blood test done later revealed raised GGT of 105 IU/L, ALT 121 IU/L and ALP 116 IU/L, and mirtazapine was stopped. One month after stopping mirtazapine the blood tests showed GGT 27, ALT 24 and ALP 62. Considered possibly related to mirtazapine.
57038/212

This 44 years old female patient was prescribed 30mg of mirtazapine for depression. Five months after starting the medication the patient was reported to have abnormal LFTs. The blood tests showed an increase in ALT at 78 IU/L and GGT of 51 IU/L. Mirtazapine was stopped. It is plausible for the event to be due to mirtazapine.
62068/307

This 39 years old male patient was prescribed 15mg mirtazapine for severe intractable depression. Two weeks after starting mirtazapine the patient's blood tests showed increased AST of 46 IU/L, but continued taking mirtazapine. Repeat blood tests done two months later showed AST 37 IU/L which was normal. The event resolved while still on mirtazapine. The consultant thinks it was due to post viral illness. Unlikely to be related to mirtazapine.
68169/186

This 38 years old female patient was prescribed 15mg mirtazapine for depression. Two months after starting mirtazapine the patients blood tests showed an increase in AST, ALT and GGT. There was no pre-existing disorder or past medical history of any liver disease. Patient still continues to take mirtazapine. Difficult to assess the causality, though it may be pharmacologically plausible for the abnormal LFTs to be due to mirtazapine.
79065/468

This 52 years old male patient was prescribed 45 mg mirtazapine. Four months after starting mirtazapine the patient was found to have elevated LFTs, and mirtazapine was stopped. Four months after stopping mirtazapine the patient continued to have persistently elevated LFTs, which is still being reviewed. Difficult to assess the causality.
80248/757

Jaundice

This 38 years old female patient was prescribed 30mg of mirtazapine. Two months after starting the medication the patient complained of two episodes of jaundice with yellowish discolouration of skin and eyes but normal LFTs, which settled in four days time, and mirtazapine was stopped. On stopping mirtazapine there have been no further episodes of jaundice. The patient had a past history of Hepatitis A. Difficult to assess the causality in this case due to limited information.
18007/671

MALE REPRODUCTIVE AND BREAST DISORDER

Loss of libido

This 27 years old male patient was prescribed 30mg of mirtazapine. A month after being on mirtazapine the patient complained of loss of libido and the drug was stopped. The patient did not have this problem prior to starting mirtazapine, and the event resolved once mirtazapine was stopped. Possibly related to mirtazapine.
25003/166

Ejaculation failure

This 69 years old male patient was prescribed 30mg of mirtazapine for depression. Few days after starting the medication the patient complained of ejaculation failure and mirtazapine was stopped. Patient also has a past history of erectile dysfunction with other antidepressants, and has a medical history of hypertension and CCF. At the time of the event the patient was also taking doxazosin, salbutamol and beclomethasone. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
52145/302

Erectile dysfunction

This 54 years old male patient was prescribed 30mg mirtazapine for depression. Five months after starting mirtazapine the patient complained of erectile dysfunction, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
90038/170

Haematospermia

This 58 years old male patient was prescribed 7.5mg mirtazapine for refractory depression. A month after starting the medication the patient complained of haematospermia, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
58053/482

Galactorrhea

This 34 years old female patient was prescribed 30mg of mirtazapine for depression. One month after starting the medication the patient complained of galactorrhea and the drug was stopped. The event resolved on stopping mirtazapine. The GP wrote that galactorrhea occurred in the left breast and that the proclactin levels were normal. The GP thinks that the event was due to mirtazapine.
04039/58

30 years old female patient was prescribed 30mg of mirtazapine for depression and anxiety. A month after starting the medication the patient developed galactorrhea. At the time of the event the patient was also taking diazepam and prozac. Galactorrhea resolved once mirtazapine was stopped. Possibly related to mirtazapine.
27080/247

IMMUNOLOGICAL

Facial rash and dizziness

This 45 years old female patient was prescribed 30mg of mirtazapine for her depression. A month after starting the drug the patient developed facial rash and swelling with headaches, dizziness and weak legs, and the drug was stopped. At the time of the event the patient was also on paroxetine and premique. The event resolved on stopping mirtazapine and the GP also thinks that the event is possibly due to mirtazapine.
16005/33

Photosensitivity

39 years old female patient prescribed 30mg of mirtazapine. Developed photosensitivity immideately on starting mirtazapine that ceased on stopping the medication. Possibly related to mirtazapine.
25064/303

Angioneurotic oedema

This 79 years old female patient was prescribed mirtazzaapine for her depression. Three days after starting the medication the patient developed oedema of the arms which spread to lips, then to the tongue and throat. The patient was admitted to the ICU for a day, and mirtazapine was stopped. At the time of the event the patient was also taking epilim, didranel, mobic, zoton and aspirin. The event resolved once mirtazapine was stopped. Possibly related to mirtazapine.
27033/350

Facial swelling

40 years old female patient was prescribed 30mg of mirtazapine. On taking the medication the patient developed facial swelling for a short duration and stopped the medication herself. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
38179/13

Allergy

This 69 years old male patient was prescribed mirtazapine for hypomania. Soon after starting mirtazapine the patient developed an allergic reaction and mirtazapine was stopped. The event resolved after stopping mirtazapine. Possibly related to mirtazapine.
34125/73

This 48 years old female patient was prescribed 15mg of mirtazapine. Three weeks after starting mirtazapine the patient developed a rash and vulvodynia and mirtazapine was stopped. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.

58029/277

This 39 years old female patient was prescribed 30 mg mirtazapine for depression. Eleven days after starting mirtazapine the patient developed itchy rash all over the body, which resolved on stopping mirtazapine. Possibly related to mirtazapine.
66113/481

UROLOGIC

This male patient was prescribed 30mg of mirtazapine. Four months after starting mirtazapine the patient developed subacute urinary retension and the drug was stopped. The GP writes that the event is possibly related to mirtazapine. The event resolved on stopping mirtazapine.
19079/147

Acute Renal failure

This female patient was prescribed mirtazapine for depression. Ten days after starting mirtazapine the patient presented with acute renal failure and was hospitalised, and mirtazapine was stopped. The patient had pre-existing peripheral vascular disease, hypothyrodism and hypertension, MI with cardiac arrest. At the time of the event the patient was also taking lisinopril, thyroxine, diltiazem, aspirin, frusemide and omeprazole. The renal function tests done prior to starting mirtazapine showed Potassium 4.34 mmol, urea 7.9, and creatinine 82. RFTs done one day after stopping mirtazapine showed potassium 8.2, urea 41.4 and creatinine 1271. The event continued even after stopping mirtazapine. Unlikely to related to mirtazapine.
22006/148

HAEMOPOEITIC

Agranulocytosis/Bone marrow toxicity

This female patient was prescribed 30mg of mirtazapine for her depression, after being admitted to the hospital with a Klebsila right lower lobe pneumonia. Two months after starting the mirtazapine the patient was detected to have agranulocytosis and disturbed LFTs and mirtazapine was stopped. The GP thought that it may be a possible bone marrow toxicity. The event resolved on stopping mirtazapine.
24070/171

This 51 years old female patient was prescribed 60mg mirtazapine for depression. Five months after starting mirtazapine the patient complained of sore throat and blood tests done at that time shoed low neutrophil counts and agranulocytosis. On stopping mirtazapine the blood picture improved. Possibly related to mirtazapine.
83133/21

Thrombocytopenia

This 83 years old female patient was prescribed 30mg of mirtazapine for depression. Three months after starting mirtazapine the patient was found to have thrombocytopenia and mirtazapine was stopped. At the time of the event the patient

was also on thyroxine and temazapam. On stopping mirtazapine the event resolved. Possibly related to mirtazapine.
57092/320

Myeoldysplasia

This 78 years old female patient was prescribed 30mg mirtazapine. Three months after starting mirtazapine the patient's blood picture showed a haemoglobin of 7, platelets 27 and the bone marrow showed ring sideroblasts, and mirtazapine was stopped. The patient later died of septicaemia in the hospital. At the time of the event the patient was also taking bendrofluazide and nitrazepam. Possibly related to mirtazapine.
75056/224

EYE

Visual disturbance

60 years old female patient was prescribed 30mg of mirtazapine for insomnia and chronic pain depression. A month after starting the drug the patient complained of visual disturbance. On examination of the visual fields the patient was diagnosed to have bi-temporal hemianopia and mirtazapine was stopped. The re was no past history or pre-existing conditions of any eye problems. The event resolved once mirtazapine was stopped. Possibly related to mirtazapine.
43096/194

Blurred vision

This 77 years old female patient was prescribed 15mg of mirtazapine. Three months after starting the medication the patient complained of blurred vision and the drug was stopped. Prior to starting mirtazapine the patient did not have any problems with vision, though she had a past history of anxiety. At the time of the event the patient was also taking thioridazine and temezapam. It is unknown whether the event resolved on stopping the medication. It is plausible that the event may be due to mirtazapine, but due to limited information difficult to assess.
47006/213

This 77 years old female patient was prescribed 30mg of mirtazapine for agitated depression. Few days after starting the medication the patient complained of blurred vision, and mirtazapine was stopped. The patient was also taking HRT and beclomethasone. The event resolved on stopping mirtazapine. Possibly related to mirtazapine.
61033/269

ADVERSE REACTION TO SPECIFIC DRUG

Withdrawal reaction

This female patient was prescribed mirtazapine for depression, and remained on treatment for seven months, after which the medication was stopped as it was

ineffective. Soon after stopping mirtazapine, the patient compalined of sevre anxiety, sleep disturbance, agitation and nausea. The GP considered the events to be withdrawal symptoms due to stopping mirtazapine. Possibly related to mirtazapine.
14015/105

This 30 years old female patient was prescribed 15mg mirtazapine for depression, and remained on treatment for seven months. Thereafter mirtazapine was stopped as the patient thought of conceiving. On stopping mirtazapine the patient complained of severe withdrawal reaction, feeling very unwell and also had nausea. The GP reported the events to CSM. Possibly related to mirtazapine.
46021/359

This 58 years old male patient was prescribed 15mg of mirtazapine, which the patient continued to take for five months. Mirtazapine was stopped subsequently as it was ineffective. A few days after stopping mirtazapine the patient complained of unpleasant symptoms, which the GP attributed to withdrawal symptoms to mirtazapine. Possibly related to mirtazapine.
48009/206

This 51 years old female patient was prescribed 30mg of mirtazapine, which she continued to take for four months. On stopping mirtazapine, the patient complained of severe headaches, unable to sleep, aching legs, which were considered as possible withdrawal symptoms attributed to mirtazapine by the GP. Possibly related to mirtazapine.
52033/31

This 56 years old male patient was prescribed 30mg of mirtazapine for depression. The patient continued to take mirtazapine for four months after which it was stopped as it was ineffective. On stopping mirtazapine the patient complained of panic attacks, extreme anxiety, which the GP attributed to withdrawal symptoms to mirtazapine. Possibly related to mirtazapine.
61137/74