Within-drug comparison for Prescription-Event Monitoring (PEM)

処方-イベントモニタリングのための同一薬剤使用者群内の比較

Kiyoshi KUBOTA

Within-drug comparison for Prescription-Event Monitoring (PEM)

Kiyoshi KUBOTA

Acknowledgement

This study is based on the data collected in Prescription-Event Monitoring (PEM) conducted by the Drug Safety Research Unit (DSRU), Southampton, England. The data obtained between 1982 and 1993 and available in early 1996 in the DSRU are used in this thesis. I have studied PEM since late 1991 till early 1996 in the DSRU and had a chance to publish several papers. In addition, I have had a plan to write a thesis using PEM data after I leave the DSRU. I have asked Dr. R.D. Mann, Director of the DSRU about the possibility that I bring the data with me when I go back to Japan. After getting permission made by the trustees' meeting, Dr. Mann has kindly allowed me to bring them with me and use them in writing a thesis. I greatly appreciate Dr. Mann and all of the trustees for this favour.

I also appreciate Professor WHW Inman, the founder of the DSRU under whom I have worked in the DSRU between 1991 and 1993. Professor Inman allowed me to work on the dictionary used in PEM and analyse the event data. Through those works, I have had a chance to know PEM to an extent which is otherwise impossible to reach. Other many staffs in the DSRU have also kindly helped me do those works and I appreciate them.

Dr. T Kusunoki, Professor of Pharmacoepidemiology in the University of Tokyo between 1993 and 1996, has given me a chance to write a Ph.D. thesis and encouraged me to complete it. After Professor Kusunoki retired in March 1996, Dr. Y Ohashi, Professor of Epidemiology and Biostatistics took over this role. I deeply appreciate these two professors who have provided me with an environment ideal to accomplish the thesis.

Last but not least, my wife Noriko and my daughter Junko have lived with me in England. Without their support, my stay in England for more than four years as well as this work would be impossible.

October 1996, Tokyo Japan

Kiyoshi Kubota, M.D.

Within-drug comparison for Prescription-Event Monitoring (PEM)

Contents

Introduction

Prescription-Event Monitoring (PEM) and Post-marketing Surveillance (PMS)

Prescription-Event Monitoring (PEM) has been in operation since 1981 as a main activity of the Drug Surveillance (later Safety) Research Unit (DSRU), Southampton, England set up in 1980 by Professor WHW Inman. PEM was designed as the second national monitoring scheme to be complementary to Voluntary Reporting System (VRS) to collect reports on suspected drug reaction known as the 'Yellow Card Scheme' in the UK[1].

The role of Post-marketing Surveillance (PMS) is usually discussed from a governmental or administrative view point where PMS is expected to generate early warning signals on the adverse drug reactions (ADRs) so far unrecognised or on any serious or unexpected problems associated with the known ADRs. The role of PMS may be also discussed from another view where the system is supposed to provide the information needed to give clinical guidance that helps practitioners decide which drug is to be prescribed to which patient[2].

A signal or a hypothesis that any previously unknown ADR or any unexpected problem with a known ADR takes place must be generated and tested as early as possible. It depends on the nature of the individual ADRs whether or not the timing when each signal is generated is rated 'early' enough. The timing may be rated too late for some frequent ADRs if they are not detected already in the pre-marketing stage. On the other hand, for some rare or late-onset ADRs, the timing of detection may be said to be early enough when the relevant information is collected and handled reasonably fast even if detected months after marketing the drug. In other words, the actual detection can be rated early or late only relatively in contrast with the possible earliest timing of detection.

It has been well recognised that no single mechanism or system can detect or confirm all of the ADRs reasonably 'early'. In general, VRS is recognised as a system good to generate hypotheses on the new ADRs[3]. However, reports

sent to VRS may be regarded as the evidence to strengthen or even test the hypotheses already generated in the pre-marketing stage. On the other hand, various multipurpose medical databases such as General Practice Research Database (GPRD) formerly called as Value Added Medical Products (VAMP)[4,5] in the UK and those created within the various Health Maintenance Organizations (HMOs) in the US[6,7] have been often used to strengthen or test the hypotheses generated in VRS or elsewhere though it is possible that a multipurpose database generates a hypothesis on the new ADR so far not recognised by anybody or any system.

PEM is not a multipurpose database and designed specifically for the drug safety[8]. As described in Appendix 1, PEM has been established as a direct result of the practolol affair where the Yellow Card Scheme failed to raise an early warning signal on muco-cutaneous syndrome due to a β-blocker, practolol (practolol syndrome)[9-11]. The possible earliest timing of detection of this late-onset ADR may be difficult to determine. However, this ADR was missed for almost 4 years after marketing and nobody would argue against that the timing of detection must be said to be too late[12]. PEM, designed to overcome the problems illuminated by the practolol case, is much more hypothesis-generating-oriented when compared with multipurpose databases mentioned above.

One of the major objectives of PEM is the detection of the ADRs unrecognised by almost all the doctors (and therefore not reported to VRS) provided that the reaction is not rare or more than 0.1 % (see Appendix 1)[12]. In PEM, a questionnaire is mailed to the practitioner 6 to 12 months after the first prescription has been issued to the individual patient. Therefore, it takes at least more than 6 months after marketing the drug that enough number of answers become available. Most ADRs with the incidence of 0.1 % or more are usually detected in the pre-marketing stage or detected by VRS until several months after marketing new drugs. If the pre-marketing clinical trials are conducted reasonably well and VRS functions also well, the fraction of new ADRs detected by PEM for the first time ever must be small. It is therefore of no surprise that the actual major contribution of PEM toward increasing the information on the drug safety has been made by using its hypothesis-strengthening or testing function rather than by its hypothesis-generating

function as detailed in Appendices 2 to 4. Nevertheless, as described in Appendix 1, the practolol case in England and the case of subacute myelo-optico-neuropathy (SMON) due to chloroquinol in Japan[13-15] indicate that ADRs which are not rare can be missed for long period by individual doctors and such ADRs could be serious. It is therefore very important to examine whether or not PEM has the hypothesis-generating function through mechanisms other than the individual doctors' recognition of the causality between the event and drug. The main subject of this thesis is to examine this hypothesis-generating function of PEM.

Study designs of pharmacoepidemiology and methods in PEM

According to Strom, at least 6 designs are available for the pharmacoepidemiology studies[16]. They are, when arranged according to the magnitude of conviction, randomized clinical study, cohort study, case-control study, 'analyses of secular trends', case series and case reports. VRS may be regarded as a scheme to collect case reports sent voluntarily from individual medical doctors or health professionals in a systematic way[17-19]. Case series are collections of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated and described. One of the typical examples of case series is a 'Drug Use Investigation' in Japan defined in 'the standard for Good Post-Marketing Surveillance Practice (GPMSP)' issued by Ministry of Health and Welfare (MHW) in June 1993. According to this standard, drug companies must provide data needed to clear the 'Reexamination of New Drugs'. Both 'analysis of secular trends' and case-control study are to test the relationship between a particular event and an exposure and therefore may be considered to be means to strengthen or test the hypotheses already generated elsewhere. A PEM study is conducted as a cohort study where multiple outcomes are studied longitudinally[20]. Usually a cohort study requires a control group and in PEM, a previous study done being independent of the current study is used as a historical control. The event rate is then compared between the study drug and control. As described in Appendices 2 and 3, this standard procedure of data analysis for the cohort study has been often employed in PEM when strengthening and testing some particular hypotheses generated elsewhere.

The method of hypothesis-generating however includes some unique problems. The ability to generate the hypotheses on the new ADRs is said to be high with VRS[3]. However, this ability is in fact more or less dependent on that of individual doctors. After individual case reports are reported to VRS or medical journals etc., the magnitude of the possibility for causal relationship between the reported suspected ADR and drug may be assessed by global introspection where the magnitude of the possibility is classified into several categories such as 'definite', 'probable', 'possible', 'doubtful' and 'unrelated' according to the subjective opinion of experts[21] Sometimes, other more 'objective' methods such as algorithms[22,23] or probabilistic methods (e.g., one based on the Bayesian probability approach)[21,24,25] may be used. According to Jones, however, there has been no consensus on the method because of several reasons[21]. Probably, when a doctor or health professional decides to report some event as a suspected ADR to VRS, the judgement on causal relationship which has been made by the individual reporter prior to the report may be similar to that in global introspection or some algorithms. However, it may be often difficult to generalise a variety of signal-generating processes employed by the individual reporters to reach a suspicion on the causal relation between the event and drug.

In theory, a cohort study where a group of patients exposed to one single agent and a comparable control group of patients not exposed to the agent are studied longitudinally, any event which occurs more frequently in the exposed cohort than in the control cohort is potentially caused by the exposure. However, in reality, there could be various difficulties in this comparison when viewed as a method to generate a hypothesis on an ADR so far not recognised by anybody as detailed in Appendix 5. In PMS, it is known that several procedures which may be evaluated to be 'informal' in terms of the established design for pharmacoepidemiology studies have been sometimes employed as adjunctive means when generating signals. They include monitoring of secular trends of the incidence of the adverse event which is sometimes employed by the Food and Drug Administration (FDA) in the US[26]. Another 'informal' procedure is the analysis of ADR pattern (i.e., examination of the fraction of the number of voluntary reports on the particular suspected reaction in the total number of reports on any suspected ADRs to the same drug) often used in the Committee

on Safety of Medicines (CSM) in the UK[27,28] and sometimes in the FDA[29].

In the DSRU, several methods have been tried as means to generate hypotheses from the data obtained in PEM studies. As detailed in Appendix 6, after trying various methods, some procedures using within-drug comparison have been found to be promising for this purpose. Particularly, a procedure using the comparison between two rates during the two time periods (i.e., the monthly rate in the first month called T1 and that in the subsequent 5 months called T2) has been thought to be efficient in picking up events which are potentially ADRs. However, as detailed in Appendix 7, the comparison between T1 and T2 itself does not give any evidence to support a hypothesis that a drug has caused that event and the hypothesis needs to be further examined by other methods. The comparison between T1 and T2 is nevertheless still invaluable if it does really pick up efficiently many events which are potentially ADRs.

What is addressed in this thesis as an original contribution to the field

In some publication from the DSRU, it is mentioned that the method of comparison between T1 and T2 can pick up most of major known ADRs[30-40]. However, in fact, this statement has not been well tested. It has been also not well tested whether or not this method can pick up ADRs which have not been widely recognised as ADRs by doctors involved in the PEM study.

In this thesis, those points so far not well addressed by anybody are examined. In addition, one new statistical approach for the comparison between T1 and T2 is advocated in this thesis for the first time ever. What is addressed in this thesis as an original and challenging contribution to the field is in methodology. New findings obtained in PEM studies associated with the safety of individual drugs, if any, have been already published elsewhere.

Method

Procedures of PEM

Collaboration with the Prescription Pricing Authority

PEM is an observational cohort study conducted by the DSRU. The DSRU has emphasised that PMS studies including cohort studies should be non-interventional and strongly campaigned against pseudo-PMS where monitoring of drugs is used for 'seeding' or promoting the sale of drugs[30-39]. In PEM patients are identified for inclusion in the study only after the decision to prescribe a particular medicine has been taken according to the principle that PMS should be observational. In addition, doctors are not informed that a particular patient will be monitored until they receive a questionnaire several months after the first prescription of the drug.

In England, the prescriptions issued by the general practitioners (GPs) employed in the National Health Service (NHS) are all gathered in a central processing system run by the Prescription Pricing Authority (PPA). Though the PPA is also available in Wales, Scotland or North Ireland, only the prescriptions gathered in the PPA in England have been used in PEM. Only the drugs newly marketed have been monitored in PEM except for some 'old' drugs such as erythromycin and 'Indocid' monitored during the developing phase of PEM[8] as detailed in Appendices 2 and 3. After the initial developing phase of PEM, most new chemical entities marketed in the UK have been included in PEM provided they were likely to be prescribed on a scale sufficient to give a study population of at least 10,000 patients within a period of perhaps one to two years. As the PPA does not have any means to identify drugs used in hospitals (e.g., drugs used by injection or infusion only) but collects only the prescriptions issued by GPs, the drugs monitored in PEM have been only those chiefly used by out-patients.

The PPA processes and prices more than 350 million prescription items each year, and, until the end of the 1970s, this task was performed manually. During the 1980s, computers have been gradually installed in the PPA and the process has been automated before 1990[41]. During a couple of years after

PEM was started, the number of drugs that could be monitored by the PPA was limited to four, since this was the maximum number of names that the clerks could memorize and, thus, reliably identify all prescriptions for those drugs[8,41]. With the computerization of the PPA, the DSRU became able to monitor nearly all new chemical entities as soon as they are marketed. However, even after 1990, the DSRU used photocopies of the prescriptions sent from the PPA. It is since 1993 that the information is brought to the DSRU on a magnetic tape but this magnetic tape is prepared in the PPA as a special file. In the electronic file routinely used in the PPA, the patient's name and address are not recorded in order to protect privacy and the PPA's clerks record the name and address only for the use in the DSRU but erase this information immediately the tape is shipped to the DSRU.

Design of green forms

The first green form (questionnaire) was sent in January 1982 in the PEM studies on fenbufen and benoxaprofen conducted at the same time. Thereafter, green form (questionnaire) was improved several times. The first type of green form used in PEM is shown in Figure 1 which was used in the first several pilot studies only. Within the same year (i.e., in 1982), a major revision was made and doctors were asked to describe events while taking the drug and events after stopping the drug in two different columns on the green form (Figure 2). In 1986, a minor revision was made where a new box for the reason for stopping the drug and the name of any other drug substituted was made, and a note "IMPORTANT: PLEASE INDICATE ANY EVENT REPORTED TO CSM OR MANUFACTURER" was added to the bottom of the form (Figure 3). In 1994, another revision was made soon after Dr. R.D. Mann took over the DSRU where doctors are specifically asked to tell the DSRU if they suspect an event to be an ADR to a drug (Figure 4). This change in the green form made in 1994 should not be considered to be major as the definition of an EVENT includes "any suspected drug reaction" and this definition was consistent since the first version of a green form as follows (Figures 1-4):

An EVENT is any new diagnosis, any reason for referral to

PLEASE DETACH THIS SECTION OF THE FORM BEFORE POSTING

PRESCRIPTION – EVENT MONITORING

DRUG SURVEILLANCE RESEARCH UNIT
34 Bassett Crescent East
Southampton
SO2 3FL
Telephone: (0703) 767841

received a prescription for 'Baratol'
dated

Definition of an EVENT

An EVENT is any new diagnosis, any reason for referral to a consultant or admission to hospital (eg operation, accident or pregnancy), any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was considered of sufficient importance to enter in the patient's notes.

Example

A broken leg is an EVENT. If more fractures were associated with this drug they could have been due to hypotension, CNS effects or metabolic bone changes.

Reference Number:

IMPORTANT — PLEASE RETURN NO-EVENT AND BLANK FORMS

INDICATION FOR 'BARATOL'	DATE OF BIRTH	SEX

'Baratol' continuing ☐
'Baratol' discontinued ☐ Date and reason if discontinued

Please record events occurring on or after the first prescription using 'key-words' (see letter) copied from the patient's records.

DATE	EVENT AND OUTCOME	
	If this is not the first prescription please indicate when drug was started	DATE

Figure 1 Original green form used in a few pilot studies in 1982

PLEASE DETACH THIS SECTION OF THE FORM BEFORE POSTING

PRESCRIPTION – EVENT MONITORING

DRUG SURVEILLANCE RESEARCH UNIT
Dr. W. H. W. Inman, FRCP, FFCM
North Croft House,
Botley, Southampton SO3 2BX
Telephone: (0703) 600263

Was first prescribed Zantac on .....

Definition of an EVENT

An EVENT is any new diagnosis, any reason for referral to a consultant or admission to hospital (eg operation, accident or pregnancy), any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was considered of sufficient importance to enter in the patient's notes.

N.B. The reason for stopping treatment and changes of treatment are important events. It is also very important to establish the pattern of events which occur after the patient has stopped treatment.

Example

A broken leg is an EVENT. If more fractures were associated with this drug they could have been due to hypotension, CNS effects or metabolic bone changes.

Reference Number:

IMPORTANT — PLEASE RETURN **NO-EVENT** AND BLANK FORMS

INDICATION FOR ZANTAC		SEX	DATE OF BIRTH OR AGE
WAS THE DRUG EFFECTIVE? YES ☐ NO ☐	PATIENT STILL ON TREATMENT? YES ☐ NO ☐	DATE DRUG STARTED? (day month year) ☐☐ ☐☐ ☐☐	STOPPED? ☐☐ ☐☐ ☐☐

DATE	EVENTS WHILE TAKING THE DRUG	DATE	EVENTS AFTER STOPPING THE DRUG

Figure 2 Second version of green form revised in 1982

PLEASE RETAIN THIS SECTION OF THE FORM FOR YOUR RECORDS

DRUG SAFETY RESEARCH UNIT
PRESCRIPTION EVENT MONITORING

CONFIDENTIAL

FOLD FOR STORAGE IN NOTES

Professor W. H. W. Inman, FRCP, FFPM,
Dorsledon Hall,
Southampton SO3 8BA.
Telephone: (0703) 40612213

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, or any other complaint which was considered of sufficient importance to enter in the patient's notes.

Example: A broken leg is an EVENT. If bone fractures were associated with this drug they could have been due to hypotension, CNS effects or metabolic bone changes.

Please note that the following are essential:

1. Date of birth, indication for this drug and dates of starting and ceasing treatment with this drug.
2. Details of all events even if this drug has been discontinued.
3. Reason for stopping this drug and name of any other drug substituted.
4. Date and cause of death (if appropriate).

Ref:

The DSRU is managed by the Drug Safety Research Trust, an independent charity (No. 327206) working in co-operation with the University of Southampton.
Trustees: Professor Sir Douglas Black MD FRCP, Professor D J. Finney CBE ScD FRS FRSE, Sir Gordon Higginson FRCP FMedSci E, Professor W.H.W. Inman FRCP FFPM
Dr. S.P. Lock CBE MD FRCP

PLEASE RETURN NO-EVENT FORMS

Ref:

SEX	DATE OF BIRTH / /	WAS THIS DRUG EFFECTIVE? Yes ☐ No ☐
INDICATION FOR PRESCRIBING		PLEASE SPECIFY THE REASON FOR STOPPING THIS DRUG AND THE NAME OF ANY OTHER DRUG SUBSTITUTED
DATE PATIENT STARTED THIS DRUG / /		DATE PATIENT STOPPED THIS DRUG / /

DATE	EVENTS WHILE TAKING THIS DRUG	DATE	EVENTS AFTER STOPPING THIS DRUG

IMPORTANT: PLEASE INDICATE ANY EVENT REPORTED TO CSM OR MANUFACTURER

Figure 3 Third version of green form revised in 1986

DRUG SAFETY RESEARCH UNIT
PRESCRIPTION EVENT MONITORING

CONFIDENTIAL

Dr Ronald D. Mann, MD, FRCP, FRCGP, FFPM, FCP
Bursledon Hall,
Southampton SO31 1AA
Telephone: (01703) 406122/3

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, 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 tell us if you suspect an EVENT to be an adverse reaction to a drug.

Please note that the following are essential:

1. Date of birth, indication for this drug and dates of starting and ceasing treatment with this drug.
2. Details of all events even if this drug has been discontinued.
3. Reason for stopping this drug and name of any other drug substituted.
4. Date and cause of death (if appropriate).

Ref:

PLEASE RETURN NO-EVENT FORMS

Ref:

SEX DATE OF BIRTH / /	WAS THIS DRUG EFFECTIVE? Yes ☐ No ☐
INDICATION FOR PRESCRIBING	PLEASE SPECIFY THE REASON FOR STOPPING THIS DRUG AND THE NAME OF ANY OTHER DRUG SUBSTITUTED
DATE PATIENT STARTED THIS DRUG / /	DATE PATIENT STOPPED THIS DRUG / /

DATE	EVENTS WHILE TAKING THIS DRUG	DATE	EVENTS AFTER STOPPING THIS DRUG

IMPORTANT: PLEASE INDICATE ANY EVENT REPORTED TO CSM OR MANUFACTURER

Figure 4 Current version of green form revised in 1994

a consultant or admission to hospital, any unexpected deterioration (or improvement) in a concurrent illness, any suspected drug reaction, or any other complaint which was considered of sufficient importance to enter in the patient's notes.

In other words, the definition of an 'EVENT' does not preclude doctors from describing that an ADR has occurred but rather recommends (though not explicitly in the above definition) them to do so if they suspect an ADR.

In the first three versions used until 1994, an example for an 'EVENT' was shown on each green form. At least during the developing phase of PEM, this example has probably helped doctors realise the distinction between an 'EVENT' and an ADR. The example has been erased in the last version (Figure 4). An example for an 'EVENT' shown in the first three versions of the green form reads as:

Example: A broken leg is an EVENT. If more fractures were associated with this drug they could have been due to hypotension, CNS effects or metabolic bone changes.

In all of the four versions, a green form consists of upper and lower parts. On the upper half the name and address of the patient are printed while on the lower half, only the patient's reference number given by the computer in the DSRU is printed. Doctors are asked to retain the upper part for their records and send back the lower part only. When detached, the lower half does not show the patient's name but only the patient's reference number so that the information becomes anonymous when sent back from the doctor. In practice, many doctors send back both of the upper and lower halves of the green form but so far the DSRU has never experienced any problem due to the break of the anonymity.

Prescriptions, green forms and cohorts

Table 1 shows 41 PEM drugs monitored between 1982 and 1994. The list

	A	B	C	D	E	F	G	H
1	No	Code	Generic Name	Drug Name	Group and Note	Total	Male	Female
2								
3								
4	1	FVX	Fluvoxamine	FAVERIN	Antidepressant	10983	3094	7694
5	2	FXT	Fluoxetine	PROZAC	Antidepressant	12692	3690	8863
6	3	PXT	Paroxetine	SEROXAT	Antidepressant	13741	4373	9279
7	4	STL	Sertraline	LUSTRAL	Antidepressant	12734	3910	8729
8	5	BPR	Buspirone	BUSPAR	Anxiolytic	11113	3500	7419
9	6	FNZ	Flunitrazepam	ROHYPNOL	Benzodiazepine	7492	2368	4951
10	7	ZPC	Zopiclone	ZIMOVANE	Hypnotics	11543	3989	7461
11	8	STP	Sumatriptan	IMIGRAN	Antimigraine	14928	2881	11948
12	9	DTZ	Diltiazem	TILDIEM	Ca-antagonist	10112	6000	3972
13	10	NDP	Nicardipine	CARDENE	Ca-antagonist	10910	5276	5484
14	11	ADP	Amlodipine	ISTIN	Ca-antagonist	12969	6085	6751
15	12	IDP	Isradipine	PRESCAL	Ca-antagonist	3679	1515	2128
16	13	DXZ	Doxazosin	CARDURA	Alpha-blocker	8482	3799	4622
17	14	BXL	Betaxolol	KERLONE	Beta-blocker	1531	644	852
18	15	XTR	Xamoterol	CORWIN	Inotropic	5373	2846	2467
19	16	ELP	Enalapril	INNOVACE	ACE-inhibitor	15361	7081	7951
20	17	LPT	Lisinopril	ZESTRIL+CARACE	ACE-inhibitor	12438	5469	6712
21	18	RMP	Ramipril	TRITACE	ACE-inhibitor	1371	618	739
22	19	EDL	Etodolac	LODINE	NSAIDs	9091	3002	5925
23	20	NBM	Nabumetone	RELIFEX	NSAIDs	10444	3437	6838
24	21	TXC	Tenoxicam	MOBIFLEX	NSAIDs	10882	3702	6940
25	22	NZD	Nizatidine	AXID	H2-blocker	7782	4098	3555
26	23	FMD	Famotidine	PEPCID	H2-blocker	9500	4899	4396
27	24	OPZ	Omeprazole	LOSEC	Proton pump inhibitor	16204	7968	8073
28	25	CPR	Cisapride	PREPULSID	Antispasmodics	13234	5485	7623
29	26	MPS	Misoprostol	CYTOTEC	Prostaglandin analog	13775	4939	8592
30	27	AVT	Acrivastine	SEMPREX	Antihistamine	7863	2833	4899
31	28	CTZ	Cetirizine	ZIRTEK	Antihistamine	9554	3945	5457
32	29	LTD	Loratadine	CLARITYN	Antihistamine	9308	3912	5179
33	30	NCM	Nedocromil	TILADE	Asthma prophylaxis	12294	6340	5768
34	31	SLM	Salmeterol	SEREVENT	Beta2 agonist	15407	7844	7445
35	32	TDL	Terodiline	TEROLIN	Anticholinergic	12444	3378	8912
36	33	ACV	Acyclovir	ZOVIRAX	Antiviral	11051	3953	6866
37	34	CXM	Cefixime	SUPRAX	Cephalosporin	11250	4799	6223
38	35	CFX	Ciprofloxacin	CIPROXIN	Quinolone	11477	4493	6612
39	36	EXC	Enoxacin	COMPRECIN	Quinolone	2790	475	2276
40	37	NFX	Norfloxacin	UTINOR	Quinolone	11110	1852	9098
41	38	OFX	Ofloxacin	TARIVID	Quinolone	11033	4263	6629
42	39	AZM	Azithromycin	ZITHROMAX	Macrolide	11275	4532	6575
43	40	FCZ	Fluconazole	DIFLUCAN	Antifungal	15015	877	14017
44	41	ICZ	Itraconazole	SPORANOX	Antifungal	13645	1482	12102
45					TOTAL	433880	159646	268022
46					MEAN	10582	3894	6537

Table 1 41 PEM drugs

	A	B	C	D	E	F	G	H	I
1	No	Generic Name	1st Rx	Last Rx	Collection	Rx on	GF sent	Last GF	Total
2					months	database	interval		time
3							approx.		months
4	1	Fluvoxamine	Feb-87	Feb-88	13	35000	12	Mar-89	26
5	2	Fluoxetine	Mar-89	Mar-90	13	53000	6	Mar-91	25
6	3	Paroxetine	Mar-91	Mar-92	13	49000	6	Feb-93	24
7	4	Sertraline	Jan-91	Sep-92	21	51000	6	Aug-93	32
8	5	Buspirone	Mar-88	Feb-89	12	41000	12	Apr-90	26
9	6	Flunitrazepam	Oct-82	Nov-83	14	0	12	Nov-84	26
10	7	Zopiclone	Mar-91	Jul-91	5	46000	6	Sep-92	19
11	8	Sumatriptan	Nov-91	Jul-92	9	59000	6	May-93	19
12	9	Diltiazem	Sep-84	Oct-86	26	64000	12	Oct-87	38
13	10	Nicardipine	Nov-86	May-88	19	83000	12	Jul-89	33
14	11	Amlodipine	Mar-90	Mar-91	13	81000	6	Jun-92	28
15	12	Isradipine	Mar-89	Feb-91	24	39000	6	Mar-92	37
16	13	Doxazosin	Mar-89	Jan-91	23	73000	6	Mar-92	37
17	14	Betaxolol	Nov-84	Jun-87	32	17000	12	Jun-88	44
18	15	Xamoterol	Aug-88	Nov-90	28	50000	6	Apr-91	33
19	16	Enalapril	Apr-85	Jan-86	10	76000	12	Jan-87	22
20	17	Lisinopril	Jun-88	Mar-89	10	60000	6	Sep-89	16
21	18	Ramipril	Apr-90	Feb-91	11	10000	12	May-92	26
22	19	Etodolac	Nov-85	Aug-86	10	30000	12	Nov-87	25
23	20	Nabumetone	Mar-87	Sep-88	7	31000	12	Nov-88	21
24	21	Tenoxicam	Nov-88	Aug-89	10	44000	6	Mar-90	17
25	22	Nizatidine	Sep-87	Sep-88	13	36000	12	Oct-89	26
26	23	Famotidine	Nov-87	Mar-88	5	37000	6	Sep-88	12
27	24	Omeprazole	Jun-89	Jun-90	13	59000	12	Oct-91	28
28	25	Cisapride	Oct-90	Apr-91	7	39000	6	May-92	20
29	26	Misoprostol	Oct-88	Jul-89	10	39000	6	May-90	20
30	27	Acrivastine	May-89	Sep-90	17	22000	6	Jan-91	21
31	28	Cetirizine	May-89	Jul-89	3	21000	6	Aug-90	16
32	29	Loratadine	May-89	Aug-89	4	24000	6	Aug-90	16
33	30	Nedocromil	Nov-86	Sep-88	23	61000	12	Oct-89	36
34	31	Salmeterol	Dec-90	May-91	6	43000	12	Dec-92	25
35	32	Terodiline	Nov-86	Sep-87	11	43000	12	Dec-88	26
36	33	Acyclovir	Nov-85	Dec-86	14	21000	6	May-87	19
37	34	Cefixime	Sep-90	May-91	9	36000	6	Jul-92	23
38	35	Ciprofloxacin	Nov-88	Jan-89	3	23000	6	Jul-89	9
39	36	Enoxacin	Apr-89	Jan-91	22	9000	12	Oct-91	31
40	37	Norfloxacin	Oct-90	Oct-91	13	31000	12	Feb-93	29
41	38	Ofloxacin	May-90	Dec-91	20	29000	12	Feb-93	34
42	39	Azithromycin	Mar-92	Jun-93	15	30000	6	Feb-94	24
43	40	Fluconazole	Sep-88	Jan-89	5	26000	6	Jun-89	10
44	41	Itraconazole	Apr-89	Apr-90	13	29000	6	Jan-91	22
45				MEAN	13	41250			25

Table 2 Study period and collection of prescriptions

	A	B	C	D	E	F	G	H	I	J
1	No	Generic Name	GF	GF		Voids		Valid		Rx per
2			sent	returned						GF sent
3			N	N	% sent	N	% returned	N	% sent	N
4	1	Fluvoxamine	20504	12279	60	1296	11	10983	54	1.7
5	2	Fluoxetine	24738	14444	58	1752	12	12692	51	2.1
6	3	Paroxetine	26194	15907	61	2166	14	13741	52	1.9
7	4	Sertraline	24632	14817	60	2083	14	12734	52	2.1
8	5	Buspirone	24185	13087	54	1974	15	11113	46	1.7
9	6	Flunitrazepam	NK	9325	NK	1833	20	7492	NK	NK
10	7	Zopiclone	24026	13177	55	1634	12	11543	48	1.9
11	8	Sumatriptan	23625	16724	71	1796	11	14928	63	2.5
12	9	Diltiazem	16665	11219	67	1107	10	10112	61	3.8
13	10	Nicardipine	19243	12048	63	1138	9	10910	57	4.3
14	11	Amlodipine	24140	14177	59	1208	9	12969	54	3.4
15	12	Isradipine	8073	4139	51	460	11	3679	46	4.8
16	13	Doxazosin	15498	9315	60	833	9	8482	55	4.7
17	14	Betaxolol	3187	1743	55	212	12	1531	48	5.3
18	15	Xamoterol	8561	5882	69	509	9	5373	63	5.8
19	16	Enalapril	24719	16875	68	1514	9	15361	62	3.1
20	17	Lisinopril	20631	13091	63	653	5	12438	60	2.9
21	18	Ramipril	3287	1556	47	185	12	1371	42	3.0
22	19	Etodolac	20725	10334	50	1243	12	9091	44	1.4
23	20	Nabumetone	21007	11540	55	1096	9	10444	50	1.5
24	21	Tenoxicam	26357	11731	45	849	7	10882	41	1.7
25	22	Nizatidine	19454	8691	45	909	10	7782	40	1.9
26	23	Famotidine	20399	10560	52	1060	10	9500	47	1.8
27	24	Omeprazole	28496	17772	62	1568	9	16204	57	2.1
28	25	Cisapride	23133	14442	62	1208	8	13234	57	1.7
29	26	Misoprostol	22034	14836	67	1061	7	13775	63	1.8
30	27	Acrivastine	15772	8911	56	1048	12	7863	50	1.4
31	28	Cetirizine	18933	10877	57	1323	12	9554	50	1.1
32	29	Loratadine	21084	10684	51	1376	13	9308	44	1.1
33	30	Nedocromil	20644	14057	68	1763	13	12294	60	3.0
34	31	Salmeterol	28019	17347	62	1940	11	15407	55	1.5
35	32	Terodiline	20069	13971	70	1527	11	12444	62	2.1
36	33	Acyclovir	17027	12611	74	1560	12	11051	65	1.2
37	34	Cefixime	32526	12880	40	1630	13	11250	35	1.1
38	35	Ciprofloxacin	20664	12394	60	917	7	11477	56	1.1
39	36	Enoxacin	7369	3281	45	491	15	2790	38	1.2
40	37	Norfloxacin	26036	13029	50	1919	15	11110	43	1.2
41	38	Ofloxacin	27787	12698	46	1665	13	11033	40	1.0
42	39	Azithromycin	23900	12535	52	1260	10	11275	47	1.3
43	40	Fluconazole	23846	16347	69	1332	8	15015	63	1.1
44	41	Itraconazole	24216	15370	63	1725	11	13645	56	1.2
45		TOTAL	821405	486703	59	52823	11	433880	53	2.0
46		MEAN	20535	11871	58	1288	11	10582	52	2.2

Table 3 Green forms sent, returned and valid

includes most drugs monitored by the PEM studies which have been 'finished' where the DSRU has judged that no more green forms will be returned and has decided to finalise the study. In reality, a small number of green forms may be returned months or even years later and the judgement that the collection of the forms has been 'finished' is rather arbitrary. New PEM studies not 'finished' before December 1995 are excluded from Table 1. Some old drugs such as piroxicam and ranitidine are also not included in the list mainly due to a practical reason. The first computer system introduced to the DSRU was that using ICL computers which have been replaced by IBM AS400 during the period between 1991 and 1992[12,42]. Most data recorded in the ICL system were transferred to AS400 but the data handled manually before the introduction of the ICL system were unable to be transferred to the new computer system. In Table 1, as well as in Tables 2 and 3 explained below, some information for flunitrazepam is lacking due to this problem of the computer system and other old drugs are not listed at all. As shown in column F of Table 1, on average, 10582 valid green forms (questionnaires) were returned from doctors per study but the number varied from 1371 (ramipril) to 16204 (omeprazole). It may be noted that sum of male patients (column G) and female patients (column H) may be smaller than total patients (column F) as sex is unknown for some patients. Small cohort size indicates that the sale of the drug was limited and the study had to be stopped in an immature stage.

Table 2 shows the time when the first prescription (Rx) of each PEM drug was issued (column C) as well as the time when the last prescription used in the PEM study was issued (column D). The prescriptions were collected on average for 13 months but the collection period ranged from 3 to 32 months (Column E). Being associated with these figures, it may be of importance to emphasise that with some drugs the data were collected during a very short period of the first year after the drug was marketed and, therefore, during the first several years the drug was probably used by far more patients than those identified in the PEM study. For such a drug, the fraction of patients monitored by PEM could be less than 10 % or even less than 5 % of all drug users. On average more than 40000 prescriptions are collected for one PEM study (column F). The green form is sent to the doctor approximately 6 months after the first prescription for each patient for some drugs but it is approximately 12 months for the other drugs (column G). The last green form

was sent to the doctor on average 25 months after the first prescription was issued by any doctor soon after the drug was marketed (column H). Most green forms are sent back from doctors within a few weeks after they are mailed to doctors if the doctor decides to respond. Therefore, almost all green forms are returned on average within 2 years after the drug is newly marketed (column I).

As shown in Table 3, the response from GPs is so far fair. On average, 58 % of the green forms have been returned but the response varies from 40 to 74 % (column E). On average 11 % of green forms were void (column G) for the following 5 reasons: (1) patient no longer registered with doctor, (2) blank forms, (3) no record of treatment with the drug, (4) the drug prescribed but not taken and (5) doctor moved or retired[30-39]. As a result, on average 52 % of green forms sent were judged to be valid (column I) PEM has been repeatedly criticised to be flawed because many green forms are not returned. Recently, a study on the issues associated with no response was published indicating that the largest factor associated with no response was the number of green forms received by one doctor[43]. Heavy prescribers who prescribe a lot of newly marketed drugs during the first several months and receive many green forms do not respond well while doctors who receive just one or two green forms respond satisfactorily[43]. This finding indicates that the major factor associated with non-responder is on the prescriber's side rather than on the patient's side; for example whether the patient had a serious adverse event. However, no studies have fully elucidated the effects of non-responders on the PEM studies.

Table 3 also shows the average number of prescriptions used to identify one patient (column J). On average 2 prescriptions are used to identify one patient but the number varies from 1.0 to 5.8. One patient who has used an antibiotic may be identified by only one prescription, while 3 or more prescriptions are needed to identify a patient who has used a cardiovascular drug.

Red Alert Scheme

As stated in Appendix 6, most ADRs occur early, typically within the first month, after the prescription of the drug. However, it takes several months until the first green form returns to the DSRU as the questionnaire is not sent and therefore not collected at least during the first 6 months. In some PEM studies, the green form is not collected at least during the first 12 months. In order to make PEM have an early alerting function, the joint CSM/DSRU 'Red Alert' scheme was tried in the PEM studies of fluvoxamine, nabumetone, famotidine and nizatidine around 1987 to 1988[44]. Special yellow cards were sent to doctors as soon after the first prescription had been written as possible and doctors were asked to send the yellow card when they observed a serious event suspected as an ADR. These special yellow cards were forwarded to the CSM by the DSRU. When 6 or 12 months elapsed after the first prescription of the drug to each particular patient, a green form was sent again to doctors asking them to report 'events' as in a usual PEM study.

Unfortunately, the 'Red Alert' scheme was not quite successful as doctors misinterpreted the scheme and sent back many yellow cards to report minor ADR or returned 'Red Alert' forms indicating that there had been no events, adverse or otherwise. In addition, the 'Red Alert' scheme was very expensive, doubling the distribution and clerical costs of the DSRU and increased demands on doctors. After 1987, the 'Red Alert' scheme was abandoned[44].

Coding the information on green forms

All of the information given in the green form (Figure 4) are coded in the DSRU when the green form is processed. In addition to events reported, sex, date of birth, subjective opinion on the effectiveness of drug, indication for prescribing the drug, reason for stopping the drug, name of the drug substituted, date patient started the drug and date patient stopped the drug are recorded. The last date of observation is defined as the 'form completion date' which is, allowing form postal delays, assumed to be 4 days prior to its receipt by the DSRU[41]. Some information is also transferred from the original prescriptions used to identify the patient. The name and sex of the patient are read from the prescriptions and they are pre-printed on the questionnaire but the sex is not printed to ask the doctor to describe it if it is unknown. Dose of the drug

monitored by PEM and co-prescribed drugs are not coded for each patient. However, when the collection of green forms is 'finished', 1000 prescriptions for 1000 individual patients are randomly selected and dose and co-prescribed drugs are recorded to know the representative pattern of dose and that of co-prescribed drugs.

Coding events

The above information is coded for all of the patients though some information such as the stop date or the reason for stopping the drug are not applicable if the patient still uses the drug on the 'form completion date'. On the other hand, many green forms do not report any event and the information is available only from a fraction of valid green forms. Where events are reported, the green form often reports two or more events, and, on average, one event is reported by one green form[45]. When the event is coded, the date of event is also coded though it is sometimes unknown. If the doctor has judged that the even is an ADR and reported this finding on the green form, a special 'flag' is given when coding the event in the DSRU. Similarly, when the doctor reported the event as an ADR to CSM or manufacturer, another special 'flag' is given. When the event is coded, a 'flag' is given to distinguish whether the event has occurred while taking the drug or after stopping drug. Where date of stopping the drug is unavailable, this information is considered to be 'unknown'.

Events are coded according to the principle as in Table 4 given below[45]

Table 4. Principles of coding events

1. Pre-existing diseases are not coded unless an exacerbation occurs.
2. Where the same event occurred more than once, only the first episode is coded.
3. If an event is a diagnosis or syndrome, related individual signs, symptoms or laboratory test results are not coded.
4. Where the events are related, only the more serious is coded, signs taking precedence over symptoms (e.g., 'nausea and vomiting' would be coded as 'vomiting')
5. More than one event in the same class (e.g., eczema and urticaria) may be coded for one patient.

The principles are made so as to avoid double-coding. For example, one event is coded only once in one patient (principle 2). This point is in fact closely associated with the analysis and when the 'on' vs 'off' comparison was the main method to analyse the data in the DSRU, two episodes of the same event were coded in one patient if applicable: i.e., the first episode of the event during the treatment and the first episode after stopping the drug. When a diagnosis is described signs, symptoms or laboratory test results are not coded (principle 3) but they may be coded if a diagnosis is not available. This means that the same event may be coded by any of signs, symptoms, laboratory test results or diagnosis, depending on the description on the green form given by the doctor. Where this is considered to be often the case, two or more terms may be lumped together before analysing the data as explained in 'Event Dictionary' below.

Indication-related events

In the above table, it is shown that pre-existing diseases are not coded unless an exacerbation occurs. In theory, 'pre-existing diseases' include indication of the drug as well as complications of the indication. However, in practice, it is sometimes difficult to judge whether or not the green form reports an 'exacerbation' when indication is repeated as an event on the green form. In

addition, as doctors are not asked to record complications of the indication or concomitant diseases on the green form in a systematic manner, it may be difficult to judge whether the event given on the green form is pre-existing disease. As a result, all of the events reported on the green form tend to be coded irrespective of whether or not they are pre-existing and irrespective of whether or not an exacerbation has really occurred. Therefore, when the rate of events is calculated, it may be apparently very big when the event is associated with indication. For instance, the crude rate of myocardial infarction with some calcium blockers may be higher than that with other drugs which may create a chance that the data are interpreted as evidences indicating that the drug has caused or exacerbated myocardial infarction even if it is virtually impossible to reach such a conclusion. After late 1992 a new principle has been added to the old principles to avoid this danger[30-39]. For instance, in the PEM report on nicardipin[30], the following is given in the section of '*Coding*':

To avoid confusion the indication is not treated as an 'event' even if it has been mentioned in the section of the green form used to list the events. The term '*hypertension*', for example, may have been used if the condition has worsened during treatment or recurred after stopping treatment. Similarly if a term describing an uncommon indication is mentioned on an individual form and then repeated as an event or as a reason for stopping testament, it is not coded as an event.

In other words, the new principle requires the indication to be not coded at all irrespective of whether or not an exacerbation of the indication has occurred. However, this principle has not been applied before late 1992 and if the event is judged to be associated with the indication, the data are shown with an index 'indication-related event' in the appendix table in the PEM reports where the data coded before 1992 are analysed[30-39]. After 1994 when Dr. R.D. Mann took directorship, the principle of coding has been resumed and events associated with the indication are now coded in a manner which is essentially the same as that employed before 1992 in the DSRU.

The issue addressed by the debate on principles of coding is in fact closely related to the problem of confounding by the indication. Indeed the increase in the rate of myocardial infarction associated with the use of calcium antagonists is one of the hot issues currently debated all over the world[46,47]. One of the original papers[47] where this problem has arisen is the report on an observational study and some criticisms addressed to this study has raised the possibility that this study has been confounded by the indication[48,49]. A principle that such event is not coded may be one of the answers to the question how to cope with confoundings by the indication. The problem will be discussed further in the discussion section in this thesis.

Fatal and non-fatal terms

For PEM studies conducted until 1986 or 1987, the distinction between fatal and non-fatal cases was not made and coded by using the same term irrespective of whether or not the event was fatal but another event 'fatal outcome' was coded if the patient was reported to have died. This was the case for the PEM studies on the following 6 drugs given in Tables 1-3; diltiazem, betaxolol, enalapril, etodolac, terodiline and acyclovir. After these 6 PEM studies, many 'fatal' terms were created and used when the patient was reported to have died while old terms were used only for 'non-fatal' events. For instance, in the above 6 old PEM studies, convulsion was coded as 'CONVULSION' irrespective of whether or not it was fatal. Thereafter, new term 'CONVULSION[F]' was created and if the patient died from convulsion, it was coded using this new fatal term but only non-fatal convulsion was coded using 'CONVULSION'. A term 'CONVULSION' included both fatal and non-fatal cases with the old 6 drugs but only non-fatal cases with new drugs. On the other hand, the number of events for 'CONVULSION[F]' is exclusively '0' with the old 6 drugs even if some patients might have died from convulsion as this term was not available during the old PEM studies. The term is therefore equivalent and comparable between 'old' and 'new' drugs only when two terms 'CONVULSION' and 'CONVULSION[F]' are lumped together. Since 1992, the event dictionary was revised where the fatal and non-fatal terms are lumped together and shown as a new term as detailed below.

Event Dictionary[45]

The original event dictionary used when the DSRU started PEM was a simple dictionary with a small number of terms based on the dictionary used in the 'Yellow Card Scheme' in the late 1970s. Thereafter, new terms have been added to the dictionary slowly when a new event was reported in a green form and when the term is considered important enough to be included as a new term in the dictionary.

In 1992, a new low- and high-level term structure was introduced to the event dictionary. The introduction of this new scheme was judged to be mandatory around 1992 when the results of more than 10 PEM studies were to be analysed and published in a consistent manner as a series of 'PEM reports'[30-39]. For example in the cardiovascular events, 6 terms CARDIAC FAILURE, CARDIAC FAILURE[F], CCF, CCF[F], LVF, LVF[F] are used to designate fatal and nonfatal cases of cardiac failure, congestive cardiac failure and left ventricular failure, respectively. If shown alphabetically, those terms are placed in different lines here and there even if these terms are closely associated with one another. Therefore, these terms must be shown as a group in the same place and it was thought to be useful to show the total number of those six events.

The introduction of the high- and low-level term scheme was done as a secondary modification of the original files in the DSRU so that the introduction of the new scheme did not affect the original procedures of coding events. The data were transferred from AS400 to personal computer (PC) and, all the terms were rewritten using full spelling. For example, CCF and LVF are rewritten as 'Congestive cardiac failure' and 'Left ventricular failure', respectively. The next step was to lump together a pair of fatal and non-fatal terms as one term and this term was considered to be a new 'low-level' terms. Thereafter 108 'high-level' terms were introduced to lump together two or more 'low-level' terms where appropriate.

The principle to relate the high-level term with the low-level terms in the event dictionary is quite different from that in the classification of diseases. For example, signs and diagnosis may be grouped as one term when judged to be

appropriate. For example, under one high-level term 'dyspepsia', 7 low-level terms, Barrett's syndrome, duodenitis, dyspepsia, gastritis, heartburn, oesophageal reflux and oesophagitis are grouped[45]. Even among diagnoses, the 'level' of high-level term is sometimes not really 'high'. For example, a new high-level term 'cardiac failure' includes the following low level terms which are not mutually exclusive; cardiac failure, congestive cardiac failure and left ventricular failure. In introducing a high-level term, many other factors are considered. For instance, many low-level terms are grouped when the chance that they might be ADRs is remote; the term 'respiratory tract infection' includes 27 low-level terms such as 'infection chest', 'upper respiratory tract infection', 'catarrh' and 'coryza'.

In March 1992 when the paper on terminology in PEM was written which was published in 1994[45], the terms were classified under 24 body classes and after grouping a pair of fatal and non-fatal terms, 1197 low-level terms were available where 549 were grouped under one of 108 high-level terms while the remaining 648 low-level terms were considered to be free-standing high-level terms. The final 756 high-level terms consisted of the 108 new high-level terms and 648 free-standing high-level terms. After 1992, about 100 new terms were added to the original event dictionary until early 1996 and a new version of low- and high-level terms scheme will be made in the near future.

In Appendix 8, the event dictionary in March 1992 is shown. If a term made from a pair of fatal and non-fatal terms is further classified under high-level term, a symbol '*' is given. If the low-level term is, in terms of spelling, the same as the high-level term or the same as the term with '*', a symbol '@' is given to a low-level term. When a high-level term includes two or more fatal terms with [F], fatal terms under the high-level term are lumped together as a term with #[F]. Normally, two different list of events defined as 'File 1' and 'File 2' are produced by PC when the data are analysed as follows.

File 1 shows the high-level terms only. All low-level terms including 'new' low-level terms with '*' under one of high-level terms are ignored. Similarly new fatal terms with '#[F]' are not shown. If no event is coded in a PEM study on a particular drug, the term is not shown in File 1 for that drug. It is File 1 that is shown as appendix table in most PEM reports.

File 2 shows both of the high-level and low-level terms. Low-level terms follow a high-level term to which those low-level terms belong. It is of note that this list does not show all of the terms given in Appendix 8. If fatal and non-fatal terms are lumped together, this pair is considered to be a low-level term in File 2 and either of the original fatal and non-fatal terms is not shown. New fatal terms with '#[F]' are also not shown. As in File 1, if no event is coded, the term is not shown in File 2 for a particular drug.

In this thesis, only 1076 low-level terms under 19 body systems are analysed. The detail is given in section 'B' which follows.

Follow-up study[8,12,41]

When the events reported on green forms are considered to be important, secondary questionnaires may be sent to the doctor to ask more detailed information on that event. For instance, the follow-up study has been done for all of the patients reported to have died till several years ago although this strategy has been suspended at least until recently mainly due to lack of resources. In Britain, when the patient dies the patient's note recorded by a GP is transferred to the Family Health Service Authority (FHSA). To examine those who died, the DSRU asks the GP to permit to see the life time patient's record and if the GP does so, the DSRU can have a chance to have the GP's note from the FHSA. When the patient was admitted to a hospital, at least one letter describing the diagnosis and major procedures made in the hospital is sent from the hospital to the GP. Therefore, some information on what happened during when the patient was admitted might be known from the GP's patient's note. If needed, more information is requested from the doctor in the hospital. Finally, the Office of Population Censuses and Surveys (OPCS) may be asked to supply copies of the death entry (based on the death certificate) for patients who have died.

Another occasion where the patient may be followed-up is when it turns out that the patient has been pregnant. This survey may not produce sufficient amount of data for some drugs normally used with old patients such as

cardiovascular drugs. However, some drugs may be preferentially used by women of the productive age. One of examples is an antifungal agent, fluconazole, mainly used for vaginal candidiasis[50].

Some other important conditions may be examined by further questionnaires. Though the DSRU does not pay for filling green forms, some small money is paid when the doctor provided the information to respond to the second questionnaire.

In this thesis, however, the follow-up study will be no longer mentioned. In the following sections, the information directly derived from green forms is examined.

Analysis of the data

Calculation of event rates

Why and when the comparison of two rates of an event during two different periods of observation has become employed as a method of screening events in the analysis of PEM studies to pick up possible ADRs are detailed in Appendices (particularly in Appendices 6 and 7).

The first monthly rate T1 and the monthly rate in the second to sixth months T2 expressed by 'per 1000 patients per month' are defined as

$$T1 = \frac{N1}{D1} \times 1000 \quad \text{and} \quad T2 = \frac{N2 + N3 + N4 + N5 + N6}{D2 + D3 + D4 + D5 + D6} \times 1000$$

where numerators, $N1$, $N2$, --- etc. are the number of events that are recorded during the first, second, --- etc. moths. Denominators, $D1$, $D2$, --- etc. are the average number of patients who are still under observation by the doctor during the first, second, --- etc. months. In the DSRU, one month is defined as 30 days and 6 months are equal to 180 days. Dr. Inman's rule of thumb is "to give a strong signal if T1/T2 is 3.0 or more but a weak signal if T1/T2 is 2.5 or more but less than 3.0". Before discussing this algorithm, some relevant issues are mentioned first.

Does the practice employed in the DSRU to code only the first episode skew the distribution of some events ?

First problem is whether the practice employed in the DSRU when coding events has undesirable effects on the estimation of the rates. As described in the earlier section, in the DSRU only the first episode of the event is coded where the same event occurs more than once. In some PEM reports, this manner of coding events is commented as[30-39]

Where the same event occurred more than once, only the first

episode is coded. This has the effect of skewing the distribution of some events so that a relative excess may be apparent during the early months of treatment.

As shown in Appendix 9, a weak 'skewing' effect produced by the current way of calculating rates (rather than the current way of coding events) can be avoided by a simple modification. Currently, when counting denominators, *D*1, *D*2, — etc., all of the patients under observation are included. This procedure has a small 'skewing' effect. The 'correct' rate of an event is calculated if the patient is excluded from the denominator once the patient has experienced that event even if the patient is still under observation by the doctor. For example, if a patient was observed for the first 180 days or the first 6 months but had the event on day 15, the contribution of this patient to *D*1 is 0.5 rather than 1 because the patient must be excluded from the denominator after the patient experienced the event. The contribution of this patient to *D*2, *D*3, —, *D*6 is 0 even if the patient is under observation by the doctor. It is of note that the contribution of this patient to the denominator could differ between events. In the calculation of another event which the above patient has not experienced, the contribution of this patient to *D*1, *D*2, *D*3, —, *D*6 is all 1. However, for most events, the rate is small and usually it is a very small fraction of the whole population that experiences one particular event. Therefore, the difference between the 'correct' denominator and 'incorrect' denominator currently used in the DSRU can be usually ignored. 'Incorrect' denominators currently used in the DSRU where all of the patients under observation are included irrespective of whether a patient has experienced any particular event are used in the analysis throughout this thesis.

Should the denominator be the number of patients treated by the drug or that under observation ?

As described in Appendix 6, when Dr. Inman abandoned the 'on' vs 'off' comparison method and switched to the use of the comparison between the first monthly rate and the monthly rate between the 2nd and 6th months within one drug, the rates were calculated in the patients on treatment. This comparison of 'T1' and 'T2' is used in a PEM report on fluvoxamine[40]. However, the method

of the calculation of rates was altered soon and the rates were measured in the patients who were under observation irrespective of whether or not the patient was treated by the drug. As described earlier, when translated into wording of statistics, in the PEM report on fluvoxamine, a patient is considered 'censored' either when treatment with the drug is stopped or when the patient is lost to follow-up, but after the fluvoxamine paper, the patient is considered 'censored' only when the patient is lost to follow-up. One of the purposes of this thesis is to evaluate the way of signalling possible ADRs by using 'T1' and 'T2' currently employed in the DSRU and therefore, throughout the thesis, the rate is calculated assuming that the patient is considered censored only when lost to follow-up.

The analysis using weekly rates for antibiotics

Recently, a new analysis has been introduced to the analysis of the PEM studies of antibiotics in the DSRU[51]. The method uses two rates, W1 and W2 defined as

$$W1 = \frac{N1}{D1} \times 1000 \quad \text{and} \quad W2 = \frac{N2 + N3 + N4 + N5 + N6}{D2 + D3 + D4 + D5 + D6} \times 1000$$

where $N1$, $N2$, --- etc. are the number of events that are recorded during the first, second, --- etc. weeks. $D1$, $D2$, --- etc. are the average number of patients who are still under observation by the doctor during the first, second, --- etc. weeks. The reason why weekly rates instead of monthly rates are used for antibiotics has been not explicitly given, but, the reason is probably associated with the short duration of the use of antibiotics monitored by PEM. It might be judged odd to calculate monthly rates when almost all patients used the drug for only 7 days or less. In this thesis, however, the comparison of weekly rates is not used because of the following reasons:

(1) The method to compare T1 and T2 is based on the observation that 'most ADRs occur early typically during the first month'. This observation is independent of the duration of drug use and may be judged to be more general. On the other hand, the new way of the comparison of weekly rates has been

introduced because antibiotics so far monitored in PEM have been used for less than 7 days by patients. If, in a future PEM study, it turns out that some fraction (e.g., 20 % or more) of patients use an antibiotic for 2 weeks or longer, for example, it will be difficult to validate the analysis using weekly rates. The use of different duration is confusing. If the critical point is whether or not the event has occurred during treatment, the 'on' vs 'off' comparison is probably the best method as described in the 'introduction' section. The 'on' vs 'off' comparison has been abandoned due to several reasons but those reasons do not prevail in the PEM studies of antibiotics used for a short period only as described in the 'introduction' section. With antibiotics, relatively reliable information may be obtainable for both 'on' and 'off' periods for almost all patients.

(2) The events picked up by the analysis of weekly rates are also picked up by the analysis of monthly rates. Some events such as vaginal candidiasis probably due to the change in vaginal normal flora caused by an antibiotic (ciprofloxacin) are observed mainly in week 2 and picked up by the analysis of monthly rates only.

Signalling and comparison of two rates

It is not clear whether the future DSRU continues using the rule of thumb of '3.0'. However, this rule will be examined in this thesis because it has been used in more than 10 papers from the DSRU. The rule is

1) to give a strong signal if $T1/T2 \geqq 3.0$ provided $T1 \geqq 1.0$/1000 patients/month

and

2) to give a weak signal if $T1/T2 \geqq 2.5$ and < 3.0 provided $T1 \geqq 1.0$/1000 patients/month.

In this thesis this rule of thumb is designated as the 'rate ratio method' as this term has been often used in the publication from the DSRU.

It has been realised that this method is not perfect because the value of T1/T2 for some known ADRs is less than 2.5. It has been also realised that some events where the above relationship is satisfied are not ADRs. Nevertheless, the method has been used because it can pick up a handful events for further evaluation from as many as 1000 or more events coded for each drug.

Statistical test on the difference between two rates

As long as a statistical significance test is considered to be just one of means to pick up possible ADRs and it is realised that the significant difference, similar to the observation T1/T2 $\geqq$ 3, does not indicate any causal relationship between the event and drug and the absence of the significant difference does not preclude the possibility that the event is in fact an ADR, there would be no reason to preclude the use of the statistical significance test on the difference between T1 and T2.

As shown in Appendix 9, when T1 and T2 are calculated in a 'correct' manner to avoid skewing effect, both T1 and T2 can be also considered to be independent of each other. Assuming the Poisson model, it is possible to test the statistical significance of the difference between T1 and T2 as described below. In general to test the statistical significance of the difference between two rates, one of the following three tests may be used as standard tests; likelihood ratio test, Wald test and Score test[52-58].

In this section of the thesis, denominators are expressed as patient-days but not patient-months. The patient-days in the first period (month 1) and the second period (month 2 to 6) are defined as $Y1$ and $Y2$, respectively. The relationship between $Y1$ and $D1$ and that between $Y2$ and ($D2 + -- + D6$) are given as

$$Y1 = 30\ D1$$

and

$$Y2 = 30(D2 + -- + D6).$$

The rates expressed as the number of events per patient per day are defined as $\lambda 1$ and $\lambda 2$, respectively. The relationship between $\lambda 1$ and T1 and that between $\lambda 2$ and T2 are given, respectively as

$$\lambda 1 = T1/30000$$

and

$\lambda 2 = T2/30000$

The log rate parameter and confidence interval

The three tests below are all based on the quadratic approximation to the Gaussian (normal) distribution. To employ such an approximation, the parameter is usually transformed and the distribution of $\log(\lambda)$ rather than λ itself is considered. Note that $\log \lambda$ is $\log_e \lambda$ but not $\log_{10} \lambda$. The confidence interval (CI) is also given using this function so that, for example, the CI of the rate for N events in D patient-days is calculated from

$\log(N/D) \pm a\,S$ where S is given as $S = \sqrt{1/N}$

in the above formula, a is 1.64, 1.96, 2.58 and 3.29 for the 90, 95, 99 and 99.9 % CI, respectively.

Therefore, the CI is given as (N/DXexp(-aS), N/DXexp(aS))

Similarly, when θ is defined as the rate ratio of two rates or

$\theta = \lambda 1/\lambda 2 = T1/T2$, S is given as $S = \sqrt{1/N1 + 1/N2}$

the most likely value of θ is $N1/Y1/N2/Y2$ and the CI of θ is given as $(N1/Y1/N2/Y2 \,X\exp(-a\sqrt{1/N1+1/N2}), N1/Y1/N2/Y2 \,X\exp(a\sqrt{1/N1+1/N2}))$ This formula has been already presented in a paper recently published from the DSRU[59].

When the difference of the log rates,(log $\lambda 1$-log $\lambda 2$) is considered, this is directly transformed to the rate ratio $\lambda 1/\lambda 2 = T1/T2$ as $\log \lambda 1 - \log \lambda 2 = \log(\lambda 1/\lambda 2)$. If the difference of the rates in the usual sense, $N1/Y1 - N2/Y2$, is considered, S is given as

$S = \sqrt{N1/(Y1)^2 + N2/(Y2)^2}$ and the CI is given as $N1/Y1 - N2/Y2 \pm aS$

This formula has been also shown in the recent publication from the DSRU[58]. In a paper from the DSRU, this CI is directly linked with the statistical test[60] which may be criticised to be not quite appropriate as the parameter λ may be transformed into log λ when the statistical test based on the Gaussian (normal) approximation is used.

Likelihood ratio test[52-58]

When LLR is defined as the log likelihood ratio, -2LLR is, under the null hypothesis $\lambda 1 = \lambda 2$ or T1 = T2, given as

$$-2LLR = 2[N1 \log \lambda 1 + N2 \log \lambda 2 - (N1 + N2)\log((N1 + N2)/(Y1 + Y2))]$$

With the Gaussian (normal) distribution, -2LLR has chi-square distribution with one degree of freedom and the relationship between the -2LLR and the p-value holds approximately for non-Gaussian log likelihoods. Thus, the above -2LLR has approximate chi-square distribution with one degree of freedom.

Wald test[52-58]

The Wald test uses the quadratic approximation to the Gaussian (normal) distribution in the region of the most likely value. By this approximation, the following value has approximate chi-square distribution with one degree of freedom under the null hypothesis $\lambda 1 = \lambda 2$ or T1 = T2.

$$\left[\log(N1/Y1/N2/Y2)\right]^2 \frac{N1N2}{N1 + N2}$$

Score test[52-58]

The Score test uses the quadratic approximation to the Gaussian (normal)

distribution in the region of the null value. By this approximation, the following value has approximate chi-square distribution with one degree of freedom under the null hypothesis $\lambda 1 = \lambda 2$ or $T1 = T2$

$$\frac{(N1Y2 - N2Y1)^2}{(N1 + N2)Y1Y2}$$

Terminology

To examine events coded in the PEM studies, only low-level terms under 19 body systems are examined in this thesis. In Appendix 8, the 1076 low-level terms in 19 body systems are listed as well as terms under other 6 categories. The 1076 low-level terms under 19 systems may be divided into two categories. 590 low-level terms designated by a symbol "F" are free-standing low-level terms and used as high-level terms as its own right in the event dictionary. 486 low-level terms designated by a symbol "G" are usually grouped under one of the high-level terms and are not shown unless this is particularly needed in the PEM report. In this thesis, however, the low-level terms which are usually grouped under the high-level term are examined individually. In the sections which follow, the results of the PEM studies are compared with the description in the British National Formula (BNF)[61] where the terminology sometimes differs from that in the event dictionary and the use of low-level terms of the event dictionary is judged to be more appropriate. When needed, some of low-level terms are grouped and compared with terms in the BNF as described below. This combination is not necessarily according to the way of grouping low-level terms to make a high-level term in the event dictionary.

Only the terms in the 19 body systems are judged to be usually relevant to the description in the BNF. Those 19 body systems include, skin, musculoskeletal, psychiatric, nervous, eye, ear, cardiovascular, respiratory, gastrointestinal and hepatobiliary, metabolic and endocrine, urologic, male reproductive and gynaecomastia, female reproductive, breast disorder, obstetric, haemopoietic, neoplasm, miscellaneous infection and immunological.

Terms under other 6 special categories are excluded with some exception.

Those 6 special categories are 'Death cause uncertain', 'Adverse reaction to specific drug', 'Accident and injury', 'Surgery', 'Referrals', and 'Social'. Most terms in those categories such as 'road traffic accident', 'nephrectomy', 'hospital referrals: cardiology', and 'bereavement' cannot be by themselves ADRs though it is possible that some of those terms are associated with ADRs.

Some comments may be needed on three terms under a special class 'Adverse reaction to specific drug'. The three terms are 'dependence', 'withdrawal symptoms' and 'adverse reaction to other drug'. The first two terms are those to the drug monitored by PEM. These two terms are examined only when the BNF describes 'dependence' or 'withdrawal symptoms' as a possible ADR. Otherwise these terms are ignored. The last term 'adverse reaction to other drug' is somewhat confusing. This term is currently seldom used and the event which has been judged to be an ADR to any drug by the doctor is now coded using a specific term with a flag indicating that the event is a suspected ADR. In any case, this term is excluded and is not considered for examination.

A special class 'Death cause uncertain' has only one term 'death cause uncertain'. If the patient is reported to have died with no more information on the green form, the event is coded by this term and the patient is usually examined in the follow-up study. There is virtually no chance that this term itself is recognised as an ADR.

The event dictionary has other 39 low-level terms under a class 'Events ignored' which are usually not shown. Those 39 terms include many unspecified terms such as 'pain', 'nodule', 'blood unspecified', 'liver unspecified' and 'haemorrhage unspecified'. Some of the terms under this category are examined only when they are given as an ADR in the BNF.

Classification of ADRs

If the event dictionary terms are judged to be the events corresponding to one of the ADRs in the BNF, they are classified into 4 categories.

1) ***Category A:*** **'Previously known ADRs'** are defined as events

corresponding to the ADRs described in the BNF available around when each PEM study was finished.

2) ***Category B:*** **'Previously unknown ADRs'** are defined as events corresponding to the ADRs described in the recent BNF (Number 31, March 1996) but not in the BNF available around when each PEM study was finished as defined above.

3) ***Category C:*** **'Questionable ADRs'** are defined as events corresponding to the ADRs which are described in the recent BNF as ADRs where the causality is uncertain.

4) ***Category D:*** **'Hard-to-detect ADRs'** are defined as events corresponding to the ADRs which are described in the recent BNF but judged to be hard to detect without laboratory test. The laboratory test is not often ordered in general practice and therefore ADRs under this category are judged to be hard to detect in PEM.

In some occasions, some of ADRs described in the old BNF are not reproduced in the recent BNF. When this is the case, such ADRs shown in the old BNF only are in general ignored. Sometimes, some ADR in the old BNF (e.g., 'rash') is replaced by a more general term in the recent BNF (e.g., 'hypersensitivity'). In such a case, the event dictionary term corresponding to the ADR in the old BNF (e.g., 'rash') is considered to be under category A (Previously known ADRs) but the other terms corresponding to the ADR in the recent BNF (e.g., 'urticaria', 'anaphylaxis' etc.) are considered to be under category B (Previously unknown ADRs).

Events signalled in PEM and ADRs described in the BNF and other literature

In this thesis, the following three points are examined.

1) Are events which have been signalled by the rate ratio method or statistical test really ADRs ?

To judge whether or not events picked up by the rate ratio method or statistical test are really ADRs, it is examined whether those events (event dictionary terms) are listed as an ADR in the BNF[61] or other literature. If events are

signalled but judged to be not an ADR (false positive), the underlying mechanisms (e.g., confounding by the indication) are examined.

2) Are known ADRs in the BNF signalled in PEM ?

Conversely, ADRs described in the recent BNF (Number 31, March 1996) are examined using the PEM data. When known ADRs are not signalled (false negative), the underlying mechanisms (e.g., rare ADR) are examined.

The terminology used to describe ADRs in the BNF is often different from that in the event dictionary of the DSRU. There could be following three combinations of terms where one to one correspondence is unavailable between the event dictionary and the BNF. It is of note that when some of terms in the BNF or event dictionary belong to one of the classes given below, total number of events signalled in the PEM study which are also known ADRs and the total number of known ADRs in the BNF which are found to be signalled in the PEM study could differ from each other.

Combination 1: When two or more ADRs in the BNF correspond to one event dictionary term (low-level term) signalled, it is judged that (i) one event dictionary term (low-level term) signalled is a known ADR and (ii) all of the ADRs in the BNF are signalled in the PEM study.

Combination 2: If one ADR in the BNF corresponds to two or more event dictionary terms (low-level terms) (i) one, two or more event dictionary terms signalled are judged to be known ADRs (one of categories A to D defined as above) signalled while those not signalled are judged to be known ADRs not signalled and (ii) the ADR is considered to be signalled when at least one of the corresponding event dictionary terms is signalled.

Combination 3: In a few cases, two or more ADRs in the BNF are judged to correspond to two or more event dictionary terms (low-level terms). This combination is complicated and avoided unless other option can be hardly accepted. For example, in the BNF, two terms 'nervousness' and 'anxiety' are described as ADRs to fluoxetine. Though a term 'agitation' is not given as an ADR to fluoxetine in the BNF, this term is included in a high level term 'anxiety' in some ADR terminology such as WHO Adverse Reaction Terminology (WHOART)[62]. The event dictionary in the DSRU has a term 'agitation' distinct

from 'anxiety' while if the green form reports 'nervousness', this is coded as 'anxiety'. Therefore, two terms in the BNF 'nervousness' and 'anxiety' are grouped which are regarded to correspond to two event dictionary terms 'anxiety' + 'agitation' as a whole. In such a case, (i) one, two or more event dictionary terms signalled are judged to be known ADRs signalled while those not signalled are judged to be known ADRs not signalled and (ii) all of the ADRs are considered to be signalled when at least one of the corresponding event dictionary terms is signalled.

3) Does the rate ratio method or statistical test pick up unknown ADRs ?

It is examined whether or not the previously unknown ADRs are signalled by PEM. Even if ADRs were not shown in the previous BNF available during the specific PEM study, the information on some 'previously unknown' ADRs could be obtained in the documents other than the BNF during the PEM study and doctors might have a chance to see it before filling the green form. However, the BNF is one of the most widely used source of information on the drugs by the practitioners in Britain. Therefore it is not a bad assumption that the description on the BNF available during the PEM study is a representative information available to most doctors. The issue number and time of publication of the BNF available around when posting the last green form in each PEM study are listed on Table 5.

PEM studies excluded

1) Small studies

Of the 41 PEM studies shown in Table 1, some studies with a small cohort size are excluded. The study is excluded from the analysis if the initial cohort size is less than 6000. Those studies (initial cohort size) include:

Isradipine (3679)
Betaxolol (1531)
Xamoterol (5373)
Ramipril (1371)

Enoxacin (2790)

2) New drugs
In the BNF the information is slowly improved as time elapses. The number of ADRs shown in the BNF usually increases with time. It may therefore take some years until a full range of ADRs are eventually listed in the BNF. In this thesis, if the time when the first prescription is issued (which is very close to the time when the drug was marketed) is 1990 or later, that PEM study is excluded from the analysis. Those studies (time when the first prescription issued) include

Paroxetine (March 1991)
Sertraline (January 1991)
Zopiclone (March 1991)
Sumatriptan (November 1991)
Amlodipine (March 1990)
Ramipril (April 1990)
Cisapride (October 1990)
Salmeterol (December 1990)
Cefixime (September 1990)
Norfloxacin (October 1990)
Ofloxacin (May 1990)
Azithromycin (March 1992)

3) Drugs withdrawn
Similarly, when the drug has been already excluded from the market, a full range of information on ADRs may have been unavailable and the study has been excluded from the analysis. Such drug is

Terodiline (excluded from the market in July 1991)

The following list summarises the PEM studies (initial cohort size, time when the first prescription issued) included in and excluded from the analysis in this thesis (see also Table 5).

PEM studies included:

1 Fluvoxamine (10983, February 1987)
2 Fluoxetine (12692, March 1989)
3 Buspirone (11113, March 1988)
4 Flunitrazepam (7492, October 1982)
5 Diltiazem (10112, September 1984)
6 Nicardipine (10910, November 1986)
7 Doxazosin (8482, March 1989)
8 Enalapril (15361, April 1985)
9 Lisinopril (12438, June 1988)
10 Etodolac (9091, November 1985)
11 Nabumetone (10444, March 1987)
12 Tenoxicam (10882, November 1988)
13 Nizatidine (7782, September 1987)
14 Famotidine (9500, November 1987)
15 Omeprazole (16204, June 1989)
16 Misoprostol (13775, October 1988)
17 Acrivastine (7863, May 1989)
18 Cetirizine (9554, May 1989)
19 Loratadine (9308, May 1989)
20 Nedocromil (12294, November 1986)
21 Acyclovir (11051, November 1985)
22 Ciprofloxacin (11477, November 1988)
23 Fluconazole (15015, September 1988)
24 Itraconazole (13645, April 1989)

PEM studies excluded:

1 Paroxetine (13741, March 1991)
2 Sertraline (12734, January 1991)
3 Zopiclone (11543, March 1991)
4 Sumatriptan (14928, November 1991)
5 Amlodipine (12969, March 1990)
6 Isradipine (3679, March 1989)
7 Betaxolol (1531, November 1984)
8 Xamoterol (5373, August 1988)
9 Ramipril (1371, April 1990)
10 Cisapride (13234, October 1990)

11 Salmeterol (15407, December 1990)
12 Terodiline (12444, November 1986 withdrawn in July 1991)
13 Cefixime (11250, September 1990)
14 Enoxacin (2790, April 1989)
15 Norfloxacin (11110, October 1990)
16 Ofloxacin (11033, May 1990)
17 Azithromycin (11275, March 1992)

	A	B	C	D	E	F	G	H
1	No	Generic Name	Cohort	1st Rx$	Last GF$$	BNF	Time when	
2			size			No	issued	
3								
4	1	Fluvoxamine	10983	Feb-87	Mar-89	17	Mar-89	
5	2	Fluoxetine	12692	Mar-89	Mar-91	21	Mar-91	
6	3	Paroxetine	13741	Mar-91	Feb-93	-	-	*
7	4	Sertraline	12734	Jan-91	Aug-93	-	-	*
8	5	Buspirone	11113	Mar-88	Apr-90	19	Mar-90	
9	6	Flunitrazepam	7492	Oct-82	Nov-84	9	Mar-85	
10	7	Zopiclone	11543	Mar-91	Sep-92	-	-	*
11	8	Sumatriptan	14928	Nov-91	May-93	-	-	*
12	9	Diltiazem	10112	Sep-84	Oct-87	14	Sep-87	
13	10	Nicardipine	10910	Nov-86	Jul-89	18	Sep-89	
14	11	Amlodipine	12969	Mar-90	Jun-92	-	-	*
15	12	Isradipine	3679	Mar-89	Mar-92	-	-	*
16	13	Doxazosin	8482	Mar-89	Mar-92	23	Mar-92	
17	14	Betaxolol	1531	Nov-84	Jun-88	-	-	*
18	15	Xamoterol	5373	Aug-88	Apr-91	-	-	*
19	16	Enalapril	15361	Apr-85	Jan-87	12	Sep-86	
20	17	Lisinopril	12438	Jun-88	Sep-89	18	Sep-89	
21	18	Ramipril	1371	Apr-90	May-92	-	-	*
22	19	Etodolac	9091	Nov-85	Nov-87	14	Sep-87	
23	20	Nabumetone	10444	Mar-87	Nov-88	16	Sep-88	
24	21	Tenoxicam	10882	Nov-88	Mar-90	19	Mar-90	
25	22	Nizatidine	7782	Sep-87	Oct-89	18	Sep-89	
26	23	Famotidine	9500	Nov-87	Sep-88	16	Sep-88	
27	24	Omeprazole	16204	Jun-89	Oct-91	22	Sep-91	
28	25	Cisapride	13234	Oct-90	May-92	-	-	*
29	26	Misoprostol	13775	Oct-88	May-90	19	Mar-90	
30	27	Acrivastine	7863	May-89	Jan-91	20	Sep-90	
31	28	Cetirizine	9554	May-89	Aug-90	19	Mar-90	
32	29	Loratadine	9308	May-89	Aug-90	19	Mar-90	
33	30	Nedocromil	12294	Nov-86	Oct-89	18	Sep-89	
34	31	Salmeterol	15407	Dec-90	Dec-92	-	-	*
35	32	Terodiline	12444	Nov-86	Dec-88	-	-	*
36	33	Acyclovir	11051	Nov-85	May-87	13	Mar-87	
37	34	Cefixime	11250	Sep-90	Jul-92	-	-	*
38	35	Ciprofloxacin	11477	Nov-88	Jul-89	17	Mar-89	
39	36	Enoxacin	2790	Apr-89	Oct-91	-	-	*
40	37	Norfloxacin	11110	Oct-90	Feb-93	-	-	*
41	38	Ofloxacin	11033	May-90	Feb-93	-	-	*
42	39	Azithromycin	11275	Mar-92	Feb-94	-	-	*
43	40	Fluconazole	15015	Sep-88	Jun-89	17	Mar-89	
44	41	Itraconazole	13645	Apr-89	Jan-91	20	Sep-90	
45	* Excluded from analysis							
46	$ When the first prescription was issued by any doctor							
47	$$ When the last green form was posted							

Table 5 PEM studies excluded from analysis and the BNF available around when PEM study was finished

Results

Rate ratio method and statistical test

p values corresponding to the rate ratio 3.0 or 2.5

When almost all patients are under observation by doctors during the first six months and when the event rate is relatively low so that the fraction of the patients who have experienced the event is supposed to be around 1 % or less, the following assumption is roughly valid

$(D2+ D3+ D4+ D5+ D6)=5 D1$

or

$Y2 = 5Y1$

In the 'rate ratio method' or a rule of thumb using the rate ratio of '3.0' or '2.5', some idea is in fact associated with statistics. When the absolute number of event is small, the rate ratio '3.0' or more can be attained just by chance. For example, one event in month 1 and no event in the succeeding months will make the rate ratio infinite. To solve this problem, the 'rate ratio method' has been used only when T1 is 1.0 per 1000 patients per month or more. This means N1 should be 10 or more when D1 = 10000. However, the method has been used even if D1 is smaller than 10000[63] Though there has been no clear guideline about the minimum number of D1 or minimum cohort size where the rate ratio method can be used, D1 may be as small as 7000 so that N1 may be as small as 7.

Table 6 shows the maximum number of N2 which gives the value of T1/T2 equal to or more than 2.5 for each N1 value between 7 and 50. The value of N2 is the maximum because when N2 is bigger than the value shown in the table, T1/T2 is less than 2.5 and all the values of N2 which are smaller than the value shown in the table make T1/T2 bigger than 2.5. In the context of the statistical test, each combination of N1 and maximum N2 in Table 6 has a chi-square value (shown in

columns C, E and G) as well as a p-value (columns D, F and H). In Table 6, the ratio of Y2 to Y1, i.e., the ratio of (D2+D3+D4+D5+D6) to D1 is fixed to be 5 and once the ratio is fixed, the critical criterion (rate ratio or chi-square value) depends on the combination of N1 and N2 but does not depend on the absolute size of Y1 or Y2 in all of the 'rate ratio method' and three statistical tests. The chi-square values for each combination of N1 and 'Maximum N2' are similar between the likelihood ratio test (LRT), Wald test (Wald) and Score test (Score) though small difference can be seen between the tests. Irrespective of which test is used, when the value of T1/T2 is fixed to be 2.5, chi-square values increase and p values decrease with the increase in N1. As mentioned above, when N1 is small, T1/T2 could be bigger than 2.5 or 3.0 just by chance. The decrease in p value with the increase in N1 shown in Table 6 indicates that this chance is still not small when T1 is around 1.0 per 1000 patients per month but remote when T1 is much bigger than 1.0 per 1000 patients per month provided that the cohort size is around 10000.

Table 7 shows the similar information to that in Table 6 but the values corresponding to the rate ratio 'T1/T2' of 3.0 are shown. The maximum N2 to make T1/T2 3.0 or more is smaller than that to make it 2.5 or more and the chi-square values (p-values) are bigger (smaller) than those in Table 6. Similar to Table 6, it can be seen that with the increase in the maximum N2, the chi-square values (columns C, E and G) increase and the p values (columns D, F and H) decrease.

In Tables 6 and 7, the values of likelihood ratio test, Wald test and Score test are shown. However, only the likelihood ratio test is used as the statistical test in the following sections of the thesis as the likelihood ratio test is the only one of the three tests which remains the same when the parameter is transformed, and is to be preferred in general[52,57].

Table 8 shows the maximum N2 for each N1 where p value is 0.001 or less with the likelihood ratio test. The value of N2 shown in Table 8 is the maximum because when N2 is bigger than that shown, p is bigger than 0.001. All of the values of N2 which are smaller than that in Table 8 make the p value smaller than 0.001. Table 8 also shows the rate ratio when the value of N2 is the maximum value which makes the p value 0.001 or less. In other words, the rate

ratio (T1/T2) shown in Table 8 is the minimum value which makes the p value 0.001 or less with the likelihood ratio test. Even if N1 is 4, the p value is less than 0.001 if N2 is 0 or the rate ratio is infinite. Where N1 is 16 or smaller, the p value is 0.001 or less only when the rate ratio is more than 3.0. Where N1 is between 17 and 21, the minimum rate ratio corresponding to the p value of 0.001 or less is between 2.5 and 3.0. Where N1 is 22 or more, the p value may be less than 0.001 even if the rate ratio is less than 2.5.

	A	B	C	D	E	F	G	H
1	N1	Maximum N2	LRT		Wald		Score	
2			chi-square		chi-square		chi-square	
3	7	14	3.5	p=0.06	3.9	p<0.05	4.2	p<0.05
4	8	16	3.9	p<0.05	4.5	p<0.05	4.8	p<0.05
5	9	18	4.4	p<0.05	5.0	p<0.05	5.4	p<0.05
6	10	20	4.9	p<0.05	5.6	p<0.05	6.0	p<0.05
7	11	22	5.4	p<0.05	6.2	p<0.05	6.6	p<0.05
8	12	24	5.9	p<0.05	6.7	p<0.01	7.2	p<0.01
9	13	26	6.4	p<0.05	7.3	p<0.01	7.8	p<0.01
10	14	28	6.9	p<0.01	7.8	p<0.01	8.4	p<0.01
11	15	30	7.4	p<0.01	8.4	p<0.01	9.0	p<0.01
12	16	32	7.9	p<0.01	9.0	p<0.01	9.6	p<0.01
13	17	34	8.4	p<0.01	9.5	p<0.01	10.2	p<0.01
14	18	36	8.9	p<0.01	10.1	p<0.01	10.8	p<0.01
15	19	38	9.4	p<0.01	10.6	p<0.01	11.4	p<0.001
16	20	40	9.9	p<0.01	11.2	p<0.001	12.0	p<0.001
17	21	42	10.4	p<0.01	11.8	p<0.001	12.6	p<0.001
18	22	44	10.9	p<0.001	12.3	p<0.001	13.2	p<0.001
19	23	46	11.4	p<0.001	12.9	p<0.001	13.8	p<0.001
20	24	48	11.8	p<0.001	13.4	p<0.001	14.4	p<0.001
21	25	50	12.3	p<0.001	14.0	p<0.001	15.0	p<0.001
22	26	52	12.8	p<0.001	14.6	p<0.001	15.6	p<0.001
23	27	54	13.3	p<0.001	15.1	p<0.001	16.2	p<0.001
24	28	56	13.8	p<0.001	15.7	p<0.001	16.8	p<0.001
25	29	58	14.3	p<0.001	16.2	p<0.001	17.4	p<0.001
26	30	60	14.8	p<0.001	16.8	p<0.001	18.0	p<0.001
27	31	62	15.3	p<0.001	17.4	p<0.001	18.6	p<0.001
28	32	64	15.8	p<0.001	17.9	p<0.001	19.2	p<0.001
29	33	66	16.3	p<0.001	18.5	p<0.001	19.8	p<0.001
30	34	68	16.8	p<0.001	19.0	p<0.001	20.4	p<0.001
31	35	70	17.3	p<0.001	19.6	p<0.001	21.0	p<0.001
32	36	72	17.8	p<0.001	20.2	p<0.001	21.6	p<0.001
33	37	74	18.3	p<0.001	20.7	p<0.001	22.2	p<0.001
34	38	76	18.8	p<0.001	21.3	p<0.001	22.8	p<0.001
35	39	78	19.3	p<0.001	21.8	p<0.001	23.4	p<0.001
36	40	80	19.7	p<0.001	22.4	p<0.001	24.0	p<0.001
37	41	82	20.2	p<0.001	22.9	p<0.001	24.6	p<0.001
38	42	84	20.7	p<0.001	23.5	p<0.001	25.2	p<0.001
39	43	86	21.2	p<0.001	24.1	p<0.001	25.8	p<0.001
40	44	88	21.7	p<0.001	24.6	p<0.001	26.4	p<0.001
41	45	90	22.2	p<0.001	25.2	p<0.001	27.0	p<0.001
42	46	92	22.7	p<0.001	25.7	p<0.001	27.6	p<0.001
43	47	94	23.2	p<0.001	26.3	p<0.001	28.2	p<0.001
44	48	96	23.7	p<0.001	26.9	p<0.001	28.8	p<0.001
45	49	98	24.2	p<0.001	27.4	p<0.001	29.4	p<0.001
46	50	100	24.7	p<0.001	28.0	p<0.001	30.0	p<0.001
47	Maximum N2: maximum number of N2 which makes T1/T2 2.5 or more							
48	It is asumed that (D2+D3+D4+D5+D6)=5D1							
49	LRT: likelihood ratio test							
50	Wald: Wald test							
51	Score: Score test							

Table 6 Chi-square and p values when T1/T2 is 2.5 or more

	A	B	C	D	E	F	G	H
1	N1	Maximum N2	LRT		Wald		Score	
2			chi-square		chi-square		chi-square	
3	7	11	5.0	p<0.05	5.7	p<0.05	6.4	p<0.05
4	8	13	5.5	p<0.05	6.3	p<0.05	6.9	p<0.01
5	9	15	6.0	p<0.05	6.8	p<0.01	7.5	p<0.01
6	10	16	7.0	p<0.01	8.0	p<0.01	8.9	p<0.01
7	11	18	7.5	p<0.01	8.5	p<0.01	9.4	p<0.01
8	12	20	8.0	p<0.01	9.1	p<0.01	10.0	p<0.01
9	13	21	9.0	p<0.01	10.3	p<0.01	11.4	p<0.001
10	14	23	9.5	p<0.01	10.8	p<0.01	11.9	p<0.001
11	15	25	9.9	p<0.01	11.3	p<0.001	12.5	p<0.001
12	16	26	11.0	p<0.001	12.5	p<0.001	13.9	p<0.001
13	17	28	11.5	p<0.001	13.0	p<0.001	14.4	p<0.001
14	18	30	11.9	p<0.001	13.6	p<0.001	15.0	p<0.001
15	19	31	13.0	p<0.001	14.8	p<0.001	16.4	p<0.001
16	20	33	13.5	p<0.001	15.3	p<0.001	16.9	p<0.001
17	21	35	13.9	p<0.001	15.8	p<0.001	17.5	p<0.001
18	22	36	15.0	p<0.001	17.0	p<0.001	18.9	p<0.001
19	23	38	15.4	p<0.001	17.6	p<0.001	19.4	p<0.001
20	24	40	15.9	p<0.001	18.1	p<0.001	20.0	p<0.001
21	25	41	17.0	p<0.001	19.3	p<0.001	21.4	p<0.001
22	26	43	17.4	p<0.001	19.8	p<0.001	21.9	p<0.001
23	27	45	17.9	p<0.001	20.4	p<0.001	22.5	p<0.001
24	28	46	18.9	p<0.001	21.6	p<0.001	23.9	p<0.001
25	29	48	19.4	p<0.001	22.1	p<0.001	24.4	p<0.001
26	30	50	19.9	p<0.001	22.6	p<0.001	25.0	p<0.001
27	31	51	20.9	p<0.001	23.8	p<0.001	26.4	p<0.001
28	32	53	21.4	p<0.001	24.4	p<0.001	26.9	p<0.001
29	33	55	21.9	p<0.001	24.9	p<0.001	27.5	p<0.001
30	34	56	22.9	p<0.001	26.1	p<0.001	28.9	p<0.001
31	35	58	23.4	p<0.001	26.6	p<0.001	29.4	p<0.001
32	36	60	23.9	p<0.001	27.2	p<0.001	30.0	p<0.001
33	37	61	24.9	p<0.001	28.3	p<0.001	31.4	p<0.001
34	38	63	25.4	p<0.001	28.9	p<0.001	31.9	p<0.001
35	39	65	25.9	p<0.001	29.4	p<0.001	32.5	p<0.001
36	40	66	26.9	p<0.001	30.6	p<0.001	33.9	p<0.001
37	41	68	27.4	p<0.001	31.1	p<0.001	34.4	p<0.001
38	42	70	27.8	p<0.001	31.7	p<0.001	35.0	p<0.001
39	43	71	28.9	p<0.001	32.9	p<0.001	36.4	p<0.001
40	44	73	29.4	p<0.001	33.4	p<0.001	36.9	p<0.001
41	45	75	29.8	p<0.001	33.9	p<0.001	37.5	p<0.001
42	46	76	30.9	p<0.001	35.1	p<0.001	38.9	p<0.001
43	47	78	31.3	p<0.001	35.7	p<0.001	39.4	p<0.001
44	48	80	31.8	p<0.001	36.2	p<0.001	40.0	p<0.001
45	49	81	32.9	p<0.001	37.4	p<0.001	41.4	p<0.001
46	50	83	33.3	p<0.001	37.9	p<0.001	41.9	p<0.001
47	Maximum N2: maximum number of N2 which makes T1/T2 3.0 or more							
48	It is asumed that (D2+D3+D4+D5+D6)=5D1							
49	LRT: likelihood ratio test							
50	Wald: Wald test							
51	Score: Score test							

Table 7 Chi-square and p values when T1/T2 is 3.0 or more

	A	B	C	D
1	N1	Maximum N2	LRT	T1/T2
2			Chi-square	
3	3	-	10.75*	-
4	4	0	14.33	INFINITE
5	5	1	12.88	25.00
6	6	3	11.14	10.00
7	7	4	12.12	8.75
8	8	6	11.73	6.67
9	9	8	11.66	5.63
10	10	10	11.76	5.00
11	11	13	11.05	4.23
12	12	15	11.38	4.00
13	13	18	10.98	3.61
14	14	20	11.39	3.50
15	15	23	11.16	3.26
16	16	26	11.00	3.08
17	17	29	10.89	2.93
18	18	32	10.83	2.81
19	19	34	11.31	2.79
20	20	37	11.29	2.70
21	21	40	11.29	2.63
22	22	44	10.86	2.50
23	23	47	10.92	2.45
24	24	50	10.98	2.40
25	25	53	11.06	2.36
26	26	56	11.15	2.32
27	27	60	10.86	2.25
28	28	63	10.97	2.22
29	29	66	11.09	2.20
30	30	70	10.86	2.14
31	31	73	10.99	2.12
32	32	76	11.12	2.11
33	33	80	10.93	2.06
34	34	83	11.08	2.05
35	35	87	10.91	2.01
36	36	90	11.06	2.00
37	37	94	10.91	1.97
38	38	97	11.07	1.96
39	39	101	10.94	1.93
40	40	104	11.10	1.92
41	41	108	10.98	1.90
42	42	112	10.87	1.88
43	43	115	11.04	1.87
44	44	119	10.94	1.85
45	45	123	10.85	1.83
46	46	126	11.03	1.83
47	47	130	10.94	1.81
48	48	134	10.87	1.79
49	49	137	11.04	1.79
50	50	141	10.97	1.77
51	* The value when N2 = 0			
52	Maximum N2: maximum value of N2 where p < 0.001			
53	or chi-square > 10.828			
54	LRT: likelihood ratio test			
55	T1/T2: value of T1/T2 with N1 and maximum N2			
56	It is assumed that (D2+D3+D4+D5+D6) = 5D1			
57	Note: Nlog(N)=0 when N=0			

Table 8 maximum N2 and minimum T1/T2 where p < 0.001 with the likelihood ratio test

Known and 'unknown' ADRs and events 'signalled'

1 Fluvoxamine

ADRs in the BNF

Description in the BNF No 17 March 1989

FLUVOXAMINE MALEATE

Side-effects: nausea and vomiting, drowsiness, agitation, headache, anorexia, tremor; constipation; bradycardia; convulsions

ADRs in the BNF No 17

1 Nausea
2 Vomiting
3 Drowsiness
4 Agitation
5 Headache
6 Anorexia
7 Tremor
8 Constipation
9 Bradycardia
10 Convulsion

Description in the BNF No 31 March 1996

FLUVOXAMINE MALEATE

Cautions; Contra-indications; Side-effects: see under Fluoxetine; may cause decrease in heart rate; rarely increase in hepatic enzymes, usually with symptoms (withdrawal advised); galactorrhoea

FLUOXETINE

Side-effects: gastro-intestinal (fairly common - include

nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, anorexia with weight loss and possible changes in blood sugar); hypersensitivity reactions (important: see also below); also dry mouth, nervousness, anxiety, headache, insomnia, palpitations, tremor, confusion, dizziness, hypotension, hypomania or mania, drowsiness, asthenia, convulsions (see Cautions above), fever, sexual dysfunction, sweating; movement disorders and dyskinesias, neuroleptic malignant syndrome-like event; hyponatraemia (may be due to inappropriate antidiuretic hormone secretion), see CSM warning on p. 169; abnormal liver function tests reported; also reported (no causal relationship established): abnormal bleeding, aplastic anaemia, cerebrovascular accident, ecchymoses, eosinophilic pneumonia, gastro-intestinal haemorrhage, hyperprolactinaemia, haemolytic anaemia, pancreatitis, pancytopenia, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding on withdrawal, violent behaviour; hair loss also reported

HYPERSENSITIVITY. Angioedema, urticaria, pruritus, and other allergic reactions including anaphylaxis have been reported (discontinue if rash occurs, may be warning of impending serious systemic reaction, possibly associated with vasculitis); pharyngitis and rarely pulmonary inflammation or fibrosis (with dyspnoea only warning sign) also reported; possible hypersensitivity signs associated with other SSRIs include arthralgia, myalgia

The event dictionary low-level terms corresponding to the terms in the BNF No 31

ADRs in the BNF No 31		described in the BNF 17 ? (Y/N)	Event Dictionary low-level term(s)
1	Bradycardia	Y	Bradycardia
2	Nausea	Y	Nausea
3	Vomiting	Y	Vomiting

4	Dyspepsia	N	Dyspepsia
5	Abdominal pain	N	Pain abdomen
6	Diarrhoea	N	Diarrhoea
7	Constipation	Y	Constipation
8	Anorexia with weight loss	Y	Anorexia
9	Hypersensitivity	N	Angioneurotic oedema + Urticaria + Pruritus + Anaphylaxis + Rash
10	Dry mouth	N	Dry mouth
11	Nervousness + Anxiety	Y	Anxiety + Agitation
12	Headache	Y	Headache
13	Insomnia	N	Insomnia
14	Palpitations	N	Palpitation
15	Tremor	Y	Tremor
16	Confusion	N	Confusion
17	Dizziness	N	Dizziness
18	Hypotension	N	Hypotension
19	Hypomania or mania	N	Hypomania + Mania
20	Drowsiness	Y	Drowsiness + Sedation
21	Asthenia	N	Lassitude + Malaise
22	Convulsions	Y	Convulsion + Epilepsy grand mal + Status epilepticus
23	Fever	N	Pyrexia of unknown origin
24	Sexual dysfunction	N	Impotence + Ejaculation failure
25	Sweating	N	Sweating
26	Movement disorders and dyskinesia	N	Akinesia + Dystonia + Extrapyramidal disease + Huntington's chorea + Movement involuntary + Parkinson's disease + Shy-Drager syndrome
27	Neuroleptic malignant syndrome-like event	N	No term available
28	Galactorrhoea	N	Galactorrhoea

Questionable ADRs where 'no causal relationship is established'

Q1	Abnormal bleeding	Coagulation disorder + Haematoma spontaneous
Q2	Aplastic anaemia + Pancytopenia	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia
Q3	Cerebrovascular accident	Cerebrovascular accident + Embolus cerebral + Haemorrhage cerebral + Haemorrhage subarachnoid + Stenosis artery cerebral + Thrombosis cerebral + Vertebrobasilar syndrome
Q4	Ecchymoses	Haemorrhage NOS
Q5	Eosinophilic pneumonia	Churg-Strauss syndrome + Respiratory NOS
Q6	Gastrointestinal haemorrhage	Haemorrhage gastrointestinal + Haematemsis + Hernia hiatus haemorrhagic + Mallory-Weiss syndrome + Melena + Oesophageal haemorrhage + Ulcer duodenal haemorrhage + Ulcer gastric haemorrhage + Ulcer oesophageal hemorrhage + Ulcer peptic haemorrhage
Q7	Hyperprolactinaemia	Hyperprolactinaemia
Q8	Haemolytic anaemia	Anaemia haemolytic
Q9	Pancreatitis	Pancreatitis
Q10	Suicidal ideation	Suicidal thought
Q11	Vaginal bleeding on withdrawal	Haemorrhage vaginal
Q12	Violent behaviour	No term available
Q13	Hair loss	Alopecia

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Liver function changes	Liver function test abnormal
N2	Hyponatraemia	Hyponatraemia
N3	Thrombocytopenia	Thrombocytopenia

Events signalled and not signalled

As shown in Table 9, 45 events (low-level terms) are signalled. Nine events are signalled by the statistical test only and 3 events are signalled by the rate ratio method only. The remaining 33 events (73 %) are signalled by both of the methods. 10 known ADRs (category A) and 12 previously unknown ADRs (category B) are signalled. Therefore 22 or 45 (49%) events signalled are currently known ADRs.

At least nine of 23 events not shown in BNF may be considered to be known ADRs.

1 'Aggression' may be associated with 'agitation' (described in the BNF 17), nervousness or anxiety (category A).
2 'Hyperventilation' may be associated with nervousness or anxiety (category A)
3 'Disorientation' may be associated with 'confusion' (category B)
4 'Heartburn' is associated with dyspepsia (category B)
5 'Dreams abnormal' is described as an ADR in literature other than the BNF[64]
6 'Hallucination' is described as an ADR in literature other than the BNF[64]
7 'Vertigo' is described as an ADR in literature other than the BNF[65]
8 'Dysuria' is described as an ADR in literature other than the BNF[66]
9 'Cystitis' may be associated with dysuria as given above[66]

If those 9 events are added to currently known ADRs, 31 of 45 events signalled (69 %) may be judged to be currently known ADRs.

No events under category C or category D were signalled.

Confounding by the indication or 'indication-related' events

See Section 3 'Four SSRIs'.

ADRs signalled

Of the 28 ADRs under categories A and B, 19 (68 %) are signalled. The

remaining 9 known ADRs are rare except for 'hypersensitivity' to which 5 event dictionary terms (angioneurotic oedema, urticaria, pruritus, anaphylaxis and rash) may correspond. Of these 5 events, T1 for 'rash' is more than 1.0 per 1000 patients per month though T1 of other 4 events is less than 1.0 per 1000 patients per month. All ADRs under categories C and D are rare and T1 was 0.6 per 1000 patients per month or less for all of the events under these categories.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		10980		54656			min	max
3	Denominator male		3094		15417				
4	Denominator female		7689		38252				
5	$ T1/T2 = or > 2.5 and $$ T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***10***	
11	**Psychiatric**								
12	Agitation	$$*	69	6.3	22	0.4	15.6	9.7	25.2
13	Anxiety@	$$*	85	7.7	88	1.6	4.8	3.6	6.5
14	**Central and Peripheral Nervous System**								
15	Drowsiness	$$*	111	10.1	41	0.8	13.5	9.4	19.3
16	Sedation	$$*	54	4.9	14	0.3	19.2	10.7	34.6
17	Headache	$$*	182	16.6	137	2.5	6.6	5.3	8.3
18	Tremor	$$*	99	9.0	29	0.5	17.0	11.2	25.7
19	**Alimentary**								
20	Anorexia	$$*	46	4.2	21	0.4	10.9	6.5	18.3
21	Constipation	$$*	46	4.2	45	0.8	5.1	3.4	7.7
22	Nausea	$$*	703	64.0	110	2.0	31.8	26.0	38.9
23	Vomiting	$$*	227	20.7	77	1.4	14.7	11.3	19.0
24									
25	***B. Previously unknown ADRs signalled***							***12***	
26	**Psychiatric**								
27	Confusion	$$*	26	2.4	13	0.2	10.0	5.1	19.4
28	Insomnia	$$*	115	10.5	64	1.2	8.9	6.6	12.1
29	Lassitude	$$*	82	7.5	63	1.2	6.5	4.7	9.0
30	Malaise	$$*	229	20.9	43	0.8	26.5	19.1	36.7
31	**Central and Peripheral Nervous System**								
32	Dizziness	$$*	192	17.5	72	1.3	13.3	10.1	17.4
33	**Cardiovascular**								
34	Palpitation	$$*	36	3.3	19	0.3	9.4	5.4	16.4
35	**Alimentary**								
36	Diarrhoea	$$*	172	15.7	88	1.6	9.7	7.5	12.6
37	Dry mouth	$$*	28	2.6	9	0.2	15.5	7.3	32.8
38	Dyspepsia@	$$*	66	6.0	55	1.0	6.0	4.2	8.5
39	Pain abdomen	$$*	120	10.9	103	1.9	5.8	4.5	7.5
40	**Metabolic and Endocrine**								
41	Sweating	$$*	26	2.4	16	0.3	8.1	4.3	15.1
42	**Miscellaneous Infection**								
43	Pyrexia of unknown origin	*	9	0.8	4	0.1	-	-	-
44									
45	***C. Questionable ADRs signalled***							***0***	
46									
47	***D. 'Hard-to-detect' ADRs signalled***							***0***	
48									
49									
50									
51									
52									
53									
54									

Table 9 Fluvoxamine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
55	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of	T1/T2
56	***E. No description in BNF but signalled***							***23***	
57	**Psychiatric**								
58	Aggression	*	7	0.6	3	0.1	-	-	-
59	Dreams abnormal	$$*	14	1.3	10	0.2	7.0	3.1	15.7
60	Euphoria	*	8	0.7	0	0.0	-	-	-
61	Globus hystericus	*	8	0.7	4	0.1	-	-	-
62	Hallucination	$$*	12	1.1	7	0.1	8.5	3.4	21.7
63	Panic attack	$$*	32	2.9	18	0.3	8.8	5.0	15.8
64	Overdose unknown drug*	$$*	25	2.3	39	0.7	3.2	1.9	5.3
65	**Central and Peripheral Nervous System**								
66	Ataxia	$$*	16	1.5	17	0.3	4.7	2.4	9.3
67	Disorientation	*	6	0.5	1	0.0	-	-	-
68	Flushing	$$*	14	1.3	10	0.2	7.0	3.1	15.7
69	Migraine	$$*	20	1.8	26	0.5	3.8	2.1	6.9
70	Hyperaesthesia	*	10	0.9	5	0.1	-	-	-
71	Paraesthesia	$$*	19	1.7	24	0.4	3.9	2.2	7.2
72	Syncope	$$*	36	3.3	29	0.5	6.2	3.8	10.1
73	**Ear**								
74	Vertigo	$	12	1.1	22	0.4	2.7	1.3	5.5
75	**Cardiovascular**								
76	Tachycardia	*	8	0.7	4	0.1	-	-	-
77	Faintness	$$*	16	1.5	8	0.1	10.0	4.3	23.3
78	**Respiratory**								
79	Dyspnoea	$$	11	1.0	18	0.3	3.0	1.4	6.4
80	Hyperventilation	*	9	0.8	7	0.1	-	-	-
81	**Alimentary**								
82	Heartburn	*	10	0.9	2	0.0	-	-	-
83	**Urologic**								
84	Dysuria	$$	12	1.1	16	0.3	3.7	1.8	7.9
85	Cystitis	$	11	1.0	21	0.4	2.6	1.3	5.4
86	**Immunological**								
87	Unspecified side effects	$$*	107	9.7	15	0.3	35.5	20.7	61.0
88									
89	***Events NOT signalled***								
90									
91	***A. Previously known ADRs NOT signalled***							***4***	
92	**Central and Peripheral Nervous System**								
93	Convulsion*		1	0.1	3	0.1	-	-	-
94	Epilepsy grand mal		4	0.4	7	0.1	-	-	-
95	Status epilepticus*		0	0.0	0	0.0	-	-	-
96	**Cardiovascular**								
97	Bradycardia		2	0.2	0	0.0	-	-	-
98									
99									
100									
101									
102									
103									
104									
105									
106									
107									
108									
109									

Table 9 Fluvoxamine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
110	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of	T1/T2
111	***B. Previously unknown ADRs NOT signalled***							***18***	
112	**Skin**								
113	Pruritus @		6	0.5	19	0.3	-	-	-
114	Rash		19	1.7	43	0.8	2.2	1.3	3.8
115	Urticaria		4	0.4	9	0.2	-	-	-
116	**Psychiatric**								
117	Hypomania		0	0.0	0	0.0	-	-	-
118	Mania		2	0.2	6	0.1	-	-	-
119	**Central and Peripheral Nervous System**								
120	Akinesia		0	0.0	0	0.0	-	-	-
121	Dystonia		0	0.0	0	0.0	-	-	-
122	Extrapyramidal disease@		0	0.0	0	0.0	-	-	-
123	Huntington's chorea		0	0.0	0	0.0	-	-	-
124	Movement involuntary		1	0.1	1	0.0	-	-	-
125	Parkinson's disease*		2	0.2	6	0.1	-	-	-
126	Shy-Drager syndrome*		0	0.0	0	0.0	-	-	-
127	**Cardiovascular**								
128	Hypotension		8	0.7	10	0.2	-	-	-
129	**Male Reproductive and Gynaecomastia**								
130	Ejaculation failure		0	0.0	0	0.0	-	-	-
131	Impotence		1	0.3	4	0.3	-	-	-
132	**Breast Disorder**								
133	Galactorrhoea		0	0.0	2	0.1	-	-	-
134	**Immunological**								
135	Anaphylaxis		0	0.0	0	0.0	-	-	-
136	Angioneurotic oedema		1	0.1	1	0.0	-	-	-
137									
138	***C. 'Questionable' ADRs NOT signalled***							***31***	
139	**Skin**								
140	Alopecia		1	0.1	1	0.0	-	-	-
141	**Psychiatric**								
142	Suicidal thought		0	0.0	0	0.0	-	-	-
143	**Cardiovascular**								
144	Cerebro-vascular accident*		7	0.6	17	0.3	-	-	-
145	Embolus cerebral		0	0.0	1	0.0	-	-	-
146	Haemorrhage cerebral*		0	0.0	3	0.1	-	-	-
147	Haemorrhage subarachnoid*		0	0.0	0	0.0	-	-	-
148	Stenosis artery cerebral		0	0.0	0	0.0	-	-	-
149	Thrombosis cerebral*		0	0.0	0	0.0	-	-	-
150	Vertebrobasilar syndrome		0	0.0	0	0.0	-	-	-
151	**Respiratory**								
152	Churg-Strauss syndrome		0	0.0	0	0.0	-	-	-
153	**Alimentary**								
154	Haemorrhage gastrointestinal		0	0.0	0	0.0	-	-	-
155	Haematemesis*		2	0.2	3	0.1	-	-	-
156	Hernia hiatus haemorrhage*		0	0.0	0	0.0	-	-	-
157	Mallory-Weiss syndrome		0	0.0	0	0.0	-	-	-
158	Melena		2	0.2	1	0.0	-	-	-
159	Oesophageal haemorrhage*		0	0.0	0	0.0	-	-	-
160	Ulcer duodenal haemorrhage*		2	0.2	1	0.0	-	-	-
161	Ulcer gastric haemorrhage*		0	0.0	0	0.0	-	-	-
162	Ulcer oesophageal haemorrahge		0	0.0	0	0.0	-	-	-
163	Ulcer peptic haemorrhage*		0	0.0	0	0.0	-	-	-
164	Pancreatitis*		3	0.3	1	0.0	-	-	-
165									

Table 9 Fluvoxamine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
166	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of	T1/T2
167	***C. 'Questionable' ADRs NOT signalled continued***								
168	**Metabolic and Endocrine**								
169	Hyperprolactinaemia		0	0.0	0	0.0	-	-	-
170	- to be continued								
171	**Female Reproductive**								
172	Haemorrhage vaginal		0	0.0	7	0.2	-	-	-
173	**Haemopoietic**								
174	Anaemia haemolytic		0	0.0	0	0.0	-	-	-
175	Coagulation disorder		0	0.0	2	0.0	-	-	-
176	Haematoma spontaneous		1	0.1	2	0.0	-	-	-
177	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
178	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
179	Pancytopenia@		0	0.0	0	0.0	-	-	-
180	**Other events usually not shown**								
181	Haemorrhage unspecified		0	0.0	0	0.0	-	-	-
182	Respiratory unspecified		5	0.5	14	0.3	-	-	-
183									
184	***D. 'Hard-to-detect' ADRs NOT signalled***							*3*	
185	**Alimentary**								
186	Liver function test abnormal		0	0.0	3	0.1	-	-	-
187	**Metabolic and Endocrine**								
188	Hyponatraemia		0	0.0	0	0.0	-	-	-
189	**Haemopoietic**								
190	Thrombocytopenia		1	0.1	1	0.0	-	-	-

Table 9 Fluvoxamine: Events signalled and not signalled

2 Fluoxetine

ADRs in the BNF

Description in the BNF No 21 March 1991

FLUVOXAMINE MALEATE

Side-effects: rash (discontinue treatment, may be associated with vasculitis, anaphylaxis, and pulmonary inflammation or fibrosis), nausea, vomiting, diarrhoea, anorexia with weight loss, headache, nervousness, insomnia, anxiety, tremor, dry mouth, dizziness, hypomania, drowsiness, convulsions, fever, sexual dysfunction, sweating; less common, raised serum transaminases, depressed leucocyte counts; other side-effects reported are vaginal bleeding on withdrawal, hyperprolactinaemia, thrombocytopenia, altered platelet function and abnormal bleeding, confusion, suicidal ideation and violent behaviour; rarely hyponatraemia

ADRs in the BNF No 21

1 Rash
2 Nausea
3 Vomiting
4 Diarrhoea
5 Anorexia
6 Headache
7,8 Nervousness + Anxiety
9 Insomnia
10 Tremor
11 Dry mouth
12 Dizziness
13 Hypomania
14 Drowsiness
15 Convulsions
16 Fever

17 Sexual dysfunction
18 Sweating
19 Vaginal bleeding on withdrawal
20 Hyperprolactinaemia
21 Abnormal bleeding
22 Confusion
23 Suicidal ideation
24 Violent behaviour

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1 Raised serum transaminases
N2 Depressed leucocyte counts
N3 Thrombocytopenia
N4 Hyponatraemia

Description in the BNF No 31 March 1996

FLUOXETINE

Side-effects: gastro-intestinal (fairly common - include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, anorexia with weight loss and possible changes in blood sugar); hypersensitivity reactions (important: see also below); also dry mouth, nervousness, anxiety, headache, insomnia, palpitations, tremor, confusion, dizziness, hypotension, hypomania or mania, drowsiness, asthenia, convulsions (see Cautions above), fever, sexual dysfunction, sweating; movement disorders and dyskinesias, neuroleptic malignant syndrome-like event; hyponatraemia (may be due to inappropriate antidiuretic hormone secretion), see CSM warning on p. 169; abnormal liver function tests reported; also reported (no causal relationship established): abnormal bleeding, aplastic anaemia, cerebrovascular accident, ecchymoses, eosinophilic pneumonia, gastro-intestinal haemorrhage, hyperprolactinaemia, haemolytic anaemia, pancreatitis, pancytopenia, suicidal ideation, thrombocytopenia,

thrombocytopenic purpura, vaginal bleeding on withdrawal, violent behaviour; hair loss also reported
HYPERSENSITIVITY. Angioedema, urticaria, pruritus, and other allergic reactions including anaphylaxis have been reported (discontinue if rash occurs, may be warning of impending serious systemic reaction, possibly associated with vasculitis); pharyngitis and rarely pulmonary inflammation or fibrosis (with dyspnoea only warning sign) also reported; possible hypersensitivity signs associated with other SSRIs include arthralgia, myalgia

The event dictionary low-level terms corresponding to the terms in the BNF No 31

ADRs in the BNF No 31		described in the BNF 21 ? (Y/N)	Event Dictionary low-level term(s)
1	Nausea	Y	Nausea
2	Vomiting	Y	Vomiting
3	Dyspepsia	N	Dyspepsia
4	Abdominal pain	N	Pain abdomen
5	Diarrhoea	N	Diarrhoea
6	Constipation	Y	Constipation
7	Anorexia with weight loss	Y	Anorexia
8	Hypersensitivity	N	Angioneurotic oedema + Urticaria + Pruritus + Anaphylaxis + Rash
9	Dry mouth	N	Dry mouth
10,11	Nervousness + Anxiety	Y	Anxiety + Agitation
12	Headache	Y	Headache
13	Insomnia	N	Insomnia
14	Palpitations	N	Palpitation
15	Tremor	Y	Tremor
16	Confusion	N	Confusion
17	Dizziness	Y	Dizziness
18	Hypotension	N	Hypotension
19	Hypomania or mania	N	Hypomania + Mania

20	Drowsiness	Y	Drowsiness + Sedation
21	Asthenia	N	Lassitude + Malaise
22	Convulsions	Y	Convulsion + Epilepsy grand mal + Status epilepticus
23	Fever	N	Pyrexia of unknown origin
24	Sexual dysfunction	N	Impotence + Ejaculation failure
25	Sweating	N	Sweating
26	Movement disorders and dyskinesia	N	Akinesia + Dystonia + Extrapyramidal disease + Huntington's chorea + Movement involuntary + Parkinson's disease + Shy-Drager syndrome
27	Neuroleptic malignant syndrome-like event	N	No term available

Questionable ADRs where 'no causal relationship is established'

Q1	Abnormal bleeding	Coagulation disorder + Haematoma spontaneous
Q2	Aplastic anaemia + Pancytopenia	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia
Q3	Cerebrovascular accident	Cerebrovascular accident + Embolus cerebral + Haemorrhage cerebral + Haemorrhage subarachnoid + Stenosis artery cerebral + Thrombosis cerebral + Vertebrobasilar syndrome
Q4	Ecchymoses	Haemorrhage NOS
Q5	Eosinophilic pneumonia	Churg-Strauss syndrome + Respiratory NOS
Q6	Gastrointestinal haemorrhage	Haemorrhage gastrointestinal + Haematemsis + Hernia hiatus haemorrhagic + Mallory-Weiss syndrome + Melena + Oesophageal haemorrhage + Ulcer duodenal haemorrhage + Ulcer gastric

		haemorrhage + Ulcer oesophageal hemorrhage + Ulcer peptic haemorrhage
Q7	Hyperprolactinaemia	Hyperprolactinaemia
Q8	Haemolytic anaemia	Anaemia haemolytic
Q9	Pancreatitis	Pancreatitis
Q10	Suicidal ideation	Suicidal thought
Q11	Vaginal bleeding on withdrawal	Haemorrhage vaginal
Q12	Violent behaviour	No term available
Q13	Hair loss	Alopecia

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Liver function changes	Liver function test abnormal
N2	Hyponatraemia	Hyponatraemia
N3	Thrombocytopenia	Thrombocytopenia

Events signalled and not signalled

As shown in Table 10, 36 events (low-level terms) are signalled. Ten events are signalled by the statistical test only and 3 events are signalled by the rate ratio method only. The remaining 23 events (64 %) are signalled by both of the methods. 16 known ADRs (category A) and 6 previously unknown ADRs (category B) are signalled. One questionable ADR (category C) is also signalled. Therefore 23 or 36 (64%) events signalled are currently known ADRs.

At least four of 13 events not shown in the BNF may be considered to be known ADRs.

1 'Anxiety/depression' may be associated with nervousness or anxiety (category A).
2 'Panic attack' may be associated with nervousness or anxiety (category A).
3 'Dysuria' is described as an ADR in literature other than the BNF[66]
4 'Retension' is described as an ADR in literature other than the BNF[66]

If those 4 events are added to currently known ADRs, 27 of 36 events signalled

(75 %) may be judged to be currently known ADRs.

No events under category D were signalled.

Confounding by the indication or 'indication-related' events

See Section 3 'Four SSRIs'.

ADRs signalled

Of the 27 ADRs under categories A and B, 20 (74 %) are signalled. The remaining 7 known ADRs are rare. According to the definition, 'hypersensitivity' is judged to be signalled because 'pruritus' is signalled. 'Rash' which is one of 5 low-level event dictionary terms which may correspond to 'hypersensitivity' is not signalled even if it is not rare (T1 = 2.6 and T2 = 1.3). One ADR under category C, 'cerebrovascular accident' is signalled though it needs more study to known any association between this event and fluoxetine. Except for 'cerebrovascular accident', all other ADRs under categories C and D are rare and T1 was 0.3 per 1000 patients per month or less.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		12686		63277			min	max
3	Denominator male		3689		18396				
4	Denominator female		8856		44176				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***16***	
11	**Psychiatric**								
12	Agitation	$$*	63	5.0	40	0.6	7.9	5.3	11.7
13	Anxiety@	$$*	94	7.4	116	1.8	4.0	3.1	5.3
14	Confusion	$$*	23	1.8	25	0.4	4.6	2.6	8.1
15	Insomnia	$$*	100	7.9	96	1.5	5.2	3.9	6.9
16	**Central and Peripheral Nervous System**								
17	Dizziness	$$*	69	5.4	84	1.3	4.1	3.0	5.6
18	Drowsiness	$$*	64	5.0	27	0.4	11.8	7.5	18.5
19	Sedation	$$*	21	1.7	15	0.2	7.0	3.6	13.5
20	Headache	$$*	119	9.4	146	2.3	4.1	3.2	5.2
21	Tremor	$$*	60	4.7	57	0.9	5.3	3.7	7.5
22	**Alimentary**								
23	Anorexia	$$*	25	2.0	29	0.5	4.3	2.5	7.3
24	Constipation	*	31	2.4	70	1.1	2.2	1.4	3.4
25	Diarrhoea	$$*	73	5.8	97	1.5	3.8	2.8	5.1
26	Dry mouth	$$*	18	1.4	7	0.1	12.8	5.4	30.7
27	Nausea	$$*	205	16.2	104	1.6	9.8	7.8	12.4
28	Vomiting	$$*	68	5.4	68	1.1	5.0	3.6	7.0
29	**Metabolic and Endocrine**								
30	Sweating	$$*	23	1.8	18	0.3	6.4	3.4	11.8
31									
32	***B. Previously unknown ADRs signalled***							***6***	
33	**Skin**								
34	Pruritus @	$	14	1.1	28	0.4	2.5	1.3	4.7
35	**Psychiatric**								
36	Lassitude	$*	38	3.0	67	1.1	2.8	1.9	4.2
37	Malaise	$$*	133	10.5	52	0.8	12.8	9.3	17.6
38	**Cardiovascular**								
39	Palpitation	$$*	22	1.7	16	0.3	6.9	3.6	13.1
40	**Alimentary**								
41	Dyspepsia@	$$*	46	3.6	66	1.0	3.5	2.4	5.1
42	Pain abdomen	*	63	5.0	142	2.2	2.2	1.6	3.0
43									
44	***C. Questionable ADRs signalled***							***1***	
45	**Cardiovascular**								
46	Cerebro-vascular accident*	*	9	0.7	8	0.1	-	-	-
47									
48	***D. 'Hard-to-detect' ADRs signalled***							***0***	
49									
50									
51									
52									
53									
54									

Table 10 Fluoxetine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
55	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
56	***E. No description in BNF but signalled***							***13***	
57	**Psychiatric**								
58	Anxiety/depression	$$*	18	1.4	19	0.3	4.7	2.5	9.0
59	Depression @	*	96	7.6	301	4.8	1.6	1.3	2.0
60	Hyperactive	*	11	0.9	4	0.1	-	-	-
61	Panic attack	$$*	27	2.1	18	0.3	7.5	4.1	13.6
62	**Central and Peripheral Nervous System**								
63	Ataxia	$$*	15	1.2	10	0.2	7.5	3.4	16.7
64	Paresis	*	11	0.9	7	0.1	-	-	-
65	Paraesthesia	*	12	0.9	15	0.2	-	-	-
66	**Cardiovascular**								
67	Faintness	*	10	0.8	6	0.1	-	-	-
68	**Respiratory**								
69	Dyspnoea	$$	13	1.0	20	0.3	3.2	1.6	6.5
70	**Alimentary**								
71	Dysphagia	*	6	0.5	2	0.0	-	-	-
72	**Urologic**								
73	Dysuria	$$	14	1.1	22	0.3	3.2	1.6	6.2
74	Retention	*	10	0.8	8	0.1	-	-	-
75	**Immunological**								
76	Unspecified side effects	$$*	24	1.9	19	0.3	6.3	3.5	11.5
77									
78	***Events NOT signalled***								
79									
80	***A. Previously known ADRs NOT signalled***							***9***	
81	**Skin**								
82	Rash		33	2.6	82	1.3	2.0	1.3	3.0
83	**Psychiatric**								
84	Hypomania		1	0.1	13	0.2	-	-	-
85	Mania		1	0.1	8	0.1	-	-	-
86	**Central and Peripheral Nervous System**								
87	Convulsion*		3	0.2	1	0.0	-	-	-
88	Epilepsy grand mal		3	0.2	6	0.1	-	-	-
89	Status epilepticus*		0	0.0	0	0.0	-	-	-
90	**Male Reproductive and Gynaecomastia**								
91	Ejaculation failure		0	0.0	0	0.0	-	-	-
92	Impotence		2	0.5	6	0.3	-	-	-
93	**Miscellaneous Infection**								
94	Pyrexia of unknown origin		1	0.1	7	0.1	-	-	-
95									
96	***B. Previously unknown ADRs NOT signalled***							***11***	
97	**Skin**								
98	Urticaria		11	0.9	17	0.3	-	-	-
99	**Central and Peripheral Nervous System**								
100	Akinesia		0	0.0	0	0.0	-	-	-
101	Dystonia		1	0.1	2	0.0	-	-	-
102	Extrapyramidal disease@		1	0.1	3	0.0	-	-	-
103	Huntington's chorea		0	0.0	0	0.0	-	-	-
104	Movement involuntary		1	0.1	5	0.1	-	-	-
105	Parkinson's disease*		4	0.3	13	0.2	-	-	-
106	Shy-Drager syndrome*		0	0.0	0	0.0	-	-	-
107									
108									

Table 10 Fluoxetine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
109	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
110	***B. Previously unknown ADRs NOT signalled continued***								
111	**Cardiovascular**								
112	Hypotension		10	0.8	13	0.2	-	-	-
113	**Immunological**								
114	Anaphylaxis		0	0.0	1	0.0	-	-	-
115	Angioneurotic oedema		1	0.1	2	0.0	-	-	-
116									
117	***C. 'Questionable' ADRs NOT signalled***							*30*	
118	**Skin**								
119	Alopecia		0	0.0	0	0.0	-	-	-
120	**Psychiatric**								
121	Suicidal thought		0	0.0	0	0.0	-	-	-
122	**Cardiovascular**								
123	Embolus cerebral		0	0.0	0	0.0	-	-	-
124	Haemorrhage cerebral*		0	0.0	0	0.0	-	-	-
125	Haemorrhage subarachnoid*		0	0.0	0	0.0	-	-	-
126	Stenosis artery cerebral		0	0.0	0	0.0	-	-	-
127	Thrombosis cerebral*		0	0.0	0	0.0	-	-	-
128	Vertebrobasilar syndrome		0	0.0	5	0.1	-	-	-
129	**Respiratory**								
130	Churg-Strauss syndrome		0	0.0	0	0.0	-	-	-
131	**Alimentary**								
132	Haemorrhage gastrointestinal		0	0.0	1	0.0	-	-	-
133	Haematemesis*		0	0.0	4	0.1	-	-	-
134	Hernia hiatus haemorrhage*		0	0.0	0	0.0	-	-	-
135	Mallory-Weiss syndrome		0	0.0	1	0.0	-	-	-
136	Melena		0	0.0	3	0.0	-	-	-
137	Oesophageal haemorrhage*		0	0.0	0	0.0	-	-	-
138	Ulcer duodenal haemorrhage*		0	0.0	1	0.0	-	-	-
139	Ulcer gastric haemorrhage*		0	0.0	0	0.0	-	-	-
140	Ulcer oesophageal haemorrahge		0	0.0	0	0.0	-	-	-
141	Ulcer peptic haemorrhage*		0	0.0	0	0.0	-	-	-
142	Pancreatitis*		2	0.2	2	0.0	-	-	-
143	**Metabolic and Endocrine**								
144	Hyperprolactinaemia		0	0.0	0	0.0	-	-	-
145	**Female Reproductive**								
146	Haemorrhage vaginal		1	0.1	12	0.3	-	-	-
147	**Haemopoietic**								
148	Anaemia haemolytic		0	0.0	0	0.0	-	-	-
149	Coagulation disorder		0	0.0	0	0.0	-	-	-
150	Haematoma spontaneous		2	0.2	4	0.1	-	-	-
151	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
152	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
153	Pancytopenia@		0	0.0	1	0.0	-	-	-
154	**Other events usually not shown**								
155	Haemorrhage unspecified		1	0.1	0	0.0	-	-	-
156	Respiratory unspecified		4	0.3	21	0.3	-	-	-
157									
158	***D. 'Hard-to-detect' ADRs NOT signalled***							*3*	
159	**Alimentary**								
160	Liver function test abnormal		0	0.0	3	0.0	-	-	-
161	**Metabolic and Endocrine**								
162	Hyponatraemia		3	0.2	4	0.1	-	-	-
163	**Haemopoietic**								
164	Thrombocytopenia		1	0.1	0	0.0	-	-	-

Table 10 Fluoxetine: Events signalled and not signalled

3 Four SSRIs

Comparison between four SSRIs

As shown in Table 9, with fluvoxamine, 22 events signalled were currently known ADRs (i.e., under one of categories A to D) while with fluoxetine it was the case for 23 events signalled (Table 10). The number of events under category A (previously known ADRs) was 10 with fluvoxamine but that was 16 with fluoxetine. On the other hand, the number of events under category B (previously unknown ADRs) was 12 with fluvoxamine while that was 6 with fluoxetine. The difference of the number of events under category A or B between fluvoxamine and fluoxetine was mainly due to the change in the description in the BNF. The BNF No 17 used to find 'previously known ADRs' (category A) for fluvoxamine was published two years earlier than the BNF No 21 used to know ADRs under category A for fluoxetine. During these two years, the number of ADRs in the BNF was increased so that the number of events under category A increased while that under category B decreased. However, events signalled were quite similar between fluvoxamine and fluoxetine.

Table 11 shows events signalled in the PEM studies of four SSRIs. The events were classified into those described and those not described in the BNF No 31 (March 1996). Events signalled, particularly those under categories A to D (ADRs described in the BNF), were similar between four SSRIs. Consistency between four SSRIs indicates that PEM can pick up possible ADRs irrespective of whether the event is known, or, more precisely, widely known as an ADR.

Confounding by the indication or 'indication-related' event

In PEM report on fluoxetine[34], the following three events are designated as those which are 'indication-related':

Anxiety
Anxiety/depression
Depression

In PEM report on paroxetine[35], the following event is designated as that which is 'indication-related':

Anxiety

The events designated as those which are 'indication-related' are not consistent between two PEM studies[34,35]. This is because the above three events are 'signalled' in the fluoxetine study when the method to signal is mechanically applied while only anxiety is 'signalled' in the paroxetine study (see Table 11).

The reason why those events are judged to be 'indication-related' is not given in these PEM reports[34,35]. It is likely that some of other events including most psychiatric events signalled in the PEM studies on four SSRIs shown in Table 11 may be in fact the manifestation of indication but not ADRs to the drug (e.g., 13 psychiatric events with fluvoxamine and 10 with fluoxetine) though some of them are also known ADRs to SSRIs. Other events such as 'Tachycardia' and 'Hyperventilation' may be also confounded by the indication as they can be manifestations of anxiety. For a small number of events which are potentially indication-related, further information is obtained by re-examination of the original green forms or by the comparison between drugs and the results are shown in those PEM reports[34,35] but they are seldom conclusive regarding the causality between the drug and event. An exception is when the result is negative. For example, in the report on the fluoxetine study[34], attempted suicides are discussed as follows:

> Of great importance was the lack of evidence of suicidal ideation suggested by *Teicher et al.* or of any difference (between fluvoxamine, fluoxetine and paroxetine) in the rates for attempted suicide which were recorded at about six times the average rate in (34 various) PEM studies.

Note: underlined description is added by the author of this thesis to clarify the context.

The description may be judged to be not conclusive but give some evidence which declines the causal relationship between fluoxetine and suicides.

	A	B	C	D	E	F	G	H	I	J	K	L	M
1		Fluvoxamine			Fluoxetine			Paroxetine			Sertraline		
2	EVENT		T1&D1	T2&D2-6		T1&D1	T2&D2-6		T1&D1	T2&D2-6		T1&D1	T2&D2-6
3	Denominator total		10980	54656		12686	63277		13736	68606		12729	63583
4	Denominator male		3094	15417		3689	18396		4369	21831		3909	19533
5	Denominator female		7689	38252		8856	44176		9275	46319		8724	43572
6	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)												
7													
8	***Events signalled***												
9													
10	***ADRs under categories A,B,C,D***												
11	**Skin**												
12	Pruritus @				$	1.1	0.4						
13	**Psychiatric**												
14	Agitation	$$*	6.3	0.4	$$*	5.0	0.6	$$*	4.3	0.6	$$*	4.2	0.7
15	Anxiety@	$$*	7.7	1.6	$$*	7.4	1.8	$$*	3.8	1.2	$$*	2.4	0.8
16	Confusion	$$*	2.4	0.2	$$*	1.8	0.4						
17	Insomnia	$$*	10.5	1.2	$$*	7.9	1.5	$$*	10.7	1.8	$$*	7.0	1.7
18	Lassitude	$$*	7.5	1.2	$*	3.0	1.1	$$*	4.6	1.1	$$*	3.2	0.9
19	Malaise	$$*	20.9	0.8	$$*	10.5	0.8	$$*	10.1	0.6	$$*	7.1	0.4
20	Suicidal thought										*	0.7	0.1
21	**Central and Peripheral Nervous System**												
22	Dizziness	$$*	17.5	1.3	$$*	5.4	1.3	$$*	9.5	1.6	$$*	7.5	1.1
23	Drowsiness	$$*	10.1	0.8	$$*	5.0	0.4	$$*	12.5	0.8	$$*	4.6	0.4
24	Sedation	$$*	4.9	0.3	$$*	1.7	0.2	$$*	4.1	0.3	$$*	1.7	0.1
25	Headache	$$*	16.6	2.5	$$*	9.4	2.3	$$*	10.8	2.1	$$*	10.1	2.3
26	Tremor	$$*	9.0	0.5	$$*	4.7	0.9	$$*	10.2	0.6	$$*	5.3	0.5
27	**Cardiovascular**												
28	Cerebro-vascular accident*				*	0.7	0.1						
29	Palpitation	$$*	3.3	0.3	$$*	1.7	0.3	$$*	1.7	0.4	$$*	1.6	0.4
30	**Alimentary**												
31	Anorexia	$$*	4.2	0.4	$$*	2.0	0.5	$$*	1.5	0.2	$$*	2.0	0.2
32	Constipation	$$*	4.2	0.8	*	2.4	1.1	*	2.7	1.2	$$*	2.7	0.8
33	Diarrhoea	$$*	15.7	1.6	$$*	5.8	1.5	$$*	6.6	2.0	$$*	10.0	3.1
34	Dry mouth	$$*	2.6	0.2	$$*	1.4	0.1	$$*	3.5	0.3	$$*	2.6	0.2
35	Dyspepsia@	$$*	6.0	1.0	$$*	3.6	1.0	$$*	3.2	0.8	$$*	3.9	1.1
36	Nausea	$$*	64.0	2.0	$$*	16.2	1.6	$$*	35.3	2.1	$$*	23.8	1.3
37	Vomiting	$$*	20.7	1.4	$$*	5.4	1.1	$$*	7.9	1.0	$$*	5.3	0.9
38	Pain abdomen	$$*	10.9	1.9	*	5.0	2.2	*	4.4	1.8	$*	5.3	1.9
39	**Metabolic and Endocrine**												
40	Sweating	$$*	2.4	0.3	$$*	1.8	0.3	$$*	5.5	0.8	$$*	3.4	0.6
41	**Miscellaneous Infection**												
42	Pyrexia of unknown origin	*	0.8	0.1									
43													
44	***No description in BNF but signalled***												
45	**Psychiatric**												
46	Aggression	*	0.6	0.1									
47	Anxiety/depression				$$*	1.4	0.3						
48	Depression @				*	7.6	4.8						
49	Dreams abnormal	$$*	1.3	0.2									
50	Euphoria	*	0.7	0.0							*	0.5	0.1
51	Globus hystericus	*	0.7	0.1									
52	Hallucination	$$*	1.1	0.1									
53	Hyperactive				*	0.9	0.1				*	0.5	0.0
54	Panic attack	$$*	2.9	0.3	$$*	2.1	0.3	$$*	2.4	0.5	$$*	2.4	0.4
55	Overdose unknown drug*	$$*	2.3	0.7				$	1.0	0.3			
56	Suicide attempt*							*	0.9	0.1			

Table 11 Comparison between four SSRIs

	A	B	C	D	E	F	G	H	I	J	K	L	M
57	***No description in BNF but signalled continued***												
58		**Fluvoxamine**			**Fluoxetine**			**Paroxetine**			**Sertraline**		
59	EVENT		T1&D1	T2&D2-6		T1&D1	T2&D2-6		T1&D1	T2&D2-6		T1&D1	T2&D2-6
60	**Central and Peripheral Nervous System**												
61	Ataxia	$$*	1.5	0.3	$$*	1.2	0.2	*	0.9	0.2			
62	Disorientation	*	0.5	0.0									
63	Feeling hot							*	0.5	0.0			
64	Flushing	$$*	1.3	0.2				$$*	1.2	0.3			
65	Migraine	$$*	1.8	0.5									
66	Hyperaesthesia	*	0.9	0.1									
67	Paresis				*	0.9	0.1						
68	Paraesthesia	$$*	1.7	0.4	*	0.9	0.2						
69	Taste abnormal							*	0.4	0.0			
70	Syncope	$$*	3.3	0.5				$	1.0	0.3			
71	**Ear**												
72	Vertigo	$	1.1	0.4									
73	**Eye**												
74	Visual disturbance							*	0.9	0.2	*	0.8	0.2
75	**Cardiovascular**												
76	Tachycardia	*	0.7	0.1									
77	Faintness	$$*	1.5	0.1	$$*	0.8	0.1	*	0.7	0.1	*	0.9	0.1
78	**Respiratory**												
79	Dyspnoea	$$	1.0	0.3	$$	1.0	0.3						
80	Hyperventilation	*	0.8	0.1							*	0.7	0.1
81	**Alimentary**												
82	Dysphagia				*	0.5	0.0						
83	Heartburn	*	0.9	0.0									
84	**Urologic**												
85	Dysuria	$$	1.1	0.3	$$	1.1	0.3	*	0.9	0.2			
86	Cystitis	$	1.0	0.4									
87	Retention				*	0.8	0.1						
88	**Male Reproductive and Gynaecomastia**												
89	Prostatism										$$	1.0	0.3
90	**Immunological**												
91	Unspecified side effects	$$*	9.7	0.3	$$*	1.9	0.3	$$*	2.0	0.1	$$*	2.1	0.2

Table 11 Comparison between four SSRIs

4 Buspirone

ADRs in the BNF

Description in the BNF No 19 March 1990

BUSPIRONE HYDROCHLORIDE
Side-effects: nausea, dizziness, headache, nervousness, lightheadedness, excitement; rarely tachycardia, palpitations, chest pain, drowsiness, confusion, dry mouth, fatigue, and sweating

ADRs in the BNF No 19

1 Nausea
2 Dizziness
3 Headache
4 Nervousness
5 Lightheadedness
6 Excitement
5 Tachycardia
6 Palpitation
7 Chest pain
8 Drowsiness
9 Confusion
10 Dry mouth
11 Fatigue
12 Sweating

Description in the BNF No 31 March 1996

The description in the BNF No 31 is exactly the same as that in the BNF No 19. Therefore, all of the ADRs are regarded to be 'Known ADRs' (category 1).

The event dictionary low-level terms corresponding to the terms in the BNF No

31

	ADRs in the BNF No 31	described in the BNF 19 ? (Y/N)	Event Dictionary low-level term(s)
1	Nausea	Y	Nausea
2	Dizziness	Y	Dizziness
3	Headache	Y	Headache
4	Nervousness	Y	Anxiety
5	Lightheadedness	Y	Dizziness
6	Excitement	Y	Agitation + Aggression + Panic attack
7	Tachycardia	Y	Tachycardia
8	Palpitation	Y	Palpitation
9	Chest pain	Y	Pain chest
10	Drowsiness	Y	Drowsiness + Sedation
11	Confusion	Y	Confusion
12	Dry mouth	Y	Dry mouth
13	Fatigue	Y	Lassitude + Malaise
14	Sweating	Y	Sweating

Events signalled and not signalled

As shown in Table 12, 25 events (low-level terms) are signalled. Three events are signalled by the statistical test only and one event is signalled by the rate ratio method only. The remaining 21 events (84 %) are signalled by both of the methods.

Fourteen events signalled are known ADRs but 11 are not shown in the BNF. Of these 11 events, at least 2 events may be considered to be known ADRs.

1 'Paraesthsia' is described as an ADR in literature other than the BNF[67]
2 'Vomiting' is described as an ADR in literature other than the BNF[67].

If those 2 events are added to currently known ADRs, 16 of 25 (64 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

Though no formally published PEM report is available for buspirone, a draft for PEM report on buspirone[68], which has been not finished by some reason, indicates that the following events signalled as well as some other events not signalled are 'indication-related'.

Agitation
Anxiety
Depression
Insomnia
Panic attack

It is possible that most of other psychiatric events may be also confounded by the indication including

'Dreams abnormal' (nightmare)
'Overdose unknown drugs' (suicide).

Some other events such as

tachycardia
palpitation
sweating

may be also manifestations of the indication (anxiety) rather than ADRs to buspirone.

ADRs signalled

All of the 14 ADRs in the BNF are considered to be under class A and of these 14 ADRs, 12 (86 %) are signalled. The remaining two terms are 'dry mouth' and 'chest pain'. An event 'dry mouth' is rather rare and T1 was 0.8 per 1000 patients per month. The value for T1 of 'chest pain' was 2.3 per 1000 patients

per month but more than 60 patients had this event in month 2 or later and the value for T2 was 1.1. It is difficult to judge whether 'chest pain' is an ADR to buspirone of which the occurrence is not confined to month 1 or is associated with the indication 'anxiety'.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI	of T1/T2
2	Denominator total		11109		55313			min	max
3	Denominator male		3497		17430				
4	Denominator female		7416		36909				
5	$ T1/T2 = or > 2.5 and $$. T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	**A. Previously known ADRs signalled**							14	
11	**Psychiatric**								
12	Agitation	$$*	29	2.6	22	0.4	6.6	3.8	11.4
13	Anxiety@	$*	85	7.7	166	3.0	2.5	2.0	3.3
14	Confusion	$$*	12	1.1	5	0.1	11.9	4.2	33.9
15	Lassitude	$$*	20	1.8	30	0.5	3.3	1.9	5.8
16	Malaise	$$*	64	5.8	23	0.4	13.9	8.6	22.3
17	Panic attack	$$*	34	3.1	41	0.7	4.1	2.6	6.5
18	**Central and Peripheral Nervous System**								
19	Dizziness	$$*	91	8.2	58	1.0	7.8	5.6	10.9
20	Drowsiness	$$*	27	2.4	12	0.2	11.2	5.7	22.1
21	Sedation	$$*	14	1.3	7	0.1	10.0	4.0	24.7
22	Headache	$$*	100	9.0	99	1.8	5.0	3.8	6.6
23	**Cardiovascular**								
24	Tachycardia	$$*	11	1.0	7	0.1	7.8	3.0	20.2
25	Palpitation	$$*	29	2.6	33	0.6	4.4	2.7	7.2
26	**Alimentary**								
27	Nausea	$$*	69	6.2	29	0.5	11.8	7.7	18.3
28	**Metabolic and Endocrine**								
29	Sweating	$$*	11	1.0	11	0.2	5.0	2.2	11.5
30									
31	**E. No description in BNF but signalled**							11	
32	**Psychiatric**								
33	Depression @	$*	99	8.9	190	3.4	2.6	2.0	3.3
34	Dreams abnormal	*	7	0.6	0	0.0	-	-	-
35	Insomnia	$$*	45	4.1	44	0.8	5.1	3.4	7.7
36	Overdose unknown drug*	$$*	23	2.1	23	0.4	5.0	2.8	8.9
37	**Central and Peripheral Nervous System**								
38	Paraesthesia	$$*	14	1.3	14	0.3	5.0	2.4	10.4
39	Tremor	$$*	30	2.7	20	0.4	7.5	4.2	13.2
40	**Respiratory**								
41	Catarrh	$$	12	1.1	19	0.3	3.1	1.5	6.5
42	**Alimentary**								
43	Anorexia	*	9	0.8	8	0.1	-	-	-
44	Vomiting	$$*	22	2.0	30	0.5	3.7	2.1	6.3
45	Pain abdomen	*	38	3.4	96	1.7	2.0	1.4	2.9
46	**Immunological**								
47	Unspecified side effects	$$*	22	2.0	6	0.1	18.3	7.4	45.0
48									
49	Note: All ADRs in the BNF are judged to be under category A (see text for detail)								
50									
51									
52									
53									
54									
55									

Table 12 Buspirone: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
56	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI	of T1/T2
57	***Events NOT signalled***								
58									
59	***A. Previously known ADRs NOT signalled***							*3*	
60	**Psychiatric**								
61	Aggression		7	0.6	7	0.1	-	-	-
62	**Cardiovascular**								
63	Pain chest		26	2.3	62	1.1	2.1	1.3	3.3
64	**Alimentary**								
65	Dry mouth		9	0.8	9	0.2	-	-	-
66	Note: All ADRs in the BNF are judged to be under category A (see text for detail)								

Table 12 Buspirone: Events signalled and not signalled

5 Flunitrazepam

ADRs in the BNF

Description in the BNF No 9 March 1985

FLUNITRAZEPAM
Cautions; Contra-indications; Side-effects: see under Nitrazepam

NITRAZEPAM
Side-effects: hangover with drowsiness, dizziness, ataxia (particularly in the elderly); occasionally confusion, dry mouth, hypersensitivity reactions. Prolonged use my give rise to cumulation, tolerance, rebound insomnia and dependence

ADRs in the BNF No 9

1 Drowsiness
2 Dizziness
3 Ataxia
4 Confusion
5 Dry mouth
6 Hypersensitivity
7 Tolerance
8 Rebound insomnia
9 Dependence

Description in the BNF No 31 March 1996

FLUNITRAZEPAM
Cautions; Contra-indications; Side-effects: see under Nitrazepam

NITRAZEPAM
Side-effects: drowsiness and lightheadedness the next day;

confusion and ataxia (especially in the elderly); amnesia may occur; dependence; see also under Diazepam

DIAZEPAM

Side-effects: drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur; dependence; paradoxical increase in aggression (see also section 4.1); occasionally: headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, rashes, visual disturbances, changes in libido, urinary retention; blood disorders and jaundice reported; on intravenous injection, pain, thrombophlebitis, and rarely apnoea

The description in the BNF No 31 is rather complicated (i.e., nitrazepam is referred in the description on flunitrazepam, and, diazepam is referred in the description on nitrazepam) but in this thesis, all of the side effects given under nitrazepam or diazepam in the BNF No 31 are regarded as currently known ADRs to flunitrazepam and those side effects not given in the BNF No 9 are regarded as 'previously unknown ADRs' (category B).

The event dictionary low-level terms corresponding to the terms in the BNF No 31

	ADRs in the BNF No 31	described in the BNF 9 ? (Y/N)	Event Dictionary low-level term(s)
1	Drowsiness the next day	Y	Drowsiness + Sedation
2	Lightheadedness the next day	Y	Dizziness
3	Confusion	Y	Confusion
4	Ataxia	Y	Ataxia
5	Amnesia	N	Amnesia
6	Dependence	Y	Dependence
7	Paradoxical increase in aggression	N	Aggression
8	Headache	N	Headache
9	Vertigo	N	Vertigo

10	Hypotension	N	Hypotension
11	Salivation change	N	Saliva increased
12	Gastrointestinal disturbances	N	Dyspepsia + Nausea + Vomiting + Diarrhoea + Pain abdomen
13	Rashes	N	Rash
14	Visual disturbances	N	Diplopia + Vision deteriorated + Visual disturbances
15	Changes in libido	N	Libido decreased
16	Urinary retention	N	Retention
17	Blood disorders	N	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
18	Jaundice	N	Jaundice

Events signalled and not signalled

As shown in Table 13, 7 events (low-level terms) are signalled. One event is signalled by the statistical test only and another event is signalled by the rate ratio method only. The remaining 5 events (71 %) are signalled by both of the methods.

Three events are known ADRs but four events signalled are not shown in the BNF. Of these 4, at least one event may be considered to be a known ADR.

1 'Malaise' is described as an ADR in literature other than BNF[69]

If this event is added to currently known ADRs, 4 of 7 (57 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

No PEM report is available for flunitrazepam. However, some of the PEM study on flunitrazepam are mentioned in the PEM report on another hypnotic,

zopiclone[23]. In the appendix of the PEM report on zopiclone, all of the psychiatric terms are considered to be 'indication-related'. The same thing may apply to the PEM study on flunitrazepam and some of psychiatric events in Table 13 are likely to be confounded by the indication.

ADRs signalled

Of the 18 ADRs under categories A and B, just 2 ADRs, drowsiness and gastro-intestinal disturbances (11 %) are signalled. The remaining 16 known ADRs are rare except for rash (T1 = 1.2 per 1000 patients per month) and headache (T1 = 2.8 per 1000 patients per month). T1 was 0.4 per 1000 patients per month or less with other 14 known ADRs. (Note that T1 of some alimentary events such as 'dyspepsia' [line 51], 'vomiting' [line 53] and 'pain abdomen' [line 54] is not small but these events are raised as those corresponding to an ADR 'gastro-intestinal disturbances' and this ADR is judged to be signalled as other two event dictionary terms 'diarrhoea' and 'nausea' corresponding to this ADR are signalled.)

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		7491		37278			min	max
3	Denominator male		2367		11787				
4	Denominator female		4950		24622				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*1*	
11	**Central and Peripheral Nervous System**								
12	Drowsiness	$$*	19	2.5	9	0.2	10.5	4.8	23.2
13									
14	***B. Previously unknown ADRs signalled***							*2*	
15	**Alimentary**								
16	Diarrhoea	$	17	2.3	32	0.9	2.6	1.5	4.8
17	Nausea	$$*	12	1.6	12	0.3	5.0	2.2	11.1
18									
19	***E. No description in BNF but signalled***							*4*	
20	**Psychiatric**								
21	Depression @	*	44	5.9	114	3.1	1.9	1.4	2.7
22	Dreams abnormal	$$*	10	1.3	5	0.1	10.0	3.4	29.1
23	Malaise	$$*	10	1.3	7	0.2	7.1	2.7	18.7
24	Overdose unknown drug*	$$	10	1.3	16	0.4	3.1	1.4	6.9
25									
26	***Events NOT signalled***								
27									
28	***A. Previously known ADRs NOT signalled***							*5*	
29	**Psychiatric**								
30	Confusion		4	0.5	10	0.3	-	-	-
31	**Central and Peripheral Nervous System**								
32	Ataxia		1	0.1	1	0.0	-	-	-
33	Dizziness		7	0.9	33	0.9	-	-	-
34	Sedation		4	0.5	4	0.1	-	-	-
35	**Adverse Reaction to Specific Drug**								
36	Dependence		1	0.1	4	0.1	-	-	-
37									
38									
39									
40									
41									
42									
43									
44									
45									
46									
47									
48									
49									
50									
51									
52									
53									
54									
55									

Table 13 Flunitrazepam: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
56	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
57	***B. Previously unknown ADRs NOT signalled***							***22***	
58	**Skin**								
59	Rash		9	1.2	21	0.6	2.1	1.0	4.7
60	**Psychiatric**								
61	Aggression		2	0.3	3	0.1	-	-	-
62	Libido decreased		0	0.0	3	0.1	-	-	-
63	**Central and Peripheral Nervous System**								
64	Amnesia		0	0.0	0	0.0	-	-	-
65	Headache		21	2.8	47	1.3	2.2	1.3	3.7
66	**Eye**								
67	Diplopia		1	0.1	2	0.1	-	-	-
68	Vision deteriorated		0	0.0	1	0.0	-	-	-
69	Visual disturbance		1	0.1	0	0.0	-	-	-
70	**Ear**								
71	Vertigo		3	0.4	15	0.4	-	-	-
72	**Cardiovascular**								
73	Hypotension		1	0.1	2	0.1	-	-	-
74	**Alimentary**								
75	Dyspepsia@		12	1.6	35	0.9	1.7	0.9	3.3
76	Jaundice		0	0.0	1	0.0	-	-	-
77	Vomiting		4	0.5	22	0.6	-	-	-
78	Pain abdomen		18	2.4	42	1.1	2.1	1.2	3.7
79	Saliva increased		0	0.0	0	0.0	-	-	-
80	**Urologic**								
81	Retention		1	0.1	3	0.1	-	-	-
82	**Haemopoietic**								
83	Leucopenia@		0	0.0	1	0.0	-	-	-
84	Neutropenia		0	0.0	0	0.0	-	-	-
85	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
86	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
87	Pancytopenia@		0	0.0	1	0.0	-	-	-
88	Thrombocytopenia		0	0.0	1	0.0	-	-	-

Table 13 Flunitrazepam: Events signalled and not signalled

6 Diltiazem

ADRs in the BNF

Description in the BNF No 14 September 1987

DILTIAZEM
Side-effects: bradycardia, hypotension, ankle oedema, rarely headache, nausea, rashes

ADRs in the BNF No 14

1 Bradycardia
2 Hypotension
3 Ankle oedema
4 Headache
5 Nausea
6 Rashes

Description in the BNF No 31 March 1996

DILTIAZEM
Side-effects: bradycardia, sino-atrial block, atrio-ventricular block, hypotension, malaise, headache, hot flushes, gastro-intestinal disturbances, oedema (notably of ankles); rarely rashes (erythema multiforme reported); altered liver function tests; hepatitis and depression reported

The event dictionary low-level terms corresponding to the terms in the BNF No 31

ADRs in the BNF No 31	described in the BNF 14 ? (Y/N)	Event Dictionary low-level term(s)

1	Bradycardia	Y	Bradycardia
2	Sino-atrial block	N	Sick sinus syndrome*
3	Atrio-ventricular block	N	Heart block
4	Hypotension	Y	Hypotension
5	Malaise	N	Malaise + Lassitude
6	Headache	Y	Headache
7	Hot flushes	N	Flushing
8	Gastrointestinal disturbances	N&Y**	Dyspepsia + Nausea + Vomiting + Diarrhoea + Pain abdomen
9	Oedema	N	Oedema + Swollen ankles + Swollen limb
10	Rashes	N&Y***	Rash + Erythema multiforme

* See below (ADRs signalled) for the reason why this term is listed as a term corresponding to 'sino-atrial block'
** Nausea given in the BNF 14
*** Rashes given in the BNF 14

Questionable ADRs

Q1	Hepatitis	Hepatitis
Q2	Depression	Depression

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Altered liver function	Liver function test abnormal

Events signalled and not signalled

As shown in Table 14, 16 events (low-level terms) are signalled. Three events are signalled by the statistical test only and one event is signalled by the rate ratio method only. The remaining 12 events (75 %) are signalled by both of the methods.

Nine events signalled are known ADRs but seven events signalled are not

shown in the BNF. Of these seven events, at least 2 events may be considered to be known ADRs.

1 'Dizziness' is described as an ADR in literature other than the BNF[70]

2 'Tachycardia' is described as an ADR in literature other than the BNF[70]

If those 2 events are added to currently known ADRs, 11 of 16 events signalled (69 %) may be judged to be currently known ADRs.

No events under category C or category D were signalled.

Confounding by the indication or 'indication-related' event

The results of the PEM study on diltiazem were reported in 1990[71]. In this report, the 'on' vs 'off' comparison was used and no comparison between T1 and T2 was employed. Interestingly, in this report some of the events under the group 'no description in BNF but signalled' such as cardiac failure, myocardial infarction and tachycardia are shown as events which have the 'on' rates being similar to the 'off' rates. This makes a clear contrast to 'bradycardia' where the 'on' rate is 14 times bigger than the 'off' rate. Similarly, the 'on' rates of rash, dizziness and headache and oedema were bigger than the 'off' rates with the factor of 2.7 or more[71]. This indicates that the 'on' vs 'off' comparison may give some evidence which suggests some of the events 'signalled' by the comparison between T1 and T2 may be confounded by the indication.

ADRs signalled

Of the 10 ADRs under categories A and B, 7 ADRs (70 %) are signalled. Of the remaining 3 known ADRs one event dictionary term 'heart block' is rare and T1 = 0.2 and T2 = 0.3 per 1000 patients per month. As shown in Table 14, 15 patients developed heart block in the first six months, but 6 other patients were reported to have experienced heart block in month 7 to month 12. One other patient developed heart block, 15 months after the first prescription. The 22 patients who developed heart block were followed-up and except for 4 patients where type of heart block was unknown all the patients had atrio-ventricular

block. For three patients there was a clearly identifiable precipitating factor for heart block, such as coronary artery surgery and myocardial infarction. Two other patients were known to have had first degree heart block prior to diltiazem treatment[71].

Five patients coded as having sick sinus syndrome were also investigated further. Two were reported to have developed sino-atrial block during diltiazem[71].

With 'hypotension', T1 and T2 were approximately the same (0.8 and 0.7 per 1000 patients per month, respectively).

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		10099		50317			min	max
3	Denominator male		5993		29869				
4	Denominator female		3966		19750				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*4*	
11	**Skin**								
12	Rash	$$*	65	6.4	70	1.4	4.6	3.3	6.5
13	**Central and Peripheral Nervous System**								
14	Headache	$$*	77	7.6	79	1.6	4.9	3.5	6.6
15	**Cardiovascular**								
16	Bradycardia	$$*	22	2.2	29	0.6	3.8	2.2	6.6
17	**Alimentary**								
18	Nausea	$$*	48	4.8	39	0.8	6.1	4.0	9.4
19									
20	***B. Previously unknown ADRs signalled***							*5*	
21	**Psychiatric**								
22	Lassitude	$$*	36	3.6	51	1.0	3.5	2.3	5.4
23	Malaise	$$*	45	4.5	52	1.0	4.3	2.9	6.4
24	**Central and Peripheral Nervous System**								
25	Flushing	$$*	17	1.7	23	0.5	3.7	2.0	6.9
26	**Cardiovascular**								
27	Swollen ankles	$$*	12	1.2	14	0.3	4.3	2.0	9.2
28	**Alimentary**								
29	Dyspepsia@	*	31	3.1	65	1.3	2.4	1.5	3.6
30									
31	***C. Questionable ADRs signalled***							*0*	
32									
33	***D. 'Hard-to-detect' ADRs signalled***							*0*	
34									
35	***E. No description in BNF but signalled***							*7*	
36	**Central and Peripheral Nervous System**								
37	Dizziness	$*	57	5.6	103	2.0	2.8	2.0	3.8
38	Tremor	$$*	11	1.1	4	0.1	13.7	4.4	43.0
39	**Cardiovascular**								
40	Left ventricular failure*	$	19	1.9	38	0.8	2.5	1.4	4.3
41	Tachycardia	$$*	11	1.1	13	0.3	4.2	1.9	9.4
42	Myocardial infarction*	*	41	4.1	107	2.1	1.9	1.3	2.7
43	**Respiratory**								
44	Dyspnoea	*	39	3.9	97	1.9	2.0	1.4	2.9
45	**Metabolic and Endocrine**								
46	Sweating	$$*	11	1.1	10	0.2	5.5	2.3	12.9
47									
48									
49									
50									
51									
52									
53									

Table 14 Diltiazem: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***Events NOT signalled***								
56									
57	***A. Previously known ADRs NOT signalled***							*1*	
58	**Cardiovascular**								
59	Hypotension		8	0.8	37	0.7	-	-	-
60									
61	***B. Previously unknown ADRs NOT signalled***							*8*	
62	**Skin**								
63	Erythema multiforme		0	0.0	0	0.0	-	-	-
64	**Cardiovascular**								
65	Sick-sinus syndrome		1	0.1	2	0.0	-	-	-
66	Heart block*		2	0.2	13	0.3	-	-	-
67	Oedema@		26	2.6	59	1.2	2.2	1.4	3.5
68	Swollen limb		0	0.0	0	0.0	-	-	-
69	**Alimentary**								
70	Diarrhoea		9	0.9	50	1.0	-	-	-
71	Vomiting		19	1.9	40	0.8	2.4	1.4	4.1
72	Pain abdomen		15	1.5	78	1.6	1.0	0.6	1.7
73									
74	***C. 'Questionable' ADRs NOT signalled***							*2*	
75	**Psychiatric**								
76	Depression @		17	1.7	90	1.8	0.9	0.6	1.6
77	**Alimentary**								
78	Hepatitis*		0	0.0	0	0.0	-	-	-
79									
80	***D. 'Hard-to-detect' ADRs NOT signalled***							*1*	
81	**Alimentary**								
82	Liver function test abnormal		1	0.1	0	0.0	-	-	-

Table 14 Diltiazem: Events signalled and not signalled

7 Nicardipine

ADRs in the BNF

Description in the BNF No 18 September 1989

NICARDIPINE HYDROCHLORIDE
Side-effects: dizziness, headache, peripheral oedema, flushing, palpitations, nausea; also gastro-intestinal disturbances, drowsiness, hypotension, rashes, salivation, frequency of micturition

ADRs in the BNF No 18

1 Dizziness
2 Headache
3 Peripheral oedema
4 Flushing
5 Palpitations
6 Nausea
7 Gastro-intestinal disturbances
8 Drowsiness
9 Hypotension
10 Rashes
11 Salivation
12 Frequency of micturition

Description in the BNF No 31 March 1996

NICARDIPINE HYDROCHLORIDE
Side-effects: dizziness, headache, peripheral oedema, flushing, palpitations, nausea; also gastro-intestinal disturbances, drowsiness, insomnia, tinnitus, hypotension, rashes, salivation, frequency of micturition; thrombocytopenia reported

The event dictionary low-level terms corresponding to the terms in BNF No 14

ADRs in BNF No 30		described in BNF 18 ? (Y/N)	Event Dictionary low-level term(s)
1	Dizziness	Y	Dizziness
2	Headache	Y	Headache
3	Peripheral oedema	Y	Oedema + Swollen ankles + Swollen limb
4	Flushing	Y	Flushing
5	Palpitations	Y	Palpitation
6	Nausea	Y	Nausea
7	Gastrointestinal disturbances	Y	Dyspepsia + Vomiting + Diarrhoea + Pain abdomen
8	Drowsiness	Y	Drowsiness + Sedation
9	Insomnia	N	Insomnia
10	Tinnitus	N	Tinnitus
11	Hypotension	Y	Hypotension
12	Rashes	Y	Rash
13	Salivation	Y	Saliva increased
14	Frequency of micturition	Y	Frequency
Questionable ADRs			
Q1	Thrombocytopenia		Thrombocytopenia

Events signalled and not signalled

As shown in Table 15, 22 events (low-level terms) are signalled. Four events are signalled by the statistical test only. The remaining 18 events (82 %) are signalled by both of the methods.

10 events signalled are known ADRs and some of them known associated with vasodilatation have been discussed in detail elsewhere[72]. On the other hand, 12 events signalled are not shown in the BNF. Of these 12 events, at least 4 events may be considered to be known ADRs.

1 'Dyspnoe' is described as an ADR in literature other than the BNF[73]

2&3 'Lassitude' and 'Malaise' are considered to be known ADRs (given as 'Fatigue' or 'Weakness') in literature other than the BNF[73]

4 'Menopausal symptoms' may be associated with 'flushing' misunderstood by doctors regarding some female patients.

If those 4 events are added to currently known ADRs, 14 of 22 events signalled (64 %) may be judged to be currently known ADRs.

No events under category C was signalled.

Confounding by the indication or 'indication-related' event

In the PEM report on nicardipine[30], 'pain chest' in Table 15 is designated as an 'indication-related' event as well as other 4 events which are not signalled. The other 4 'indication-related' events are 'angina', 'ischaemic heart disease', 'myocardial infarction' and 'hypertension' and all of them are in fact major indications themselves rather than the 'indication-related' events. Even if those events are not 'signalled' by the comparison between T1 and T2, the rates are remarkably high when compared with other drugs. Currently, several authors suggest a possibility that calcium antagonists (particularly dihydropyridine calcium antagonists including nicardipine) increase the rate of myocardial infarction[46,47]. However, the fact that the rate of myocardial infarction etc. with nicardipine is significantly higher than that with other drugs observed in PEM cannot be used as an evidence to support this hypothesis. As in the current PEM where concurrent control is not available and the information on the confounding variables is scarce, it is quite difficult or actually impossible to give any reliable evidence which may support or deny the hypothesis that dihydropyridine antagonists increase the rate of myocardial infarction.

ADRs signalled

Of the 14 ADRs under categories A or B, 8 ADRs (57 %) are signalled. Of the remaining 6 known ADRs 'salivation' is rare (only 1 event is coded during the

first 6 months) and T1 of 'drowsiness' is 0.6 per 1000 patients per month. With hypotension, T1 and T2 were similar to each other (0.9 and 0.7 per 1000 patients per month, respectively). T1 for 'frequency', 'tinnitus' and 'insomnia' were between 0.5 and 0.7 per 1000 patients per month.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		10906		54342			min	max
3	Denominator male		5274		26284				
4	Denominator female		5481		27310				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***10***	
11	**Skin**								
12	Rash	$$*	32	2.9	50	0.9	3.2	2.0	5.0
13	**Central and Peripheral Nervous System**								
14	Dizziness	$$*	113	10.4	153	2.8	3.7	2.9	4.7
15	Flushing	$$*	190	17.4	135	2.5	7.0	5.6	8.7
16	Headache	$$*	222	20.4	183	3.4	6.0	5.0	7.4
17	**Cardiovascular**								
18	Oedema@	$$*	88	8.1	127	2.3	3.5	2.6	4.5
19	Swollen ankles	$$*	26	2.4	38	0.7	3.4	2.1	5.6
20	Palpitation	$$*	99	9.1	73	1.3	6.8	5.0	9.1
21	**Alimentary**								
22	Dyspepsia@	$*	46	4.2	83	1.5	2.8	1.9	4.0
23	Nausea	$$*	81	7.4	55	1.0	7.3	5.2	10.3
24	Vomiting	$$*	24	2.2	26	0.5	4.6	2.6	8.0
25									
26	***B. Previously unknown ADRs signalled***							***0***	
27									
28	***C. Questionable ADRs signalled***							***0***	
29									
30	***E. No description in BNF but signalled***							***12***	
31	**Musculoskeletal**								
32	Pain limb	*	23	2.1	47	0.9	2.4	1.5	4.0
33	**Psychiatric**								
34	Lassitude	$*	45	4.1	90	1.7	2.5	1.7	3.6
35	Malaise	$$*	91	8.3	70	1.3	6.5	4.7	8.8
36	**Central and Peripheral Nervous System**								
37	Feeling cold	*	6	0.6	2	0.0	-	-	-
38	Hyperaesthesia	$$*	15	1.4	15	0.3	5.0	2.4	10.2
39	Tremor	$$*	25	2.3	14	0.3	8.9	4.6	17.1
40	**Cardiovascular**								
41	Tachycardia	$$*	53	4.9	34	0.6	7.8	5.0	11.9
42	Faintness	*	10	0.9	5	0.1	-	-	-
43	Pain chest	$$*	59	5.4	98	1.8	3.0	2.2	4.1
44	**Respiratory**								
45	Dyspnoea	*	38	3.5	84	1.5	2.3	1.5	3.3
46	**Female Reproductive**								
47	Menopausal symptoms	$$*	8	1.5	6	0.2	6.6	2.3	19.1
48	**Immunological**								
49	Unspecified side effects	$$*	32	2.9	12	0.2	13.3	6.8	25.8
50									
51									
52									
53									
54									

Table 15 Nicardipine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
55	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
56	***Events NOT signalled***								
57									
58	***A. Previously known ADRs NOT signalled***							*8*	
59	**Central and Peripheral Nervous System**								
60	Drowsiness		7	0.6	10	0.2	-	-	-
61	Sedation		0	0.0	1	0.0	-	-	-
62	**Cardiovascular**								
63	Hypotension		10	0.9	40	0.7	-	-	-
64	Swollen limb		3	0.3	5	0.1	-	-	-
65	**Alimentary**								
66	Diarrhoea		13	1.2	50	0.9	1.3	0.7	2.4
67	Pain abdomen		23	2.1	62	1.1	1.8	1.1	3.0
68	Saliva increased		0	0.0	1	0.0	-	-	-
69	**Urologic**								
70	Frequency		8	0.7	17	0.3	-	-	-
71									
72	***B. Previously unknown ADRs NOT signalled***							*2*	
73	**Psychiatric**								
74	Insomnia		8	0.7	20	0.4	-	-	-
75	**Ear**								
76	Tinnitus		5	0.5	14	0.3	-	-	-
77									
78	***C. 'Questionable' ADRs NOT signalled***							*1*	
79	**Haemopoietic**								
80	Thrombocytopenia		0	0.0	0	0.0	-	-	-

Table 15 Nicardipine: Events signalled and not signalled

8 Doxazosin

ADRs in the BNF

Description in the BNF No 23 March 1992

DOXAZOSIN
Side-effects: postural hypotension (rarely associated with fainting); dizziness, vertigo, headache, fatigue, asthenia, oedema

ADRs in the BNF No 23

1 Postural hypotension rarely with fainting
2 Dizziness
3 Vertigo
4 Headache
5 Fatigue
6 Asthenia
7 Oedema

Description in the BNF No 31 March 1996

DOXAZOSIN
Side-effects: postural hypotension (rarely associated with fainting); dizziness, vertigo, headache, fatigue, asthenia, oedema, somnolence, nausea, rhinitis, urinary incontinence reported

ADRs in the BNF No 31	described in the BNF 23 ? (Y/N)	Event Dictionary low-level term(s)
1 Postural hypotension rarely with fainting	Y	Hypotension + Faintness + Syncope
2 Dizziness	Y	Dizziness
3 Vertigo	Y	Vertigo

4	Headache	Y	Headache
5&6	Fatigue and Asthenia	Y	Malaise + Lassitude
7	Oedema	Y	Oedema
8	Somnolence	N	Drowsiness + Sedation
9	Nausea	N	Nausea
10	Rhinitis	N	Rhinitis
11	Urinary incontinence	N	Incontinence

Events signalled and not signalled

As shown in Table 16, 19 events (low-level terms) are signalled. One event is signalled by the statistical test only and the four events are signalled by the rate ratio method only. The remaining 14 events (74 %) are signalled by both of the methods.

Seven events signalled are known ADRs but 12 events signalled are not shown in the BNF. Of these 12 events, at least 6 events may be considered to be known ADRs.

1 'Tachycardia' is described as an ADR in literature other than BNF[74]
2 'Paraesthesia' is described as an ADR in literature other than BNF[74]
3 'Sweating' is described as an ADR in literature other than BNF[74]
4 'Diarrhoea' is described as an ADR in literature other than BNF[74]
5 'Palpitation' is described as an ADR in literature other than BNF[74]
6 'Dyspnoe' is described as an ADR in literature other than BNF[74]

If those 6 events are added to currently known ADRs, 13 of 19 events signalled (68 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

Though the formal PEM report is not available on doxazosin, in a draft of the PEM report on doxazosin made in January 1995[75], two events 'hypertension' and 'ischaemic heart disease' are designated as 'indication-related events'. However, these two events are not signalled and not shown in Table 16.

ADRs signalled

Of the 11 ADRs under category A, 7 ADRs (64 %) are signalled. Of the remaining 4 known ADRs 'rhinitis' and 'incontinence' are rare (T1 = 0.6 per 1000 patients per month or less). With two events 'vertigo' and 'hypotension', T1 is similar to T2. 'Syncope' and 'faintness' which are said to 'rarely' accompany with postural hypotension are not signalled. However, if these two events are lumped together as a new event, T1/T2 = 2.6 and the likelihood ratio test is significant ($p < 0.001$).

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		8481		42328			min	max
3	Denominator male		3798		18956				
4	Denominator female		4621		23064				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	***A. Previously known ADRs signalled***							***5***	
11	**Psychiatric**								
12	Lassitude	*	51	6.0	106	2.5	2.4	1.7	3.4
13	Malaise	$$*	102	12.0	84	2.0	6.1	4.5	8.1
14	**Central and Peripheral Nervous System**								
15	Dizziness	$$*	120	14.1	141	3.3	4.2	3.3	5.4
16	Headache	$$*	149	17.6	167	3.9	4.5	3.6	5.6
17	**Cardiovascular**								
18	Oedema@	$$*	46	5.4	57	1.3	4.0	2.7	5.9
19									
20	***B. Previously unknown ADRs signalled***							***2***	
21	**Central and Peripheral Nervous System**								
22	Drowsiness	$$*	19	2.2	17	0.4	5.6	2.9	10.7
23	**Alimentary**								
24	Nausea	$$*	34	4.0	34	0.8	5.0	3.1	8.0
25									
26	***E. No description in BNF but signalled***							***12***	
27	**Central and Peripheral Nervous System**								
28	Flushing	$$*	14	1.7	19	0.4	3.7	1.8	7.3
29	Migraine	$$	9	1.1	13	0.3	3.5	1.5	8.1
30	Paraesthesia	$	10	1.2	18	0.4	2.8	1.3	6.0
31	Tremor	$$*	19	2.2	11	0.3	8.6	4.1	18.1
32	**Cardiovascular**								
33	Tachycardia	$$*	14	1.7	14	0.3	5.0	2.4	10.5
34	Swollen ankles	$$*	15	1.8	8	0.2	9.4	4.0	22.1
35	Palpitation	$$*	53	6.2	40	0.9	6.6	4.4	10.0
36	**Respiratory**								
37	Dyspnoea	$*	26	3.1	46	1.1	2.8	1.7	4.6
38	**Alimentary**								
39	Diarrhoea	$$*	18	2.1	27	0.6	3.3	1.8	6.0
40	Vomiting	$	13	1.5	23	0.5	2.8	1.4	5.6
41	**Metabolic and Endocrine**								
42	Sweating	$$	9	1.1	13	0.3	3.5	1.5	8.1
43	**Immunological**								
44	Unspecified side effects	$$*	12	1.4	15	0.4	4.0	1.9	8.5
45									
46									
47									
48									
49									
50									
51									
52									
53									
54									
55									

Table 16 Doxazosin: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
56	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
57	***Events NOT signalled***								
58									
59	***A. Previously known ADRs NOT signalled***							*4*	
60	**Central and Peripheral Nervous System**								
61	Syncope		14	1.7	29	0.7	2.4	1.3	4 6
62	**Ear**								
63	Vertigo		8	0.9	37	0.9	-	-	-
64	**Cardiovascular**								
65	Faintness		7	0.8	11	0 3	-	-	-
66	Hypotension		13	1.5	49	1.2	1.3	0.7	2.4
67									
68	***B. Previously unknown ADRs NOT signalled***							*3*	
69	**Central and Peripheral Nervous System**								
70	Sedation		1	0.1	5	0.1	-	-	-
71	**Respiratory**								
72	Rhinitis		2	0.2	10	0.2	-	-	-
73	**Urologic**								
74	Incontinence		5	0.6	13	0.3	-	-	-

Table 16 Doxazosin: Events signalled and not signalled

9 Enalapril

ADRs in the BNF

Description in the BNF No 12 September 1986

ENALAPRIL MALEATE

Side-effects: dizziness, headache, fatigue, weakness, hypotension (see also Cautions), alteration of taste, nausea, diarrhoea, muscle cramps, cough, rash and angioedema; increases in blood urea and plasma creatinine more common in renal impairment

'Cautions' for enalapril in the BNF No 12 are given as below

Cautions: where possible reduce dose of any diuretic being given concurrently; first dose may cause hypotension especially in patients taking diuretics, on a low-sodium diet, on dialysis, or dehydrated; reduce dose in renal impairment; pregnancy (toxicity in *animal* studies). Drug interactions: see Appendix 1 (sections 2.5, *8*)

ADRs in the BNF No 12

1 Dizziness
2 Headache
3 Fatigue
4 Weakness
5 Hypotension (first dose)
6 Alteration of taste
7 Nausea
8 Diarrhoea
9 Muscle cramps
10 Cough
11 Rash
12 Angioedema

13 Increases in blood urea
14 Increases in creatinine

Description in the BNF No 31 March 1996

ENALAPRIL MALEATE
Cautions; Contra-indications; Side-effects: see under Captopril and notes above

CAPTOPRIL
Side-effects: hypotension (see Cautions); dizziness, headache, fatigue, asthenia, nausea (occasionally vomiting), diarrhoea (occasionally constipation), muscle cramps, persistent dry cough, throat discomfort, voice changes, taste alteration (may be associated with weight loss), stomatitis, dyspepsia, abdominal pain; renal impairment (see Cautions and notes above); hyperkalaemia (more common in renal impairment, see notes above); angioedema, urticaria, rashes (erythema multiforme and toxic epidermal necrolysis reported), and hypersensitivity reaction (see below for Symptom Complex), blood disorders (including thrombocytopenia, neutropenia, agranulocytosis and aplastic anaemia); other side-effects reported include upper respiratory tract symptoms, hyponatraemia, tachycardia, palpitations, arrhythmias, myocardial infarction and cerebrovascular accident (possibly associated with severe hypotension), back pain, flushing, jaundice (hepatocellular or cholestatic), pancreatitis, sleep paraesthesia, impotence, onycholysis, alopecia
SYMPTOM COMPLEX. A symptom complex has been reported for ACE inhibitors which may include fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis; rash, photosensitivity or other skin reactions may occur.

'Cautions' for captopril in BNF No 31 are given below for a reference

Cautions: diuretics (important: see notes above); first doses may cause hypotension especially in patients taking diuretics, on a low-sodium diet, on dialysis, or dehydrated; peripheral vascular disease or generalised atherosclerosis owing to risk of clinically silent renovascular disease (see also notes above); monitor renal function before and during treatment, and reduce dose in renal impairment (see also notes above); possible increased risk of agranulocytosis in collagen vascular disease (blood counts recommended); anaphylactoid reactions (see below); breast-feeding (see Appendix 5); interactions: Appendix 1 (ACE inhibitors)

ANAPHYLACTOID REACTIONS. To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis, with dextran sulphate; they should also be withheld before desensitisation with wasp or venom

ADRs in the BNF No 31		described in the BNF 12 ? (Y/N)	Event Dictionary low-level term(s)
1	Hypotension (first dose)	Y	Hypotension
2	Dizziness	Y	Dizziness
3	Headache	Y	Headache
4&5	Fatigue and Asthenia	Y	Malaise + Lassitude
6	Nausea	Y	Nausea
7	Vomiting	N	Vomiting
8	Diarrhoea	Y	Diarrhoea
9	Constipation	N	Constipation
10	Muscle cramps	Y	Cramp
11	Persistent dry cough	Y	Cough
12	Throat discomfort	N	Pharynx irritation + Pharyngitis + Laryngitis
13	Voice changes	N	Hoarseness
14	Taste alteration	Y	Taste abnormal
15	Stomatitis	N	Stomatitis
16	Dyspepsia	N	Dyspepsia

17	Abdominal pain	N	Pain abdomen
18	Renal impairment	Y&N	Renal failure + Renal failure acute + Renal failure chronic + Uraemia + Urea raised + Renal function test abnormal
19	Hyperkalaemia	N	Hyperkalaemia
20	Angioedema	Y	Angioneurotic oedema
21	Urticaria	N	Urticaria
22	Rashes	Y	Rash
23	Erythema multiforme	N	Erythema Multiforme
24	Toxic epidermal necrolysis	N	no term available
25	Hypersensitivity reactions	N	Allergy
26	Blood disorders	N	Thrombocytopenia + Leucopenia + Neutropenia + Anaemia aplastic + Anaemia hypoplastic + Pancytopenia
27	Upper respiratory tract symptoms	N	no term available
28	Tachycardia	N	Tachycardia
29	Palpitations	N	Palpitation
30	Arrhythmias	N	Arrhythmia
31	Myocardial infarction	N	Myocardial infarction
32	Cerebrovascular accident	N	Cerebrovascular accident + Stenosis artery cerebral + Vertebrobasilar syndrome
33	Back pain	N	Pain back
34	Flushing	N	Flushing
35	Jaundice	N	Jaundice + Jaundice cholestatic
36	Pancreatitis	N	Pancreatitis
37	Sleep paraesthesia	N	Paraesthesia
38	Impotence	N	Impotence
39	Onycholysis	N	Onycholysis
40	Alopecia	N	Alopecia

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Hyponatraemia	Hyponatraemia

Events signalled

As shown in Table 17, 12 events (low-level terms) are signalled. One event is signalled by the statistical test only. The remaining 11 events (92 %) are signalled by both of the methods.

Of the 12 events signalled, 10 events (83 %) are known ADRs but two events signalled are not shown in the BNF.

Confounding by the indication or 'indication-related' event

Oedema which is signalled may be confounded by the indication (cardiac failure).

ADRs signalled

Of the 40 ADRs under category A or B, 10 ADRs (25 %) are signalled of which 3 are judged to be previously unknown (Category B). In a paper published in BMJ in 1988[76], some more information was given on hypotension; 120 patients stopped treatment because of it, 36 continued at a reduced dose, and 61 continued at the same dose. 92 reports stated that the hypotension was postural. Elderly patients in heart failure were particularly likely to develop hypotension after small doses.

Of the 30 known ADRs not signalled, the event with the largest rate is cough (T1 = 3.5). As discussed in detail elsewhere[77], cough was not widely accepted as an ADR to ACE-inhibitor when the PEM study of enalapril was conducted even if this ADR was already written in BNF No 12. The rate of cough with enalapril was approximately one third of the rate with other ACE-inhibitors monitored later after cough was widely accepted as a class effect to ACE-inhibitors. This indicates that under-reporting prevails when an event is not serious and is commonplace so that it does not provoke doctors to suspect an ADR. What is more important is that with ACE-inhibitor-induced cough, the first occurrence of

cough does not necessarily occur in the first month after the prescription. However, it has been also shown that ACE-inhibitor-induced cough is characterised by its rapid disappearance after discontinuation of the drug[53,54]. Though the results of the 'on' vs 'off' comparison is not available for enalapril, if this comparison is done for all of the events signalled by the comparison between T1 and T2, cough may be illuminated as an event with high ratio of 'on' to 'off' rates.

Nine other known ADRs occurring relatively frequently are not signalled. For example, T1 is more than 1.0 per 1000 patients per month for rash, muscle cramp, pain back, paraestheia, myocardial infarction, dyspepsia, vomiting and pain abdomen all of which are not signalled. Some may represent just 'background' rates of non-specific events (e.g., pain back or paraesthesia) but some may be ADRs where the first occurrence is not necessarily confined to the first month after the prescription as with cough. With other 20 known ADRs not signalled, the rate was small. This includes renal failure and problems associated with renal failure[76,78] have been already discussed in the introduction section.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		15349		73792			min	max
3	Denominator male		7076		34063				
4	Denominator female		7944		38200				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*7*	
11	**Psychiatric**								
12	Lassitude	$$*	61	4.0	96	1.3	3.1	2.2	4.2
13	Malaise	$$*	108	7.0	100	1.4	5.2	4.0	6.8
14	**Central and Peripheral Nervous System**								
15	Dizziness	$$*	158	10.3	182	2.5	4.2	3.4	5.2
16	Headache	$$*	97	6.3	139	1.9	3.4	2.6	4.3
17	**Cardiovascular**								
18	Hypotension	$$*	75	4.9	105	1.4	3.4	2.6	4.6
19	**Alimentary**								
20	Diarrhoea	$$*	66	4.3	100	1.4	3.2	2.3	4.3
21	Nausea	$$*	75	4.9	84	1.1	4.3	3.1	5.9
22									
23	***B. Previously unknown ADRs signalled***							*3*	
24	**Central and Peripheral Nervous System**								
25	Flushing	$$*	18	1.2	25	0.3	3.5	1.9	6.3
26	**Cardiovascular**								
27	Tachycardia	$$*	28	1.8	27	0.4	5.0	2.9	8.5
28	Palpitation	$$*	40	2.6	41	0.6	4.7	3.0	7.3
29									
30	***D. 'Hard-to-detect' ADRs signalled***							*0*	
31									
32	***E. No description in BNF but signalled***							*2*	
33	**Central and Peripheral Nervous System**								
34	Drowsiness	*	10	0.7	10	0.1	-	-	-
35	**Cardiovascular**								
36	Oedema@	$*	30	2.0	53	0.7	2.7	1.7	4.3
37									
38									
39									
40									
41									
42									
43									
44									
45									
46									
47									
48									
49									
50									
51									
52									
53									
54									
55									

Table 17 Enalapril: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
56	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
57	***Events NOT signalled***								
58									
59	***A. Previously known ADRs NOT signalled***							*7*	
60	**Skin**								
61	Rash		30	2.0	96	1.3	1.5	1.0	2.3
62	**Musculoskeletal**								
63	Cramp		19	1.2	39	0.5	2.3	1.4	4.1
64	**Central and Peripheral Nervous System**								
65	Taste abnormal		3	0.2	15	0.2	-	-	-
66	**Respiratory**								
67	Cough		53	3.5	197	2.7	1.3	1.0	1.8
68	**Urologic**								
69	Renal function test abnormal		7	0.5	18	0.2	-	-	-
70	Urea raised		8	0.5	20	0.3	-	-	-
71	**Immunological**								
72	Angioneurotic oedema		2	0.1	5	0.1	-	-	-
73									
74	***B. Previously unknown ADRs NOT signalled***							*36*	
75	**Skin**								
76	Alopecia		1	0.1	2	0.0	-	-	-
77	Erythema multiforme		1	0.1	1	0.0	-	-	-
78	Onycholysis		0	0.0	0	0.0	-	-	-
79	Urticaria		5	0.3	14	0.2	-	-	-
80	**Musculoskeletal**								
81	Pain back		17	1.1	86	1.2	1.0	0.6	1.6
82	**Central and Peripheral Nervous System**								
83	Paraesthesia		16	1.0	32	0.4	2.4	1.3	4.4
84	**Cardiovascular**								
85	Cerebro-vascular accident*		13	0.8	43	0.6	-	-	-
86	Stenosis artery cerebral		0	0.0	0	0.0	-	-	-
87	Vertebrobasilar syndrome		0	0.0	1	0.0	-	-	-
88	Arrhythmia		3	0.2	11	0.1	-	-	-
89	Myocardial infarction*		18	1.2	69	0.9	1.3	0.7	2.1
90	**Respiratory**								
91	Hoarseness		1	0.1	6	0.1	-	-	-
92	Laryngitis		3	0.2	7	0.1	-	-	-
93	Pharyngitis		8	0.5	48	0.7	-	-	-
94	**Alimentary**								
95	Constipation		10	0.7	40	0.5	-	-	-
96	Dyspepsia@		32	2.1	78	1.1	2.0	1.3	3.0
97	Jaundice		1	0.1	1	0.0	-	-	-
98	Jaundice cholestatic		0	0.0	0	0.0	-	-	-
99	Vomiting		31	2.0	73	1.0	2.0	1.3	3.1
100	Pain abdomen		33	2.1	111	1.5	1.4	1.0	2.1
101	Pancreatitis*		0	0.0	1	0.0	-	-	-
102	Pharynx irritation		1	0.1	8	0.1	-	-	-
103	Stomatitis		0	0.0	2	0.0	-	-	-
104	**Metabolic and Endocrine**								
105	Hyperkalaemia		4	0.3	23	0.3	-	-	-
106	**Urologic**								
107	Renal failure acute		0	0.0	0	0.0	-	-	-
108	Renal failure chronic*		0	0.0	0	0.0	-	-	-
109	Renal failure*		10	0.7	51	0.7	-	-	-
110	Uraemia*		1	0.1	3	0.0	-	-	-

Table 17 Enalapril: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
111	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
112	***B. Previously unknown ADRs NOT signalled continued***								
113	**Male Reproductive and Gynaecomastia**								
114	Impotence		2	0.3	21	0.6	-	-	-
115	**Haemopoietic**								
116	Leucopenia@		1	0.1	0	0.0	-	-	-
117	Neutropenia		0	0.0	1	0.0	-	-	-
118	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
119	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
120	Pancytopenia@		0	0.0	0	0.0	-	-	-
121	Thrombocytopenia		0	0.0	1	0.0	-	-	-
122	**Immunological**								
123	Allergy		4	0.3	8	0.1	-	-	-
124									
125	***D. 'Hard-to-detect' ADRs NOT signalled***							*1*	
126	**Metabolic and Endocrine**								
127	Hyponatraemia		1	0.1	2	0.0	-	-	-

Table 17 Enalapril: Events signalled and not signalled

10 Lisinopril

ADRs in the BNF

Description in the BNF No 18 September 1989

LISINOPRIL
Side-effects: see under Captopril; palpitations and chest pain also reported.

ENALAPRIL MALEATE
Side-effects: persistent dry cough; dizziness, headache, fatigue, weakness, hypotension (see Cautions), change of taste, nausea, diarrhoea, muscle cramps, rash, and angioedema; renal impairment, see notes above

ADRs in the BNF No 18

1 Persistent dry cough
2 Dizziness
3 Headache
4 Fatigue
5 Weakness
6 Hypotension (first dose)
7 Change of taste
8 Nausea
9 Diarrhoea
10 Muscle cramps
11 Rash
12 Angioedema
13 Renal impairment
14 Palpitation
15 Chest pain

Description in the BNF No 31 March 1996

LISINOPRIL

Cautions; Contra-indications; Side-effects: see under Captopril and notes above

CAPTOPRIL

Side-effects: hypotension (see Cautions); dizziness, headache, fatigue, asthenia, nausea (occasionally vomiting), diarrhoea (occasionally constipation), muscle cramps, persistent dry cough, throat discomfort, voice changes, taste alteration (may be associated with weight loss), stomatitis, dyspepsia, abdominal pain; renal impairment (see Cautions and notes above); hyperkalaemia (more common in renal impairment, see notes above); angioedema, urticaria, rashes (erythema multiforme and toxic epidermal necrolysis reported), and hypersensitivity reaction (see below for Symptom Complex), blood disorders (including thrombocytopenia, neutropenia, agranulocytosis and aplastic anaemia); other side-effects reported include upper respiratory tract symptoms, hyponatraemia, tachycardia, palpitations, arrhythmias, myocardial infarction and cerebrovascular accident (possibly associated with severe hypotension), back pain, flushing, jaundice (hepatocellular or cholestatic), pancreatitis, sleep paraesthesia, impotence, onycholysis, alopecia
SYMPTOM COMPLEX. A symptom complex has been reported for ACE inhibitors which may include fever, serositis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis; rash, photosensitivity or other skin reactions may occur.

'Cautions' for captopril in BNF No 31 are given below for a reference

Cautions: diuretics (important: see notes above); first doses may cause hypotension especially in patients taking diuretics, on a low-sodium diet, on dialysis, or dehydrated; peripheral

vascular disease or generalised atherosclerosis owing to risk of clinically silent renovascular disease (see also notes above); monitor renal function before and during treatment, and reduce dose in renal impairment (see also notes above); possible increased risk of agranulocytosis in collagen vascular disease (blood counts recommended); anaphylactoid reactions (see below); breast-feeding (see Appendix 5); interactions: Appendix 1 (ACE inhibitors)

ANAPHYLACTOID REACTIONS. To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile membranes and during low-density lipoprotein apheresis, with dextran sulphate; they should also be withheld before desensitisation with wasp or venom

ADRs in the BNF No 31		described in the BNF 18? (Y/N)	Event Dictionary low-level term(s)
1	Hypotension (first dose)	Y	Hypotension
2	Dizziness	Y	Dizziness
3	Headache	Y	Headache
4&5	Fatigue and Asthenia	Y	Malaise + Lassitude
6	Nausea	Y	Nausea
7	Vomiting	N	Vomiting
8	Diarrhoea	Y	Diarrhoea
9	Constipation	N	Constipation
10	Muscle cramps	Y	Cramp
11	Persistent dry cough	Y	Cough
12	Throat discomfort	N	Pharynx irritation + Pharyngitis + Laryngitis
13	Voice changes	N	Hoarseness
14	Taste alteration	Y	Taste abnormal
15	Stomatitis	N	Stomatitis
16	Dyspepsia	N	Dyspepsia
17	Abdominal pain	N	Pain abdomen
18	Renal impairment	Y	Renal failure + Renal failure acute + Renal failure chronic + Uraemia + Urea raised + Renal function test

			abnormal
19	Hyperkalaemia	N	Hyperkalaemia
20	Angioedema	Y	Angioneurotic oedema
21	Urticaria	N	Urticaria
22	Rashes	Y	Rash
23	Erythema multiforme	N	Erythema Multiforme
24	Toxic epidermal necrolysis	N	no term available
25	Hypersensitivity reactions	N	Allergy
26	Blood disorders	N	Thrombocytopenia + Leucopenia + Neutropenia + Anaemia aplastic + Anaemia hypoplastic + Pancytopenia
27	Upper respiratory tract symptoms	N	no term available
28	Tachycardia	N	Tachycardia
29	Palpitations	Y	Palpitation
30	Arrhythmias	N	Arrhythmia
31	Myocardial infarction	N	Myocardial infarction
32	Cerebrovascular accident	N	Cerebro vascular accident + Stenosis artery cerebral + Vertebrobasilar syndrome
33	Back pain	N	Pain back
34	Flushing	N	Flushing
35	Jaundice	N	Jaundice + Jaundice cholestatic
36	Pancreatitis	N	Pancreatitis
37	Sleep paraesthesia	N	Paraesthesia
38	Impotence	N	Impotence
39	Onycholysis	N	Onycholysis
40	Alopecia	N	Alopecia

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Hyponatraemia	Hyponatraemia

Events signalled

As shown in Table 18, 21 events (low-level terms) are signalled. Five events

are signalled by the statistical test only while three events are signalled by the rate ratio method only. The remaining 13 events (62 %) are signalled by both of the methods.

Of the 21 events signalled, 11 events are known ADRs but 10 events signalled are not shown in the BNF. Of these 10 events, at least two events may be regarded as known ADRs.

1 'Pain chest' is given as an ADR in the BNF No 18.
2 'Dyspnoea' is described as an ADR in literature other than the BNF[79,80]

If these two events are added to currently known ADRs, 13 of 21 events signalled (62 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

In the PEM report on lisinopril[81], four events, 'cardiac failure', 'hypertension', 'ischaemic heart disease' and 'pain chest, tight chest' are designated as indication-related events. Therefore, in Table 18, 'pain chest' may be confounded by the indication though this is raised as an ADR in the BNF No 18. 'Oedema' may be also confounded by the indication.

ADRs signalled

Of the 40 ADRs under category A or B, 11 ADRs (25 %) are signalled of which 2 are judged to be previously unknown (Category B). It may be noted that cough has the rate ratio 1.5 which is similar to the value with enalapril, 1.3. When lisinopril was monitored by PEM, cough was already widely accepted as class effect to ACE-inhibitors[77]. Due to the increase in absolute number of green forms reporting 'cough', this event is signalled by the statistical test even if the rate ratio is similar to that with enalapril.

Of the 29 known ADRs not signalled, 10 ADRs occur relatively frequently. T1 is more than 1.0 per 1000 patients per month for rash, muscle cramp, pain back,

flushing, paraestheia, myocardial infarction, pharyngitis, dyspepsia, vomiting and 'pain abdomen' all of which are not signalled. The list is quite similar to that of enalapril and may share the underlying mechanisms though they cannot be clarified fully in this thesis. With other 19 known ADRs not signalled, the rate was small. They include renal failure and the rate of renal failure with lisinopril is smaller than that with enalapril.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		12432		51243			min	max
3	Denominator male		5465		22562				
4	Denominator female		6708		27573				
5	$. T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	**A. Previously known ADRs signalled**							9	
11	**Psychiatric**								
12	Lassitude	$*	82	6.6	128	2.5	2.6	2.0	3.5
13	Malaise	$$*	106	8.5	80	1.6	5.5	4.1	7.3
14	**Central and Peripheral Nervous System**								
15	Dizziness	$$*	164	13.2	162	3.2	4.2	3.4	5.2
16	Headache	$$*	179	14.4	172	3.4	4.3	3.5	5.3
17	**Cardiovascular**								
18	Hypotension	*	31	2.5	54	1.1	2.4	1.5	3.7
19	Palpitation	$$*	59	4.7	69	1.3	3.5	2.5	5.0
20	**Respiratory**								
21	Cough	*	169	13.6	450	8.8	1.5	1.3	1.8
22	**Alimentary**								
23	Diarrhoea	$*	62	5.0	87	1.7	2.9	2.1	4.1
24	Nausea	$$*	72	5.8	65	1.3	4.6	3.3	6.4
25									
26	**B. Previously unknown ADRs signalled**							2	
27	**Cardiovascular**								
28	Cerebro-vascular accident*	$	14	1.1	22	0.4	2.6	1.3	5.1
29	Tachycardia	$$*	34	2.7	21	0.4	6.7	3.9	11.5
30									
31	**D. 'Hard-to-detect' ADRs signalled**							0	
32									
33	**E. No description in BNF but signalled**							10	
34	**Central and Peripheral Nervous System**								
35	Drowsiness	$$*	15	1.2	11	0.2	5.6	2.6	12.2
36	Tremor	$$*	18	1.4	17	0.3	4.4	2.2	8.5
37	**Ear**								
38	Tinnitus	$	12	1.0	20	0.4	2.5	1.2	5.1
39	**Cardiovascular**								
40	Oedema@	$*	26	2.1	43	0.8	2.5	1.5	4.1
41	Pain chest	*	44	3.5	91	1.8	2.0	1.4	2.9
42	**Respiratory**								
43	Dyspnoea	$$*	51	4.1	68	1.3	3.1	2.2	4.4
44	**Alimentary**								
45	Anorexia	*	11	0.9	10	0.2	-	-	-
46	**Metabolic and Endocrine**								
47	Gout	$$	16	1.3	22	0.4	3.0	1.6	5.7
48	**Urologic**								
49	Nocturia	*	5	0.4	1	0.0	-	-	-
50	**Immunological**								
51	Unspecified side effects	$$*	21	1.7	14	0.3	6.2	3.1	12.2
52									
53									

Table 18 Lisinopril: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***Events NOT signalled***								
56									
57	***A. Previously known ADRs NOT signalled***							*10*	
58	**Skin**								
59	Rash		34	2.7	72	1.4	1.9	1.3	2.9
60	**Musculoskeletal**								
61	Cramp		13	1.0	36	0.7	1.5	0.8	2.8
62	**Central and Peripheral Nervous System**								
63	Taste abnormal		5	0.4	9	0.2	-	-	-
64	**Urologic**								
65	Renal failure acute		1	0.1	1	0.0	-	-	-
66	Renal failure chronic*		0	0.0	1	0.0	-	-	-
67	Renal failure*		3	0.2	15	0.3	-	-	-
68	Uraemia*		0	0.0	3	0.1	-	-	-
69	Renal function test abnormal		3	0.2	11	0.2	-	-	-
70	Urea raised		2	0.2	12	0.2	-	-	-
71	**Immunological**								
72	Angioneurotic oedema		4	0.3	4	0.1	-	-	-
73									
74	***B. Previously unknown ADRs NOT signalled***							*32*	
75	**Skin**								
76	Alopecia		1	0.1	0	0.0	-	-	-
77	Erythema multiforme		0	0.0	0	0.0	-	-	-
78	Onycholysis		0	0.0	0	0.0	-	-	-
79	Urticaria		6	0.5	3	0.1	-	-	-
80	**Musculoskeletal**								
81	Pain back		18	1.4	83	1.6	0.9	0.5	1.5
82	**Central and Peripheral Nervous System**								
83	Flushing		12	1.0	32	0.6	1.5	0.8	3.0
84	Paraesthesia		14	1.1	35	0.7	1.6	0.9	3.1
85	**Cardiovascular**								
86	Stenosis artery cerebral		0	0.0	0	0.0	-	-	-
87	Vertebrobasilar syndrome		0	0.0	2	0.0	-	-	-
88	Arrhythmia		3	0.2	8	0.2	-	-	-
89	Myocardial infarction*		16	1.3	48	0.9	1.4	0.8	2.4
90	**Respiratory**								
91	Hoarseness		0	0.0	11	0.2	-	-	-
92	Laryngitis		3	0.2	11	0.2	-	-	-
93	Pharyngitis		13	1.0	52	1.0	1.0	0.6	1.9
94	**Alimentary**								
95	Constipation		8	0.6	27	0.5	-	-	-
96	Dyspepsia@		38	3.1	94	1.8	1.7	1.1	2.4
97	Jaundice		0	0.0	1	0.0	-	-	-
98	Jaundice cholestatic		0	0.0	0	0.0	-	-	-
99	Vomiting		23	1.9	50	1.0	1.9	1.2	3.1
100	Pain abdomen		39	3.1	95	1.9	1.7	1.2	2.5
101	Pancreatitis*		1	0.1	1	0.0	-	-	-
102	Pharynx irritation		3	0.2	17	0.3	-	-	-
103	Stomatitis		0	0.0	4	0.1	-	-	-
104	**Metabolic and Endocrine**								
105	Hyperkalaemia		1	0.1	9	0.2	-	-	-
106	**Male Reproductive and Gynaecomastia**								
107	Impotence		5	0.9	23	1.0	-	-	-
108									

Table 18 Lisinopril: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
109	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
110	***B. Previously unknown ADRs NOT signalled continued***								
111	**Haemopoietic**								
112	Leucopenia@		0	0.0	0	0.0	-	-	-
113	Neutropenia		0	0.0	1	0.0	-	-	-
114	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
115	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
116	Pancytopenia@		0	0.0	1	0.0	-	-	-
117	Thrombocytopenia		0	0.0	0	0.0	-	-	-
118	**Immunological**								
119	Allergy		0	0.0	1	0.0	-	-	-
120									
121	***D. 'Hard-to-detect' ADRs NOT signalled***							*1*	
122	**Metabolic and Endocrine**								
123	Hyponatraemia		0	0.0	2	0.0	-	-	-

Table 18 Lisinopril: Events signalled and not signalled

11 Etodolac

ADRs in the BNF

Description in the BNF No 14 September 1987

ETODOLAC
Cautions; Side-effects: see notes above.

Etodolac is given under section 10.1.1 and the beginning of the section reads as follows:

10.1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding occur and may be minimised by advising that these drugs should always be taken with food or milk. Hypersensitivity reactions (particularly angioedema, asthma, and rashes), headache, dizziness, vertigo, and hearing disturbances such as tinnitus. Blood disorders have occurred. Fluid retention may occur (rarely precipitating congestive heart failure in elderly patients). Rarely reversible acute renal failure may be provoked by NSAIDs especially in patients with pre-existing renal disease, as may chronic renal failure due to papillary necrosis or intestinal fibrosis.

ADRs in the BNF No 14

1 Gastro-intestinal discomfort
2 Nausea
3 Diarrhoea
4 Bleeding
5 Hypersensitivity reactions (angioedema, asthma, and rashes)
6 Headache
7 Dizziness
8 Vertigo

9 Hearing disturbances (tinnitus etc.)
10 Blood disorders
11 Fluid retention (rarely with cardiac failure)
12 Renal failure acute or chronic

Description in the BNF No 31 March 1996

ETODOLAC

Cautions; Contra-indications; Side-effects: see under Ibuprofen and notes above

IBUPROFEN

Side-effects: gastro-intestinal discomfort - also nausea, diarrhoea and occasionally bleeding and ulceration (important: see also CSM advice above), hypersensitivity reactions - notably with bronchospasm, rashes and angioedema (important: see also under Hypersensitivity, above); other side-effects associated with NSAIDs include fluid retention, headache, dizziness, vertigo, hearing disturbances such as tinnitus, photosensitivity, haematuria,; blood disorders, reversible acute renal failure, renal papillary necrosis (or interstitial fibrosis), alveolitis, hepatic damage, pancreatitis, eye changes, and aseptic meningitis may also rarely occur; for further details of these side-effects see also notes above.

General note for NSAIDs in the BNF No 31

SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur; dyspepsia may be minimised by taking these drugs with food or milk. Other side-effects include hypersensitivity reactions (particularly angioedema, bronchospasm, and rashes), headache, dizziness, vertigo, hearing disturbances such as tinnitus, and haematuria. Blood disorders have also occurred. Fluid retention may occur

(rarely precipitating congestive heart failure in elderly patients). Reversible acute renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment (important, see also under Cautions above). Rarely, papillary necrosis or intestinal fibrosis associated with NSAIDs may lead to renal failure. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible. Hepatic damage is another rare side-effect.

ADRs in the BNF No 31		described in the BNF 14? (Y/N)	Event Dictionary low-level term(s)
1	Gastro-intestinal discomfort	Y	Dyspepsia + Vomiting + Pain abdomen
2	Nausea	Y	Nausea
3	Diarrhoea	Y	Diarrhoea
4&5	Bleeding & Ulceration	Y	Melena + Haematemesis + Ulcer duodenal haemorrhage + Ulcer gastric haemorrhage + Ulcer peptic haemorrhage + Ulcer duodenal + Ulcer gastric + Ulcer peptic + Ulcer duodenal perforated + Ulcer gastric perforated + Ulcer peptic perforated
6	Hypersensitivity	Y	Bronchospasm + Asthma + Rash + Angioneurotic oedema
7	Fluid retention (rarely with congestive heart failure)	Y	Fluid retention + Congestive Cardiac failure + Cardiac failure + Left ventricular failure
8	Headache	Y	Headache
9	Dizziness	Y	Dizziness
10	Vertigo	Y	Vertigo
11	Hearing disturbances		

	such as tinnitus	Y	Tinnitus
12	Photosensitivity	N	Photosensitivity
13	Haematuria	N	Haematuria
14	Blood disorders	Y	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
15&16	Acute renal failure & Renal papillary necrosis (interstitial fibrosis)	Y	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
17	Alveolitis	N	Alveolitis fibrosing
18	Hepatic damage	N	Hepatitis + Hepatic failure
19	Pancreatitis	N	Pancreatitis
20	Eye change	N	Retinopathy + Diplopia + Vision deteriorated + Visual disturbance*
21	Aseptic meningitis	N	Meningitis

* Not detailed in BNF and some of event dictionary terms compatible with eye reactions to indomethacin in Meyler's textbook[127] are listed

Events signalled

As shown in Table 19, 13 events (low-level terms) are signalled. One event is signalled by the statistical test only while two events are signalled by the rate ratio method only. The remaining 10 events (77 %) are signalled by both of the methods.

Of the 13 events signalled, 7 events are known ADRs but 6 events signalled are not shown in the BNF. All of these 6 events may be regarded as known ADRs.

1 'Pruritus' is given as an ADR in literature other than BNF[83].
2 'Confusion' is given as an ADR in literature other than BNF[83].
3 'Malaise' is described as an ADR in literature other than BNF[83].
4 'Oedema' is associated with fluid retention.

5 'Gastritis' is associated with gastro-intestinal discomfort.
6 'Heartburn' is associated with gastro-intestinal discomfort.

If these 6 events are added to currently known ADRs, 13 of 13 events signalled (100 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

No event signalled is considered to be likely confounded by the indication.

ADRs signalled

Of the 21 ADRs under category A or B, 6 ADRs (29 %) are signalled all of which are judged to be previously known (Category A). With all of the 15 known ADRs not signalled, the rate is low except for 'diarrhoea' (T1 = 2.9 and T2 = 1.4 per 1000 patients per month). As in the previous paper from the DSRU[84], the data indicate that peptic ulcer which is clinically significant including haemorrhagic or perforated ulcer does not occur frequently associated with the use of NSAIDs.

EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
							min	max
Denominator total		9090		45330				
Denominator male		3001		14961				
Denominator female		5924		29548				
$ T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
Events signalled								
A. Previously known ADRs signalled							7	
Skin								
Rash	$$*	40	4.4	35	0.8	5.7	3.6	9.0
Central and Peripheral Nervous System								
Dizziness	$$*	32	3.5	29	0.6	5.5	3.3	9.1
Headache	$$*	25	2.8	28	0.6	4.5	2.6	7.6
Alimentary								
Dyspepsia@	$$*	140	15.4	120	2.6	5.8	4.6	7.4
Nausea	$$*	42	4.6	35	0.8	6.0	3.8	9.4
Vomiting	$$*	31	3.4	28	0.6	5.5	3.3	9.2
Pain abdomen	$$*	44	4.8	68	1.5	3.2	2.2	4.7
B. Previously unknown ADRs signalled							0	
E. No description in BNF but signalled							6	
Skin								
Pruritus @	$$*	10	1.1	8	0.2	6.2	2.5	15.8
Psychiatric								
Confusion	*	7	0.8	4	0.1	-	-	-
Malaise	$$*	13	1.4	12	0.3	5.4	2.5	11.8
Cardiovascular								
Oedema@	$	12	1.3	24	0.5	2.5	1.2	5.0
Alimentary								
Gastritis	$	9	1.0	17	0.4	2.6	1.2	5.9
Heartburn	$$*	20	2.2	16	0.4	6.2	3.2	12.0
Events NOT signalled								
A. Previously known ADRs NOT signalled							31	
Ear								
Tinnitus		1	0.1	8	0.2	-	-	-
Vertigo		7	0.8	14	0.3	-	-	-
Cardiovascular								
Cardiac failure*		0	0.0	2	0.0	-	-	-
Congestive cardiac failure*		4	0.4	4	0.1	-	-	-
Left ventricular failure*		0	0.0	6	0.1	-	-	-
Fluid retention		0	0.0	1	0.0	-	-	-
Respiratory								
Asthma*		0	0.0	6	0.1	-	-	-
Bronchospasm		0	0.0	0	0.0	-	-	-

Table 19 Etodolac: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***A. Previously known ADRs NOT signalled continued***								
56	**Alimentary**								
57	Diarrhoea		26	2.9	65	1.4	2.0	1.3	3.1
58	Haematemesis*		1	0.1	2	0.0	-	-	-
59	Melena		0	0.0	4	0.1	-	-	-
60	Ulcer duodenal haemorrhage*		0	0.0	1	0.0	-	-	-
61	Ulcer gastric haemorrhage*		0	0.0	0	0.0	-	-	-
62	Ulcer peptic haemorrhage*		0	0.0	1	0.0	-	-	-
63	Ulcer duodenal perforated*		0	0.0	1	0.0	-	-	-
64	Ulcer duodenal*		1	0.1	5	0.1	-	-	-
65	Ulcer gastric		1	0.1	1	0.0	-	-	-
66	Ulcer gastric perforated*		0	0.0	0	0.0	-	-	-
67	Ulcer peptic perforated*		0	0.0	0	0.0	-	-	-
68	Ulcer peptic*		1	0.1	1	0.0	-	-	-
69	**Urologic**								
70	Renal failure acute		0	0.0	0	0.0	-	-	-
71	Renal failure chronic*		0	0.0	0	0.0	-	-	-
72	Renal failure*		0	0.0	1	0.0	-	-	-
73	Uraemia*		0	0.0	0	0.0	-	-	-
74	**Haemopoietic**								
75	Leucopenia@		0	0.0	0	0.0	-	-	-
76	Neutropenia		0	0.0	1	0.0	-	-	-
77	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
78	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
79	Pancytopenia@		0	0.0	0	0.0	-	-	-
80	Thrombocytopenia		0	0.0	0	0.0	-	-	-
81	**Immunological**								
82	Angioneurotic oedema		0	0.0	0	0.0	-	-	-
83									
84	***B. Previously unknown ADRs NOT signalled***							*11*	
85	**Skin**								
86	Photosensitivity		1	0.1	1	0.0	-	-	-
87	**Central and Peripheral Nervous System**								
88	Meningitis *		0	0.0	0	0.0	-	-	-
89	**Eye**								
90	Retinopathy		0	0.0	0	0.0	-	-	-
91	Diplopia		0	0.0	3	0.1	-	-	-
92	Vision deteriorated		1	0.1	3	0.1	-	-	-
93	Visual disturbance		2	0.2	0	0.0	-	-	-
94	**Respiratory**								
95	Alveolitis fibrosing*		0	0.0	0	0.0	-	-	-
96	**Alimentary**								
97	Hepatic Failure*		0	0.0	0	0.0	-	-	-
98	Hepatitis*		0	0.0	0	0.0	-	-	-
99	Pancreatitis*		0	0.0	1	0.0	-	-	-
100	**Urologic**								
101	Haematuria		1	0.1	3	0.1	-	-	-

Table 19 Etodolac: Events signalled and not signalled

12 Nabumetone

ADRs in the BNF

Description in the BNF No 16 September 1988

NABUMETONE

Cautions; Side-effects: see notes above.

Nabumetone is given under section 10.1.1 and the beginning of the section reads as follows:

10.1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)

SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding occur and may be minimised by advising that these drugs should always be taken with food or milk. Hypersensitivity reactions (particularly angioedema, asthma, and rashes), headache, dizziness, vertigo, and hearing disturbances such as tinnitus. Blood disorders have occurred. Fluid retention may occur (rarely precipitating congestive heart failure in elderly patients). Rarely reversible acute renal impairment; papillary necrosis or interstitial fibrosis associated with NSAIDs may also lead to chronic renal failure (analgesic nephropathy).

ADRs in the BNF No 16

1 Gastro-intestinal discomfort
2 Nausea
3 Diarrhoea
4 Bleeding
5 Hypersensitivity reactions (angioedema, asthma, and rashes)
6 Headache
7 Dizziness

8 Vertigo
9 Hearing disturbances (tinnitus etc.)
10 Blood disorders
11 Fluid retention (rarely with cardiac failure)
12 Renal failure acute or chronic

Description in the BNF No 31 March 1996

NABUMETONE

Cautions; Contra-indications; Side-effects: see under Ibuprofen and notes above

IBUPROFEN

Side-effects: gastro-intestinal discomfort - also nausea, diarrhoea and occasionally bleeding and ulceration (important: see also CSM advice above), hypersensitivity reactions - notably with bronchospasm, rashes and angioedema (important: see also under Hypersensitivity, above); other side-effects associated with NSAIDs include fluid retention, headache, dizziness, vertigo, hearing disturbances such as tinnitus, photosensitivity, haematuria,; blood disorders, reversible acute renal failure, renal papillary necrosis (or interstitial fibrosis), alveolitis, hepatic damage, pancreatitis, eye changes, and aseptic meningitis may also rarely occur; for further details of these side-effects see also notes above.

General note for NSAIDs in the BNF No 30

SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur; dyspepsia may be minimised by taking these drugs with food or milk. Other side-effects include hypersensitivity reactions (particularly angioedema, bronchospasm, and rashes), headache, dizziness, vertigo, hearing disturbances such as tinnitus, and haematuria.

Blood disorders have also occurred. Fluid retention may occur (rarely precipitating congestive heart failure in elderly patients). Reversible acute renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment (important, see also under Cautions above). Rarely, papillary necrosis or intestinal fibrosis associated with NSAIDs may lead to renal failure. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible. Hepatic damage is another rare side-effect.

ADRs in the BNF No 31		described in the BNF 16? (Y/N)	Event Dictionary low-level term(s)
1	Gastro-intestinal discomfort	Y	Dyspepsia + Vomiting + Pain abdomen
2	Nausea	Y	Nausea
3	Diarrhoea	Y	Diarrhoea
4&5	Bleeding & Ulceration	Y	Melena + Haematemesis + Ulcer duodenal haemorrhage + Ulcer gastric haemorrhage + Ulcer peptic haemorrhage + Ulcer duodenal + Ulcer gastric + Ulcer peptic + Ulcer duodenal perforated + Ulcer gastric perforated + Ulcer peptic perforated
6	Hypersensitivity	Y	Bronchospasm + Asthma + Rash + Angioneurotic oedema
7	Fluid retention (rarely with congestive heart failure)	Y	Fluid retention + Congestive Cardiac failure + Cardiac failure + Left ventricular failure
8	Headache	Y	Headache
9	Dizziness	Y	Dizziness
10	Vertigo	Y	Vertigo

11	Hearing disturbances such as tinnitus	Y	Tinnitus
12	Photosensitivity	N	Photosensitivity
13	Haematuria	N	Haematuria
14	Blood disorders	Y	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
15&16	Acute renal failure & Renal papillary necrosis (interstitial fibrosis)	Y	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
17	Alveolitis	N	Alveolitis fibrosing
18	Hepatic damage	N	Hepatitis + Hepatic failure
19	Pancreatitis	N	Pancreatitis
20	Eye change	N	Retinopathy + Diplopia + Vision deteriorated + Visual disturbance*
21	Aseptic meningitis	N	Meningitis

* Not detailed in BNF and some of event dictionary terms compatible with eye reactions to indomethacin in Meyler's textbook[127] are listed

Events signalled

As shown in Table 20, 17 events (low-level terms) are signalled. Two events are signalled by the statistical test only while one event is signalled by the rate ratio method only. The remaining 14 events (82 %) are signalled by both of the methods.

Of the 17 events signalled, 9 events are known ADRs but 8 events signalled are not shown in the BNF. Of these 8 events, 4 may be regarded as known ADRs.

1 'Drowsiness' is associated with 'somnolence' which is an ADR shown in literature other than BNF[85].

2 'Constipation' is given as an ADR in literature other than BNF[85].

3 'Gastritis' is associated with gastro-intestinal discomfort.
4 'Heartburn' is associated with gastro-intestinal discomfort.

If these 4 events are added to currently known ADRs, 13 of 17 events signalled (76 %) may be judged to be currently known ADRs.

An event signalled with nabumetone, 'dreams abnormal' is probably an ADR detected by the PEM study for the first time[86]. However, no other study has confirmed this finding so far.

Confounding by the indication or 'indication-related' event

No event signalled is considered to be likely confounded by the indication.

ADRs signalled

Of the 21 ADRs under category A or B, 7 ADRs (33 %) are signalled all of which are judged to be previously known (Category A). With all of the 14 known ADRs not signalled, the rate is low. As in the PEM study of etodolac, the data indicate that peptic ulcer which is clinically significant including haemorrhagic or perforated ulcer does not occur frequently associated with the use of NSAIDs.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		10440		52032			min	max
3	Denominator male		3435		17135				
4	Denominator female		6833		34041				
5	$ T1/T2 = or > 2.5 and $$ T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***9***	
11	**Skin**								
12	Rash	$$*	39	3.7	60	1.2	3.2	2.2	4.8
13	**Central and Peripheral Nervous System**								
14	Dizziness	$$*	39	3.7	41	0.8	4.7	3.1	7.3
15	Headache	$$*	42	4.0	43	0.8	4.9	3.2	7.4
16	**Ear**								
17	Vertigo	$	10	1.0	17	0.3	2.9	1.3	6.4
18	**Alimentary**								
19	Diarrhoea	$$*	72	6.9	81	1.6	4.4	3.2	6.1
20	Dyspepsia@	$$*	138	13.2	169	3.2	4.1	3.3	5.1
21	Nausea	$$*	69	6.6	42	0.8	8.2	5.6	12.0
22	Vomiting	$$*	29	2.8	30	0.6	4.8	2.9	8.0
23	Pain abdomen	$*	53	5.1	92	1.8	2.9	2.0	4.0
24									
25	***B. Previously unknown ADRs signalled***							***0***	
26									
27	***E. No description in BNF but signalled***							***8***	
28	**Psychiatric**								
29	Dreams abnormal	$$*	10	1.0	2	0.0	24.9	5.5	113.7
30	Lassitude	$$*	15	1.4	18	0.3	4.2	2.1	8.2
31	Malaise	$$*	25	2.4	15	0.3	8.3	4.4	15.8
32	**Central and Peripheral Nervous System**								
33	Drowsiness	*	7	0.7	2	0.0	-	-	-
34	**Alimentary**								
35	Constipation	$$*	18	1.7	26	0.5	3.5	1.9	6.3
36	Gastritis	$$*	22	2.1	24	0.5	4.6	2.6	8.1
37	Heartburn	$$*	14	1.3	13	0.2	5.4	2.5	11.4
38	**Immunological**								
39	Unspecified side effects	*	9	0.9	4	0.1	-	-	-
40									
41	***Events NOT signalled***								
42									
43	***A. Previously known ADRs NOT signalled***							***29***	
44	**Ear**								
45	Tinnitus		2	0.2	6	0.1	-	-	-
46	**Cardiovascular**								
47	Cardiac failure*		1	0.1	5	0.1	-	-	-
48	Congestive cardiac failure*		3	0.3	14	0.3	-	-	-
49	Left ventricular failure*		0	0.0	4	0.1	-	-	-
50	Fluid retention		0	0.0	4	0.1	-	-	-
51									
52									
53									

Table 20 Nabumetone: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***A. Previously known ADRs NOT signalled continued***								
56	**Respiratory**								
57	Asthma*		3	0.3	21	0.4	-	-	-
58	Bronchospasm		0	0.0	4	0.1	-	-	-
59	**Alimentary**								
60	Haematemesis*		1	0.1	5	0.1	-	-	-
61	Melena		2	0.2	3	0.1	-	-	-
62	Ulcer duodenal haemorrhage*		1	0.1	0	0.0	-	-	-
63	Ulcer gastric haemorrhage*		0	0.0	1	0.0	-	-	-
64	Ulcer peptic haemorrhage*		0	0.0	0	0.0	-	-	-
65	Ulcer duodenal perforated*		0	0.0	0	0.0	-	-	-
66	Ulcer duodenal*		1	0.1	4	0.1	-	-	-
67	Ulcer gastric		0	0.0	2	0.0	-	-	-
68	Ulcer gastric perforated*		0	0.0	0	0.0	-	-	-
69	Ulcer peptic perforated*		0	0.0	0	0.0	-	-	-
70	Ulcer peptic*		0	0.0	2	0.0	-	-	-
71	**Urologic**								
72	Renal failure acute		0	0.0	0	0.0	-	-	-
73	Renal failure chronic*		0	0.0	0	0.0	-	-	-
74	Renal failure*		0	0.0	2	0.0	-	-	-
75	Uraemia*		0	0.0	0	0.0	-	-	-
76	**Haemopoietic**								
77	Leucopenia@		1	0.1	1	0.0	-	-	-
78	Neutropenia		0	0.0	1	0.0	-	-	-
79	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
80	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
81	Pancytopenia@		0	0.0	0	0.0	-	-	-
82	Thrombocytopenia		1	0.1	1	0.0	-	-	-
83	**Immunological**								
84	Angioneurotic oedema		0	0.0	1	0.0	-	-	-
85									
86	***B. Previously unknown ADRs NOT signalled***							*11*	
87	**Skin**								
88	Photosensitivity		1	0.1	3	0.1	-	-	-
89	**Central and Peripheral Nervous System**								
90	Meningitis *		0	0.0	0	0.0	-	-	-
91	**Eye**								
92	Retinopathy		0	0.0	0	0.0	-	-	-
93	Diplopia		0	0.0	0	0.0	-	-	-
94	Vision deteriorated		1	0.1	3	0.1	-	-	-
95	Visual disturbance		3	0.3	4	0.1	-	-	-
96	**Respiratory**								
97	Alveolitis fibrosing*		0	0.0	0	0.0	-	-	-
98	**Alimentary**								
99	Hepatic Failure*		0	0.0	0	0.0	-	-	-
100	Hepatitis*		0	0.0	0	0.0	-	-	-
101	Pancreatitis*		0	0.0	1	0.0	-	-	-
102	**Urologic**								
103	Haematuria		2	0.2	2	0.0	-	-	-

Table 20 Nabumetone: Events signalled and not signalled

13 Tenoxicam

ADRs in the BNF

Description in the BNF No 19 March 1990

TENOXICAM
Cautions; Side-effects: see notes above.

Nabumetone is given under section 10.1.1 and the beginning of the section reads as follows:
10.1.1 Non-steroidal anti-inflammatory drugs (NSAIDs)
SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding occur and may be minimised by advising that these drugs should always be taken with food or milk. Hypersensitivity reactions (particularly angioedema, asthma, and rashes), headache, dizziness, vertigo, and hearing disturbances such as tinnitus. Blood disorders have occurred. Fluid retention may occur (rarely precipitating congestive heart failure in elderly patients). Rarely reversible acute renal impairment; papillary necrosis or interstitial fibrosis associated with NSAIDs may also lead to chronic renal failure (analgesic nephropathy).

ADRs in the BNF No 19

1 Gastro-intestinal discomfort
2 Nausea
3 Diarrhoea
4 Bleeding
5 Hypersensitivity reactions (angioedema, asthma, and rashes)
6 Headache
7 Dizziness
8 Vertigo

9 Hearing disturbances (tinnitus etc.)
10 Blood disorders
11 Fluid retention (rarely with cardiac failure)
12 Renal failure acute or chronic

Description in the BNF No 31 March 1996

TENOXICAM

Cautions; Contra-indications; Side-effects: see under Ibuprofen and notes above

IBUPROFEN

Side-effects: gastro-intestinal discomfort - also nausea, diarrhoea and occasionally bleeding and ulceration (important: see also CSM advice above), hypersensitivity reactions - notably with bronchospasm, rashes and angioedema (important: see also under Hypersensitivity, above); other side-effects associated with NSAIDs include fluid retention, headache, dizziness, vertigo, hearing disturbances such as tinnitus, photosensitivity, haematuria,; blood disorders, reversible acute renal failure, renal papillary necrosis (or interstitial fibrosis), alveolitis, hepatic damage, pancreatitis, eye changes, and aseptic meningitis may also rarely occur; for further details of these side-effects see also notes above.

General note for NSAIDs in the BNF No 31

SIDE-EFFECTS. Side-effects are variable in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur; dyspepsia may be minimised by taking these drugs with food or milk. Other side-effects include hypersensitivity reactions (particularly angioedema, bronchospasm, and rashes), headache, dizziness, vertigo, hearing disturbances such as tinnitus, and haematuria. Blood disorders have also occurred. Fluid retention may occur

(rarely precipitating congestive heart failure in elderly patients). Reversible acute renal failure may be provoked by NSAIDs especially in patients with pre-existing renal impairment (important, see also under Cautions above). Rarely, papillary necrosis or intestinal fibrosis associated with NSAIDs may lead to renal failure. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible. Hepatic damage is another rare side-effect.

ADRs in the BNF No 31		described in the BNF 19? (Y/N)	Event Dictionary low-level term(s)
1	Gastro-intestinal discomfort	Y	Dyspepsia + Vomiting + Pain abdomen
2	Nausea	Y	Nausea
3	Diarrhoea	Y	Diarrhoea
4&5	Bleeding & Ulceration	Y	Melena + Haematemesis + Ulcer duodenal haemorrhage + Ulcer gastric haemorrhage + Ulcer peptic haemorrhage + Ulcer duodenal + Ulcer gastric + Ulcer peptic + Ulcer duodenal perforated + Ulcer gastric perforated + Ulcer peptic perforated
6	Hypersensitivity	Y	Bronchospasm + Asthma + Rash + Angioneurotic oedema
7	Fluid retention (rarely with congestive heart failure)	Y	Fluid retention + Congestive Cardiac failure + Cardiac failure + Left ventricular failure
8	Headache	Y	Headache
9	Dizziness	Y	Dizziness
10	Vertigo	Y	Vertigo
11	Hearing disturbances		

	such as tinnitus	Y	Tinnitus
12	Photosensitivity	N	Photosensitivity
13	Haematuria	N	Haematuria
14	Blood disorders	Y	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
15&16	Acute renal failure & Renal papillary necrosis (interstitial fibrosis)	Y	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
17	Alveolitis	N	Alveolitis fibrosing
18	Hepatic damage	N	Hepatitis + Hepatic failure
19	Pancreatitis	N	Pancreatitis
20	Eye change	N	Retinopathy + Diplopia + Vision deteriorated + Visual disturbance*
21	Aseptic meningitis	N	Meningitis

* Not detailed in BNF and some of event dictionary terms compatible with eye reactions to indomethacin in Meyler's textbook are listed

Events signalled

As shown in Table 21, 15 events (low-level terms) are signalled. One event is signalled by the statistical test only while two events are signalled by the rate ratio method only. The remaining 12 events (80 %) are signalled by both of the methods.

Of the 15 events signalled, 8 events are known ADRs but 7 events signalled are not shown in the BNF. Of these 7 events, 3 may be regarded as known ADRs.

1 'Oedema' is an ADR shown in literature other than BNF[87].
2 'Gastritis' is associated with gastro-intestinal discomfort.
3 'Ulcer mouth' is given as an ADR in literature other than BNF[87].

If these 3 events are added to currently known ADRs, 11 of 15 events signalled (73 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

No event signalled is considered to be likely confounded by the indication.

ADRs signalled

Of the 21 ADRs under category A or B, 6 ADRs (29 %) are signalled all of which are judged to be previously known (Category A). With all of the 15 known ADRs not signalled, the rate is low. As in the PEM study of etodolac or nabumetone, the data indicate that peptic ulcer which is clinically significant including haemorrhagic or perforated ulcer does not occur frequently associated with the use of NSAIDs.

	A	B	C	D	E	F	G	H	J
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		10878		52617			min	max
3	Denominator male		3697		17841				
4	Denominator female		6937		33602				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	**A. Previously known ADRs signalled**							8	
11	**Skin**								
12	Rash	$$*	45	4.1	59	1.1	3.7	2.5	5.4
13	**Central and Peripheral Nervous System**								
14	Dizziness	$*	29	2.7	53	1.0	2.6	1.7	4.2
15	Headache	$$*	26	2.4	40	0.8	3.1	1.9	5.2
16	**Alimentary**								
17	Diarrhoea	*	29	2.7	61	1.2	2.3	1.5	3.6
18	Dyspepsia@	$$*	106	9.7	131	2.5	3.9	3.0	5.1
19	Nausea	$$*	50	4.6	35	0.7	6.9	4.5	10.6
20	Vomiting	$$*	28	2.6	37	0.7	3.7	2.2	6.0
21	Pain abdomen	$*	67	6.2	115	2.2	2.8	2.1	3.8
22									
23	**B. Previously unknown ADRs signalled**							0	
24									
25	**E. No description in BNF but signalled**							7	
26	**Musculoskeletal**								
27	Pain limb	$$*	19	1.7	27	0.5	3.4	1.9	6.1
28	**Psychiatric**								
29	Malaise	$$	11	1.0	15	0.3	3.5	1.6	7.7
30	**Central and Peripheral Nervous System**								
31	Drowsiness	*	9	0.8	1	0.0	-	-	-
32	**Cardiovascular**								
33	Oedema@	$$*	20	1.8	28	0.5	3.5	1.9	6.1
34	**Alimentary**								
35	Gastritis	$$*	18	1.7	21	0.4	4.1	2.2	7.8
36	Ulcer mouth	$	11	1.0	21	0.4	2.5	1.2	5.3
37	**Immunological**								
38	Unspecified side effects	$$*	11	1.0	2	0.0	26.6	5.9	120.0
39									
40	**Events NOT signalled**								
41									
42	**A. Previously known ADRs NOT signalled**							30	
43	**Ear**								
44	Tinnitus		1	0.1	12	0.2	-	-	-
45	Vertigo		6	0.6	18	0.3	-	-	-
46	**Cardiovascular**								
47	Cardiac failure*		2	0.2	4	0.1	-	-	-
48	Congestive cardiac failure*		4	0.4	12	0.2	-	-	-
49	Left ventricular failure*		1	0.1	6	0.1	-	-	-
50	Fluid retention		2	0.2	2	0.0	-	-	-
51									
52									
53									

Table 21 Tenoxicam: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***A. Previously known ADRs NOT signalled continued***								
56	**Respiratory**								
57	Asthma*		5	0.5	18	0.3	-	-	-
58	Bronchospasm		0	0.0	3	0.1	-	-	-
59	**Alimentary**								
60	Haematemesis*		1	0.1	3	0.1	-	-	-
61	Melena		1	0.1	4	0.1	-	-	-
62	Ulcer duodenal haemorrhage*		1	0.1	1	0.0	-	-	-
63	Ulcer gastric haemorrhage*		0	0.0	2	0.0	-	-	-
64	Ulcer peptic haemorrhage*		0	0.0	0	0.0	-	-	-
65	Ulcer duodenal perforated*		0	0.0	1	0.0	-	-	-
66	Ulcer duodenal*		3	0.3	5	0.1	-	-	-
67	Ulcer gastric		1	0.1	4	0.1	-	-	-
68	Ulcer gastric perforated*		0	0.0	0	0.0	-	-	-
69	Ulcer peptic perforated*		0	0.0	0	0.0	-	-	-
70	Ulcer peptic*		0	0.0	1	0.0	-	-	-
71	**Urologic**								
72	Renal failure acute		0	0.0	0	0.0	-	-	-
73	Renal failure chronic*		0	0.0	1	0.0	-	-	-
74	Renal failure*		0	0.0	1	0.0	-	-	-
75	Uraemia*		0	0.0	0	0.0	-	-	-
76	**Haemopoietic**								
77	Leucopenia@		0	0.0	1	0.0	-	-	-
78	Neutropenia		1	0.1	0	0.0	-	-	-
79	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
80	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
81	Pancytopenia@		0	0.0	0	0.0	-	-	-
82	Thrombocytopenia		0	0.0	1	0.0	-	-	-
83	**Immunological**								
84	Angioneurotic oedema		0	0.0	0	0.0	-	-	-
85									
86	***B. Previously unknown ADRs NOT signalled***							*11*	
87	**Skin**								
88	Photosensitivity		0	0.0	1	0.0	-	-	-
89	**Central and Peripheral Nervous System**								
90	Meningitis *		0	0.0	1	0.0	-	-	-
91	**Eye**								
92	Retinopathy		0	0.0	0	0.0	-	-	-
93	Diplopia		0	0.0	1	0.0	-	-	-
94	Vision deteriorated		1	0.1	3	0.1	-	-	-
95	Visual disturbance		2	0.2	6	0.1	-	-	-
96	**Respiratory**								
97	Alveolitis fibrosing*		0	0.0	0	0.0	-	-	-
98	**Alimentary**								
99	Hepatic Failure*		0	0.0	0	0.0	-	-	-
100	Hepatitis*		0	0.0	0	0.0	-	-	-
101	Pancreatitis*		0	0.0	0	0.0	-	-	-
102	**Urologic**								
103	Haematuria		2	0.2	14	0.3	-	-	-

Table 21 Tenoxicam: Events signalled and not signalled

14 Nizatidine

ADRs in the BNF

Description in the BNF No 18 September 1989

NIZATIDINE

Side-effects: reported, headache, asthenia, chest pain, myalgia, abnormal dreams, somnolence, rhinitis, pharyngitis, cough, pruritus, and sweating; reversible increases in liver enzymes also reported; does not have anti-androgenic effects

ADRs in the BNF No 18

1 Headache
2 Asthenia
3 Chest pain
4 Myalgia
5 Abnormal dreams
6 Somnolence
7 Rhinitis
8 Pharyngitis
9 Cough
10 Pruritus
11 Sweating
12 Liver enzyme increase

Description in the BNF No 31 March 1996

NIZATIDINE

Side-effects: see under Cimetidine and notes above; sweating also reported; rare reports of gynaecomastia

CIMETIDINE

Side-effects: altered bowel habit, dizziness, rash, tiredness; reversible confusional states, reversible liver damage,

headache; rarely, blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia), muscle or joint pain, hypersensitivity, bradycardia and AV block; interstitial nephritis and acute pancreatitis reported; gynaecomastia is also an occasional problem with cimetidine (but usually only in high dosage), and reversible impotence has also been reported (see also notes above)

General note for H_2-receptor antagonists in the BNF No 31

SIDE-EFFECTS. H_2-receptor antagonists are well tolerated and side-effects are uncommon with few significant differences between available drugs. Dizziness, somnolence or fatigue, and rash have occasionally been reported with all of them, and there are rare reports of headache, liver dysfunction, and blood disorders. Other rare reports include bradycardia or AV block, confusion, interstitial nephritis (cimetidine), and urticaria and angioedema. Cimetidine is also associated with occsasional gynaecomastia and rare reports of impotence and myalgia. Causal relationships of other reports, such as pancreatitis, are unclear.

ADRs in the BNF No 31	described in the BNF 18? (Y/N)	Event Dictionary low-level term(s)
1 Altered bowel habit	N	Constipation + Diarrhoea
2 Dizziness	N	Dizziness
3 Rash	N	Rash
4 Tiredness	Y[a]	Malaise + Lassitude
5 Reversible confusional state	N	Confusion
6 Headache	Y	Headache
7 Blood disorders	N	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia

8	Muscle pain	Y	Myalgia
9	Joint pain	N	Pain joint
10	Hypersensitivity	Y&N	Rhinitis[b] + Pharyingitis[b] + Cough[b] + Pruritus[b] + Asthma + Urticaria[c] + Angioneurotic oedema[c]
11	Bradycardia	N	Bradycardia
12	AV block	N	Heart block
13	Interstitial nephritis	N	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
14	Gyanaecomastia	N	Gynaecomastia
15	Impotence	N	Impotence
16	Sweating	Y	Sweating
17	Somnolence	Y	Drowsiness + Sedation

[a] Described as 'Asthenia' in the BNF No 18

[b] Description in the BNF No 18

[c] Description in 'General note for H_2-receptor antagonists in the BNF No 31'

Questionable ADRs where 'causal relationships are unclear'

Q1	Pancreatitis[d]	Pancreatitis

[d] Classified under this category according to 'General note for H_2-receptor antagonists in the BNF No 31'

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Liver dysfunction	Liver function test abnormal

Events signalled

As shown in Table 22, 13 events (low-level terms) are signalled. One event is signalled by the statistical test only while four events are signalled by the rate ratio method only. The remaining 8 events (62 %) are signalled by both of the methods.

Of the 13 events signalled, 8 events (62 %) are known ADRs (category A or B)

but 5 events signalled are not shown in the BNF. None of these 5 events are given as ADRs in any literature.

Confounding by the indication or 'indication-related' event[63]

It is likely that two cardiovascular events 'angina' and 'myocardial infarction' are confounded by the indication. Abdominal pain and chest pain due to these diseases can be judged to be (potentially) caused by peptic ulcer. Anti-peptic ulcer drugs may be prescribed to those patients with abdominal or chest pain and the underlying diseases may be diagnosed and reported soon after the first prescription of nizatidine. Two alimentary events 'Nausea' and 'Vomiting' can be confounded by the indication as the underlying gastro-intestinal diseases which lead the prescription of anti-peptic ulcer drugs may be closely associated with these events. However, these two events are commonplace ADRs to many drugs and it is difficult to draw a clear conclusion. Lastly, 'vaginal candidiasis' may be also confounded by the indication because this disease is often associated with pelvic inflammatory disease or other sexually transmitted diseases of females leading to abdominal pain or discomfort potentially interpreted as symptoms caused by peptic ulcer disease.

ADRs signalled

Of the 17 ADRs under category A or B, 6 ADRs (35 %) are signalled. Three of them are previously known (Category A) but the other three are previously unknown (Category B). Of the 11 known ADRs not signalled, the rate is low except for 'pharyngitis' and 'pain joint' where T1 is more than 1 in 1000 patients per month. It is likely that most of these events coded in the PEM study of nizatidine are non-specific and not associated with the drug.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		7779		38810			min	max
3	Denominator male		4097		20459				
4	Denominator female		3552		17700				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	**A. Previously known ADRs signalled**							4	
11	**Psychiatric**								
12	Lassitude	$$	10	1.3	12	0.3	4.2	1.8	9.6
13	Malaise	$$*	12	1.5	9	0.2	6.7	2.8	15.8
14	**Central and Peripheral Nervous System**								
15	Drowsiness	*	7	0.9	4	0.1	-	-	-
16	Headache	$$*	25	3.2	29	0.7	4.3	2.5	7.3
17									
18	**B. Previously unknown ADRs signalled**							4	
19	**Skin**								
20	Rash	$$*	21	2.7	20	0.5	5.2	2.8	9.7
21	**Central and Peripheral Nervous System**								
22	Dizziness	$	12	1.5	24	0.6	2.5	1.2	5.0
23	**Alimentary**								
24	Constipation	$$*	16	2.1	12	0.3	6.7	3.1	14.1
25	Diarrhoea	$$*	27	3.5	36	0.9	3.7	2.3	6.2
26									
27	**C. Questionable ADRs signalled**							0	
28									
29	**D. 'Hard-to-detect' ADRs signalled**							0	
30									
31	**E. No description in BNF but signalled**							5	
32	**Cardiovascular**								
33	Angina	$	12	1.5	23	0.6	2.6	1.3	5.2
34	Myocardial infarction*	$$*	13	1.7	11	0.3	5.9	2.6	13.2
35	**Alimentary**								
36	Nausea	$$*	23	3.0	16	0.4	7.2	3.8	13.6
37	Vomiting	$*	20	2.6	37	1.0	2.7	1.6	4.6
38	**Female Reproductive**								
39	Vaginal candidiasis	$$	6	1.7	9	0.5	3.3	1.2	9.3
40									
41	**Events NOT signalled**								
42									
43	**A. Previously known ADRs NOT signalled**							7	
44	**Skin**								
45	Pruritus @		3	0.4	5	0.1	-	-	-
46	**Musculoskeletal**								
47	Myalgia		6	0.8	5	0.1	-	-	-
48	**Central and Peripheral Nervous System**								
49	Sedation		0	0.0	0	0.0	-	-	-
50									
51									
52									

Table 22 Nizatidine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
53	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
54	***A. Previously known ADRs NOT signalled continued***								
55	**Respiratory**								
56	Cough		4	0.5	25	0.6	-	-	-
57	Pharyngitis		9	1.2	33	0.9	1.4	0.7	2.8
58	Rhinitis		1	0.1	0	0.0	-	-	-
59	**Metabolic and Endocrine**								
60	Sweating		3	0.4	7	0.2	-	-	-
61									
62	***B. Previously unknown ADRs NOT signalled***							***19***	
63	**Skin**								
64	Urticaria		1	0.1	4	0.1	-	-	-
65	**Musculoskeletal**								
66	Pain joint@		13	1.7	40	1.0	1.6	0.9	3.0
67	**Psychiatric**								
68	Confusion		0	0.0	1	0.0	-	-	-
69	**Cardiovascular**								
70	Bradycardia		0	0.0	0	0.0	-	-	-
71	Heart block*		1	0.1	0	0.0	-	-	-
72	**Respiratory**								
73	Asthma*		2	0.3	7	0.2	-	-	-
74	**Urologic**								
75	Renal failure acute		0	0.0	1	0.0	-	-	-
76	Renal failure chronic*		0	0.0	0	0.0	-	-	-
77	Renal failure*		0	0.0	1	0.0	-	-	-
78	Uraemia*		0	0.0	0	0.0	-	-	-
79	**Male Reproductive and Gynaecomastia**								
80	Gynaecomastia		1	0.2	2	0.1	-	-	-
81	Impotence		0	0.0	2	0.1	-	-	-
82	**Haemopoietic**								
83	Leucopenia@		0	0.0	1	0.0	-	-	-
84	Neutropenia		0	0.0	0	0.0	-	-	-
85	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
86	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
87	Pancytopenia@		0	0.0	1	0.0	-	-	-
88	Thrombocytopenia		0	0.0	1	0.0	-	-	-
89	**Immunological**								
90	Angioneurotic oedema		2	0.3	0	0.0	-	-	-
91									
92	***C. 'Questionable' ADRs NOT signalled***							***1***	
93	**Alimentary**								
94	Pancreatitis*		2	0.3	4	0.1	-	-	-
95									
96	***D. 'Hard-to-detect' ADRs NOT signalled***							***1***	
97	**Alimentary**								
98	Liver function test abnormal		1	0.1	3	0.1	-	-	-

Table 22 **Nizatidine: Events signalled and not signalled**

15 Famotidine

ADRs in the BNF

Description in the BNF No 16 September 1988

FAMOTIDINE

Side-effects: rarely, headache, dizziness, constipation, and diarrhoea: also reported dry mouth, nausea, vomiting, abdominal discomfort, anorexia, rash, and fatigue

ADRs in the BNF No 16

1 Headache
2 Dizziness
3 Constipation
4 Diarrhoea
5 Dry mouth
6 Nausea
7 Vomiting
8 Abdominal discomfort
9 Anorexia
10 Rash
11 Fatigue

Description in the BNF No 31 March 1996

FAMOTIDINE

Side-effects: see under Cimetidine and notes above

CIMETIDINE

Side-effects: altered bowel habit, dizziness, rash, tiredness; reversible confusional states, reversible liver damage, headache; rarely, blood disorders (including thrombocytopenia, agranulocytosis and aplastic anaemia), muscle or joint pain, hypersensitivity, bradycardia and AV block; interstitial

nephritis and acute pancreatitis reported; gynaecomastia is also an occasional problem with cimetidine (but usually only in high dosage), and reversible impotence has also been reported (see also notes above)

General note for H_2-receptor antagonists in the BNF No 31

SIDE-EFFECTS. H_2-receptor antagonists are well tolerated and side-effects are uncommon with few significant differences between available drugs. Dizziness, somnolence or fatigue, and rash have occasionally been reported with all of them, and there are rare reports of headache, liver dysfunction, and blood disorders. Other rare reports include bradycardia or AV block, confusion, interstitial nephritis (cimetidine), and urticaria and angioedema. Cimetidine is also associated with occasional gynaecomastia and rare reports of impotence and myalgia. Causal relationships of other reports, such as pancreatitis, are unclear.

	ADRs in the BNF No 31	described in the BNF 16? (Y/N)	Event Dictionary low-level term(s)
1	Altered bowel habit	Y	Constipation + Diarrhoea
2	Dizziness	Y	Dizziness
3	Rash	Y	Rash
4	Tiredness or Fatigue	Y	Malaise + Lassitude
5	Reversible confusional state	N	Confusion
6	Headache	Y	Headache
7	Blood disorders	N	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
8	Muscle pain	N	Myalgia
9	Joint pain	N	Pain joint
10	Hypersensitivity	N	Rhinitis[a] + Pharyingitis[a] + Cough[a] +

			Pruritus[a] + Asthma + Urticaria[b] + Angioneurotic oedema[b]
11	Bradycardia	N	Bradycardia
12	AV block	N	Heart block
13	Interstitial nephritis	N	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
14	Gyanaecomastia	N	Gynaecomastia
15	Impotence	N	Impotence
16	Somnolence	N	Drowsiness + Sedation

[a] Terms for nizatidine are shown for famotidine as well (see 14 Nizatidine)
[b] Description in 'General note for H_2-receptor antagonists in the BNF No 31'

Questionable ADRs where 'causal relationships are unclear'

Q1	Pancreatitis[d]	Pancreatitis

[d] Classified under this category according to 'General note for H_2-receptor antagonists in the BNF No 31'

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Liver dysfunction	Liver function test abnormal

Events signalled

As shown in Table 23, 8 events (low-level terms) are signalled. Two events are signalled by the rate ratio method only. The remaining 6 events (75 %) are signalled by both of the methods.

Of the 8 events signalled, 5 events are known ADRs (category A or B) but 3 events signalled are not shown in the BNF. Of these 3 events, 2 may be regarded as known ADRs.

1 'Nausea' is an ADR shown in the BNF No 16 (see above).
2 'Vomiting' is an ADR shown in the BNF No 16 (see above).

If these two events are added to currently known ADRs, 7 of 8 events signalled

(88 %) may be judged to be currently known ADRs. The last event 'mastalgia' is probably an ADR detected by PEM for the first time[63]. This is distinct from 'gynaecomastia' in males as all of the patients with 'mastalgia' are females.

Confounding by the indication or 'indication-related' event

As with nizatidine, two alimentary events 'Nausea' and 'Vomiting' can be confounded by the indication as the underlying gastro-intestinal diseases which lead the prescription of anti-peptic ulcer drugs may be closely associated with these events. However, these two events are shown in the BNF No 16 as ADRs to nizatidine (see above) and it is difficult to draw a clear conclusion.

ADRs signalled

Of the 16 ADRs under category A or B, 5 ADRs (31 %) are signalled all of which are judged to be previously known (Category A). Of the 11 known ADRs not signalled, the rate is low except for 'constipation' and 'pain joint' where T1 is more than 1 in 1000 patients per month. 'Impotence' is relatively rare and is not signalled. Though the rate is small, after examining the original green forms, it is concluded that 'impotence' is probably an ADR to famotidine[63].

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		9500		47386			min	max
3	Denominator male		4899		24420				
4	Denominator female		4396		21941				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*5*	
11	**Skin**								
12	Rash	$	12	1.3	24	0.5	2.5	1.2	5.0
13	**Psychiatric**								
14	Malaise	$$*	16	1.7	15	0.3	5.3	2.6	10.8
15	**Central and Peripheral Nervous System**								
16	Dizziness	$$*	22	2.3	30	0.6	3.7	2.1	6.3
17	Headache	$$*	31	3.3	52	1.1	3.0	1.9	4.6
18	**Alimentary**								
19	Diarrhoea	$$*	32	3.4	52	1.1	3.1	2.0	4.8
20									
21	***B. Previously unknown ADRs signalled***							*0*	
22									
23	***C. Questionable ADRs signalled***							*0*	
24									
25	***D. 'Hard-to-detect' ADRs signalled***							*0*	
26									
27	***E. No description in BNF but signalled***							*3*	
28	**Alimentary**								
29	Nausea	$$*	31	3.3	28	0.6	5.5	3.3	9.2
30	Vomiting	$$*	25	2.6	41	0.9	3.0	1.8	5.0
31	**Breast Disorder**								
32	Mastalgia	$$	5	1.1	2	0.1	12.5	2.4	64.3
33									
34	***Events NOT signalled***								
35									
36	***A. Previously known ADRs NOT signalled***							*2*	
37	**Psychiatric**								
38	Lassitude		9	0.9	26	0.5	-	-	-
39	**Alimentary**								
40	Constipation		12	1.3	29	0.6	2.1	1.1	4.0
41									
42	***B. Previously unknown ADRs NOT signalled***							*26*	
43	**Skin**								
44	Pruritus @		2	0.2	13	0.3	-	-	-
45	Urticaria		2	0.2	1	0.0	-	-	-
46	**Musculoskeletal**								
47	Myalgia		4	0.4	13	0.3	-	-	-
48	Pain joint@		17	1.8	62	1.3	1.4	0.8	2.3
49	**Psychiatric**								
50	Confusion		2	0.2	3	0.1	-	-	-
51									

Table 23 Famotidine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
52	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
53	***B. Previously unknown ADRs NOT signalled continued***								
54	**Central and Peripheral Nervous System**								
55	Drowsiness		3	0.3	1	0.0	-	-	-
56	Sedation		0	0.0	0	0.0	-	-	-
57	**Cardiovascular**								
58	Bradycardia		0	0.0	0	0.0	-	-	-
59	Heart block*		0	0.0	1	0.0	-	-	-
60	**Respiratory**								
61	Asthma*		8	0.8	14	0.3	-	-	-
62	Cough		6	0.6	37	0.8	-	-	-
63	Pharyngitis		9	0.9	44	0.9	-	-	-
64	Rhinitis		0	0.0	1	0.0	-	-	-
65	**Urologic**								
66	Renal failure acute		0	0.0	0	0.0	-	-	-
67	Renal failure chronic*		0	0.0	0	0.0	-	-	-
68	Renal failure*		1	0.1	2	0.0	-	-	-
69	Uraemia*		0	0.0	0	0.0	-	-	-
70	**Male Reproductive and Gynaecomastia**								
71	Gynaecomastia		1	0.2	2	0.1	-	-	-
72	Impotence		3	0.6	1	0.0	-	-	-
73	**Haemopoietic**								
74	Leucopenia@		0	0.0	0	0.0	-	-	-
75	Neutropenia		0	0.0	0	0.0	-	-	-
76	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
77	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
78	Pancytopenia@		0	0.0	0	0.0	-	-	-
79	Thrombocytopenia		0	0.0	0	0.0	-	-	-
80	**Immunological**								
81	Angioneurotic oedema		0	0.0	1	0.0	-	-	-
82									
83	***C. 'Questionable' ADRs NOT signalled***							*1*	
84	**Alimentary**								
85	Pancreatitis*		2	0.2	0	0.0	-	-	-
86									
87	***D. 'Hard-to-detect' ADRs NOT signalled***							*1*	
88	**Alimentary**								
89	Liver function test abnormal		0	0.0	1	0.0	-	-	-

Table 23 Famotidine: Events signalled and not signalled

16 Omeprazole

ADRs in the BNF

Description in the BNF No 22 September 1991

OMEPRAZOLE
Side-effects: diarrhoea, headache (both may be severe); also nausea, constipation, and flatulence; skin reactions (some serious), photosensitivity reported

ADRs in the BNF No 22

1 Diarrhoea
2 Headache
3 Nausea
4 Constipation
5 Flatulence
6 Skin reactions
7 Photosensitivity

Description in the BNF No 31 March 1996

OMEPRARZOLE
Side-effects: rashes, urticaria, pruritus, bullous eruption, erythema multiforme, angioedema, alopecia and photosensitivity reported; diarrhoea, headache (both may be severe); also nausea, constipation, flatulence, abdominal pain, dizziness, faintness, vertigo, somnolence, malaise, insomnia and paraesthesia; muscle and joint pain, blurred vision, peripheral oedema, increased sweating, gynaecomastia and rarely impotence, loss of taste, stomatitis, gastro-intestinal candidiasis, leucopenia, thrombocytopenia, fever, bronchospasm, interstitial nephritis, liver enzyme changes and liver dysfunction also reported (and encephalopathy in pre-existing severe liver disease); reversible mental confusion, agitation,

depression and hallucinations have been noted in the severely ill

	ADRs in the BNF No 31	described in the BNF 22 ? (Y/N)	Event Dictionary low-level term(s)
1	Rashes	Y[a]	Rash
2	Urticaria	Y[a]	Urticaria
3	Pruritus	Y[a]	Pruritus
4	Bullous eruption	Y[a]	Eruption bullous + Blister + Dermatitis herpetiformis + Pemphigoid + Pemphigus
5	Erythema multiforme	Y[a]	Erythema multiforme
6	Angioedema	Y[a]	Angioneurotic oedema
7	Alopecia	N	Hair loss
8	Photosensitivity	Y	Photosensitivity
9	Diarrhoea	Y	Diarrhoea
10	Headache	Y	Headache
11	Nausea	Y	Nausea
12	Constipation	Y	Constipation
13	Flatulence	Y	Flatulence
14	Abdominal pain	N	Pain abdomen
15	Dizziness	N	Dizziness
16	Faintness	N	Syncope + Faintness
17	Vertigo	N	Vertigo
18	Somnolence	N	Drowsiness + Sedation
19	Malaise	N	Malaise
20	Insomnia	N	Insomnia
21	Paraesthesia	N	Paraesthesia
22	Muscle pain	N	Myalgia
23	Joint pain	N	Pain joint
24	Blurred vision	N	Vision deteriorated + Visual disturbance
25	Peripheral oedema	N	Oedema + Swollen ankle + Swollen limb

26	Increased sweating	N	Sweating
27	Gynaecomastia	N	Gynaecomastia
28	Impotence	N	Impotence
29	Loss of taste	N	Taste abnormal
30	Stomatitis	N	Stomatitis
31	Gastro-intestinal candidiasis	N	Candidiasis
32	Leucopenia	N	Leucopenia + Neutropenia
33	Thrombocytopenia	N	Thrombocytopenia
34	Fever	N	Pyrexia of unknown origin
35	Bronchospasm	N	Asthma + Bronchospasm + Wheezing
36	Interstitial nephritis	N	Renal failure acute + Renal failure chronic + Renal failure + Uraemia
37	Reversible mental confusion	N	Confusion
38	Agitation	N	Agitation
39	Depression	N	Depression
40	Hallucinations	N	Hallucination

[4] Described as 'Skin reaction' in the BNF No 22

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1	Liver dysfunction	Liver function test abnormal

Events signalled

As shown in Table 24, 10 events (low-level terms) are signalled. Four events are signalled by the statistical test only. The remaining 6 events (60 %) are signalled by both of the methods.

Of the 10 events signalled, 7 events are known ADRs (category A or B) but 3 events signalled are not shown in the BNF. Of these 3 events, 1 may be regarded as a known ADR.

1 'Vomiting' may be associated with 'Nausea' under category A

If this is added to currently known ADRs, 8 of 10 events signalled (80 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

Two events signalled, 'myocardial infarction' and 'oesophagitis', are likely to be confounded by the indication as they may produce chest or abdominal pain which may be considered to be potentially caused by peptic ulcer disease. In the PEM report on omeprazole, 'dyspepsia', which is a high-level term and includes 'oesophagitis' as one of the low-level terms belonging to this high-level term, 'dysphagia', 'oesophageal spasm', 'oesophageal stricture', 'pain abdomen', 'ulcer oesophageal' and 'ulcer peptic' are designated as 'Indication-related events' though most of them are not signalled[38].

ADRs signalled

Of the 40 ADRs under category A or B, 7 ADRs (18 %) are signalled. Four are judged to be previously known (Category A) but three are judged to be previously unknown (Category B). Of the 33 known ADRs not signalled, the rate is low except for 'rash', 'pain joint', 'depression' and 'malaise' where T1 is more than 1 in 1000 patients per month.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		16199		80904			min	max
3	Denominator male		7967		39783				
4	Denominator female		8069		40304				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	**A. Previously known ADRs signalled**							4	
11	**Central and Peripheral Nervous System**								
12	Headache	*	56	3.5	135	1.7	2.1	1.5	2.8
13	**Alimentary**								
14	Constipation	*	37	2.3	82	1.0	2.3	1.5	3.3
15	Diarrhoea	$$*	139	8.6	179	2.2	3.9	3.1	4.8
16	Nausea	$$*	60	3.7	64	0.8	4.7	3.3	6.7
17									
18	**B. Previously unknown ADRs signalled**							3	
19	**Central and Peripheral Nervous System**								
20	Dizziness	$*	31	1.9	63	0.8	2.5	1.6	3.8
21	**Cardiovascular**								
22	Oedema@	$*	26	1.6	51	0.6	2.5	1.6	4.1
23	**Alimentary**								
24	Pain abdomen	*	112	6.9	310	3.8	1.8	1.5	2.2
25									
26	**D. 'Hard-to-detect' ADRs signalled**							0	
27									
28	**E. No description in BNF but signalled**							3	
29	**Cardiovascular**								
30	Myocardial infarction*	$*	21	1.3	36	0.4	2.9	1.7	5.0
31	**Alimentary**								
32	Oesophagitis	*	8	0.5	157	1.9	-	-	-
33	Vomiting	$*	68	4.2	119	1.5	2.9	2.1	3.8
34									
35	**Events NOT signalled**								
36									
37	**A. Previously known ADRs NOT signalled**							12	
38	**Skin**								
39	Blister		2	0.1	2	0.0	-	-	-
40	Dermatitis herpetiformis		0	0.0	0	0.0	-	-	-
41	Eruption bullous@		0	0.0	1	0.0	-	-	-
42	Pemphigoid		0	0.0	0	0.0	-	-	-
43	Pemphigus		0	0.0	0	0.0	-	-	-
44	Erythema multiforme		0	0.0	1	0.0	-	-	-
45	Photosensitivity		0	0.0	2	0.0	-	-	-
46	Pruritus @		7	0.4	34	0.4	-	-	-
47	Rash		24	1.5	79	1.0	1.5	1.0	2.4
48	Urticaria		4	0.2	17	0.2	-	-	-
49	**Alimentary**								
50	Flatulence		12	0.7	23	0.3	-	-	-
51	**Immunological**								
52	Angioneurotic oedema		0	0.0	0	0.0	-	-	-
53									

Table 24 Omeprazole: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
54	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
55	***B. Previously unknown ADRs NOT signalled***							***36***	
56	**Skin**								
57	Hair loss		0	0.0	2	0.0	-	-	-
58	**Musculoskeletal**								
59	Myalgia		14	0.9	26	0.3	-	-	-
60	Pain joint@		34	2.1	196	2.4	0.9	0.6	1.2
61	**Psychiatric**								
62	Agitation		4	0.2	8	0.1	-	-	-
63	Confusion		2	0.1	9	0.1	-	-	-
64	Depression @		39	2.4	158	2.0	1.2	0.9	1.8
65	Hallucination		0	0.0	3	0.0	-	-	-
66	Insomnia		15	0.9	24	0.3	-	-	-
67	Malaise		23	1.4	50	0.6	2.3	1.4	3.8
68	**Central and Peripheral Nervous System**								
69	Drowsiness		2	0.1	3	0.0	-	-	-
70	Sedation		0	0.0	0	0.0	-	-	-
71	Paraesthesia		9	0.6	19	0.2	-	-	-
72	Taste abnormal		3	0.2	3	0.0	-	-	-
73	Syncope		10	0.6	20	0.2	-	-	-
74	**Eye**								
75	Vision deteriorated		0	0.0	0	0.0	-	-	-
76	Visual disturbance		3	0.2	6	0.1	-	-	-
77	**Ear**								
78	Vertigo		11	0.7	36	0.4	-	-	-
79	**Cardiovascular**								
80	Faintness		2	0.1	5	0.1	-	-	-
81	Swollen ankles		5	0.3	12	0.1	-	-	-
82	Swollen limb		0	0.0	4	0.0	-	-	-
83	**Respiratory**								
84	Asthma*		13	0.8	64	0.8	-	-	-
85	Bronchospasm		2	0.1	7	0.1	-	-	-
86	Wheezing		2	0.1	18	0.2	-	-	-
87	**Alimentary**								
88	Stomatitis		0	0.0	3	0.0	-	-	-
89	**Metabolic and Endocrine**								
90	Sweating		2	0.1	16	0.2	-	-	-
91	**Urologic**								
92	Renal failure acute		0	0.0	0	0.0	-	-	-
93	Renal failure chronic*		0	0.0	1	0.0	-	-	-
94	Renal failure*		3	0.2	3	0.0	-	-	-
95	Uraemia*		0	0.0	0	0.0	-	-	-
96	**Male Reproductive and Gynaecomastia**								
97	Gynaecomastia		0	0.0	2	0.1	-	-	-
98	Impotence		2	0.3	4	0.1	-	-	-
99	**Haemopoietic**								
100	Leucopenia@		0	0.0	1	0.0	-	-	-
101	Neutropenia		0	0.0	2	0.0	-	-	-
102	Thrombocytopenia		0	0.0	1	0.0	-	-	-
103	**Miscellaneous Infection**								
104	Candidiasis		2	0.1	8	0.1	-	-	-
105	Pyrexia of unknown origin		5	0.3	10	0.1	-	-	-
106									
107	***D. 'Hard-to-detect' ADRs NOT signalled***							***1***	
108	**Alimentary**								
109	Liver function test abnormal		0	0.0	6	0.1	-	-	-

Table 24 Omeprazole: Events signalled and not signalled

17 Misoprostol

ADRs in the BNF

Description in the BNF No 19 March 1990

MISOPROSTOL

Side-effects: diarrhoea (may be severe, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids); also reported: abdominal pain, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding (including intermenstrual bleeding, menorrhagia, and postmenopausal bleeding)

ADRs in the BNF No 19

1 Diarrhoea
2 Abdominal pain
3 Dyspepsia
4 Flatulence
5 Nausea
6 Vomiting
7 Abnormal vaginal bleeding

Description in the BNF No 31 March 1996

MISOPROSTOL

Side-effects: diarrhoea (may occasionally be severe and require withdrawal, reduced by giving single doses not exceeding 200 micrograms and by avoiding magnesium-containing antacids); also reported: abdominal pain, dyspepsia, flatulence, nausea and vomiting, abnormal vaginal bleeding (including intermenstrual bleeding, menorrhagia, and postmenopausal bleeding), rashes, dizziness

ADRs in the BNF No 31		described in the BNF 19 ? (Y/N)	Event Dictionary low-level term(s)
1	Diarrhoea	Y	Diarrhoea
2	Abdominal pain	Y	Pain abdomen
3	Dyspepsia	Y	Dyspepsia
4	Flatulence	Y	Flatulence
5	Nausea	Y	Nausea
6	Vomiting	Y	Vomiting
7	Abnormal vaginal bleeding	Y	Haemorrhage postmenopausal + Haemorrhage vaginal + Dysmenorrhoea + Menorrhagia
8	Rashes	N	Rash
9	Dizziness	N	Dizziness

Events signalled

As shown in Table 25, 23 events (low-level terms) are signalled. Nine events are signalled by the statistical test only but two events are signalled by the rate ratio method only. The remaining 12 events (52 %) are signalled by both of the methods.

Of the 23 events signalled, 9 events are known ADRs (category A or B) but 14 events signalled are not shown in the BNF. Of these 14 events, 3 may be regarded as known ADRs.

1 'Malaise' is an ADR listed in literature other than BNF[88].

2 'Distension abdominal' may be associated with abdominal pain or diarrhoea.

3 'Heartburn' is associated with dyspepsia.

If these 3 are added to currently known ADRs, 12 of 23 events signalled (52 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

The following four events, 'haematemesis', 'melena', 'haemorrhage rectal' and 'anaemia' are associated with haemorrhage of gastro-intestinal tract and may be confounded by the indication.

ADRs signalled

Of the 9 ADRs under category A or B, all of 9 ADRs (100 %) are signalled. Seven are judged to be previously known (Category A) but two are judged to be previously unknown (Category B).

EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
Denominator total		13768		68350			min	max
Denominator male		4933		24495				
Denominator female		8589		42638				
$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
Events signalled								
A. Previously known ADRs signalled							*7*	
Alimentary								
Diarrhoea	$$*	598	43.4	330	4.8	9.0	7.9	10.3
Dyspepsia@	$$*	342	24.8	301	4.4	5.6	4.8	6.6
Flatulence	$$*	49	3.6	30	0.4	8.1	5.1	12.8
Nausea	$$*	242	17.6	123	1.8	9.8	7.9	12.1
Vomiting	$$*	141	10.2	85	1.2	8.2	6.3	10.8
Pain abdomen	$$*	330	24.0	318	4.7	5.2	4.4	6.0
Female Reproductive								
Haemorrhage vaginal	*	8	0.9	4	0.1	-	-	-
B. Previously unknown ADRs signalled							*2*	
Skin								
Rash	*	38	2.8	92	1.3	2.1	1.4	3.0
Central and Peripheral Nervous System								
Dizziness	*	40	2.9	90	1.3	2.2	1.5	3.2
E. No description in BNF but signalled							*14*	
Psychiatric								
Malaise	$$*	87	6.3	56	0.8	7.7	5.5	10.8
Central and Peripheral Nervous System								
Flushing	*	7	0.5	4	0.1	-	-	-
Paraesthesia	*	12	0.9	14	0.2	-	-	-
Cardiovascular								
Congestive cardiac failure*	$	15	1.1	26	0.4	2.9	1.5	5.4
Alimentary								
Anorexia	*	12	0.9	15	0.2	-	-	-
Constipation	$*	53	3.8	90	1.3	2.9	2.1	4.1
Distension abdominal	$$*	35	2.5	23	0.3	7.6	4.5	12.8
Heartburn	$$*	32	2.3	30	0.4	5.3	3.2	8.7
Haematemesis*	*	12	0.9	15	0.2	-	-	-
Melena	*	12	0.9	14	0.2	-	-	-
Haemorrhage rectal	$	15	1.1	28	0.4	2.7	1.4	5.0
Pharynx irritation	*	6	0.4	2	0.0	-	-	-
Haemopoietic								
Anaemia	$$*	18	1.3	26	0.4	3.4	1.9	6.3
Immunological								
Unspecified side effects	$$*	33	2.4	18	0.3	9.1	5.1	16.2

Table 25 Misoprostol: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
56	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
57	***Events NOT signalled***								
58									
59	***A. Previously known ADRs NOT signalled***							*3*	
60	**Female Reproductive**								
61	Haemorrhage postmenopausal		2	0.2	7	0.2	-	-	-
62	Dysmenorrhoea		0	0.0	2	0.0	-	-	-
63	Menorrhagia		7	0.8	21	0.5	-	-	-
64									
65	***B. Previously unknown ADRs NOT signalled***							*0*	

Table 25 Misoprostol: Events signalled and not signalled

18 Acrivastine

ADRs in the BNF

Description in the BNF No 20 September 1990

ACRIVASTINE
Side-effects: see notes above; incidence of sedation and antimuscarinic effects low

In the beginning of section 3.4.1 Antihistamines, the following description is given:

DISADVANTAGES OF ANTIHISTAMINES. With most antihistamines drowsiness is a serious disadvantage; patients should be warned that their ability to drive or operate machinery may be impaired, and that the effects of alcohol may be increased. Other side-effects include headache, psychomotor impairment, antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances; occasional rashes and photosensitivity reactions have been reported; paradoxical stimulation may rarely occur, especially in high dosage or in children.

ADRs in the BNF No 20

1 Drowsiness
2 Headache
3 Psychomotor impairment
4 Urinary retention
5 Dry mouth
6 Blurred vision
7 Gastro-intestinal disturbances
8 Rashes
9 Photosensitivity
10 Paradoxical stimulation

Description in the BNF No 31 March 1996

ACRIVASTINE

Side-effects: see notes above; incidence of sedation and antimuscarinic effects low

In the beginning of section 3.4.1 Antihistamines, the following description is given:

DISADVANTAGES OF ANTIHISTAMINES. Drowsiness is a particular disadvantage with most of the older antihistamines (although paradoxical stimulation may rarely occur, especially in high dosage or in children); drowsiness is considerably less of a problem with the newer ones (see also notes above).

Other side-effects that are more common with the older antihistamines include headache, psychomotor impairment, antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances.

Other side-effects of antihistamines reported include rashes and photosensitivity reactions, palpitations and arrhythmias (important: see especially risks associated with astemizole and terfenadine, p. 136), hypersensitivity reactions (including bronchospasm, angioedema, and anaphylaxis), convulsions, sweating, myalgia, paraesthesia, blood disorders, extrapyramidal effects, tremor, liver dysfunction, sleep disturbances, depression, hypotension, and hair loss.

ADRs in the BNF No 31		described in the BNF 20 ? (Y/N)	Event Dictionary low-level term(s)
1	Drowsiness	Y	Drowsiness + Sedation
2	Headache	Y	Headache
3	Psychomotor impairment	Y	Akinesia[a] + Movement involuntary[a] + Dysphagia + Blephalospasm
4	Urinary retention	Y	Retention

5	Dry mouth	Y	Dry mouth
6	Blurred vision	Y	Vision deteriorated + Visual disturbance
7	Gastro-intestinal disturbances	Y	Anorexia[b] + Nausea[b] + Vomiting[b] + Pain abdomen[b] + Constipation[b] + Diarrhoea[b]
8	Rashes	Y	Rash
9	Photosensitivity	Y	Photosensitivity
10	Palpitation	N	Palpitation
11	Arrhythmia	N	Arrhythmia
12	Hypersensitivity	N	Bronchospasm + Wheezing + Angioneurotic oedema + Allergy + anaphylaxis
13	Convulsions	N	Convulsion + Epilepsy + Epilepsy grand mal
14	Sweating	N	Sweating
15	Myalgia	N	Myalgia
16	Paraesthesia	N	Paraesthesia
17	Blood disorders	N	Anaemia aplastic + Anaemia hypoplastic + Pancytopenia + Neutropenia + Leucopenia + Thrombocytopenia
18	Extrapyramidal effects	N	Dystonia + Extrapyramidal disease + Parkinson's disease
19	Tremor	N	Tremor
20	Sleep disturbances	N	Insomnia
21	Depression	N	Depression
22	Hypotension	N	Hypotension
23	Hair loss	N	Alopecia

[a]Facial dyskinesia, a known ADR to some antihistamines, may have been coded by this term if reported as the term 'dyskinesia' is not available in the event dictionary.

[b]Gastro-intestinal ADRs to antihistamines given in a textbook[89] even if some of them may be not really 'antimuscarinic'

ADRs hard to detect without laboratory test and unexpected to be detected in the usual general practice

N1 Liver dysfunction Liver function test abnormal

Events signalled

As shown in Table 26, 14 events (low-level terms) are signalled. Two events are signalled by the statistical test only but eight events are signalled by the rate ratio method only. The remaining 4 events (29 %) are signalled by both of the methods.

Of the 14 events signalled, 5 events are known ADRs (all of them are under category A) but 9 events signalled are not shown in the BNF. Of these 9 events, 1 may be regarded as a known ADR.

1 'Dizziness' is an ADR listed in literature other than BNF[90].
2 'Lassitude' may be associated with drowsiness
3 'Malaise' may be associated with drowsiness

If this event is added to currently known ADRs, 8 of 14 events signalled (57 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

After excluding the above 3 events ('dizziness', 'lassitude' and 'malaise'), all of the remaining 6 events may be confounded by the indication. 'Pruritus', and 'urticaria' may be the reason of administrating acrivastine though a possibility that they are in fact allergic reactions to acrivastine cannot be entirely excluded. 'Asthma' may be a manifestation of atopic diathesis which may be closely associated with allergic rhinits or others where antihistamines are often prescribed, though it is again not impossible that this event is in fact an ADR to acrivastine. 'Vaginal candidiasis' and 'scabies' may be diseases causing pruritus for which the antihistamine has been prescribed. 'Vaginal candidiasis' may be also associated with pelvic inflammatory diseases and other sexually

transmitted disease with 'menorrhagia'.

ADRs signalled

Of the 23 ADRs under category A or B, only 3 (13 %) are signalled. Of these three, 'rash' can be in fact confounded by the indication because 'rash' is often associated with conditions with pruritus for which an antihistamine is prescribed. The remaining 20 events are rare except for 'headache', 'diarrhoea', 'pain abdomen' and 'depression' where T1 is 1 per 1000 patients per month or more.

	A	B	C	D	E	F	G	H	I
1	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
2	Denominator total		7861		37950			min	max
3	Denominator male		2833		13712				
4	Denominator female		4897		23607				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***5***	
11	**Skin**								
12	Rash	$*	23	2.9	40	1.1	2.8	1.7	4.6
13	**Central and Peripheral Nervous System**								
14	Drowsiness	$$*	31	3.9	12	0.3	12.5	6.4	24.3
15	Sedation	*	5	0.6	0	0.0	-	-	-
16	**Alimentary**								
17	Nausea	$$	11	1.4	17	0.4	3.1	1.5	6.7
18	Vomiting	$	10	1.3	18	0.5	2.7	1.2	5.8
19									
20	***B. Previously unknown ADRs signalled***							***0***	
21									
22	***D. 'Hard-to-detect' ADRs signalled***							***0***	
23									
24	***E. No description in BNF but signalled***							***9***	
25	**Skin**								
26	Pruritus @	$$*	12	1.5	13	0.3	4.5	2.0	9.8
27	Scabies	*	6	0.8	1	0.0	-	-	-
28	Urticaria	$	15	1.9	27	0.7	2.7	1.4	5.0
29	**Psychiatric**								
30	Lassitude	$$	10	1.3	12	0.3	4.0	1.7	9.3
31	Malaise	$	8	1.0	14	0.4	2.8	1.2	6.6
32	**Central and Peripheral Nervous System**								
33	Dizziness	$	11	1.4	21	0.6	2.5	1.2	5.2
34	**Respiratory**								
35	Asthma*	$$*	21	2.7	34	0.9	3.0	1.7	5.1
36	**Female Reproductive**								
37	Menorrhagia	$$	7	1.4	8	0.3	4.2	1.5	11.6
38	Vaginal candidiasis	$	12	2.5	21	0.9	2.8	1.4	5.6
39									
40	***Events NOT signalled***								
41									
42	***A. Previously known ADRs NOT signalled***							***14***	
43	**Skin**								
44	Photosensitivity		0	0.0	1	0.0	-	-	-
45	**Central and Peripheral Nervous System**								
46	Akinesia		0	0.0	0	0.0	-	-	-
47	Movement involuntary		0	0.0	0	0.0	-	-	-
48	Headache		10	1.3	39	1.0	1.2	0.6	2.5
49	**Eye**								
50	Blepharospasm		0	0.0	0	0.0	-	-	-
51	Vision deteriorated		0	0.0	2	0.1	-	-	-
52	Visual disturbance		1	0.1	1	0.0	-	-	-

Table 26 Acrivastine: Events signalled and not signalled

	A	B	C	D	E	F	G	H	I
53	EVENT	Criteria	N1 & D1	T1	N2&D2-6	T2	T1/T2	95% CI of T1/T2	
54	***A. Previously known ADRs NOT signalled continued***								
65	**Alimentary**								
56	Anorexia		2	0.3	0	0.0	-	-	-
57	Constipation		2	0.3	11	0.3	-	-	-
58	Diarrhoea		12	1.5	40	1.1	1.4	0.8	2.8
59	Dry mouth		2	0.3	2	0.1	-	-	-
60	Dysphagia		1	0.1	1	0.0	-	-	-
61	Pain abdomen		19	2.4	53	1.4	1.7	1.0	2.9
62	**Urologic**								
63	Retention		0	0.0	0	0.0	-	-	-
64									
65	***B. Previously unknown ADRs NOT signalled***							***27***	
66	**Skin**								
67	Alopecia		0	0.0	0	0.0	-	-	-
68	**Musculoskeletal**								
69	Myalgia		5	0.6	15	0.4	-	-	-
70	**Psychiatric**								
71	Depression @		13	1.7	28	0.7	2.2	1.2	4.3
72	Insomnia		2	0.3	15	0.4	-	-	-
73	**Central and Peripheral Nervous System**								
74	Convulsion*		0	0.0	0	0.0	-	-	-
75	Epilepsy *		0	0.0	0	0.0	-	-	-
76	Epilepsy grand mal		0	0.0	0	0.0	-	-	-
77	Dystonia		0	0.0	0	0.0	-	-	-
78	Extrapyramidal disease@		0	0.0	0	0.0	-	-	-
79	Parkinson's disease*		0	0.0	0	0.0	-	-	-
80	Paraesthesia		1	0.1	5	0.1	-	-	-
81	Tremor		2	0.3	5	0.1	-	-	-
82	**Cardiovascular**								
83	Arrhythmia		0	0.0	0	0.0	-	-	-
84	Hypotension		0	0.0	0	0.0	-	-	-
85	Palpitation		1	0.1	6	0.2	-	-	-
86	**Respiratory**								
87	Bronchospasm		5	0.6	5	0.1	-	-	-
88	Wheezing		0	0.0	1	0.0	-	-	-
89	**Metabolic and Endocrine**								
90	Sweating		3	0.4	0	0.0	-	-	-
91	**Haemopoietic**								
92	Leucopenia@		0	0.0	0	0.0	-	-	-
93	Neutropenia		0	0.0	0	0.0	-	-	-
94	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
95	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
96	Pancytopenia@		0	0.0	0	0.0	-	-	-
97	Thrombocytopenia		0	0.0	0	0.0	-	-	-
98	**Immunological**								
99	Allergy		1	0.1	4	0.1	-	-	-
100	Anaphylaxis		0	0.0	0	0.0	-	-	-
101	Angioneurotic oedema		1	0.1	0	0.0	-	-	-
102									
103	***D. 'Hard-to-detect' ADRs NOT signalled***							***1***	
104	**Alimentary**								
105	Liver function test abnormal		0	0.0	1	0.0	-	-	-

Table 26 Acrivastine: Events signalled and not signalled