19 Cetirizine

ADRs in the BNF

Description in the BNF No 19 March 1990

CETIRIZINE
Side-effects: see notes above

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 19

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

CETIRIZINE

Side-effects: see notes above

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 19 ? (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 27, 5 events (low-level terms) are signalled. Two events are signalled by the rate ratio method only. The remaining 3 events (60 %) are signalled by both of the methods.

Of the 5 events signalled, 2 events (40 %) are known ADRs (all of them are under category A) but 3 events signalled are not shown in the BNF. Of these three,

1 'Dizziness' may be an ADR to cetirizine as with acrivastine

though in one clinical trial, the incidence of dizziness did not differ between cetirizine and placebo[91].

Confounding by the indication or 'indication-related' event

After excluding 'dizziness', both of the remaining two events may be confounded by the indication. 'Conjunctivitis', may be manifestation of allergic rhinitis or hay fever for which an antihistamine is often prescribed. '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 not impossible that this event is in fact an ADR to cetirizine.

ADRs signalled

Of the 23 ADRs under category A or B, only 1 (4 %) are signalled. The remaining 22 events are rare except for 'rash', 'headache', 'diarrhoea', 'pain abdomen', 'vomiting' and 'pain abdomen' where T1 is 1 per 1000 patients per month or more. Those results may indicate that some of known ADRs to some antihistamines, such as anti-muscarinic effect, extrapyramidal diseases, psychomotor impairment, or arrhythmogenesis may be rather unique to particular antihistamines but may not be really considered to be a class effect.

	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		9550		47682			min	max
3	Denominator male		3943		19685				
4	Denominator female		5454		27231				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7		U							
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*2*	
11	**Central and Peripheral Nervous System**								
12	Drowsiness	$$*	42	4.4	13	0.3	16.1	8.7	30.0
13	Sedation	$$*	12	1.3	0	0.0	infinite	-	-
14									
15	***B. Previously unknown ADRs signalled***							*0*	
16									
17	***D. 'Hard-to-detect' ADRs signalled***							*0*	
18									
19	***E. No description in BNF but signalled***							*3*	
20	**Central and Peripheral Nervous System**								
21	Dizziness	$$	12	1.3	17	0.4	3.5	1.7	7.4
22	**Eye**								
23	Conjunctivitis	$	13	1.4	25	0.5	2.6	1.3	5.1
24	**Respiratory**								
25	Asthma*	$$*	40	4.2	63	1.3	3.2	2.1	4.7
26									
27	***Events NOT signalled***								
28									
29	***A. Previously known ADRs NOT signalled***							*17*	
30	**Skin**								
31	Photosensitivity		1	0.1	3	0.1	-	-	-
32	Rash		16	1.7	40	0.8	2.0	1.1	3.6
33	**Central and Peripheral Nervous System**								
34	Akinesia		0	0.0	0	0.0	-	-	-
35	Movement involuntary		0	0.0	0	0.0	-	-	-
36	Headache		17	1.8	50	1.0	1.7	1.0	2.9
37	**Eye**								
38	Blepharospasm		0	0.0	0	0.0	-	-	-
39	Vision deteriorated		0	0.0	0	0.0	-	-	-
40	Visual disturbance		0	0.0	2	0.0	-	-	-
41	**Alimentary**								
42	Anorexia		1	0.1	5	0.1	-	-	-
43	Constipation		1	0.1	12	0.3	-	-	-
44	Diarrhoea		17	1.8	47	1.0	1.8	1.0	3.1
45	Dry mouth		1	0.1	0	0.0	-	-	-
46	Dysphagia		2	0.2	1	0.0	-	-	-
47	Nausea		9	0.9	17	0.4	-	-	-
48	Vomiting		10	1.0	30	0.6	1.7	0.8	3.4
49	Pain abdomen		19	2.0	64	1.3	1.5	0.9	2.5
50	**Urologic**								
51	Retention		1	0.1	0	0.0	-	-	-
52									
53									

Table 27 Cetirizine: 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***							***27***	
56	**Skin**								
57	Alopecia		0	0.0	2	0.0	-	-	-
58	**Musculoskeletal**								
59	Myalgia		3	0.3	11	0.2	-	-	-
60	**Psychiatric**								
61	Depression @		5	0.5	35	0.7	-	-	-
62	Insomnia		0	0.0	4	0.1	-	-	-
63	**Central and Peripheral Nervous System**								
64	Convulsion*		0	0.0	0	0.0	-	-	-
65	Epilepsy *		0	0.0	5	0.1	-	-	-
66	Epilepsy grand mal		0	0.0	0	0.0	-	-	-
67	Dystonia		0	0.0	0	0.0	-	-	-
68	Extrapyramidal disease@		0	0.0	0	0.0	-	-	-
69	Parkinson's disease*		0	0.0	0	0.0	-	-	-
70	Paraesthesia		2	0.2	2	0.0	-	-	-
71	Tremor		0	0.0	2	0.0	-	-	-
72	**Cardiovascular**								
73	Arrhythmia		0	0.0	0	0.0	-	-	-
74	Hypotension		0	0.0	3	0.1	-	-	-
75	Palpitation		1	0.1	3	0.1	-	-	-
76	**Respiratory**								
77	Bronchospasm		2	0.2	5	0.1	-	-	-
78	Wheezing		0	0.0	0	0.0	-	-	-
79	**Metabolic and Endocrine**								
80	Sweating		0	0.0	3	0.1	-	-	-
81	**Haemopoietic**								
82	Leucopenia@		0	0.0	0	0.0	-	-	-
83	Neutropenia		0	0.0	1	0.0	-	-	-
84	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
85	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
86	Pancytopenia@		0	0.0	0	0.0	-	-	-
87	Thrombocytopenia		0	0.0	0	0.0	-	-	-
88	**Immunological**								
89	Allergy		1	0.1	7	0.1	-	-	-
90	Anaphylaxis		0	0.0	0	0.0	-	-	-
91	Angioneurotic oedema		0	0.0	0	0.0	-	-	-
92									
93	***D. 'Hard-to-detect' ADRs NOT signalled***							***1***	
94	**Alimentary**								
95	Liver function test abnormal		1	0.1	1	0.0	-	-	-

Table 27 Cetirizine: Events signalled and not signalled

20 Loratadine

ADRs in the BNF

Description in the BNF No 19 March 1990

LORATADINE
Cautions; Side-effects: see notes above; incidence of sedation and antimuscarinic effects low; pregnancy (toxicity at high doses in *animal* studies)

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 19

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

LORATADINE

Cautions; Side-effects: see notes above; incidence of sedation and antimuscarinic effects low; pregnancy (toxicity at high doses in *animal* studies)

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. 134), 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 19 ? (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 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 28, 6 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 4 events (67 %) are signalled by both of the methods.

Of the 6 events signalled, 2 events (33 %) are known ADRs (both of them are under category A) but 4 events signalled are not shown in the BNF.

Confounding by the indication or 'indication-related' event

All of the four events signalled but not shown in the BNF as ADRs may be confounded by the indication. 'Conjunctivitis', may be manifestation of allergic rhinitis or hay fever for which an antihistamine is often prescribed. 'Asthma' which is often associated with 'cough' may be a manifestation of atopic diathesis which may be closely associated with 'rhinitis allergic' or others where antihistamines are often prescribed, though it is not impossible that this event is in fact an ADR to loratadine.

ADRs signalled

Of the 23 ADRs under category A or B, only 1 (4 %) are signalled. The remaining 22 events are rare except for 'rash', 'headache', 'diarrhoea', 'pain abdomen' and 'depression' where T1 is 1 per 1000 patients per month or more. The results are similar to those with other two antihistamines.

	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		9304		46419			min	max
3	Denominator male		3908		19503				
4	Denominator female		5177		25825				
5	$ T1/T2 = or > 2.5 and $$ T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*2*	
11	**Central and Peripheral Nervous System**								
12	Drowsiness	$$*	12	1.3	2	0.0	29.9	6.7	133.8
13	Sedation	*	4	0.4	0	0.0	-	-	-
14									
15	***B. Previously unknown ADRs signalled***							*0*	
16									
17	***D. 'Hard-to-detect' ADRs signalled***							*0*	
18									
19	***E. No description in BNF but signalled***							*4*	
20	**Eye**								
21	Conjunctivitis	$$	12	1.3	19	0.4	3.2	1.5	6.5
22	**Respiratory**								
23	Asthma*	$$*	47	5.1	55	1.2	4.3	2.9	6.3
24	Cough	$*	21	2.3	38	0.8	2.8	1.6	4.7
25	Rhinitis allergic	$$*	17	1.8	12	0.3	7.1	3.4	14.8
26									
27	***Events NOT signalled***								
28									
29	***A. Previously known ADRs NOT signalled***							*17*	
30	**Skin**								
31	Photosensitivity		0	0.0	1	0.0	-	-	-
32	Rash		12	1.3	30	0.6	2.0	1.0	3.9
33	**Central and Peripheral Nervous System**								
34	Akinesia		0	0.0	0	0.0	-	-	-
35	Movement involuntary		0	0.0	0	0.0	-	-	-
36	Headache		15	1.6	54	1.2	1.4	0.8	2.5
37	**Eye**								
38	Blepharospasm		0	0.0	0	0.0	-	-	-
39	Vision deteriorated		0	0.0	1	0.0	-	-	-
40	Visual disturbance		1	0.1	2	0.0	-	-	-
41	**Alimentary**								
42	Anorexia		0	0.0	0	0.0	-	-	-
43	Constipation		4	0.4	14	0.3	-	-	-
44	Diarrhoea		11	1.2	36	0.8	1.5	0.8	3.0
45	Dry mouth		0	0.0	0	0.0	-	-	-
46	Dysphagia		0	0.0	2	0.0	-	-	-
47	Nausea		7	0.8	11	0.2	-	-	-
48	Vomiting		7	0.8	25	0.5	-	-	-
49	Pain abdomen		10	1.1	46	1.0	1.1	0.5	2.1
50	**Urologic**								
51	Retention		1	0.1	2	0.0	-	-	-
52									
53									

Table 28 Loratadine: 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***							***27***	
56	**Skin**								
57	Alopecia		0	0.0	2	0.0	-	-	-
58	**Musculoskeletal**								
59	Myalgia		3	0.3	9	0.2	-	-	-
60	**Psychiatric**								
61	Depression @		10	1.1	36	0.8	1.4	0.7	2.8
62	Insomnia		0	0.0	7	0.2	-	-	-
63	**Central and Peripheral Nervous System**								
64	Convulsion*		0	0.0	2	0.0	-	-	-
65	Epilepsy *		1	0.1	0	0.0	-	-	-
66	Epilepsy grand mal		0	0.0	0	0.0	-	-	-
67	Dystonia		0	0.0	0	0.0	-	-	-
68	Extrapyramidal disease@		0	0.0	0	0.0	-	-	-
69	Parkinson's disease*		0	0.0	0	0.0	-	-	-
70	Paraesthesia		1	0.1	3	0.1	-	-	-
71	Tremor		1	0.1	1	0.0	-	-	-
72	**Cardiovascular**								
73	Arrhythmia		0	0.0	0	0.0	-	-	-
74	Hypotension		0	0.0	1	0.0	-	-	-
75	Palpitation		0	0.0	0	0.0	-	-	-
76	**Respiratory**								
77	Bronchospasm		6	0.6	7	0.2	-	-	-
78	Wheezing		0	0.0	0	0.0	-	-	-
79	**Metabolic and Endocrine**								
80	Sweating		0	0.0	6	0.1	-	-	-
81	**Haemopoietic**								
82	Leucopenia@		0	0.0	0	0.0	-	-	-
83	Neutropenia		0	0.0	0	0.0	-	-	-
84	Anaemia aplastic*		0	0.0	0	0.0	-	-	-
85	Anaemia hypoplastic		0	0.0	0	0.0	-	-	-
86	Pancytopenia@		0	0.0	0	0.0	-	-	-
87	Thrombocytopenia		0	0.0	0	0.0	-	-	-
88	**Immunological**								
89	Allergy		1	0.1	2	0.0	-	-	-
90	Anaphylaxis		0	0.0	0	0.0	-	-	-
91	Angioneurotic oedema		1	0.1	2	0.0	-	-	-
92									
93	***C. 'Questionable' ADRs NOT signalled***							***0***	
94									
95	***D. 'Hard-to-detect' ADRs NOT signalled***							***1***	
96	**Alimentary**								
97	Liver function test abnormal		0	0.0	2	0.0	-	-	-

Table 28 Loratadine: Events signalled and not signalled

21 Nedocromil

ADRs in the BNF

Description in the BNF No 18 September 1989

NEDOCROMIL
Side-effects: see under Sodium Cromoglycate; also headache, nausea (both mild and transient); bitter taste

SODIUM CROMOGLYCATE
Side-effects: coughing, transient bronchospasm, and throat irritation due to inhalation of powder.

ADRs in the BNF No 18

1 Irritation due to inhalation (coughing, transient bronchospasm, throat irritation)
2 Headache
3 Nausea
4 Bitter taste

Description in the BNF No 31 March 1996

NEDOCROMIL SODIUM
Side-effects: see under Sodium Cromoglycate; also headache, nausea, vomiting, dyspepsia, abdominal pain (mild and transient); bitter taste (masked by mint flavour)

SODIUM CROMOGLYCATE
Side-effects: coughing, transient bronchospasm, and throat irritation due to inhalation of powder

ADRs in the BNF No 31		described in the BNF 18 ? (Y/N)	Event Dictionary low-level term(s)
1	Irritation due to inhalation	Y	Cough + Bronchospasm + Wheezing + Pharynx irritation
2	Headache	Y	Headache
3	Nausea	Y	Nausea
4	Vomiting	N	Vomiting
5	Dyspepsia	N	Dyspepsia
6	Abdominal pain	N	Pain abdomen
7	Bitter taste	Y	Drug unpalatable

Events signalled

As shown in Table 29, 10 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 6 events (60 %) are signalled by both of the methods.

Of the 10 events signalled, 5 events are known ADRs (4 are under category A and one is under category B) but 5 events signalled are not shown in the BNF. Of these 5 events, 1 may be regarded as a known ADR

1 'Sore mouth' may be associated with 'bitter taste' or 'irritation due to inhalation'

If this event is added to currently known ADRs, 6 of 10 (60 %) may be judged to be currently known ADRs.

Confounding by the indication or 'indication-related' event

Two events 'asthma' and 'infection chest' are likely to be confounded by the indication. It is well known that chest infection can worsen asthma or induce asthma attack. 'Cough' shown as a previously known ADR signalled may be in fact confounded by the indication as cough is a common manifestation of

asthma.

ADRs signalled

Of the 7 ADRs under category A or B, 5 (71 %) are signalled if 'sore mouth' is considered to be associated with 'bitter taste'. With the remaining 2 events, 'dyspepsia' and 'pain abdomen', T1 = 0.8 and 2.0 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		12292		61270			min	max
3	Denominator male		6337		31597				
4	Denominator female		5765		28731				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*4*	
11	**Central and Peripheral Nervous System**								
12	Headache	$$*	72	5.9	92	1.5	3.9	2.9	5.3
13	**Respiratory**								
14	Cough	$*	55	4.5	93	1.5	2.9	2.1	4.1
15	**Alimentary**								
16	Nausea	$$*	73	5.9	45	0.7	8.1	5.6	11.7
17	Pharynx irritation	$$	12	1.0	20	0.3	3.0	1.5	6.1
18									
19	***B. Previously unknown ADRs signalled***							*1*	
20	**Alimentary**								
21	Vomiting	$$*	33	2.7	49	0.8	3.4	2.2	5.2
22									
23	***E. No description in BNF but signalled***							*5*	
24	**Psychiatric**								
25	Malaise	$$*	22	1.8	17	0.3	6.5	3.4	12.1
26	**Respiratory**								
27	Asthma*	*	156	12.7	457	7.5	1.7	1.4	2.0
28	Infection chest*	*	98	8.0	310	5.1	1.6	1.3	2.0
29	**Alimentary**								
30	Sore mouth	$$*	12	1.0	8	0.1	7.5	3.1	18.3
31	**Immunological**								
32	Unspecified side effects	*	10	0.8	9	0.1	-	-	-
33									
34	***Events NOT signalled***								
35									
36	***A. Previously known ADRs NOT signalled***							*3*	
37	**Respiratory**								
38	Bronchospasm		15	1.2	38	0.6	2.0	1.1	3.6
39	Wheezing		0	0.0	0	0.0	-	-	-
40	**Other events usually not shown**								
41	Drug unpalatable		2	0.2	1	0.0	-	-	-
42									
43	***B. Previously unknown ADRs NOT signalled***							*2*	
44	**Alimentary**								
45	Dyspepsia@		10	0.8	56	0.9	-	-	-
46	Pain abdomen		24	2.0	72	1.2	1.7	1.0	2.6

Table 29 Nedocromil: Events signalled and not signalled

22 Acyclovir

ADRs in the BNF

Description in the BNF No 13 March 1987

ACYCLOVIR

Side-effects: rashes; gastro-intestinal disturbances; rises in bilirubin and liver-related enzymes, increases in blood urea and creatinine, decreases in haematological indices, headache, neurological reactions, fatigue

ADRs in the BNF No 13

1 Rashes
2 Gastro-intestinal disturbances
3 Rises in bilirubin and liver-related enzymes
4 Increases in blood urea and creatinine
5 Decreases in haematological indices
6 Headache
7 Neurological reactions
8 Fatigue

Description in the BNF No 31 March 1996

ACYCLOVIR

Side-effects: rashes; gastro-intestinal disturbances; rises in bilirubin and liver-related enzymes, increases in blood urea and creatinine, decreases in haematological indices, headache, neurological reactions (including dizziness), fatigue; on intravenous infusion, severe local inflammation (sometimes leading to ulceration), also confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma

ADRs in the BNF No 31		described in the BNF 13 ? (Y/N)	Event Dictionary low-level term(s)
1	Rashes	Y	Rash
2	Gastro-intestinal disturbances	Y	Dyspepsia + Nausea + Vomiting + Pain abdomen + Constipation + Diarrhoea
3	Rises in bilirubin	Y	Jaundice
4	Headache	Y	Headache
5	Neurological reactions	Y	Dizziness + Paraesthesia + Extrapyramidal disease
6	Fatigue	Y	Malaise + Lassitude
7	Confusion	N	Confusion
8	Hallucinations	N	Hallucination
9	Agitation	N	Agitation
10	Tremors	N	Tremor
11	Somnolence	N	Drowsiness + Sedation
12	Psychosis	N	Psychosis
13	Convulsions	N	Convulsion + Epilepsy + Epilepsy grand mal
14	Coma	N	Coma

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

N1	Rises in liver-related enzymes	Liver function test abnormal
N2	Increases in blood urea	Urea raised
N3	Increases in creatinine	Renal function test abnormal
N4	Decreases in haematological indices	Thrombocytopenia[a] + Anaemia + Anaemia macrocytic[b]

[a]Description in a textbook[92]
[b]Description in a textbook[93]

Events signalled

As shown in Table 30, 16 events (low-level terms) are signalled. Six events are signalled by the statistical test only and two events are signalled by the rate ratio

method only. The remaining 8 events (50 %) are signalled by both of the methods.

Of the 16 events signalled, 6 events (38 %) are known ADRs (5 are under category A and one is under category B) but 10 events signalled are not shown in the BNF.

Confounding by the indication or 'indication-related' event

All of the 10 events signalled but not shown as ADRs in the BNF may be confounded by the indication. They are infections often accompanied by herpes simplex ('infection', 'impetigo', 'infection skin', 'vaginal candidiasis', 'vaginal discharge' and 'dysuria') or sign concomitant with herpes simplex ('pyrexia of unknown origin') or sequelae of herpes zoster ('Bell's palsy', 'neuralgia' and 'neuralgia postherpetic',)

ADRs signalled

Of the 14 ADRs under category A or B, 3 (21 %) are signalled. The other 13 ADRs are rare except for 'headache', 'diarrhoea' and 'pain abdomen' where T1 is 1.0 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		11046		54810			min	max
3	Denominator male		3950		19602				
4	Denominator female		6863		34054				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							***5***	
11	**Skin**								
12	Rash	$$*	31	2.8	37	0.7	4.2	2.6	6.7
13	**Psychiatric**								
14	Malaise	$$*	21	1.9	14	0.3	7.4	3.8	14.6
15	**Alimentary**								
16	Constipation	$$*	23	2.1	18	0.3	6.3	3.4	11.7
17	Nausea	$$*	14	1.3	14	0.3	5.0	2.4	10.4
18	Vomiting	$$*	27	2.4	28	0.5	4.8	2.8	8.1
19									
20	***B. Previously unknown ADRs signalled***							***1***	
21	**Psychiatric**								
22	Confusion	*	6	0.5	3	0.1	-	-	-
23									
24	***D. 'Hard-to-detect' ADRs signalled***							***0***	
25									
26	***E. No description in BNF but signalled***							***10***	
27	**Skin**								
28	Impetigo	*	9	0.8	2	0.0	-	-	-
29	Infection skin	$$	12	1.1	16	0.3	3.7	1.8	7.9
30	**Central and Peripheral Nervous System**								
31	Bell's palsy	*	6	0.5	1	0.0	-	-	-
32	Neuralgia	*	7	0.6	4	0.1	-	-	-
33	Neuralgia postherpetic	$$*	160	14.5	90	1.6	8.8	6.8	11.4
34	**Urologic**								
35	Dysuria	$$*	14	1.3	13	0.2	5.3	2.5	11.4
36	**Female Reproductive**								
37	Vaginal candidiasis	$*	25	3.6	47	1.4	2.6	1.6	4.3
38	Vaginal discharge	$$	12	1.7	20	0.6	3.0	1.5	6.1
39	**Miscellaneous Infection**								
40	Infection	*	10	0.9	4	0.1	-	-	-
41	Pyrexia of unknown origin	*	7	0.6	2	0.0	-	-	-
42									
43									
44									
45									
46									
47									
48									
49									
50									
51									
52									
53									
54									
55									

Table 30 Acyclovir: 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***							*9*	
60	**Psychiatric**								
61	Lassitude		10	0.9	17	0.3	-	-	-
62	**Central and Peripheral Nervous System**								
63	Dizziness		7	0.6	17	0.3	-	-	-
64	Extrapyramidal disease@		0	0.0	0	0.0	-	-	-
65	Headache		17	1.5	37	0.7	2.3	1.3	4.0
66	Paraesthesia		4	0.4	8	0.1	-	-	-
67	**Alimentary**								
68	Diarrhoea		17	1.5	41	0.7	2.1	1.2	3.6
69	Dyspepsia@		8	0.7	14	0.3	-	-	-
70	Jaundice		0	0.0	0	0.0	-	-	-
71	Pain abdomen		23	2.1	53	1.0	2.2	1.3	3.5
72									
73	***B. Previously unknown ADRs NOT signalled***							*10*	
74	**Psychiatric**								
75	Agitation		0	0.0	0	0.0	-	-	-
76	Hallucination		0	0.0	0	0.0	-	-	-
77	Psychosis		0	0.0	0	0.0	-	-	-
78	**Central and Peripheral Nervous System**								
79	Coma		0	0.0	0	0.0	-	-	-
80	Convulsion*		0	0.0	1	0.0	-	-	-
81	Epilepsy *		1	0.1	2	0.0	-	-	-
82	Epilepsy grand mal		0	0.0	1	0.0	-	-	-
83	Drowsiness		1	0.1	0	0.0	-	-	-
84	Sedation		0	0.0	0	0.0	-	-	-
85	Tremor		1	0.1	1	0.0	-	-	-
86									
87	***D. 'Hard-to-detect' ADRs NOT signalled***							*6*	
88	**Alimentary**								
89	Liver function test abnormal		0	0.0	1	0.0	-	-	-
90	**Urologic**								
91	Renal function test abnormal		0	0.0	0	0.0	-	-	-
92	Urea raised		0	0.0	0	0.0	-	-	-
93	**Haemopoietic**								
94	Anaemia		1	0.1	2	0.0	-	-	-
95	Anaemia macrocytic@		0	0.0	0	0.0	-	-	-
96	Thrombocytopenia		1	0.1	0	0.0	-	-	-

Table 30 Acyclovir: Events signalled and not signalled

23 Ciprofloxacin

ADRs in the BNF

Description in the BNF No 17 March 1989

CIPROFLOXACIN

Side-effects: nausea, vomiting, diarrhoea, dyspepsia, abdominal pain: dizziness, headache, fatigue, confusion, convulsions; rashes, pruritus, joint pain, photosensitivity; increases in liver enzymes (particularly in those with previous liver damage) and in serum bilirubin, urea or creatinine)

ADRs in the BNF No 17

1 Nausea
2 Vomiting
3 Diarrhoea
4 Dyspepsia
5 Abdominal pain
6 Dizziness
7 Headache
8 Fatigue
9 Confusion
10 Convulsions
11 Rashes
12 Pruritus
13 Joint pain
14 Photosensitivity
15 Increases in liver enzymes
16 Increases in serum bilirubin
17 Increases in urea
18 Increases in creatinine

Description in the BNF No 31 March 1996

CIPROFLOXACIN

Cautions; Side-effects: see notes above; avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); not recommended in children of growing adolescents; caution in G6PD deficiency (see section 9.1.5); anaphylaxis reported, also reported dyspepsia, flatulence, dysphagia, tremor, convulsions, jaundice and hepatitis with necrosis, renal failure, nephritis, vasculitis, erythema nodosum, Stevens-Johnson syndrome, Lyell syndrome, petechiae, haemorrhagic bullae, tenosynovitis and tachycardia; pain and phlebitis at injection site

In the beginning of the section 5.1.12 4-Quinolones, the following description is given

SIDE-EFFECTS. Common side-effects of the 4-quinolones include nausea, vomiting, abdominal pain, diarrhoea (rarely pseudomembranous colitis), headache, dizziness, sleep disorders, rash, pruritus, fever, anaphylaxis, photosensitivity, increase in blood urea and creatinine, transient disturbances in liver enzymes and bilirubin, arthralgia and myalgia, blood disorders (including eosinophilia, leucopenia, thrombocytopenia, and altered prothrombin concentrations). Less frequent side-effects include anorexia, restlessness, depression, hallucinations, confusion, and disturbances in vision, taste, hearing and smell; also isolated reports of intracranial hypertension and tendon damage (see CSM advice above). Side-effects that have been reported to the CSM also include haemolytic anaemia, renal impairment, hepatic dysfunction, anaphylaxis, and hypoglycaemia. The drug should be discontinued if mental, neurological of hypersensitivity reactions occur with the first dose.

	ADRs in the BNF No 31	described in the BNF 17 ? (Y/N)	Event Dictionary low-level term(s)
Side effects common to 4-Quinolones			
1	Nausea	Y	Nausea
2	Vomiting	Y	Vomiting
3	Abdominal pain	Y	Pain abdomen
4	Diarrhoea	Y	Diarrhoea + Colitis pseudomembranous
5	Headache	Y	Headache
6	Dizziness	Y	Dizziness
7	Sleep disorders	N	Insomnia
8	Rash	Y	Rash
9	Pruritus	Y	Pruritus
10	Fever	N	Pyrexia of unknown origin
11	Anaphylaxis	N	Anaphylaxis
12	Photosensitivity	Y	Photosensitivity
13	Arthralgia	Y	Pain joint
14	Myalgia	N	Myalgia
15	Blood disorders	N	Eosinophilia + Leucopenia + Neutropenia + Thrombocytopenia + Coagulation disorder
16	Anorexia	N	Anorexia
17	Restlessness	N	Hyperactive
18	Depression	N	Depression
19	Hallucinations	N	Hallucination
20	Confusion	Y	Confusion
21	Disturbances in vision	N	Vision deteriorated + Visual disturbance
22	Disturbances in taste	N	Taste abnormal
23	Disturbances in hearing	N	Deafness + Ear unspecified
24	Disturbances in smell	N	Smell abnormal
25	Intracranial hypertension	N	No term available
26	Tendon damage	N	Tendinitis + Tenosynovitis
27	Haemolytic anaemia	N	Anaemia haemolytic
28	Renal impairment	N	Renal failure acute + Renal failure

			chronic + Renal failure + Uraemia
29	Hypoglycaemia	N	Hypoglycaemia

Side effects specifically for ciprofloxacin

30	Dyspepsia	Y	Dyspepsia
31	Flatulence	N	Flatulence
32	Dysphagia	N	Dysphagia
33	Tremor	N	Tremor
34	Convulsions	Y	Convulsion + Epilepsy + Epilepsy grand mal
35	Jaundice and hepatitis	N	Hepatitis + Jaundice
36	Nephritis	N	Nephritis + Nephropathy
37	Vasculitis	N	Vasculitis
38	Erythema nodosum	N	Erythema nodosum
39	Stevens-Johnson syndrome	N	Stevens-Johnson syndrome
40	Lyell syndrome	N	no term available
41	Petechiae	N	Purpura
42	Haemorrhagic bullae	N	Blister + Eruption bullous
43	Tachycardia	N	Tachycardia

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

N1	Increase in blood urea and creatinine	Urea raised + Renal function test abnormal
N2	Transient disturbances in liver enzymes and bilirubin	Liver function test abnormal

Events signalled

As shown in Table 31, 14 events (low-level terms) are signalled. Five events are signalled by the statistical test only and two events are signalled by the rate ratio method only. The remaining 7 events (50 %) are signalled by both of the methods.

Of the 14 events signalled, 6 events are known ADRs (all of them are under category A) but 8 events signalled are not shown in the BNF.

At least the following 2 events not shown in the BNF may be considered to be known ADRs.

1 'Malaise' is associated with 'Weakness' described in literature other than BNF[94].
2 'Vaginal candidiasis' may be also regarded to be known ADR as 'vaginitis' is described in literature other than BNF[94].

If these two are added to previously known ADRs, 8 of 14 events (57 %) may be regarded to be currently known ADRs.

'Vaginal candidiasis' is probably due to the change in the normal vaginal flora induced by ciprofloxacin and should be an ADR to ciprofloxacin. It is difficult to judge whether or not 'vaginal candidiasis' signalled in the PEM study is identical to 'vaginitis' given in one literature with no detailed information[94]. 'Vaginal candidiasis' may be regarded as an ADR detected by the PEM study for the first time and has been not widely recognised as an ADR to ciprofloxacin even if the secondary infection due to the change in the normal flora is always a likely scenario brought by any antibiotic.

Confounding by the indication or 'indication-related' event

Some of events signalled but not described as ADRs in the BNF may be confounded by the indication. 'Cough', 'tonsillitis', 'abscess' are closely associated with the indication.

ADRs signalled

Of the 43 ADRs under category A or B, 6 (14 %) are signalled. The other 37 ADRs are rare except for 'pain joint', 'headache', 'dyspepsia' and 'depression' where T1 is 1.0 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		11475		48461			min	max
3	Denominator male		4493		18976				
4	Denominator female		6607		27900				
5	$ T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	**Events signalled**								
9									
10	***A. Previously known ADRs signalled***							*6*	
11	**Skin**								
12	Rash	$*	32	2.8	52	1.1	2.6	1.7	4.0
13	**Central and Peripheral Nervous System**								
14	Dizziness	$$*	21	1.8	30	0.6	3.0	1.7	5.2
15	**Alimentary**								
16	Diarrhoea	$*	52	4.5	84	1.7	2.6	1.8	3.7
17	Nausea	$$*	39	3.4	25	0.5	6.6	4.0	10.9
18	Vomiting	$$*	53	4.6	55	1.1	4.1	2.8	5.9
19	Pain abdomen	*	59	5.1	105	2.2	2.4	1.7	3.3
20									
21	***B. Previously unknown ADRs signalled***							*0*	
22									
23	***D. 'Hard-to-detect' ADRs signalled***							*0*	
24									
25	***E. No description in BNF but signalled***							*8*	
26	**Psychiatric**								
27	Malaise	$	17	1.5	25	0.5	2.9	1.6	5.3
28	**Cardiovascular**								
29	Left ventricular failure*	$	15	1.3	22	0.5	2.9	1.5	5.6
30	Cyanosis	*	4	0.3	0	0.0	-	-	-
31	**Respiratory**								
32	Cough	*	39	3.4	73	1.5	2.3	1.5	3.3
33	Tonsillitis	$$*	15	1.3	15	0.3	4.2	2.1	8.6
34	**Female Reproductive**								
35	Vaginal candidiasis	$$*	50	7.6	36	1.3	5.9	3.8	9.0
36	**Miscellaneous Infection**								
37	Abscess	*	8	0.7	3	0.1	-	-	-
38	**Immunological**								
39	Unspecified side effects	*	6	0.5	0	0.0	-	-	-
40									
41	**Events NOT signalled**								
42									
43	***A. Previously known ADRs NOT signalled***							*10*	
44	**Skin**								
45	Photosensitivity		1	0.1	3	0.1	-	-	-
46	Pruritus @		9	0.8	19	0.4	-	-	-
47	**Musculoskeletal**								
48	Pain joint@		19	1.7	76	1.6	1.1	0.6	1.7
49	**Psychiatric**								
50	Confusion		9	0.8	13	0.3	-	-	-
51									
52									

Table 31 Ciprofloxacin: 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	**Central and Peripheral Nervous System**								
56	Convulsion*		1	0.1	1	0.0	-	-	-
57	Epilepsy *		2	0.2	4	0.1	-	-	-
58	Epilepsy grand mal		0	0.0	1	0.0	-	-	-
59	Headache		24	2.1	52	1.1	1.9	1.2	3.2
60	**Alimentary**								
61	Dyspepsia@		13	1.1	48	1.0	1.1	0.6	2.1
62	Colitis pseudomembranous*		0	0.0	0	0.0	-	-	-
63									
64	***B. Previously unknown ADRs NOT signalled***							*41*	
65	**Skin**								
66	Blister		0	0.0	2	0.0	-	-	-
67	Eruption bullous@		0	0.0	0	0.0	-	-	-
68	Erythema nodosum		0	0.0	0	0.0	-	-	-
69	Purpura		0	0.0	2	0.0	-	-	-
70	Stevens-Johnson syndrome		0	0.0	0	0.0	-	-	-
71	**Musculoskeletal**								
72	Myalgia		7	0.6	29	0.6	-	-	-
73	Tendinitis		1	0.1	0	0.0	-	-	-
74	Tenosynovitis		0	0.0	3	0.1	-	-	-
75	**Psychiatric**								
76	Depression @		26	2.3	77	1.6	1.4	0.9	2.2
77	Hallucination		3	0.3	1	0.0	-	-	-
78	Hyperactive		0	0.0	0	0.0	-	-	-
79	Insomnia		5	0.4	18	0.4	-	-	-
80	**Central and Peripheral Nervous System**								
81	Smell abnormal		0	0.0	0	0.0	-	-	-
82	Taste abnormal		1	0.1	1	0.0	-	-	-
83	Tremor		2	0.2	7	0.1	-	-	-
84	**Eye**								
85	Vision deteriorated		0	0.0	0	0.0	-	-	-
86	Visual disturbance		1	0.1	3	0.1	-	-	-
87	**Ear**								
88	Deafness		5	0.4	5	0.1	-	-	-
89	**Cardiovascular**								
90	Tachycardia		3	0.3	3	0.1	-	-	-
91	Vasculitis		0	0.0	0	0.0	-	-	-
92	**Alimentary**								
93	Anorexia		4	0.3	7	0.1	-	-	-
94	Dysphagia		2	0.2	6	0.1	-	-	-
95	Flatulence		4	0.3	8	0.2	-	-	-
96	Hepatitis*		0	0.0	1	0.0	-	-	-
97	Jaundice		0	0.0	3	0.1	-	-	-
98	**Metabolic and Endocrine**								
99	Hypoglycaemia		1	0.1	5	0.1	-	-	-
100	**Urologic**								
101	Nephritis		0	0.0	0	0.0	-	-	-
102	Nephropathy		0	0.0	0	0.0	-	-	-
103	Renal failure acute		0	0.0	0	0.0	-	-	-
104	Renal failure chronic*		1	0.1	3	0.1	-	-	-
105	Renal failure*		1	0.1	4	0.1	-	-	-
106	Uraemia*		0	0.0	0	0.0	-	-	-
107									
108									

Table 31 Ciprofloxacin: 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	Anaemia haemolytic		0	0.0	0	0.0	-	-	-
113	Coagulation disorder		0	0.0	0	0.0	-	-	-
114	Eosinophilia@		0	0.0	0	0.0	-	-	-
115	Leucopenia@		1	0.1	0	0.0	-	-	-
116	Neutropenia		0	0.0	0	0.0	-	-	-
117	Thrombocytopenia		1	0.1	1	0.0	-	-	-
118	**Miscellaneous Infection**								
119	Pyrexia of unknown origin		8	0.7	13	0.3	-	-	-
120	**Immunological**								
121	Anaphylaxis		0	0.0	0	0.0	-	-	-
122	**Other events usually not shown**								
123	Ear unspecified		1	0.1	10	0.2	-	-	-
124									
125	***D. 'Hard-to-detect' ADRs NOT signalled***							*3*	
126	**Alimentary**								
127	Liver function test abnormal		0	0.0	2	0.0	-	-	-
128	**Urologic**								
129	Renal function test abnormal		0	0.0	0	0.0	-	-	-
130	Urea raised		1	0.1	4	0.1	-	-	-

Table 31 Ciprofloxacin: Events signalled and not signalled

24 Fluconazole

ADRs in the BNF

Description in the BNF No 17 March 1989

FLUCONAZOLE
Side-effects: nausea, abdominal discomfort, headache; occasionally abnormalities of liver enzymes

ADRs in the BNF No 17

1 Nausea
2 Abdominal discomfort
3 Headache
4 Abnormalities of liver enzymes

Description in the BNF No 31 March 1996

FLUCONAZOLE
Side-effects: nausea, abdominal discomfort, diarrhoea, and flatulence; occasionally abnormalities of liver enzymes; rarely rash (discontinue treatment or monitor closely if infection invasive or systemic); angioedema, anaphylaxis, bullous lesions, and Stevens-Johnson syndrome reported; severe cutaneous reactions in AIDS patients also reported.

ADRs in the BNF No 31	described in the BNF 17 ? (Y/N)	Event Dictionary low-level term(s)
1 Nausea	Y	Nausea
2 Abdominal discomfort	Y	Vomiting
3 Diarrhoea	N	Diarrhoea
4 Flatulence	N	Flatulence
5 Rash	N	Rash
6 Angioedema	N	Angioneurotic oedema
7 Anaphylaxis	N	Anaphylaxis

8	Bulluos lesions	N	Blister + Eruption bullous
9	Stevens-Johnson syndrome	N	Stevens-Johnson syndrome

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

N1	Transient disturbances in liver enzymes and bilirubin	Liver function test abnormal

Events signalled

As shown in Table 32, 13 events (low-level terms) are signalled. Eight events are signalled by the statistical test only and two events are signalled by the rate ratio method only. The remaining 2 events (15 %) are signalled by both of the methods.

Of the 13 events signalled, 2 events (15 %) are known ADRs (one is under category A and the other is under category B) but 11 events signalled are not shown in the BNF. It may be noted that in the PEM report of fluconazole, the following is described as conclusion[32].

The concept of a one-dose treatment for an important disease is novel and it has been rewarding to note the excellent response of doctors who were requested to participate in the monitoring of fluconazole and their high opinion of its efficacy. --- Fluconazole has been almost completely free from adverse reactions in this group of more than 15,000 patients who represent a large proportion of the earliest population to receive this drug immediately after its release for use in general practice.

The above conclusion has been augmented by the succeeding study following up 289 women taking fluconazole at some time during the months before or during pregnancy. In this study examining the outcome of pregnancy, fluconazole is concluded to be without harmful effect[50].

Confounding by the indication or 'indication-related' event

Most events signalled but not described as ADRs in the BNF may be confounded by the indication except for 'rhinitis allergic'. 'Prutitus vulvae' is a manifestation of the indication, vaginal candidiasis and most of unspecified 'pruritus' is probably vulval pruritus. Vaginal candidiasis is a frequent complication with 'diabetes mellitus'. Vaginal candidiasis is also sometimes accompanied by other infections such as 'urinary tract infection' with 'frequency', 'infection vaginal bacterial', 'vaginitis trichomonas' and 'gardenerella infection'. 'vaginal discharge' and 'vaginitis' are manifestations of vaginal candidiasis and other associated vaginal infections.

Very few events are signalled because T2 > T1 rather than T1 > T2. 'Rhinitis allergic' with fluconazole is one of such few events. It is unlikely that this event is confounded by the indication. It is unclear whether this event has any relationship with fluconazole

ADRs signalled

Of the 9 ADRs under category A or B, 2 (22 %) are signalled. The other 7 ADRs are rare except for 'rash' where T1 is more than 1.0 per 1000 patients.

	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		15007		68492			min	max
3	Denominator male		877		4129				
4	Denominator female		14009		63795				
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*1*	
11	**Alimentary**								
12	Nausea	$	18	1.2	32	0.5	2.6	1.4	4.6
13									
14	***B. Previously unknown ADRs signalled***							*1*	
15	**Alimentary**								
16	Diarrhoea	*	44	2.9	92	1.3	2.2	1.5	3.1
17									
18	***D. 'Hard-to-detect' ADRs signalled***							*0*	
19									
20	***E. No description in BNF but signalled***							*11*	
21	**Skin**								
22	Pruritus @	$$*	15	1.0	19	0.3	3.6	1.8	7.1
23	Pruritus vulvae	*	46	3.1	112	1.6	1.9	1.3	2.6
24	**Respiratory**								
25	Rhinitis allergic	*	1	0.1	65	0.9	-	-	-
26	**Metabolic and Endocrine**								
27	Diabetes mellitus*	*	7	0.5	3	0.0	-	-	-
28	**Urologic**								
29	Frequency	$$*	19	1.3	21	0.3	4.1	2.2	7.7
30	Urinary tract infection*	*	71	4.7	154	2.2	2.1	1.6	2.8
31	**Female Reproductive**								
32	Infection vaginal bacterial	$	17	1.2	29	0.5	2.7	1.5	4.9
33	Vaginal discharge	*	100	7.1	245	3.8	1.9	1.5	2.3
34	Vaginitis	*	42	3.0	89	1.4	2.1	1.5	3.1
35	Vaginitis trichomonas	*	12	0.9	12	0.2	-	-	-
36	**Miscellaneous Infection**								
37	Gardnerella infection	$$*	22	1.5	29	0.4	3.5	2.0	6.0
38									
39	***Events NOT signalled***								
40									
41	***A. Previously known ADRs NOT signalled***							*1*	
42	**Alimentary**								
43	Pain abdomen		60	4.0	188	2.7	1.5	1.1	1.9
44									
45	***B. Previously unknown ADRs NOT signalled***							*7*	
46	**Skin**								
47	Blister		1	0.1	3	0.0	-	-	-
48	Eruption bullous@		0	0.0	0	0.0	-	-	-
49	Rash		37	2.5	95	1.4	1.8	1.2	2.6
50	Stevens-Johnson syndrome		0	0.0	0	0.0	-	-	-
51	**Alimentary**								
52	Flatulence		1	0.1	7	0.1	-	-	-

Table 32 Fluconazole: 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	***B. Previously unknown ADRs NOT signalled continued***								
55	**Immunological**								
56	Anaphylaxis		1	0.1	0	0.0	-	-	-
57	Angioneurotic oedema		2	0.1	1	0.0	-	-	-
58									
59	***D. 'Hard-to-detect' ADRs NOT signalled***							*1*	
60	**Alimentary**								
61	Liver function test abnormal		0	0.0	2	0.0	-	-	-

Table 32 Fluconazole: Events signalled and not signalled

25 Itraconazole

ADRs in the BNF

Description in the BNF No 20 September 1990

ITRACONAZOLE
Side-effects: nausea, abdominal pain, dyspepsia, headache

ADRs in the BNF No 20

1 Nausea
2 Abdominal pain
3 Dyspepsia
4 Headache

Description in the BNF No 31 March 1996

ITRACONAZOLE
Side-effects: nausea, abdominal pain, dyspepsia, constipation, headache, dizziness, raised liver enzymes, menstrual disorders; allergic reactions (including pruritus, rash, urticaria and angioedema), hepatitis and cholestatic jaundice (especially if treatment exceeds 1 month), peripheral neuropathy (discontinue treatment), and Stevens Johnson syndrome reported; on prolonged use hypokalaemia, oedema and hair loss reported

ADRs in the BNF No 31		described in the BNF 20 ? (Y/N)	Event Dictionary low-level term(s)
1	Nausea	Y	Nausea
3	Abdominal pain	Y	Pain abdomen
4	Dyspepsia	Y	Dyspepsia
5	Constipation	N	Constipation
6	Headache	Y	Headache

7	Dizziness	N	Dizziness
8	Menstrual disorders[a]	N	Irregular periods + Oligomenorrhoea + Polymenorrhoea
9	Allergic reactions	N	Pruritus + Rash + Urticaria + Angioneurotic oedema
10	Hepatitis	N	Hepatitis
11	Cholestatic jaundice	N	Jaundice + Jaundice cholestatic
12	Peripheral neuropathy	N	Neuropathy + Neuropathy peripheral + Neuritis + Neuritis peripheral
13	Stevens-Johnson syndrome	N	Stevens-Johnson syndrome
14	Oedema	N	Oedema + Swollen limb + Swollen ankle
15	Hair loss	N	Alopecia

[a]Though the detail is not specified in the BNF, 'menstrual irregularities' is given in literature[95].

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

N1	Raised liver enzymes	Liver function test abnormal
N2	Hypokalaemia	Hypokalaemia

Events signalled

As shown in Table 33, 9 events (low-level terms) are signalled. Four events are signalled by the statistical test only. The remaining 5 events (56 %) are signalled by both of the methods.

Of the 9 events signalled, 3 events (33 %) are known ADRs (One is under category A and two are under category B) but 5 events signalled are not shown in the BNF.

Confounding by the indication or 'indication-related' event

All of the 6 events signalled but not given as ADRs in the BNF may be

confounded by the indication. 'Pruritus vulvae' and 'vaginal discharge' are manifestations of vaginal candidiasis. Vaginal candidiasis is sometimes accompanied by 'infection vaginal bacterial', 'gardnerella infection' and 'herpes simplex genital' . Around 7 % of the indications were tinea while the early manifestation of 'psoriasis' can be misdiagnosed as tinea corporis.

ADRs signalled

Of the 15 ADRs under category A or B, 3 (20 %) are signalled. The other 12 ADRs are rare and T1 is less than 1.0 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		13637		68119			min	max
3	Denominator male		1480		7397				
4	Denominator female		12096		60415				
5	$ T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)								
6	When T1 < 1.0, above criteria for T1/T2 not applied and '-' given instead of the value of T1/T2								
7									
8	***Events signalled***								
9									
10	***A. Previously known ADRs signalled***							*1*	
11	**Alimentary**								
12	Nausea	$$*	22	1.6	35	0.5	3.1	1.8	5.4
13									
14	***B. Previously unknown ADRs signalled***							*2*	
15	**Skin**								
16	Rash	*	43	3.2	106	1.6	2.0	1.4	2.9
17	**Central and Peripheral Nervous System**								
18	Dizziness	$$*	19	1.4	32	0.5	3.0	1.7	5.2
19									
20	***D. 'Hard-to-detect' ADRs signalled***							*0*	
21									
22	***E. No description in BNF but signalled***							*6*	
23	**Skin**								
24	Pruritus vulvae	$$*	53	3.9	88	1.3	3.0	2.1	4.2
25	Psoriasis	*	10	0.7	8	0.1	-	-	-
26	**Female Reproductive**								
27	Infection vaginal bacterial	$$*	32	2.6	31	0.5	5.2	3.1	8.4
28	Vaginal discharge	*	89	7.4	207	3.4	2.1	1.7	2.8
29	**Miscellaneous Infection**								
30	Gardnerella infection	$$*	31	2.3	28	0.4	5.5	3.3	9.2
31	Herpes simplex genital	*	9	0.7	5	0.1	-	-	-
32									
33	***Events NOT signalled***								
34									
35	***A. Previously known ADRs NOT signalled***							*3*	
36	**Central and Peripheral Nervous System**								
37	Headache		22	1.6	112	1.6	1.0	0.6	1.5
38	**Alimentary**								
39	Dyspepsia@		8	0.6	31	0.5	-	-	-
40	Pain abdomen		53	3.9	188	2.8	1.4	1.0	1.9
41									
42	***B. Previously unknown ADRs NOT signalled***							*19*	
43	**Skin**								
44	Alopecia		0	0.0	2	0.0	-	-	-
45	Pruritus @		12	0.9	25	0.4	-	-	-
46	Stevens-Johnson syndrome		0	0.0	1	0.0	-	-	-
47	Urticaria		7	0.5	22	0.3	-	-	-
48	**Central and Peripheral Nervous System**								
49	Neuritis peripheral		0	0.0	0	0.0	-	-	-
50	Neuritis*		0	0.0	0	0.0	-	-	-
51	Neuropathy peripheral		0	0.0	0	0.0	-	-	-
52	Neuropathy@		0	0.0	0	0.0	-	-	-

Table 33 Itraconazole: 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	***B. Previously unknown ADRs NOT signalled continued***								
55	**Cardiovascular**								
56	Oedema@		3	0.2	12	0.2	-	-	-
57	Swollen ankles		1	0.1	2	0.0	-	-	-
58	Swollen limb		0	0.0	2	0.0	-	-	-
59	**Alimentary**								
60	Constipation		8	0.6	47	0.7	-	-	-
61	Hepatitis*		0	0.0	0	0.0	-	-	-
62	Jaundice		0	0.0	0	0.0	-	-	-
63	Jaundice cholestatic		0	0.0	0	0.0	-	-	-
64	**Female Reproductive**								
65	Irregular periods		6	0.5	34	0.6	-	-	-
66	Oligomenorrhoea		0	0.0	3	0.0	-	-	-
67	Polymenorrhoea		0	0.0	5	0.1	-	-	-
68	**Immunological**								
69	Angioneurotic oedema		1	0.1	3	0.0	-	-	-
70									
71	***D. 'Hard-to-detect' ADRs NOT signalled***							2	
72	**Alimentary**								
73	Liver function test abnormal		0	0.0	0	0.0	-	-	-
74	**Metabolic and Endocrine**								
75	Hypokalaemia		0	0.0	1	0.0	-	-	-

Table 33 Itraconazole: Events signalled and not signalled

26 Comparison between monthly and weekly analyses

Tables 34-36 show the results of the monthly and weekly analyses for the last three drugs (ciprofloxacin, fluconazole and itraconazole). The number of events in the first period with the monthly analysis (i.e., the first month) is always bigger than that with the weekly analysis (i.e., the first week) because the former includes the latter. Similarly, the number of events coded either in the first or second period (i.e., the first six months) with the monthly analysis is always bigger than that in the first six weeks with the weekly analysis. Because of this difference in the number of events, the events signalled by the weekly analysis are in general those with a fairly high incidence. Two known ADRs with ciprofloxacin, 'diarrhoea' and 'pain abdomen', signalled by the monthly analysis are not signalled by the weekly analysis (Table 34). Similarly, one known ADR with fluconazole, 'diarrhoea' (Table 35) and two known ADRs with itraconazole, 'rash' and 'dizziness' (Table 36) signalled by the monthly analysis are not signalled by the weekly analysis. However, there is no opposite case (i.e., known ADR signalled by the weekly analysis only).

With most events signalled by the monthly or weekly analysis, the rate in the first period is bigger than that in the second period. However, 'vaginal candidiasis' with ciprofloxacin, which is probably an ADR to ciprofloxacin due to the change in the normal vaginal flora, is not the case. With 'vaginal candidiasis' for ciprofloxacin, T1 = 7.6 and T2 = 1.3 while W1 = 1.4 and W2 = 1.5. As shown in Figure 14, the weekly rate of 'vaginal candidiasis' has the largest value in week 2 which is more than twice bigger than the first weekly rate. Therefore, to signal 'vaginal candidiasis', the comparison between the first weekly rate and the weekly rate during the succeeding weeks may be not appropriate. Some ADR may appear several days or even several weeks after the first prescription of the drug. In some other analysis such as the 'on' vs 'off' comparison, this point may be important. In such an analysis, some days after stopping the drug may be included in the 'on' period.

Because of the above two reasons, it is concluded that there is no definite reasons which require the weekly analysis specifically applied to antimicrobial drugs.

	A	B	C	D	E	F	G	H	I	J	K
1	EVENT	**Monthly**	N1 & D1	**T1**	N2&D2-6	**T2**	**Weekly**	N1 & D1	**W1**	N2&D2-6	**W2**
2	Denominator total		11475		48461			11475		57371	
3	Denominator male		4493		18976			4493		22461	
4	Denominator female		6607		27900			6607		33035	
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)										
6	T1 is given in 'N per 1000 patients per month'										
7	W1 is given in 'N per 1000 patients per week'										
8											
9	***Known ADRs signalled (Categories A & B)***										
10	**Skin**										
11	Rash	$*	32	2.8	52	1.1	$	14	1.2	26	0.5
12	**Central and Peripheral Nervous System**										
13	Dizziness	$$*	21	1.8	30	0.6	$$*	11	1.0	13	0.2
14	**Alimentary**										
15	Diarrhoea	$*	52	4.5	84	1.7		21	1.8	44	0.8
16	Nausea	$$*	39	3.4	25	0.5	$$*	23	2.0	17	0.3
17	Vomiting	$$*	53	4.6	55	1.1	$$*	31	2.7	34	0.6
18	Pain abdomen	*	59	5.1	105	2.2		22	1.9	51	0.9
19											
20	***No description in BNF but signalled***										
21	**Psychiatric**										
22	Malaise	$	17	1.5	25	0.5		9	0.8	11	0.2
23	**Cardiovascular**										
24	Left ventricular failure*	$	15	1.3	22	0.5		2	0.2	17	0.3
25	Cyanosis	*	4	0.3	0	0.0		1	0.1	3	0.1
26	**Respiratory**										
27	Cough	*	39	3.4	73	1.5		11	1.0	40	0.7
28	Dyspnoea		26	2.3	50	1.0	$	12	1.0	24	0.4
29	Bronchitis*		28	2.4	118	2.4	*	1	0.1	49	0.9
30	Tonsillitis	$$*	15	1.3	15	0.3		0	0.0	17	0.3
31	**Urologic**										
32	Urinary tract infection*		54	4.7	214	4.4	*	2	0.2	75	1.3
33	**Female Reproductive**										
34	Vaginal candidiasis	$$*	50	7.6	36	1.3		9	1.4	49	1.5
35	**Miscellaneous Infection**										
36	Abscess	*	8	0.7	3	0.1		3	0.3	6	0.1
37	**Immunological**										
38	Unspecified side effects	*	6	0.5	0	0.0	*	5	0.4	1	0.0

Table 34 Ciprofloxacin: Comparison between monthly and weekly analyses

	A	B	C	D	E	F	G	H	I	J	K
1	EVENT	**Monthly**	N1 & D1	**T1**	N2&D2-6	**T2**		**Weekly**	N1 & D1	**W1**	N2&D2-6	**W2**
2	Denominator total		15007		68492				15007		75025	
3	Denominator male		877		4129				877		4385	
4	Denominator female		14009		63795				14007		70025	
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)											
6	T1 is given in 'N per 1000 patients per month'											
7	W1 is given in 'N per 1000 patients per week'											
8												
9	***Known ADRs signalled (Categories A & B)***											
10	**Alimentary**											
11	Diarrhoea	*	44	2.9	92	1.3		11	0.7	44	0.6	
12	Nausea	$	18	1.2	32	0.5	*	14	0.9	5	0.1	
13												
14	***No description in BNF but signalled***											
15	**Skin**											
16	Pruritus @	$$*	15	1.0	19	0.3		7	0.5	11	0.1	
17	Pruritus vulvae	*	46	3.1	112	1.6		9	0.6	52	0.7	
18	**Respiratory**											
19	Rhinitis allergic	*	1	0.1	65	0.9		0	0.0	2	0.0	
20	**Alimentary**											
21	Anorexia		4	0.3	4	0.1	*	4	0.3	0	0.0	
22	**Metabolic and Endocrine**											
23	Diabetes mellitus*	*	7	0.5	3	0.0		1	0.1	6	0.1	
24	**Urologic**											
25	Frequency	$$*	19	1.3	21	0.3		5	0.3	16	0.2	
26	Urinary tract infection*	*	71	4.7	154	2.2		19	1.3	72	1.0	
27	**Female Reproductive**											
28	Infection vaginal bacterial	$	17	1.2	29	0.5	*	11	0.8	11	0.2	
29	Vaginal candidiasis		269	19.2	1225	19.2	*	19	1.4	391	5.6	
30	Vaginal discharge	*	100	7.1	245	3.8		18	1.3	117	1.7	
31	Vaginitis	*	42	3.0	89	1.4		14	1.0	32	0.5	
32	Vaginitis trichomonas	*	12	0.9	12	0.2		4	0.3	9	0.1	
33	**Miscellaneous Infection**											
34	Gardnerella infection	$$*	22	1.5	29	0.4		9	0.6	16	0.2	

Table 35 Fluconazole: Comparison between monthly and weekly analyses

	A	B	C	D	E	F	G	H	I	J	K
1	EVENT	**Monthly**	N1 & D1	**T1**	N2&D2-6	**T2**	**Weekly**	N1 & D1	**W1**	N2&D2-6	**W2**
2	Denominator total		13637		68119			13637		68177	
3	Denominator male		1480		7397			1480		7400	
4	Denominator female		12096		60415			12096		60470	
5	$: T1/T2 = or > 2.5 and $$: T1/T2 = or > 3.0, * p < 0.001 (likelihood ratio test)										
6	T1 is given in 'N per 1000 patients per month'										
7	W1 is given in 'N per 1000 patients per week'										
8											
9	***Known ADRs signalled (Categories A & B)***										
10	**Skin**										
11	Rash	*	43	3.2	106	1.6		13	1.0	35	0.5
12	**Central and Peripheral Nervous System**										
13	Dizziness	$$*	19	1.4	32	0.5		6	0.4	16	0.2
14	**Alimentary**										
15	Nausea	$$*	22	1.6	35	0.5	$$*	15	1.1	11	0.2
16											
17	***No description in BNF but signalled***										
18	**Skin**										
19	Pruritus vulvae	$$*	53	3.9	88	1.3		13	1.0	53	0.8
20	Psoriasis	*	10	0.7	8	0.1		3	0.2	8	0.1
21	**Female Reproductive**										
22	Infection vaginal bacterial	$$*	32	2.6	31	0.5	$$*	18	1.5	20	0.3
23	Vaginal discharge	*	89	7.4	207	3.4	*	17	1.4	283	4.7
24	**Miscellaneous Infection**										
25	Gardnerella infection	$$*	31	2.3	28	0.4	$	13	1.0	23	0.3
26	Herpes simplex genital	*	9	0.7	5	0.1	*	7	0.5	2	0.0

Table 36 Itraconazole: Comparison between monthly and weekly analyses

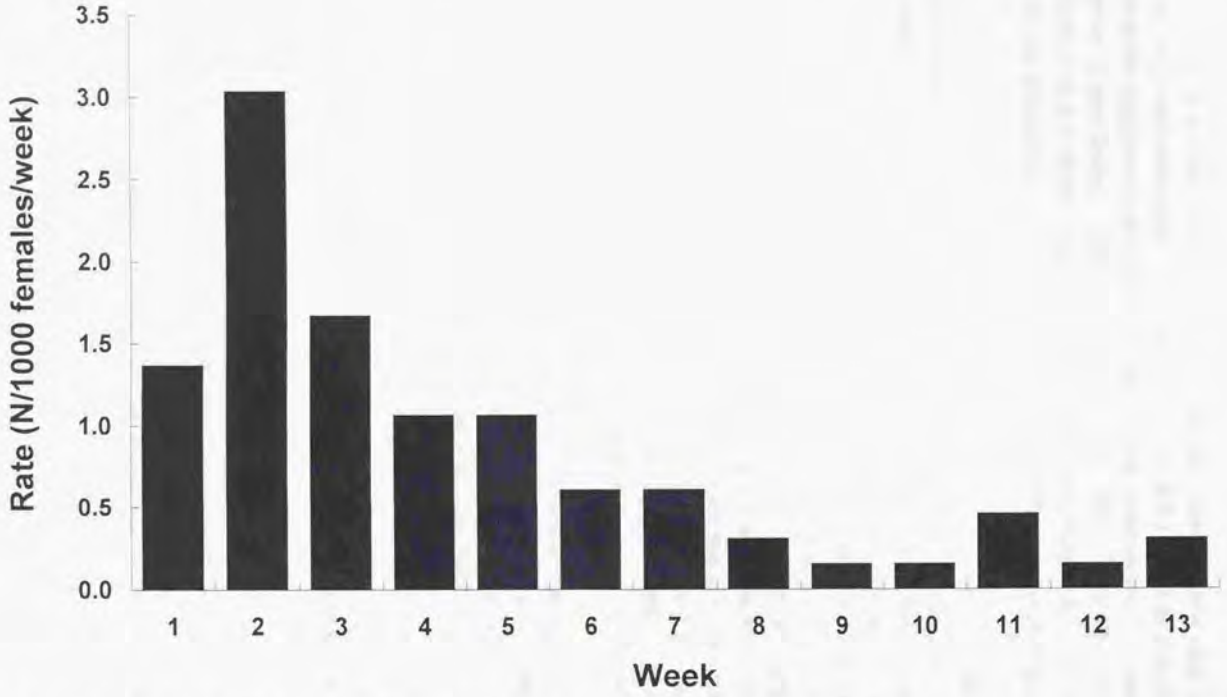


Figure 5 Weekly rates of vaginal candidiasis with ciprofloxacin

27 Summary of the results

Table 37 shows summary of the results obtained from the within-drug comparison of the monthly rates (i.e., T1 vs T2). 1,076 low-level terms in 19 body systems are examined for 24 drugs. Therefore, a total of about 26,000 low-level terms are examined.

Events known as ADRs and signalled

With 24 drugs analysed by the rate ratio method and the statistical test (likelihood ratio test), a total of 389 events (1.5 % of all of the low-level terms examined) are signalled (line 7 of Table 37). 84 (22 %) are signalled by the statistical test only and 50 (13 %) by the rate ratio method only. The remaining 255 (66 %) are signalled by both of the methods. In other words, one third (134) of 389 events are signalled by one method only.

193 events (50 %) of these 389 events signalled are described in the recent BNF (No 31, March 1996) as ADRs (line 12). These 193 terms correspond to 166 (33 %) of 504 ADRs described in the BNF (note 193 events signalled are low-level terms in the event dictionary known as ADRs while 166 ADRs are given in the BNF and signalled in the PEM study; see 'Events signalled in PEM and ADRs described in the BNF and other literature' in the 'Method' of this thesis). Of the 193 events which are known ADRs, 21 (11 %) are signalled by the statistical test only and 12 (6 %) by the rate ratio method only. The remaining 160 (83 %) events known as ADRs are signalled by both of the methods. Therefore, one sixth of the 193 events known as ADRs are signalled by one method only. This finding may support the use of two methods but not one method only.

193 events which are known ADRs and signalled may be also divided into 146 under Category A (previously known ADRs), 46 under Category B (previously unknown ADRs), 1 under Category C (Questionable ADRs) and 0 under Category D ('Hard-to-detect ADRs). 46 ADRs (24 % of known ADRs signalled and 12 % of all events signalled) with 14 drugs are judged to be under Category B, i.e., they were not described as ADRs in the BNF available when the PEM

CODE OF DRUGS		FVX	FXT	BPR	FNZ	DTZ	NDP	DXZ	ELP	LPT	EDL	NBM	TXC	NZD	FMD	OPZ	MPS	AVT	CTZ	LTD	NCM	ACV	CFX	FCZ	ICZ	TOTAL
ADRs in the BNF (Category A-D)		*28*	*27*	*14*	*18*	*10*	*14*	*11*	*40*	*40*	*21*	*21*	*21*	*17*	*16*	*40*	*9*	*23*	*23*	*23*	*7*	*14*	*43*	*9*	*15*	*504*
Signalled*		19	20	12	2	7	8	7	10	11	6	7	6	6	5	7	9	3	1	1	5	3	6	2	3	166
Not signalled		9	7	2	16	3	6	4	30	29	15	14	15	11	11	33	0	20	22	22	2	11	37	7	12	338
Events (low-level terms in the event dictionary) signalled	*TOTAL*	*45*	*36*	*25*	*7*	*16*	*22*	*19*	*12*	*21*	*13*	*17*	*15*	*13*	*8*	*10*	*23*	*14*	*5*	*6*	*10*	*16*	*14*	*13*	*9*	*389*
Statistical test only	*TOTAL*	*9*	*10*	*3*	*1*	*3*	*4*	*0*	*1*	*5*	*1*	*2*	*2*	*1*	*0*	*4*	*9*	*2*	*0*	*1*	*3*	*6*	*5*	*8*	*4*	*84*
Rate ratio method only	*TOTAL*	*4*	*3*	*1*	*2*	*1*	*0*	*5*	*0*	*3*	*2*	*1*	*2*	*4*	*2*	*0*	*2*	*8*	*2*	*1*	*1*	*2*	*2*	*2*	*0*	*50*
Both statistical test and rate ratio method	*TOTAL*	*32*	*23*	*21*	*4*	*12*	*18*	*14*	*11*	*13*	*10*	*14*	*11*	*8*	*6*	*6*	*12*	*4*	*3*	*4*	*6*	*8*	*7*	*3*	*5*	*255*
Known ADRs (Category A-D)#	*TOTAL*	*22*	*23*	*14*	*3*	*9*	*10*	*7*	*10*	*11*	*7*	*9*	*8*	*8*	*5*	*7*	*9*	*5*	*2*	*2*	*5*	*6*	*6*	*2*	*3*	*193*
Statistical test only	*TOTAL*	*1*	*3*	*0*	*0*	*1*	*0*	*0*	*0*	*2*	*0*	*0*	*1*	*1*	*0*	*3*	*3*	*1*	*0*	*1*	*0*	*1*	*1*	*1*	*1*	*21*
Rate ratio method only	*TOTAL*	*0*	*1*	*0*	*1*	*0*	*0*	*1*	*0*	*1*	*0*	*1*	*0*	*2*	*1*	*0*	*0*	*2*	*0*	*0*	*1*	*0*	*0*	*1*	*0*	*12*
Both statistical test and rate ratio method	*TOTAL*	*21*	*19*	*14*	*2*	*8*	*10*	*6*	*10*	*8*	*7*	*8*	*7*	*5*	*4*	*4*	*6*	*2*	*2*	*1*	*4*	*5*	*5*	*0*	*2*	*160*
Category A Previously known ADRs		*10*	*16*	*14*	*1*	*4*	*10*	*5*	*7*	*9*	*7*	*9*	*8*	*4*	*5*	*4*	*7*	*5*	*2*	*2*	*4*	*5*	*6*	*1*	*1*	*146*
Statistical test only		0	1	0	0	0	0	0	0	2	0	0	1	1	0	2	1	1	0	1	0	0	1	0	0	11
Rate ratio method only		0	0	0	0	0	0	1	0	0	0	1	0	1	1	0	0	2	0	0	1	0	0	1	0	8
Both statistical test and rate ratio method		10	15	14	1	4	10	4	7	7	7	8	7	2	4	2	6	2	2	1	3	5	5	0	1	127
Category B Previously unknown ADRs		*12*	*6*	*0*	*2*	*5*	*0*	*2*	*3*	*2*	*0*	*0*	*0*	*4*	*0*	*3*	*2*	*0*	*0*	*0*	*1*	*1*	*0*	*1*	*2*	*46*
Statistical test only		1	1	0	0	1	0	0	0	0	0	0	0	0	0	1	2	0	0	0	0	1	0	1	1	9
Rate ratio method only		0	1	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	4
Both statistical test and rate ratio method		11	4	0	1	4	0	2	3	1	0	0	0	3	0	2	0	0	0	0	1	0	0	0	1	33
Category C Questionable ADRs		*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*
Statistical test only		0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Rate ratio method only		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Both statistical test and rate ratio method		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Category D 'Hard-to-detect' ADRs		*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*
Statistical test only		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rate ratio method only		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Both statistical test and rate ratio method		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No description in the BNF but signalled		*23*	*13*	*11*	*4*	*7*	*12*	*12*	*2*	*10*	*6*	*8*	*7*	*5*	*3*	*3*	*14*	*9*	*3*	*4*	*5*	*10*	*8*	*11*	*6*	*196*
Statistical test only		8	7	3	1	2	4	0	1	3	1	2	1	0	0	1	6	1	0	0	3	5	4	7	3	63
Rate ratio method only		4	2	1	1	1	0	4	0	2	2	0	2	2	1	0	2	6	2	1	0	2	2	1	0	38
Both statistical test and rate ratio method		11	4	7	2	4	8	8	1	5	3	6	4	3	2	2	6	2	1	3	2	3	2	3	3	95
Events which may be considered to be known ADRs		9	4	2	1	2	4	6	0	2	6	4	3	0	2	1	5	3	1	0	1	0	1	0	0	57
ADRs so far not recognised in other literature		0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	0	3
Events potentially confounded by the indication		4	2	4	3	2	1	0	1	1	0	0	0	5	0	2	4	6	2	4	2	10	3	10	6	72
'Unspecified side effects'		1	1	1	0	0	1	1	0	1	0	1	1	0	0	0	1	0	0	0	1	0	1	0	0	11
Others		9	6	4	0	3	6	5	1	6	0	2	3	0	0	0	4	0	0	0	1	0	2	1	0	53

* If the event is also a known ADR, that event is not included.
# ADRs in the BNF and corresponding low-level terms in the event dictionary

Table 37 Summary of results (see Table 1 for drug name represented by each code of drug)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA
45	CODE OF DRUGS		FVX	FXT	BPR	FNZ	DTZ	NDP	DXZ	ELP	LPT	EDL	NBM	TXC	NZD	FMD	OPZ	MPS	AVT	CTZ	LTD	NCM	ACV	CFX	FCZ	ICZ	TOTAL
46	**ADRs in the BNF (Category A-D)**		*28*	*27*	*14*	*18*	*10*	*14*	*11*	*40*	*40*	*21*	*21*	*21*	*17*	*16*	*40*	*9*	*23*	*23*	*23*	*7*	*14*	*43*	*9*	*15*	*504*
47	**Signalled**		19	20	12	2	7	8	7	10	11	6	7	6	6	5	7	9	3	1	1	5	3	6	2	3	166
48	**Not signalled[$]**		9	7	2	16	3	6	4	30	29	15	14	15	11	11	33	0	20	22	22	2	11	37	7	12	338
49																											
50	**Events (low-level terms in the**																										
51	**event dictionary) known as ADRs**																										
52	**but not signalled[$]**	***TOTAL***	*56*	*53*	*3*	*27*	*12*	*10*	*7*	*44*	*43*	*42*	*40*	*41*	*28*	*30*	*49*	*3*	*42*	*45*	*45*	*5*	*25*	*54*	*9*	*24*	*737*
53	N of events with T1 > 1 per 1000 patients per month	***TOTAL***	*1*	*1*	*1*	*4*	*4*	*2*	*2*	*9*	*10*	*1*	*0*	*0*	*2*	*2*	*4*	*0*	*4*	*5*	*5*	*2*	*3*	*4*	*2*	*2*	*70*
54																											
55	**Category A Previously known ADRs**		*4*	*9*	*3*	*5*	*1*	*8*	*4*	*7*	*10*	*31*	*29*	*30*	*7*	*2*	*12*	*3*	*14*	*17*	*17*	*3*	*9*	*10*	*1*	*3*	*239*
56	N of events with T1 > 1 per 1000 patients per month		0	1	1	0	0	2	2	3	2	1	0	0	1	1	1	0	3	5	4	1	3	3	1	2	37
57	**Category B Previously unknown ADRs**		*18*	*11*	*0*	*22*	*8*	*0*	*3*	*36*	*32*	*11*	*11*	*11*	*19*	*26*	*36*	*0*	*27*	*27*	*27*	*2*	*10*	*41*	*7*	*19*	*404*
58	N of events with T1 > 1 per 1000 patients per month		1	0	0	4	3	0	0	6	8	0	0	0	1	1	3	0	1	0	1	1	0	1	1	0	32
59	**Category C Questionable ADRs**		*31*	*30*	*0*	*0*	*2*	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*67*
60	N of events with T1 > 1 per 1000 patients per month		0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
61	**Category D 'Hard-to-detect' ADRs**		*3*	*3*	*0*	*0*	*1*	*0*	*0*	*1*	*1*	*0*	*0*	*0*	*1*	*1*	*1*	*0*	*1*	*1*	*1*	*0*	*6*	*3*	*1*	*2*	*27*
62	N of events with T1 > 1 per 1000 patients per month		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63	[$]ADRs in the BNF and corresponding low-level terms in the event dictionary																										
64	Note: data on line 46-48 are the same as those on line 2-4																										

Table 37 Summary of results (see Table 1 for drug name represented by each code of drug)

study had been almost finished but are given as ADRs in the BNF No 31, March 1996 which is currently available. This proves that PEM has the ability to signal ADRs which are not widely recognised as ADRs during the study.

A total of 504 ADRs (Category A-D) to one of 24 PEM drugs are described in the current BNF (line 2 and 46 of Table 37). A total of 930 low-level terms are judged to correspond to those 504 ADRs described in the BNF. Of 930 low-level terms known as ADRs including 193 signalled (line 12) and 737 not signalled (line 52), 68 questionable ADRs (1 signalled plus 67 not signalled) under Category C may be in fact not ADRs and 27 ADRs under Category D are, by definition, unlikely to be detected in general practice. When excluding 95 ADRs under Category C or D, a total of 835 events are judged to be known ADRs under Category A or B. Figure 6 shows the distribution of T1 with 835 ADRs under Category A and B where the events signalled and those not signalled are given separately. Figure 7 is the same as Figure 6 but given using a different scale for Y-axis (Number of ADRs). When T1 is 4.0 per 1000 patients per month or more, all of the known ADRs are signalled. The likelihood ratio test signalls all of them. However, five known ADRs with T1 more than 4.0 per 1000 patients are missed by the 'rate ratio method'. They are 'cough' with lisinopril (T1 = 13.6/1000 patients/month, Table 18), 'pain abdomen' with omeprazole (T1 = 6.9, Table 24), 'lassitude' with doxazosin (T1 = 6.0, Table 16), 'pain abdomen with ciprofloxacin (T1 = 5.1, Table 31) and 'pain abdomen' with fluvoxamine (T1 = 5.0, Table 9).

In most literature, the rate of an ADR is given as the fraction of all patients (e.g., just in '%') but not the fraction per unit time. Such information is often derived from several studies conducted under a variety of study designs observed for various periods. Figure 8 shows % of patients with specific events under Category A and B within the first 6 months. The rate (%) shown in Figure 8 may be roughly equivalent to the fraction of patients with a specific ADR often shown in literature. Figure 9 is the same as Figure 8 but given using a different scale for Y-axis (Number of ADRs). When the rate in the first 6 months is 1.8 % or more, all of the known ADRs are signalled. The likelihood ratio test signalls all of them. However, three known ADRs with the rate more than 1.8 % are missed by the 'rate ratio method'. They are 'cough' with lisinopril (5.0 %, Table 18), 'pain abdomen' with omeprazole (2.6 %, Table 24), and 'lassitude' with

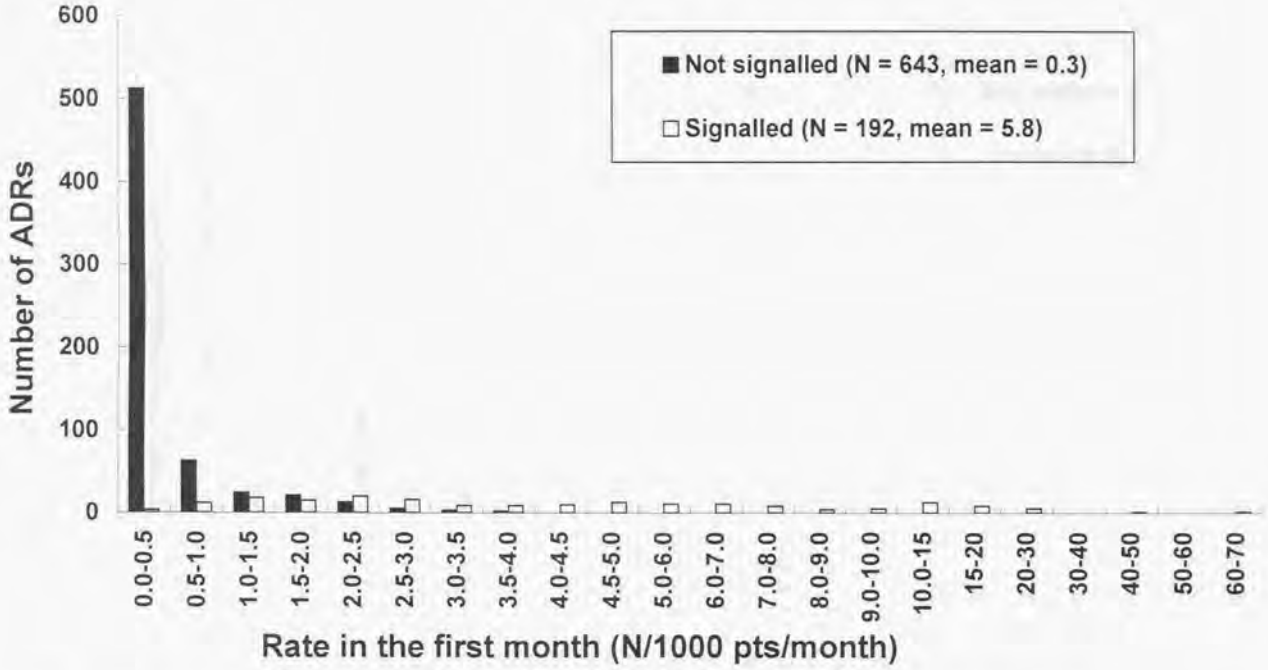


Figure 6 The first monthly rate with 835 events known as ADRs (Categories A and B)

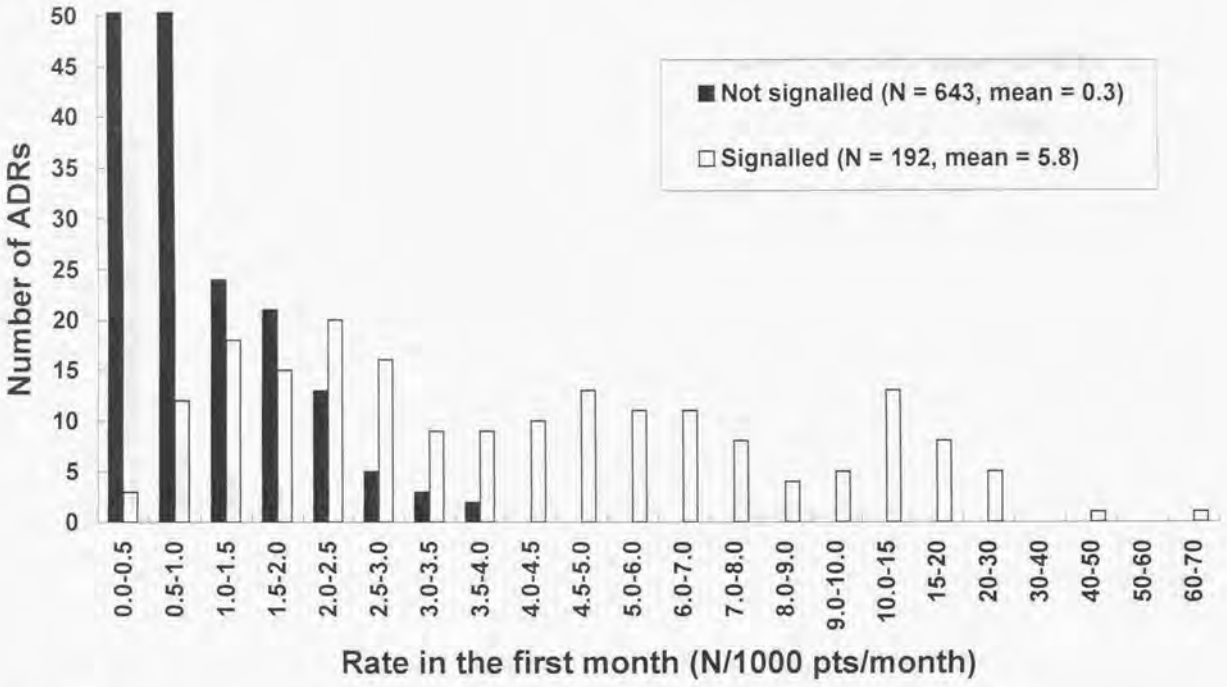


Figure 7 The first monthly rate with 835 events known as ADRs (Categories A and B)

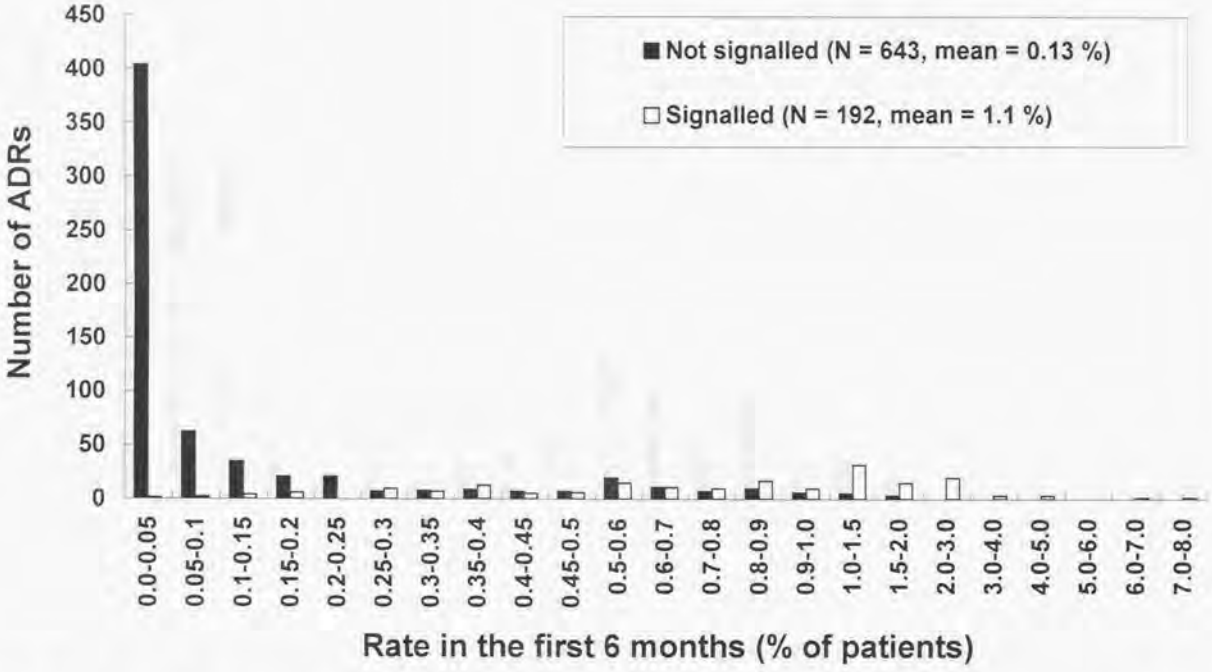


Figure 8 The rate in the first 6 months with 835 events known as ADRs (*Categories A and B*)

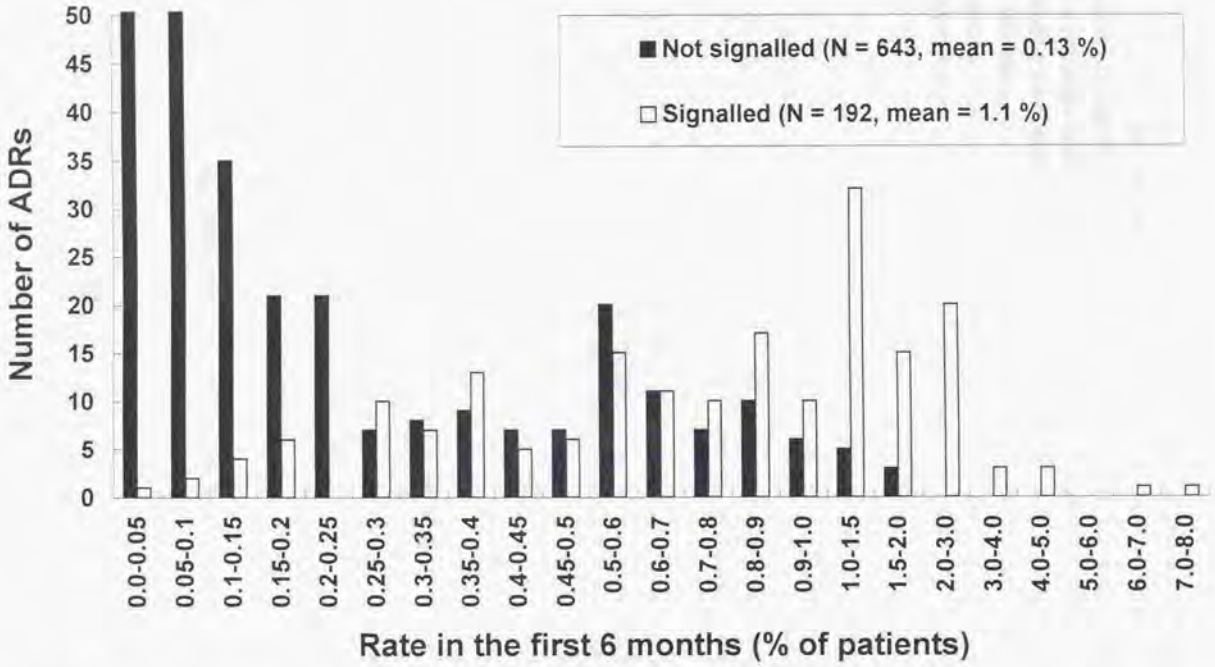


Figure 9 The rate in the first 6 months with 835 events known as ADRs (*Categories A and B*)

doxazosin (1.9%, Table 16). Those findings suggest that the use of the 'likelihood ratio test' in addition to the 'rate ratio method' is mandatory not to miss the major ADRs.

Events not described as ADRs in the current BNF but signalled

196 events signalled are not shown in the BNF No 31, March 1996 (line 33 of Table 37). They may be classified into 57 which are probably ADRs (e.g., those described in some literature other than the BNF), 3 ADRs detected in PEM but not yet widely recognised as ADRs, 72 events likely to be confounded by the indication, 11 'unspecified side effects' and other 53 events. More on the features associated with those five groups are discussed below.

At least 57 of those 196 events may be regarded as ADRs because they are described as ADRs in other literature or they are closely associated with known ADRs (e.g., 'distension abdominal' may be associated with 'abdominal pain' or 'diarrhoea'). When they are added to 193 ADRs (50 % of 389 events signalled) shown in the BNF, 250 (64 %) of 389 events signalled may be regarded to be known ADRs described in some literature (BNF or other literature).

Three events ('dreams abnormal' with nabumetone[86], 'mastalgia' in female patients with famotidine[53] and 'vaginal candidiasis' with ciprofloxacin[51]) are probably ADRs detected for the first time in the PEM study which have been not yet widely accepted and therefore not shown as ADRs in the literature other than that published from the DSRU[51,63,86].

At least 72 (19 %) of 389 events signalled are likely to be confounded by the indication although it is not easy to judge whether or not an event is confounded by the indication. 29 (40 %) of 72 such events are signalled in the PEM studies of four antimicrobials as shown in Table 37 (ACV: acyclovir; CFX: ciprofloxacin; FCZ: fluconazole; ICZ: itraconazole). These four antimicrobials are prescribed to patients with acute infections and events associated with acute infections may occur preferentially in the early period. On the contrary, when chronic disease is the indication as with cardiovascular drugs, the occurrence of events associated with the indication may not necessarily confined to the early period.

Events coded as 'unspecified side effects' are signalled with 11 drugs. The term is used where the event is described just as 'side effect' or 'adverse reactions' on the green form.

It is difficult to know whether the remaining 53 events signalled (13 % of a total of 389 events signalled) are ADRs, events confounded by the indication or those signalled by other mechanisms. In the extreme case where all of these 53 events are not ADRs, they may be added to 72 events likely confounded by the indication to measure the magnitude of false positive results in PEM. In such a case, 125 (32 %) of 389 events signalled may be judged to be events which are not ADRs (false positive). In other words, 19 to 32 % (one in five to one in three) of all events signalled may be in fact not ADRs.

The mechanism of false positive results

As given above, of 196 events not shown in the BNF but signalled, 57 are known ADRs described in some literature other than BNF and 3 ADRs detected in the PEM for the first time (line 38-40). On the other hand, at least 72 events are likely to be confounded by the indication. The remaining 53 events may be also confounded by the indication but may be signalled by other mechanisms such as so called 'placebo' effect and the decrease in reporting rate as time elapses or signalled just by chance. It is impossible to discriminate events confounded by the indication or those mistakenly signalled by other mechanisms from the true ADRs just by examining the values of rates or rate ratio. In the current PEM studies, very few data are available to distinguish ADRs from 'pseudo-signals' and in the PEM reports so far published, a note that some events are likely to be confounded by the indication is usually given from the consideration on the possible relationship between the event and indication and such note is rarely supported by the results obtained by examining the PEM data themselves.

The mechanism of false negative results

Of a total of 504 ADRs (Category A-D) to one of 24 PEM drugs described in the current BNF, 338 (67 %) are not signalled. Similarly, 737 (79 %) of a total of 930 low-level terms corresponding to those 504 ADRs described in the BNF are not signalled (i.e., false negative).

In the BNF, the causality is said to be questionable for 68 ADRs under Category C and the reason why some of them are not signalled may be that they are in fact not ADRs. 27 ADRs are classified under Category D ('Hard-to-detect' ADRs) and the reason why they are not signalled is, first of all, that the laboratory test required to detect them is not often conducted in general practice.

As shown in Figures 6-9, 193 (23 %) of 835 ADRs under Category A or B are signalled but 643 (77 %) including 239 under Category A (line 55) and 404 under Category B (line 57) are not signalled. The major reason why 643 events known as ADRs are not signalled is obviously that they are rare. In other words, the cohort size of 10,000 is not enough to detect many of them. As shown in Figure 6, T1 of more than 500 ADRs not signalled is less than 0.5 per 1000 patients per month. It is clear that with the increase in T1, the chance that they are not signalled decreases. When T1 is 2.0 per 1000 patients per month or more, at least more than half of known ADRs are signalled.

Similarly, as shown in Figure 8, approximately 400 known ADRs not signalled have the rate in the first six months which is less than 0.05 % of patients. As illuminated in Figure 9, when the rate is around 0.1 %, most of them are not signalled. The area around 0.5 % is a 'gray zone' where the chance to be signalled is even with that not signalled.

In addition to the mechanism of the rarity of ADRs (or small cohort size), there may be some other minor mechanisms leading to false negative results. Those minor mechanisms may be of particular importance with events which are known ADRs with relatively high rates but not signalled. For example, some of known ADRs are not signalled even if T1 is between 1 and 4 per 1000 patients per month or the rate in the first 6 months is between 0.5 and 1.8 % (note that

when T1 $\geqq$ 4/1000 patients/month or the rate in the first 6 months $\geqq$ 1.8 %, all of the known ADRs are signalled as in Figures 6-9).

One of such mechanisms may be that the event is in general non-specific and commonplace. For example, as shown in Figure 10, T2 of 'rash' is around 1.0 per 1000 patients per month with 41 drugs under a variety of classes. With 9 antimicrobials located on the right hand side (ACV: acyclovir; ---; ICZ: itraconazole) on Figure 10 which are normally prescribed to the patients just for several days, most of the events in the second period take place weeks or even months after patients stop the drug and therefore almost certainly unrelated to the drug. The rate of T2 in these 9 drugs may be regarded as the non-specific 'background' rate[60]. Figure 10 indicates that other drugs have T2 similar to this 'background' rate. Therefore, T2 of most drugs in the figure may be interpreted as a 'background' rate due to nonspecific mechanisms (e.g., viral eruption, rash induced by other drugs, that by chemicals in environment, etc.). In such a case, when the difference between T1 and T2 is small, the contribution of specific ADRs to the overall rate of the event should be, if any, small. The same mechanism may apply to 'back pain' and 'joint pain' as shown in Figure 11 and Figure 12 where T2 is quite similar between 41 drugs. With these two events, T1 is also similar to T2 with most drugs.

The other possible mechanism is that most events coded may be in fact specific ADRs but T1 is not much larger than T2. As shown in Figure 13, T2 of cough with enalapril (ELP) is the highest among a variety of drugs when two other ACE-inhibitors, lisinopril (LPT) and ramipril (RMP) monitored later are excluded. However, the difference between T1 and T2 is small and therefore not signalled. As discussed in detail elsewhere[77], the first occurrence of cough due to ACE-inhibitors is often observed several months after a patient begins to take the drug. With lisinopril, the ratio of T1 to T2 is 1.5 but signalled (by the statistical test only) because the number of cough reported and coded is bigger than that with enalapril. Though difficult to reach a clear conclusion, hypotension with doxazosin (Figure 14), oedema with diltiazem (Figure 15), muscle cramp with enalapril and lisinopril (Figure 16) may be not signalled by the same mechanism.

The third possible mechanism leading to false negative results is that most

events coded are in fact chronic manifestation of the indication which may not necessarily occur early after the first prescription of the drug. For example, as shown in Figure 17, in most patients who had 'bronchospasm' after taking nedocromil (NCM), 'bronchospasm' might be associated with the indication itself (asthma) rather than an ADR.

However, with many cases, the mechanisms for false negative results are likely to be complicated. For instance, 'abdominal pain' is a known ADR with 20 of 24 drugs examined. 'Abdominal pain' is signalled with 8 drugs but not with 12 drugs (Figure 18). With fluconazole and itraconazole, T2 probably represents the rate not associated with ADRs because most patients used those anti-fungals according to the 'single-dose' regimen or at most for a few days only. The major indication of these two anti-fungals, vaginal candidiasis, is closely associated with pelvic inflammatory disease or other infections which are often associated with abdominal pain. Therefore, the mechanism underlying the false negative results for 'abdominal pain' with fluconazole and itraconazole may be similar to that for 'bronchospasm' with nedocromil as above (chronic manifestation of the indication-related event). However, the mechanism leading to false negative results for 'abdominal pain' is not clear with other 10 drugs.

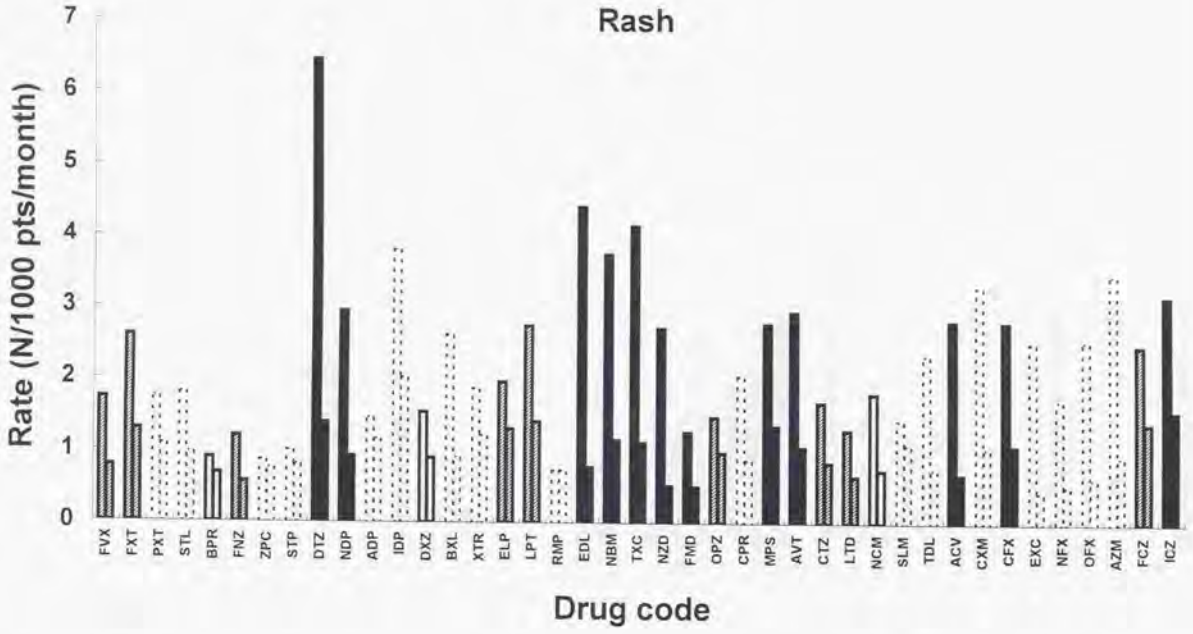


Figure 10 T1 (left column) and T2 (right column) for rash ---- closed: known ADRs signalled; hatched: known ADRs not signalled; open: not described as ADRs; *broken line: not examined*

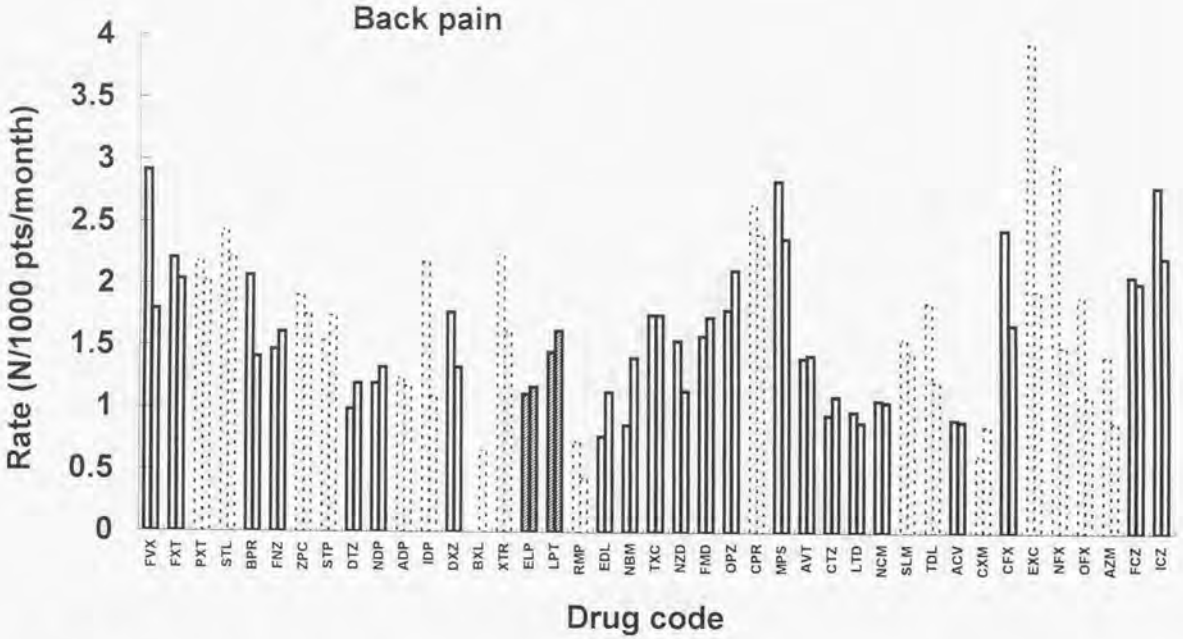


Figure 11 T1 (left column) and T2 (right column) for back pain --- hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined

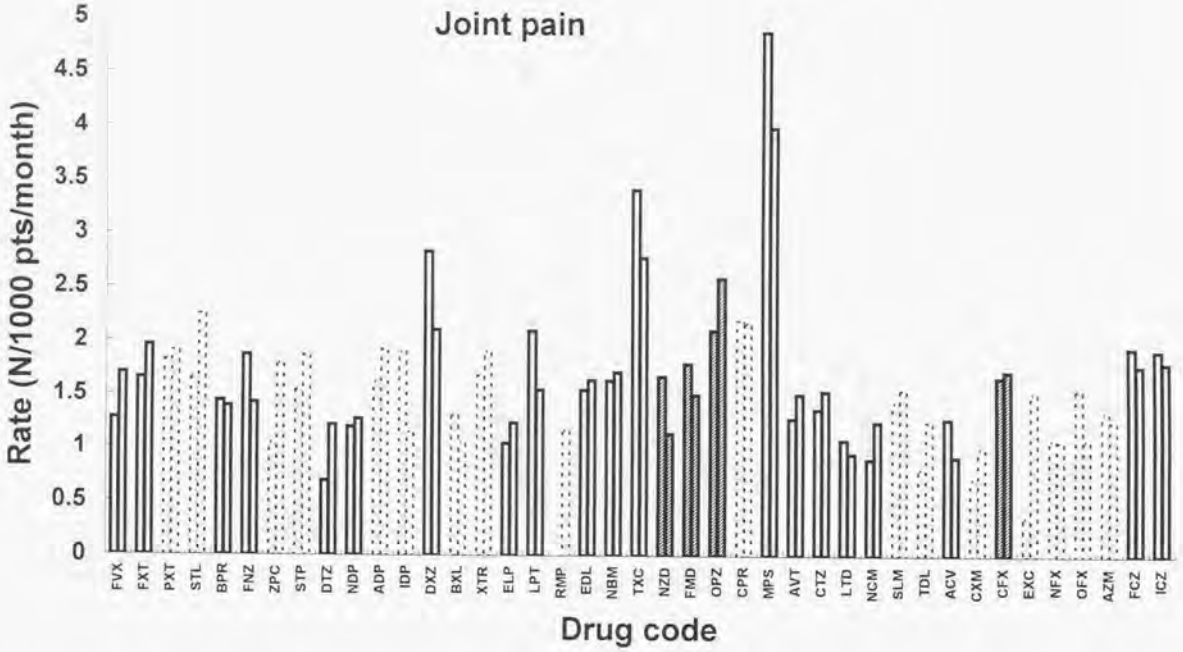


Figure 12 T1 (left column) and T2 (right column) for joint pain --- hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined

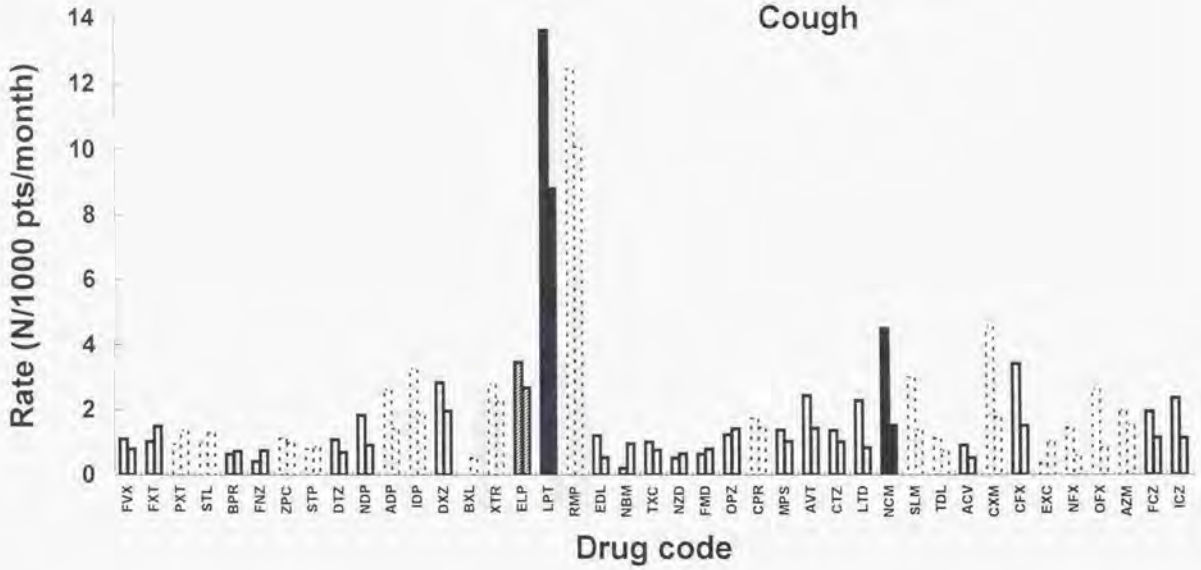


Figure 13 T1 (left column) and T2 (right column) for cough --- closed: known ADRs signalled; hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined; ELP: enalapril; LPT: lisinopril; RMP: ramipril

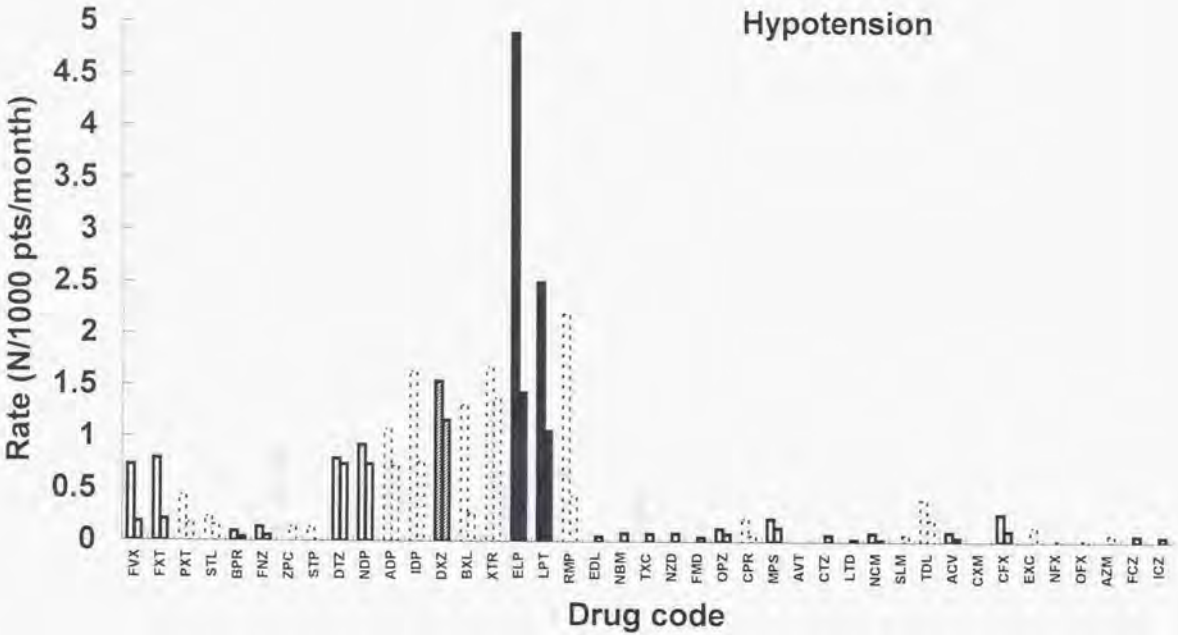


Figure 14 T1 (left column) and T2 (right column) for hypotension --- closed: known ADRs signalled; hatched: known ADRs not signalled; open: not described as ADRs; *broken line: not* examined; DXZ: doxazosin

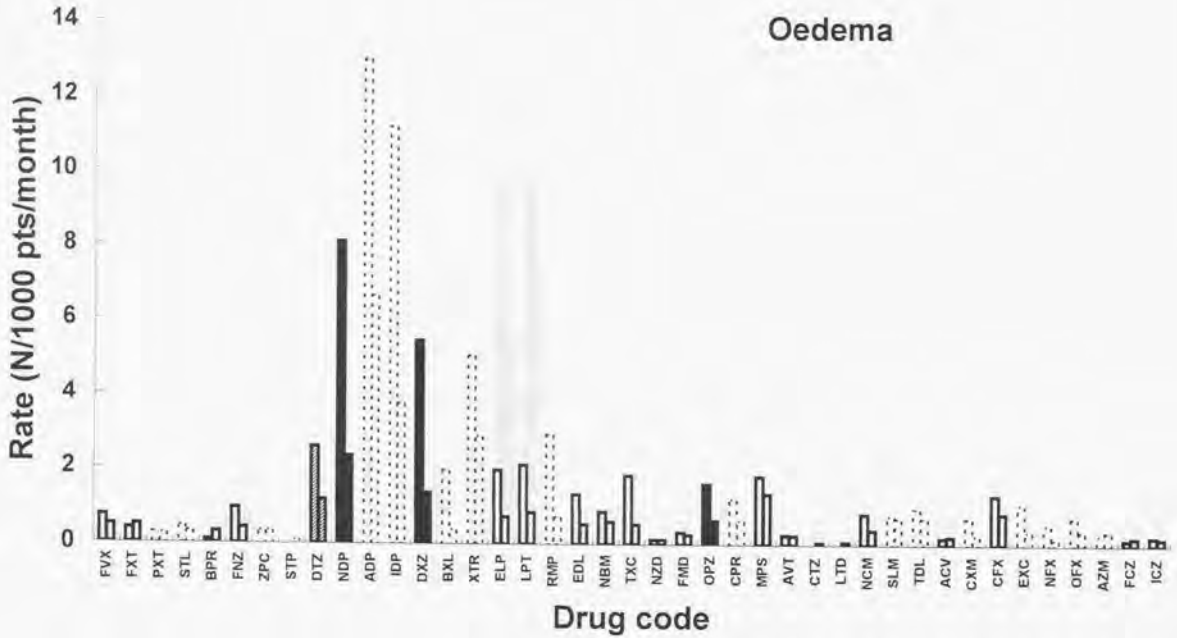


Figure 15 T1 (left column) and T2 (right column) for oedema --- closed: known ADRs signalled; hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined; DTZ: diltiazem

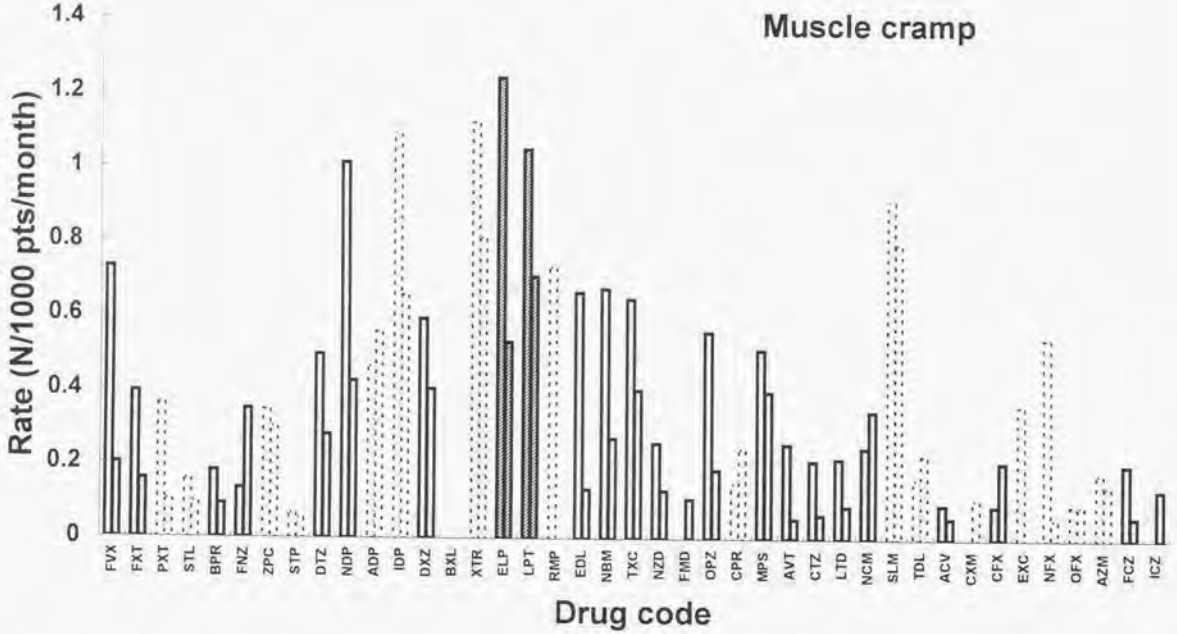


Figure 16 T1 (left column) and T2 (right column) for muscle cramp --- hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined;
ELP: enalapril; LPT: lisinopril

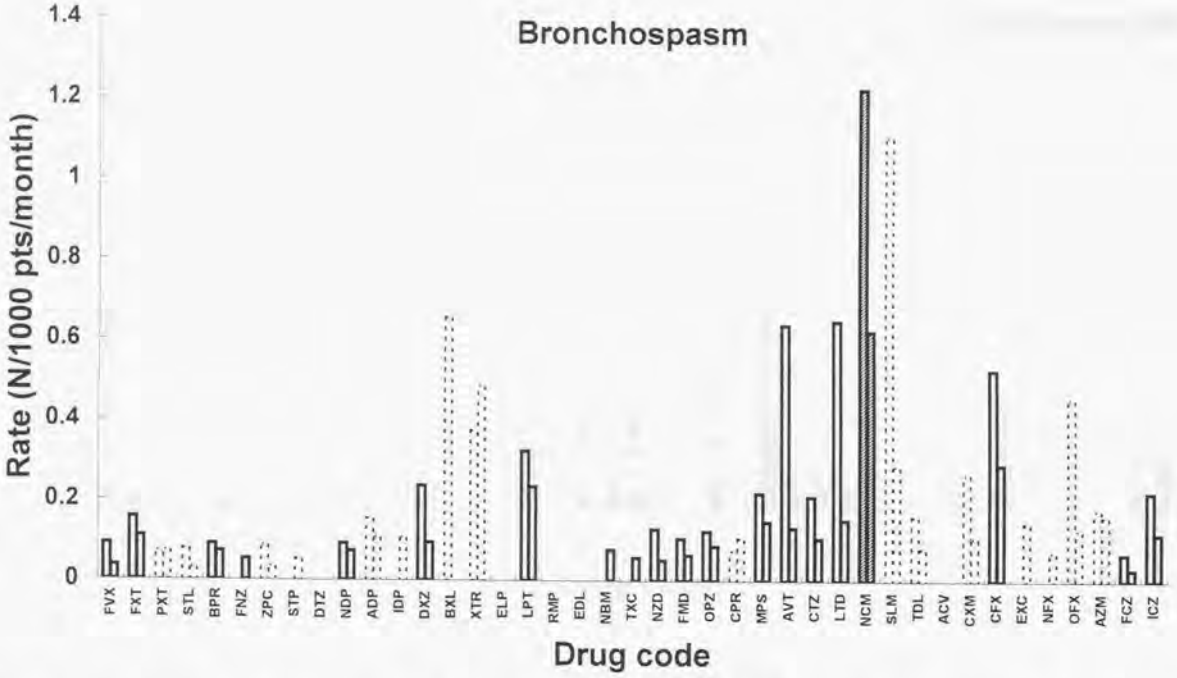


Figure 17 T1 (left column) and T2 (right column) for brochospasm --- hatched: known ADRs *not* signalled; open: not described as ADRs; broken line: not examined; NCM: *nedocromil*

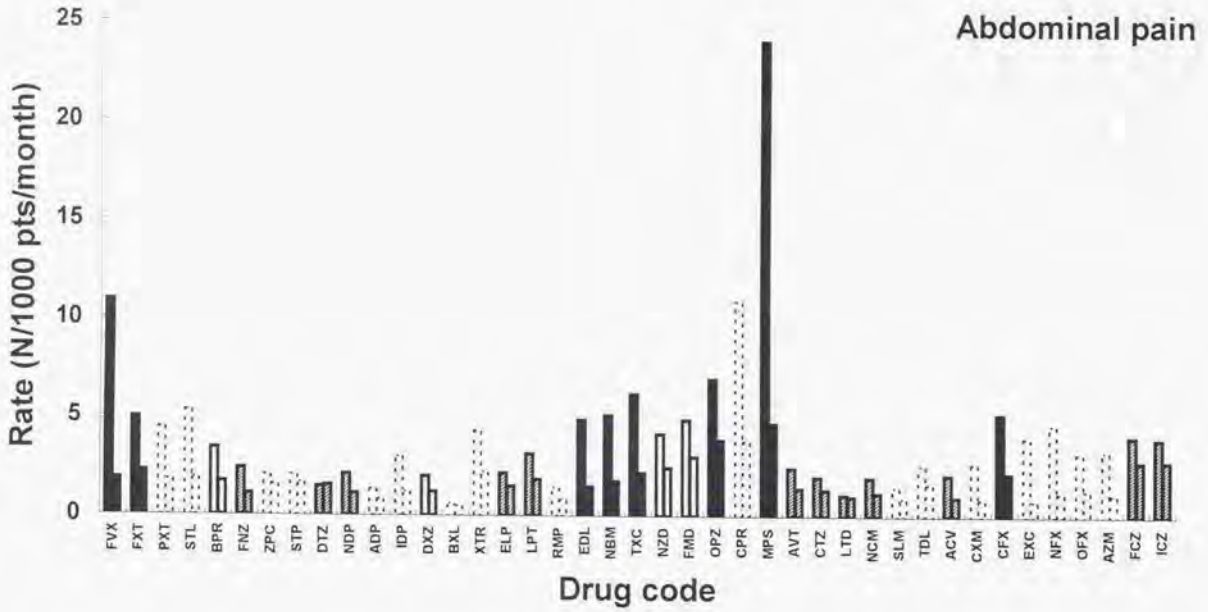


Figure 18 T1 (left column) and T2 (right column) for abdominal pain --- closed: known ADRs signalled; hatched: known ADRs not signalled; open: not described as ADRs; broken line: not examined; FCZ: fluconazole; ICZ: itraconazole

Discussion

What is clarified in this thesis

When the system for PMS is viewed as that raising warning signals for the previously undetected problems associated with the drug safety, it must have rapid and efficient mechanisms for hypothesis-generating, strengthening and testing. As described in the introduction section and Appendices 2 and 3, PEM has hypothesis-strengthening and testing functions and many of actual publications from the DSRU have been relevant to those functions. Nevertheless, in this thesis, a hypothesis-generating function of PEM is examined because some ADRs which are not rare and not trivial can be missed by individual doctors for long and it is very important to examine whether or not PEM works in such a case.

As shown in the results section, many known ADRs are missed by the comparison between T1 and T2 when the event rate is low. However, it is of note that any single known ADR to any of 24 various drugs examined in this thesis is not missed by this method, provided that the first monthly rate is more than 0.4 % per month (Figures 6 and 7) or provided that the rate in the first 6 months is more than 1.8 % (Figures 8 and 9). To obtain this result, the simultaneous use of the likelihood ratio test together with the 'rate ratio' method may be important as some frequent known ADRs such as lassitude with doxazosin (Table 16), cough with lisinopril (Table 18) and abdominal pain with omeprazole (Table 24) may be missed if only the 'rate ratio' method is used. The lowest incidence above which no known ADRs are missed (i.e., the rates of 0.4 and 1.8 % in the first month and first 6 months, respectively) could be reduced if the size of the study population is increased because the criterion depends on the combination of N1 and N2 but does not depend on the size of Y1 or Y2 (patient-days) as shown in Tables 6-8. It is also very promising that 46 (12 %) of 389 events picked up by the comparison between T1 and T2 are classified under Category B (previously unknown ADRs) which may indicate that PEM is able to detect ADRs not widely recognised as ADRs by individual doctors. The fact that the comparison between T1 and T2 does not miss any frequent known ADRs to as many as 24 drugs including those previously

unrecognised has been firmly documented in this thesis for the first time.

Several points to be improved in PEM in the future

The comparison between T1 and T2 cannot be regarded as a method which has been widely recognised to be valid or authorised. It may be difficult to test this method by applying it to other databases because the method may be rather unique to PEM. In PEM, particular attention is paid to obtain the correct date of the first prescription which is critical in the comparison between T1 and T2 as described in Appendix 6. As shown in this thesis, the comparison between T1 and T2 is one of the useful methods for screening PEM data which can be used as the first step in the hypothesis-generating processes. However, before publishing the hypothesis, the events selected by this comparison may be further examined by other methods. Many events which are not ADRs may be 'signalled' if the comparison between T1 and T2 is mechanically applied to the data. There is a need to differentiate a true 'signal' from the event confounded by the indication. In addition, some methods other than the comparison between T1 and T2 may be needed to generate more reliable 'signals'. The following points may be important to improve PEM.

(1) Information on concomitant diseases

In order to increase the ability to differentiate the event confounded by the indication from the 'true' signal, green forms may be improved so that they ask concurrent diseases or concurrent abnormal findings in a systematic way in addition to the indication of the drug studied by PEM. This question may be added as one of the formal questions on the green form so that doctors recognise that they are expected to answer to the question. Some of concurrent diseases may be in fact complication of the indication (e.g., impaired renal function when the indication is hypertension).

(2) Information on the severity of the indication

Similarly, some simple but good questions associated with the severity of the indication may be added to the current green form. In order to get consistent information, the same green form has been used in all PEM studies so far. However, a few special additional questions were sometimes added in the

individual PEM studies. For instance, a question "the use of steroid (yes/no) and, if 'yes', (oral/inhaled)" was added to the green form used in the PEM study of salmeterol[96,97]. Similar to those special additional questions, the best question on the severity of the indication may differ between individual indications. For instance, the date of the first diagnosis may be of help with hypertension but may not be of great help with acute infections to know the severity of the indication. The design must be careful so that the same kind of information is obtained for the same indication throughout various PEM studies conducted over years. The information on the concomitant diseases and severity of the indication may be obtained from all of the patients. However, even if the information is available only from the restricted number of patients who have experienced a particular event, a method to show the effect of possible confounding variables exists[96]

(3) Dose-effect relationship

Though the magnitude of drug effect is not always dependent on the drug dose as with many of so called 'type B' ADRs[99], if the positive (or sometimes negative) correlation between the event rate (incidence) and dose could be shown, this might become a strong evidence to support a causal relationship between the drug and event[16] though the dose-effect relationship could be also confounded by the indication (e.g., larger dose is used with critically ill patients or those who have not responded to smaller dose). Currently, the information on the drug dose is not used in PEM even if it is shown on the prescription. Although the dose may be changed (e.g., the initial small dose may be gradually increased, or the dose initially used may be decreased when the patient recovers), some guess may be made from the prescriptions which are currently used to identify the patient, drug and doctor at least for a certain fraction of the patients. For example, in a PEM study of the drug used for a chronic condition, on average, two or more prescriptions are available for one patient as shown in Table 3. It is also possible to make a simple question on the typical daily dose on the green form.

(4) 'On' vs 'off' comparison

As shown in the PEM study of diltiazem, the 'off' rate may be not so smaller than the 'on' rate when the event is confounded by the indication[71] even if it is 'signalled' by the comparison between T1 and T2. With some of other drugs

used for chronic conditions, the comparison of 'on' vs 'off' rates may provide some evidence which helps distinguish an ADR from the event confounded by the indication.

(5) Disappearance of an event after stopping the drug
As shown in the study of cough with ACE-inhibitors[77], when doctors recognise a clear temporal relationship that the event disappeared after stopping the drug and describe this observation on the green form, this information should be coded in a systematic way.

(6) Modification of the comparison between T1 and T2 for late-onset ADRs
There is a need to develop a new way to pick up possible late-onset ADRs where the event may be coded preferentially in the later months. It is of note that in the 'results' section, a few events are 'signalled' by the statistical test because the rate in the first period is significantly smaller than that in the second period. It is possible that the best first and second periods to pick up possible late-onset ADRs (e.g., month 1-3 vs month 4-12) differ from those to pick up possible early acute ADRs currently employed (i.e., month 1 vs. month 2-6).

(7) Testing hypotheses raised in PEM by other database
Questions raised by PEM may be tested by using other data sources such as GPRD[4,5]. Such a test may be of value particularly when conducted by researchers in the DSRU in collaboration with those involved in other database. With multipurpose database, it is usually possible to get concurrent control and the hypotheses raised by PEM may be further scrutinised.

(8) Concurrent control in PEM
As described in Appendix 2, when the original idea of PEM was published in 1981[100,101], it was planned to use the concurrent control. Difficulties encountered in the early PEM studies of several NSAIDs including 'Indocid' seem to have made the DSRU give up the use of the concurrent control[8]. However, as pointed out in Appendix 3, in the PEM study on NSAIDs, the way to identify the patients with 'Indocid' was different from that planned in the original paper published in BMJ[101]. In the original idea, it was intended to identify only 'new' users of the 'old' drug while in the PEM study on 'Indocid', users of the 'old' drug ('Indocid') were identified irrespective of whether they were 'new' or 'old'[8].

It may be worth reconsidering the original idea of the concurrent control at least in some selected studies. Particularly when the drug is the first member of the new class of drugs, the concurrent users of a drug of the old class with the same indication will be of help. For instance, the value of PEM studies of SSRIs might have been much augmented if the results of the concurrent study on a tricyclic antidepressant had been available. Even if the concurrent control is available, the comparison between two groups may be still not easy in the observational study, but, some of the problems may be avoided by careful design and analysis[98,102].

Possibility of the introduction of PEM into Japan

What is focused in this thesis is the hypothesis-generating function of PEM even if what PEM has actually contributed to the field of the drug safety has been mainly associated with its hypothesis-strengthening and testing functions. The hypothesis-generating function of PEM may become more and more important in the UK as other multipurpose databases are developing which are particularly good in hypothesis-strengthening and testing. On the other hand, in Japan, it is not easy to encourage the development of a large database. In the last decade some of the university hospitals and other large hospitals have developed a system for computer-recorded medical information. However, the driving force is weak to unify the information across several hospitals to lead a single large database. Therefore, if a system similar to PEM becomes available in Japan, its hypothesis-strengthening and testing functions will be unique and may be stronger than other available data sources at least for a while. Currently, many studies of case series called 'Drug Use Investigations' are conducted by drug companies as a legal duty, but, they are conducted by the individual companies independently and one study cannot be compared with the other even as a historical control.

PEM uses a mechanism of the collection of prescriptions issued by GPs by the PPA. In Japan, three fourths to four fifths of all the drugs prescribed in out-patient clinics are given to patients directly from clinics and hospitals via hospital pharmacists and only the rest (one fifth to one fourth) is dispensed by pharmacists in independent pharmacies (i.e., pharmacies outside and

independent of clinics and hospitals) according to the prescription issued by doctors. Nevertheless, at least in theory, it is possible to know almost all of the relatively expensive drugs prescribed by doctors irrespective of whether or not they are dispensed by the independent pharmacies because the drugs are listed in the monthly claims called 'Rezept' (a term derived from a German word meaning 'prescription') issued by hospitals and clinics requiring reimbursement of various diagnostic and therapeutic procedures. The monthly claims are also issued by independent pharmacies. However, the use of monthly claims for the purpose of drug monitoring may be not easy. For instance, many struggles do happen between hospitals and insurers associated with whether or not costs are to be reimbursed according to the original requests and the use of monthly claims for any other purposes than reimbursement may be sort of 'hot potato'. In addition, Japanese health case system is not quite simple in terms of flow of money (and, therefore, flow of monthly claims) which provides another difficulty in the use of monthly claims for the purpose of drug monitoring. The detailed discussion for those difficulties is far beyond the scope of this thesis and some of the related information may be obtained elsewhere[103]. What may be stressed here is the basic mechanism which can be used to get the information on prescribed drugs is available in Japan though there will be several difficulties when the mechanism is used for the drug safety monitoring.

Another possible mechanism to be used to identify drug, patient and prescribing doctor may be that via independent pharmacies. As a legal duty an independent pharmacy should keep a patient record for each individual patient and the information on the time when the drug is dispensed and whether the patient has received other drugs from any other pharmacists or hospitals must be recorded. Therefore, if pharmacists in independent pharmacies co-operate in identifying the patients using particular drugs, this may provide a basic mechanism useful in the drug monitoring. This mechanism may be also useful when the concurrent control is to be found because the 'new' users of 'old' drugs may be difficult to find from prescriptions or monthly claims and the information on the date when the patient has started the drug may be best obtained by somebody who is normally expected to ask individual patients the issues relevant to drugs. However, the cohort identified by this mechanism may not represent the whole drug users particularly in Japan as the fraction of outpatient drugs dispensed by independent pharmacies is small (between 1/5 and 1/4 as

described earlier).

There may be some differences of available medical information obtained from doctors in a PEM-like system in Japan compared with that in England. For instance, laboratory examination is done much more frequently in Japan even in small clinics when compared with that in general practice in the UK. Therefore, laboratory data may become an important portion of the body of the event data available in Japan and the analysis of the laboratory data may provide some important findings in Japan.

Another problem sometimes raised associated with the introduction of PEM into Japan is the fact that the number of co-prescribed drugs is on average greater than that in the US or UK and when embarking on a system like PEM, particular attention may be paid to the problems associated with polypharmacy including drug interaction. Regarding drug interaction, problems associated with hypothesis-generating and hypothesis-strengthening or testing may be discussed separately. In hypothesis-strengthening or testing, the information on the patients who took particular combination of two drugs may be collected and for this end, methods other than PEM may be more useful; e.g., multipurpose database or, if ethically acceptable, clinical trials. In hypothesis-generating, co-prescribed drugs may be handled as risk factors similar to other factors such as age, sex, severity of the indication and concomitant diseases etc. In any case, the key issue is the availability of the complete information on co-prescribed drugs. It is true that in the current PEM in England, the information on co-prescribed drugs is incomplete. In green forms no formal questions on the co-prescribed drugs are made as the burden would become extraordinary if requiring doctors to give the information on co-prescribed drugs eventually lowering the response rate. Some information on co-prescribed drugs is available from the prescriptions collected to identify the patients in PEM in England. However, there is a possibility that the patient has received other prescriptions which do not list the drug monitored by PEM. In Japan if the patient is identified by pharmacists in independent pharmacies and if enough co-operation of the pharmacists is available who keep good records on individual patients, the detailed information on the co-prescribed drugs may be available.

Two different approaches may be tested separately or simultaneously before determining which one of those (or both) approaches would be suitable when PEM is introduced into Japan. One approach is to find the patients who are representative of all drug users identified by monthly claims issued by hospitals, clinics and independent pharmacies. In the other approach, the patients are identified by pharmacists in as many independent pharmacies as possible. In the latter approach, the detailed information on co-prescribed drugs may be obtained and a concurrent control group may be also identified.

Other possible troubles are also associated with Japanese health care system. For instance, in Japan it is quite often a patient himself/herself that decides which hospital or clinic to visit and the medical cost is any way reimbursed irrespective of the hospital or clinic the patient has visited. A patient sometimes changes the hospital or clinic suddenly and seek new one without noticing the doctor in the previous hospital or clinic to which he/she has visited. Some patients even wander from hospital to hospital. Therefore, the patient follow-up is often difficult in any clinical study conducted in Japan particularly if the study period is not short. Some means to overcome this difficulty must be found when PEM is introduced into Japan

In 1996, a study group sponsored by MHW has been formed to study 'the conditions available in Japan for conducting event monitoring similar to PEM in England' (Chief, Professor Kiyoshi Kurokawa, Faculty of Medicine, Tokai University). The final report will be made probably after conducting some pilot studies somewhere in Japan and will be available around March 1998. It is expected that the issues which are not detailed in this thesis will be clarified in the final report issued by the study group.

Summary and conclusion

1) Prescription-Event Monitoring (PEM) developed in the Drug Safety Research Unit (DSRU), Southampton, England is not a multipurpose database but a scheme specifically designed for the drug safety to complement voluntary reporting system (VRS). One of the major objectives of PEM is to detect adverse drug reactions (ADRs) unrecognised by individual doctors provided that the reaction is not rare. Most ADRs which are not rare are detected in the pre-marketing stage or by VRS before PEM data are available. Nevertheless, history indicates that some ADRs which are not rare and not trivial could be missed by most doctors for long and it is therefore important to examine whether PEM has a good hypothesis-generating function.

2) A PEM study is an observational cohort study where a historical control is used. The between-drug comparison is the basic strategy of the data analysis in the cohort study and in PEM this standard procedure has been often used to strengthen or test hypotheses already generated elsewhere. However, the standard way of the data analysis is not necessarily a good means in hypothesis-generating. In the DSRU, a within-drug comparison to compare two rates during the two time periods called as T1 and T2 has been recognised to be useful though this comparison has not yet been widely accepted. This comparison itself does not provide any evidence that a drug may have caused the event and the events are to be further examined by other standard methods. In the publication from the DSRU, the comparison between T1 and T2 is said to be efficient in picking up almost all major known ADRs but this statement has not been well tested. In this thesis, whether or not this statement is really correct is examined. Furthermore, whether it picks up ADRs so far unrecognised by doctors is also examined. In addition to a rule of thumb based on the ratio of two rates known as the 'rate ratio method', a statistical test (likelihood ratio test) is advocated in this thesis and employed in the data analysis.

3) The data of the PEM studies on 24 drugs are scrutinised. These 24 drugs are selected because the cohort size is 6000 or more, the first prescription has been issued (i.e., the drug has been marketed) before 1990 so that the full range of information on the drug is now likely to be available, and, they are still used in

the UK. When more than 1000 terms are examined for each of those 24 PEM drugs, a total of 389 events are signalled of which 193 events are known ADRs given in the latest issue of the British National Formulary (BNF) No 31, March 1996. Any single known ADR to any of 24 various drugs examined in this thesis is not missed by the comparison between T1 and T2 provided that the first monthly rate is more than 0.4 % per month. Therefore, the statement that the comparison between T1 and T2 can pick up most major ADRs has been confirmed. To get this figure, the concomitant use of the likelihood ratio test is important as some ADRs where the first monthly rate is more than 0.4 % are otherwise missed. In addition, 46 of 389 events picked up by the comparison between T1 and T2 are ADRs given in the current BNF but not in the old BNF available during the individual PEM studies, indicating that PEM has a potential to detect ADRs not widely accepted as ADRs.

4) Nevertheless, there are several points to be improved in PEM in order to generate more reliable signals. It is preferable to get more information on concomitant diseases and the severity of the indication in order to differentiate events confounded by the indication from the true signals. It may be also needed to examine dose-effect relationship to signal ADRs of 'type A'. Other points include to use 'on' vs 'off' comparison, to record disappearance of an event after stopping the drug, to find the modified comparison between T1 and T2 to detect late-onset ADRs, to test hypotheses raised in PEM by other databases and to consider the possibility to find a concurrent control.

5) Lastly, the possibility of the introduction of PEM into Japan is discussed. In Japan, if a system like PEM is established, it will be particularly valuable in hypothesis-strengthening and testing because any huge multipurpose database made across several hospitals is unlikely to be developed in the near future in Japan. Several relevant problems such as how to identify drug, patient and prescribing doctor and problems associated with the difference of medical care between the UK and Japan are discussed. A study group supported by Ministry of Health and Welfare (MHW) is now examining 'the conditions available in Japan for conducting event monitoring similar to PEM in England' and the results will be published elsewhere around March 1998.

References

1 Inman WHW. *PEM News No.1*, Southampton: Drug Surveillance Research Unit, 1983.

2 Feinstein AR. The biostatistical problems of pharmaceutical surveillance. *Clin Pharmcol Ther* 1974; **16**: 110-123.

3 Strom BL. How should one perform pharmacoepidemiology studies ?: choosing among the available alternatives. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 337-350.

4 Jick SS, Dean AD, Jick H. Antidepressants and suicide. *Br Med J* 1995; **310**: 215-218.

5 Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progetagen components. *Lancet* 1995; **346**: 1589-1593.

6 Saunders KW, Stergachis A, VonKorff M. Group Health cooperative of Puget Sound. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 171-185.

7 Friedman GD. Kaiser Permanente medical care program: northern California and other regions. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 187-197.

8 Inman WHW, Rawson NSB, Wilton LV. Prescription-Event Monitoring. In: Inman WHW, ed. *Monitoring for Drug Safety, 2nd ed.* Lancaster: MTP Press, 1985: 213-35.

9 Felix RH, Ive FA. Cutaneous and ocular reactions to practolol. *Br Med J* 1974; **4**: 321-324.

10 Wright P. Untoward effects associated with practolol administration: oculomucocutaneous syndrome. *Br Med J* 1975; **1**: 595-598.

11 Brown P, Baddely H, Read AE, Davies DJ, McGarry J. Sclerosing peritonitis, an unusual reaction to a b-adrenergic-working drug (practolol). *Lancet* 1974; **2**: 1477-1481.

12 Inman WHW. *PEM News No.7*, Southampton: Drug Safety Research Unit, 1991.

13 Tsubaki T, Homma Y, Hoshi M. Neurological syndrome associated with clioquinol. *Lancet* 1971; **1**, 696-697.

14 Tsubaki T. Etiology of SMON: an early study and its development. In: Soda T, ed. *Drug-Induced Sufferings*. Amsterdam, Excerpta Medica, 1980: 423-428.

15 Kono R. SMON research. In: Soda T, ed. *Drug-Induced Sufferings*. Amsterdam, Excerpta Medica, 1980: 11-19.

16 Strom BL. Study Designs Available for Pharmacoepidemiology Studies. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 15-27.

17 Davies DM. History. In: Davies DM, ed. *Textbook of Adverse Drug Reactions, 4th ed.* Oxford: Oxford Medical Publications, 1991: 1-4.

18 Inman WHW. Post-marketing surveillance in the general population. In: Inman WHW, ed. *Monitoring for Drug Safety, 2nd ed.* Lancaster: MTP Press, 1985: 3-11.

19 Ahmad SR, Freiman JP, Graham DJ, Nelson RC. Quality of adverse drug experience reports submitted by pharmacists and physicians to the FDA. *Pharmacoepidemiol Drug Safety* 1996; **5**: 1-7.

20 Breslow NE, Day NE. The role of cohort studies in cancer epidemiology. In: *Statistical Methods in Cancer Research, Volume II: The Design and Analysis of Cohort Studies*. Lyon: IARC Scientific Publications, 1987: 1-46.

21 Jones JK. Determining causation from case reports. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 365-378.

22 Karch FE, Lasagna L. Adverse drug reactions: a critical review. *JAMA* 1975; **234**: 1236-1241.

23 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30**: 239-245.

24 Naranjo CA, Lanctot KL. Microcomputer-assisted Bayesian differential diagnosis of severe adverse reactions to new drugs: A 4-year experience. *Drug Inf J* 1991; **25**: 243-250.

25 Hutchinson TA, Dawid AP, Spiegelhalter DJ, Cowell RG, Roden S. Computerized aids for probabilistic assessment of drug safety I: a spreadshhe program. *Drug Inf J* 1991; **25**: 29-39.

26 Rossi AC, Bosco L, Faich GA, Tanner A, Temple R. The importance of adverse reaction reporting by physicians: suprofen and the flank pain

syndrome. *JAMA* 1988; **259**: 1203-1204.

27 Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed ? *J R Coll Physicians London* 1995; **29**: 41-49.

28 Inman WHW. The United Kingdom. In: Inman WHW, ed. *Monitoring for Drug Safety, 2nd ed.* Lancaster: MTP Press, 1985: 13-47.

29 Baum C, Kweder SL, Anello C. The spontaneous reporting system in the United States. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 125-155.

30 Inman W, Kubota K, Wilton L, Pearce G. Nicardipine: PEM report number 1. *Pharmacoepidemiol Drug Safety* 1993; **2**: 259-285.

31 Inman W, Clarke J, Wilton L, Pearce G, Veldhuis GJ. Terodiline: PEM report number 2. *Pharmacoepidemiol Drug Safety* 1993; **2**: 287-319.

32 Inman W, Kubota K, Pearce G, Wilton L. Fluconazole: PEM report number 3. *Pharmacoepidemiol Drug Safety* 1993; **2**: 321-340.

33 Inman W, Kubota K, Pearce G, Wilton L. Ciprofloxacin: PEM report number 4. *Pharmacoepidemiol Drug Safety* 1993; **2**: 341-364.

34 Inman W, Kubota K, Pearce G, Wilton L. Fluoxetine: PEM report number 5. *Pharmacoepidemiol Drug Safety* 1993; **2**: 365-391.

35 Inman W, Kubota K, Pearce G, Wilton L. Paroxetine: PEM report number 6. *Pharmacoepidemiol Drug Safety* 1993; **2**: 393-422.

36 Inman W, Kubota K, Pearce G, Wilton L. Itraconazole: PEM report number 7. *Pharmacoepidemiol Drug Safety* 1993; **2**: 423-443.

37 Inman W, Kubota K, Pearce G, Wilton L. Cisapride: PEM report number 8. *Pharmacoepidemiol Drug Safety* 1993; **2**: 445-471.

38 Wilton L, Inman W, Kubota K, Pearce G, Skipp M. Omeprazole: PEM report number 9. *Pharmacoepidemiol Drug Safety* 1993; **2**: 473-498.

39 Inman W, Kubota K, Pearce G, Wilton L. Zopiclone: PEM report number 10. *Pharmacoepidemiol Drug Safety* 1993; **2**: 499-521.

40 Edwards JG, Inman WHW, Wilton L, Pearce G. Prescription-Event Monitoring of 10401 patients treated with fluvoxamine. *Br J Pscyichiatr* 1994; **164**: 387-395.

41 Rawson NSB, Pearce GL, Inman WH. Prescription-Event Monitoring: Methodology and recent progress. *J Clin Epidemiol* 1990; **43**: 509-522.

42 Inman WHW. *PEM News No.6*, Southampton: Drug Safety Research Unit, 1990.

43 Inman W, Pearce G. Prescriber profile and post-marketing surveillance. *Lancet* 1993; **342**: 658-661.

44 Inman WHW. *PEM News No.5*, Southampton: Drug Safety Research Unit, 1988.

45 Kubota K, Inman WHW. Terminology in prescription-event monitoring. *Eur J Clin Pharmacol* 1994; **46**: 497-500.

46 Furberg CD, Psaty BM, Meyer JV. Nifedipine: dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92**: 1326-1331.

47 Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274**: 620-625.

48 Buring JE, Glynn RJ, Hennekens CH. Calcium channel blockers and myocardial infarction: a hypothesis formulated but not yet tested. *JAMA* 1995; **274**: 654-655.

49 Messerli FH. Case-control study, meta-analysis, and bouillabaisse: putting the calcium antagonist scare into context. *Ann Intern Med* 1995; **123**: 888-889.

50 Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis. *Eur J Clin Pharmacol* 1994; **46**: 115-118.

51 Wilton LV, Pearce GL, Mann RD. A comparison of ciprofloxacin, norfloxacin, ofloxacin, azithromycin and cefixime by observational cohort studies. *Br J Clin Pharmacol* 1996; **41**: 277-284.

52 Clayton D, Hills M. *Statistical Models in Epidemiology*. Oxford: Oxford University Press. 1993.

53 Kalbfleisch JD, Prentice RL. *The Statisical Analysis of Failure Time Data*. New York: John Wiley & Sons., 1980.

54 Cox DR, Oakes D. *Analysis of Survival Data*. London: Chapman & Hall, 1984.

55 Collet D. *Modelling Survival Data in Medical Research*. London: Chapman & Hall, 1994.

56 Oakes D. Life-table analysis. In: Hinkley DV, Reid N, Snell EJ, ed. *Statistical Theory and Modelling*. London: Chapman & Hall, 1991: 107-128.

57 Lee ET. *Statistical Methods for Survival Data Analysis, 2nd ed.* New York: John Wiley & Sons, 1992.

58 Kleinbaum DG. *Logistic Regression*. New York: Springer-Verlag. 1994.

59 Andrew JE, Prescott P, Smith TMF, Inman WHW, Kubota K. Testing for adverse reactions using prescription event monitoring. *Stats Med* 1996; **15**: 987-1002.

60 Kubota K, Kubota N, Pearce GL, Prescott P, Mann RD. Signalling drug-induced rash with 36 drugs recently marketed in the United Kingdom and studied by Prescription-Event Monitoring. *Int J Clin Pharmacol Ther* 1995; **33**: 219-225.

61 British Medical Association, Royal Pharmaceutical society of Great Britain. British National Formulary No. 9, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 31. London: The Pharmaceutical Press. 1985, 1986, 1987, 1988, 1989, 1990, 1991,1992, 1996.

62 WHO. *International monitoring of adverse drug reactions to drugs: adverse reaction terminology*. Uppsala: WHO collaborating Centre for International Drug monitoring, 1991.

63 Kubota K, Inman W, Pearce G, Wilton L. *Famotidine & Nizatidine: PEM report number 13*. Southampton: Drug Safety Research Unit, 1994.

64 Fisher S, Bryant SG, Kent TA. Postmarketing surveillance by patient self-monitoring: trazodone versus fluoxetine. *J Clin Psychopharmacol* 1993; **13**: 235-242.

65 Wagner W, Zaborny BA, Gray TE. Fluvoxamine. A review of its safety profile in world-wide study. *Int Clin Psychopharmacol*; 1994; **9**: 223-227.

66 Grimsley SR, Jann MW. Paroxetine, sertraline, and fluvoxamine: new selective serotonin reuptake inhibitors. *Clin Pharm* 1992; **11**: 930-957.

67 Newton RE, Marunycz JD, Aderdice MT, Napoliello MJ. Review of the side-effect profile of buspirone. *Am J Med* 1986; **80 (suppl 3B)**: 17-21.

68 Inman W, Kubota K, Wilton L, Pearce G. *Buspirone: PEM report. (draft)* Southampton: Drug Safety Research Unit, 1994.

69 Mattila MAK, Larni HM. Flunitrazepma. *Drugs* 1980; **20**: 353-374.

70 Chaffman M, Brogden RN. Diltiazem: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1985; **29**: 387-454.

71 Waller PC, Pearce GL, Rawson NSB, Wilton LV, Inman WHW. Post-marketing surveillance of diltiazem by Prescription-event Monitoring. *Pharmaceut Med* 1990; **4**: 319-328.

72 Kubota K, Pearce GL, Inman WHW. Vasodilation-related adverse events in diltiazem and dihydropyridine calcium antagonists studied by

prescription-event monitoring. *Eur J Clin Pharmacol* 1995; **48**: 1-7.

73 Sorkin EM, Clissold SP. Nicardipine: A review of its efficacy, in the treatment of angina pectoris, hypertension and related cardiovascular disorders. *Drugs* 1987; **33**: 296-345.

74 Young RA, Bogden RN. Doxazosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in mild or moderate hypertension. *Drugs* 1988; **35**: 525-541.

75 Inman W, Kubota K, Wilton L, Pearce G. *Doxazosin: PEM report. (draft)* Southampton: Drug Safety Research Unit, 1995.

76 Inman WHW, Rawson NSB, Wilton LV, Pearce GL, Speirs CJ. Postmarketing surveillance of enalapril. I: Results of prescription-event monitoring. *Br Med J* 1988; **297**: 826-829.

77 Kubota K, Kubota N, Pearce GL, Inman WHW. ACE-inhibitor-induced cough, an adverse drug reaction unrecognised for several years: studies in Prescription-Event Monitoring. *Eur J Clin Pharmacol* 1996; **49**: 431-437.

78 Speirs CJ, Dollery CT, Inman WHW, Rawson NSB, Wilton LV. Postmarketing surveillance of enalapril. II: Investigation of the potential role of enalapril in deaths with renal failure. *Br Med J* 1988; **297**: 830-832.

79 Lunde H, Hedner T, Samuelsson O, Lötvall J, Andrén L, Lindholm L, Wilhoml BE. Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitors. *Br Med J* 1994; **308**: 18-21.

80 Herlitz J. Comparison of lisinopril versus digoxin for congestive heart failure during maintenance diuretic therapy. *Am J Cardiol* 1992; **70**: 84C-90C.

81 Inman W, Kubota K, Pearce G, Wilton L. *Lisinopril: PEM report number 11.* Southampton: Drug Safety Research Unit, 1993.

82 Biscarini L. Anti-inflammatory analgesics and drugs used in gout. In: Dukes MNG ed. *Meyler's Side Effects of Drugs, 12th ed.* Amsterdam, Elsevier, 1992: 181-234.

83 Datasheet for 'Lodine'.

84 Inman WHW, Rawson NSB. Prescription-event monitoring of five non-steroidal anti-inflammatory drugs. In: Rainsford KD, Velo GP ed. *Side-Effects of Anti-Inflammatory Drugs: Proceedings of the 2nd International*

Meeting on the Side-Effects of Anti-Inflammatory Analgesic Drugs held at Cambridge, England, 31st July - 2nd August, 1985. Lancaster: MTP Press, 1987: 111-124.

85 Bernhard GC. Worldwide safety experience with nabumetone. *J Rheumatol* 1992; **19 (suppl 36)**: 48-57.

86 Inman WHW, Wilton LV, Pearce G, Waller PC. Prescription-event monitoring of nabumetone. *Pharmaceut Med* 1990; **4**: 309-317.

87 Datasheet for 'Mobiflex'.

88 Monk JP, Clissold SP. Misoprostol: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficiency in the treatment of peptic ulcer disease. *Drugs* 1987; **33**: 1-30.

89 Babe KS, Serafin WE. Histamine, bradykinin, and their antagonists. In: Hardman JE, Limbird LE ed. *Goodman & Gilman's the Pharmacological Basis of Therapeutics, 9th ed.* New York, McGraw-Hill, 1996: 581-600.

90 Brogden RN, McTavish D. Acrivastine: A review of its pharmacological properties and therapeutic efficacy in allergic rhinitis, urticaria and related disorders. *Drugs* 1991, **41**: 927-940.

91 Spencer CM, Faulds D, Peterd DH. Cetirizine: A reappraisal of its pharmacological properties and therapeutic use in selected allergic disorders. *Drugs* 1993; **46**: 1055-1080.

92 Hayden FG. Antimicrobial agents: Antiviral agents. In: Hardman JE, Limbird LE ed. *Goodman & Gilman's the Pharmacological Basis of Therapeutics, 9th ed.* New York, McGraw-Hill, 1996: 1191-1223.

93 Jackson GH, Proctor SJ. Disorders of blood cells and haemostasis: Part 1 disorders of blood cells. In: Davies DM, ed. *Textbook of Adverse Drug Reactions, 4th ed.* Oxford: Oxford Medical Publications, 1991: 643-655.

94 Schacht P, Arcieri G, Hullmann R. Safety or oral ciprofloxacin: An update based on clinical trial results. *Am J Med* 1989; **87 (suppl 5A)**: 98S-102S.

95 Como JA, Dismukes WE. Oral azole drugs as systemic antifungal therapy. *N Engl J Med* 1994; **330**: 263-272.

96 Mann RD, Kubota K, Pearce G, Wilton L. *Salmeterol: PEM report number 25.* Southampton: Drug Safety Research Unit, 1994

97 Mann RD, Kubota K, Pearce G, Wilton L. Salmeterol: a study by Prescription-Event Monitoring in a UK cohort of 15,407 patients. *J Clin*

Epidemiol 1996; **49**: 247-250.

98 Suissa S. Novel approaches to pharmacoepidemiology study design and statistical analysis. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 629-645.

99 Rawlins MD, Thompson JW. Mechanisms of adverse drug reactions. In: Davies DM, ed. *Textbook of Adverse Drug Reactions, 4th ed.* Oxford: Oxford Medical Publications, 1991: 18-45.

100 Inman WHW. Postmarketing surveillance of adverse drug reactions in general practice. I: Search for new methods. *Br Med J* 1981; **282**: 1131-1132.

101 Inman WHW. Postmarketing surveillance of adverse drug reactions in general practice. II: Prescription-event monitoring at the University of Southampton. *Br Med J* 1981; **282**: 1216-1217.

102 Collet JP, Boivin JF, Spitzer WO. Bias and confounding in pharmacoepidemiology. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 609-627.

103 Ikegami N, Campbell JC. Medical care in Japan. *N Engl J Med* 1995; **333**: 1295-1299.

104 Inman B: 30 years in postmarketing surveillance: a personal perspective. *Pharmacoepidemiol Drug Safety* 1993; **2**: 239-258.

105 Inman WHW, Rawson NSB. Erythromycin estolate and jaundice. *Br Med J* 1983; **286**: 1954-1955.

106 Committee on Safety of Medicines. Jaundice and erythromycin. *Adverse Reactions Series No 10.* London: DHSS, 1973.

107 Inman WHW, Rawson NSB. Peptic ulcer and piroxicam. Br Med J 1985; 290: 932-933.

108 Fox KH, George PJM, Vicary FR. Peptic ulcers induced by piroxicam. *Br Med J* 1985; **290**: 117.

109 Inman WHW. *PEM News No.4*, Southampton: Drug Safety Research Unit, 1987.

110 Teicher MH, Glod C, Cole JO. Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; **147**: 207-210.

111 Inman WHW. *PEM News No.8*, Southampton: Drug Safety Research Unit, 1993.

112 Olsson S, Edwards IR. Tachycardia during cisapride treatment. *Br*

Med J 1992; **305**: 748-749.

113 Inman W, Kubota K. Tachycardia during cisapride treatment. *Br Med J* 1992; **305**: 1019.

114 Haramburu F. Estimation of underreporting. In: Association pour la Recherche Methodologique en Pharmacovigilance ed. *Methodological Approaches in Pharmacoepidemiology*. Amsterdam: Elsevier, 1993: 39-49.

115 Fletcher RH, Fletcher SW, Wagner EH. Risk. In: *Clinical Epidemiology 3rd ed*. Baltimore: Williams & Wilkins, 1996: 94-110.

116 Feinstein AR. Additional principles of cause-effect research. In: *Clinical Epidemiology: the Architecture of Clinical Research*. Philadelphia: W.B. Saunders, 1985: 191-236.

117 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Deciding whether your treatment has done harm. In: *Clinical Epidemiology: A Basic Science for Clinical Medicine. 2nd ed*. Boston: Little, Brown Co., 1991: 283-302.

118 Veldhuis GJ, Inman WHW. Terodiline and torsades de pointes. *Br Med J* 1991; **303**: 519.

119 McLeod AA, Thorogood S, Barnett S. Torsades de pointes complicating treatment with terodiline. *Br Med J* 1991; **302**: 1469.

120 Committee on Safety of Medicines. Terodiline (Micturin) and adverse cardiac reactions. London: CSM, 1991.

121 Inman WHW. *PEM News No.2*, Southampton: Drug Surveillance Research Unit, 1984.

122 Inman WHW. *PEM News No3*, Southampton: Drug Surveillance Research Unit, 1985.

123 Fletcher RH, Fletcher SW, Wagner EH. Prognosis. In: *Clinical Epidemiology. 3rd ed*. Baltimore: Williams & Wilkins, 1996: 111-135.

124 Björck S, Mulec H, Johnsen SA, Nordén G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *Br Med J* 1992; **304**: 339-343.

125 Chan JCN, Cockram CS, Nicholls MG, Cheung CK, Swaminathan R. Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: one year analysis. *Br Med J* 1992; **305**: 981-985.

126 Hallab M, Gallois Y, Chatellier G, Rohmer V, Fressinaud P, Marre M. Comparison of reduction in microalbuminuria by enalapril and

hydrochlorothiazide in normotensive patients with insulin dependent diabetes. *Br Med J* 1993; **306**: 175-182.

127 Lewis E, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; **329**: 1456-1462.

128 Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch Intern Med* 1996; **156**: 286-289.

129 Maschio G. Protecting the residual renal function: How do ACE inhibitors and calcium antagonist compare ? *Nephron* 1994; **67**: 257-262.

130 Fluck RJ, Raine AEG. ACE inhibitors in non diabetic renal disease. *Br Heart J* 1994; **72 (Suppl)**: 46-51.

131 Hricik DE, Browning PJ, Kopelman R, et al. Captopril-induced functional renal insufficiency in patients with bilateral renal artery stenosis or renal artery stenosis in a solitary kidney. *N Engl J Med* 1983; **308**:373-376.

132 Ravid M, Ravid D. ACE inhibitors in elderly patients with hypertension. *Drugs & Aging* 1996; **8**: 29-37.

133 Hoontje SJ, Weaning JJ, Donker AJM et al. Immune-complex glomerulopathy in patients treated with captopril. *Lancet* 1980; **1**: 1212-1215.

134 Todd PA, Heel RC. Enalapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs* 1986; **31**: 198-248.

135 Strom BL, Melmon KL. The use of pharmacoepidemiology to study beneficial drug effects. In: Strom BL ed. *Pharmacoepidemiology, 2nd ed.* Chichester: John Wiley & Sons Ltd, 1994: 449-467.

136 Havelka J, Vetter H, Studer A, et al. Acute and chronic effects of the angiotensin-converting enzyme inhibitor captopril in severe hypertension. *Am J Cardiol* 1982; **49**:1467-1474.

137 Havelka J, Boerlin HJ, Studer A, et al. Long-term experience with captopril in severe hypertension. *Br J Clin Pharmacol* 1982; **14**: 71S-76S.

138 Leier CV, Bambach D, Nelson S, et al. Captopril in primary pulmonary hypertension. *Circulation* 1983; **67**: 155-161.

139 Soseko, Kaneko Y. Cough associated with the use of captopril. *Arch Intern Med* 1985; **145**: 1524.

140 Mitchel A, Gillies A, Carney S, Smith AJ. Cough and captopril. *Arch Intern Med* 1985; **146**: 1017.

141 Carruthers SG. Severe coughing during captopril and enalapril therapy. *Can Med Assoc J* 1986; **135**: 217-218.

142 Israel-Biet D, Delaisements C, Chretien J. Enalapril-induced cough. *Lancet* 1986; **2**: 918.

143 Semple PF, Herd GW. Cough and wheeze caused by inhibitors of angiotensin-converting enzyme. *N Engl J Med* 1986; **314**: 61.

144 Webb D, Benjamin N, Collier J, Robinson B. Enalapril-induced cough. *Lancet* 1986; **2**: 1094.

145 Inman WHW. Enalapril-induced cough. *Lancet* 1986; **2**: 1218.

146 Inman W, Kubota K, Pearce G, Wilton L. *Acyclovir: PEM report number 12.* Southampton: Drug Safety Research Unit, 1994.

147 Feinstein AR. Statistical communication of cross-sectional evidence. In: *Clinical Epidemiology: the Architecture of Clinical Research.* Philadelphia: W.B. Saunders, 1985: 414-457.

148 Mann RD. Editorial. *Pharmacoepidemiol Drug Safety* 1993; **2**: i-ii.

149 Jick H. The discovery of drug-induced illness. *N Engl J Med* 1977; **296**: 481-485.

150 Venning GR. Identification of adverse reactions to new drugs. I-IV. *Br Med J* 1983; **286**: 199-202, 289-292, 365-368, 458-460, 544-547.

151 Skegg DCG, Doll R. Frequency of eye complaints and rashes among patients receiving practolol and propranolol. *Lancet!* 1977; **ii**: 475-478.

152 Inman W, Kubota K, Pearce G, Wilton L. *Amlodipine: PEM report number 16.* Southampton: Drug Safety Research Unit, 1995.

153 Lee ET. *Statistical Methods for Survival Data Analysis, 2nd ed.* New York: John Wiley & Sons, 1992.

154 Miller RG. *Survival Analysis.* New York: John Wiley & sons, 1981.

155 Rawson NSB. An acute adverse drug reaction alerting scheme using the Saskatchewan health datafiles. *Drug Invest* 1993; **6**: 245-256.

156 Fletcher RH, Fletcher SW, Wagner EH. Cause. In: *Clinical Epidemiology. 3rd ed.* Baltimore: Williams & Wilkins, 1996: 228-248.

157 Rothman KJ. Causal inference in epidemiology. In: *Modern Epidemiology.* Boston: Little, Brown and Co., 1986: 7-21.

158 MacMahon B, Trichopoulos D. Concepts of cause. In: *Epidemiology: principles and methods. 2nd ed.* Boston: Little, Brown and Co., 1996: 19-29.

159 Hennekens CH, Buring JE. Statistical association and cause-effect relationships. In: *Epidemiology in medicine.* Boston: Little, Brown and Co., 1987: 30-53.

Appendices

Appendix 1

Historical consideration of Prescription-Event Monitoring (PEM) with particular attention to 'signalling'

It was in 1980 that the Drug Surveillance (later Safety) Research Unit (DSRU) was set up at the University of Southampton by Professor WHW Inman. He was also one of the original members of the Committee on Safety of Drugs (later Medicines), abbreviated as CSD (later as CSM), established in 1964 in the United Kingdom[1]. In order to understand the role of the DSRU and Prescription-Event Monitoring (PEM) which has been the main activity of the DSRU, it is important to know why the DSRU has been set up in 1980 and why PEM has been designed as a new national scheme for postmarketing surveillance (PMS). This is not just a historical matter but a key to understanding the difference and relationship between PEM and the 'Yellow Card Scheme'.

Practolol syndrome and PEM

It is well known that the thalidomide disaster has led the 'Yellow Card Scheme', the first national scheme in the United Kingdom proposed by the subcommittee on adverse reactions of the CSD in 1964 to collect reports on suspected drug reactions. Similar schemes were also established in some other countries in mid to late 1960s[17]. The system is often called as 'spontaneous' or voluntary reporting system (VRS)[18] as it depends on the voluntary reporting from medical doctors (and other health professionals including pharmacists in some countries such as USA[19]) who have suspected adverse drug reactions (ADRs) in their daily practice. On the other hand, PEM was designed to complement VRS after the 'Yellow Card Scheme' was found to have failed to give early warning signals to 'oculomucocutaneous syndrome' caused by a beta-blocker, practolol[8]. The 'Yellow Card Scheme' failed to detect practolol syndrome during the first four years after practolol was marketed in 1970 because its major manifestations such as dry eye, deafness and psoriasis-like eruption mimicked commonplace illnesses which doctors often encountered in their clinical practice. In addition, in many cases, this ADR developed months or

even years later after the first prescription of the causative agent. Because of these factors, most doctors did not suspect the possibility of the causal relationship between those adverse events and the drug. It was only after 1974 to 1975 when a couple of astute authors sent case reports of this new ADR to medical journals[9-11] that hundreds of 'Yellow Cards' on the cases of suspected practolol syndrome were rushed to VRS[12].

When most doctors miss the causal relationship, that ADR has only few chances to be reported to VRS so that VRS tends to fail to give an early warning signal.

Practolol syndrome and subacute myelo-optico-neuropathy (SMON)

Interestingly, subacute myelo-optico-neuropathy (SMON) due to chloroquinol, having clustered from late 1960s to early 1970s particularly in Japan[13], had a similar feature to practolol syndrome and other ADRs difficult to recognise. In typical SMON, patients had acute abdominal symptoms such as diarrhoea and abdominal pain suddenly at some specific time point before neurological signs developed even if patients had started taking the causative agent long before the first manifestation of this ADR[14]. Although thousands of patients suffered from SMON, virtually no Japanese practitioners recognised the causal relationship from the clinical observation. The crucial key event leading to the recognition of the relationship between SMON and chloroquinol is said to be the detection of the causative agent from green pigment in the urine and feces as well as from peculiar green fur of the tongue of some patients[15].

When no doctors recognise the causal relationship, VRS does not work at all.

Four objectives of the DSRU

The DSRU had the following four objectives when it was established in 1980[104]

1 To establish a second nationwide drug safety screening programme called Prescription-Event Monitoring (PEM) in collaboration with the Prescription

Pricing Authority.

2 To conduct epidemiological investigations into specific drug safety problems on a local or national scale.

3 To develop training and conference facilities.

4 To study methods for improving the public's perception of the balance of drug risks and benefits.

Ten objectives of PEM

The establishment of PEM was raised as the first of the above four objectives of the DSRU. It was designed to achieve the following 10 objectives set by Professor Inman[12].

1) It should enable us to estimate the incidence of adverse events.

2) It should record all events and not merely those which have been thought to have been drug-induced.

3) It should include all the users of a drug for at least as long as required to assemble a population capable of revealing comparatively uncommon drug-events (eg in the range 1% to 0.1%).

4) It should permit long-term follow-up.

5) It should not influence prescribing (ie no inducements).

6) It should not increase medico-legal risk.

7) It should permit fast communication between researchers, prescribers, regulatory authorities and manufacturers.

8) It should be standardized so that groups of patients treated with one drug

could readily be compared with other groups.

9) It should be 'doctor-friendly'.

10) It should be inexpensive.

Hypothesis-generating function is critical with PEM

Even if not explicitly described in 10 objectives of PEM above, one of the most important functions which PEM is expected to exert is obviously that of generating hypotheses on the new ADRs so far unrecognised or the new problems associated with the known ADRs. In addition, being different from VRS, PEM should have some mechanism providing a hypothesis-generating function by analysing 'events' without depending on the individual doctors' suspicion on the causal relationship between the event and drug. Unless PEM has such a mechanism, PEM cannot be regarded to meet its mission as nobody can predict which new chemical will turn out to be another practolol.

It took years for the DSRU to find an effective methodological way to detect possible ADRs to the drug from the data recorded as 'events' because the validity of the method could be fully examined and established only by using the data collected from many PEM studies. In these two to three years, there has been a debate on the methodology in the DSRU which has been not yet completely resolved. It seems that even by now the methodology has not been firmly established and an effort to find a better way of signalling possible ADRs is still on-going.

Appendix 2

PEM as a tool of hypothesis testing

A hypothesis-generating function is one of the most important features which PEM is expected to have as described in Appendix 1. In this regard, it is interesting to see that in a textbook edited by Strom, *Pharmacoepidemiology*, PEM is evaluated as a system characterised as[3]:

Hypothesis generating (+)
Hypothesis strengthening (++)
Hypothesis testing (+++)

where hypothesis-testing studies are defined as studies designed to evaluate in detail hypotheses raised elsewhere, hypothesis-strengthening studies are defined as those designed to provide support for, although not definitive evidence for, existing hypotheses and hypothesis-generating studies are defined as those designed to raise new questions about possible unexpected drug effects, whether adverse or beneficial. At least in a textbook, *Pharmacoepidemiology*, PEM is regarded as a tool of hypothesis testing or hypothesis strengthening rather than hypothesis generating. Some of contributions of PEM to the field of the drug safety have been so far made indeed through its hypothesis-strengthening or testing function. In this section, PEM is viewed as a tool of hypothesis testing.

Some examples where PEM works as a tool of hypothesis testing

PEM has been sometimes used as a tool of hypothesis testing. Several examples are shown as follows.

1. Erythromycin estolate and jaundice[105]

A hypothesis on the relationship between erythromycin estolate and jaundice was generated by VRS. In 1973, the CSM published a report suggesting that the relative risk of jaundice might be as much as 20 times as great with

erythromycin estolate than other preparation of this antibiotic[106]. In the PEM study conducted in 1982, 4373 patients using erythromycin estolate and 5386 patients using erythromycin stearate were identified[105]. Simple questionnaires to ask whether the patients had developed jaundice were sent to doctors and 3314 forms for erythromycin estolate and 4095 forms for erythromycin stearate were returned. Eight cases who took the estolate and six cases with the stearate developed jaundice. In three patients who took erythromycin stearate but no patients with the estolate, the antibiotic could be considered to have been a possible cause of jaundice. The hypothesis raised from VRS was rejected by this PEM study.

2. Gastro-intestinal ulceration and piroxicam[107]

The hypothesis that piroxicam may cause more gastro-intestinal ulceration than other NSAIDs was originally derived from reports to the CSM and raised by letters to medical journals in 1985[108] and exaggerated by lay press with such a headline as "Arthritis Drug Alert after 77 Patients Die"[109]. Being different from testing the relationship between erythromycin and jaundice as shown example 1 above, the PEM study on piroxicam had been finished independently before this hypothesis was raised. The majority of questionnaires (green forms) were returned by the end of January 1984 in the PEM study on piroxicam and the results were published in *Proceeding of the 2nd International Meeting on the Side-effects of Anti-inflammatory Analgesic Drugs* held at Cambridge, England, 31st July - 2nd August, 1985. In that report where five NSAIDs, i.e., benoxaprofen, fenbufen, zomepirac, piroxicam and 'Osomsin' (indomethacin slow-release) were compared with one another, the following conclusion was already made[84].

While we would not deny that NSAIDs may occasionally cause serious gastrointestinal complications such as bleeding or perforation, one important result of this study is the observation that the distribution of cases both during and following treatment seemed to be very similar. This leads us to conclude that any differences caused by treatment are likely to have been small.

PEM played an important part in allaying public fears for piroxicam and the results of the PEM studies on five NSAIDs were also presented at the FDA hearing[109].

3. Fluoxetine and suicide

The hypothesis was raised by a letter to medical journal reporting case series of six patients who took fluoxetine, one of selective serotonin-reuptake inhibitors (SSRIs), and had suicidal thought or homicidal behaviour[110]. It was also complicated by lay press and a lawsuit in USA and major influence from lay press occurred in the UK during the PEM study on fluoxetine. Towards the end of the PEM study and immediately after a TV programme, screened on December 1990, presenting a number of anecdotes portraying homicidal or suicidal behaviour among patients in USA, the DSRU added supplementary questions to about the last 4000 patients selected for study[12,34,111]. There was no evidence to suggest that patients had become more violent or more self-destructive during or following treatment with fluoxetine. Though no data of the PEM studies on antidepressants of other classes (e.g., tricyclics) were available, the rate of suicidal behaviour was similar between three SSRIs (fluvoxamine, fluoxetine and paroxetine) studied by PEM.

General Practice Research Database (GPRD) in UK, formerly called as Value Added Medical Product (VAMP), one of the biggest record linkage systems in the world, was also used to test this hypothesis[4]. The rate of suicide was compared among 10 antidepressants prescribed between January 1988 to February 1993. Crude rates of suicide was within a factor of 4; i.e., 4.7 (lofepramine) to 19.0 (fluoxetine) per 10,000 patients. Though the results indicate that only fluoxetine has a rate that seems to be substantially higher than that of the other antidepressants, when the analysis was restricted to those without a history of having felt suicidal or who had taken only one antidepressant, the increased risk for those who took fluoxetine was reduced. The authors concluded that the increased risk associated with fluoxetine might be explained by selection bias and the risk of suicide was similar among the 10 study antidepressants[4].

4. Cisapride and tachycardia

Though not comparable to other three examples in terms of the magnitude of the influence to public, this example shows clearly how a hypothesis raised by VRS could be tested by PEM. A hypothesis was raised by VRS and seven cases of tachycardia or palpitations associated with treatment with cisapride were reported from WHO collaborating centre for drug monitoring[112]. When compared among 23 drugs monitored by PEM, cisapride was the twelfth when the rates of palpitations, tachycardia and extrasystoles with these drugs were ranked in descending order[113]. Five non-cardiovascular drugs as well as six cardiovascular drugs had the rates higher than that of cisapride. The rate of tachycardia with cisapride was estimated to be extremely low.

PEM works as a tool of hypothesis testing particularly when rejecting the hypothesis

In all of the four examples shown above, PEM can be considered as a tool of hypothesis testing where a positive hypothesis "a drug A causes an ADR B frequently (or more frequently than other drugs)" is rejected. It may be stressed that this type of hypothesis testing is almost impossible in VRS as the rejection of the hypothesis is based on the comparison of the rates estimated in the population while the rate of an ADR is difficult to know in VRS. A reliable estimation of denominator (number of patients exposed to the drug) is difficult in VRS. An estimation of numerator or number of ADRs is more troublesome as only a small fraction of ADRs which have occurred is known to be reported to VRS[27] and therefore 'reported' rate is heavily influenced by various factors such as publicity of an ADR[114].

Between-drug comparison as a means to test and reject a hypothesis

The above four examples also illuminate an important role of the between-drug comparison in the analysis of the PEM data. In PEM, the between-drug comparison, a standard approach in the cohort study[115-117], provides a useful means when rejecting a hypothesis as illustrated above. This is particularly true when the event is proven to be rare. On the other hand, in PEM the

between-drug comparison may not necessarily provide a clear support to raise a positive hypothesis whether in hypothesis strengthening (where the same hypothesis has been already raised elsewhere) or in hypothesis generating (where the hypothesis raised is new and has not been raised anywhere else) as mentioned more in the following section.

This feature of PEM (i.e., good in showing a negative result with small rates while clumsy in drawing a positive conclusion) may be common to most other database used in the pharmacoepidemiological studies made by gathering data from large number of subjects. The feature may be contrasted with a randomised clinical trial (RCT) using relatively small number of patients. In an RCT where randomisation and other procedures are done reasonably well, a positive result with a significant difference between groups can be usually shown unambiguously even if its clinical implication and possibility to generalise the results may be sometimes questionable. On the other hand, when no difference is detected between groups, the conclusion is not so clear particularly when the number of study subjects is small. The result is often described with such an excuse that "the difference did not reach statistical significance because of the small number of subjects ---" but not shown as an evidence to verify that two groups are equal to each other. In general, to reach a negative conclusion on the events with small rates, an observational study on large number of patients is more powerful and more feasible than an RCT with a small number of subjects.

Appendix 3

Hypothesis-generating and strengthening by the between-drug comparison in PEM

PEM is an observational cohort study. In a standard observational cohort study, the basic strategy used in the analysis of data is the comparison of patient groups classified according to possible risk factors and followed over time[115-117]. In the cohort study of drug effect (either adverse or beneficial) the comparison is usually made between those who used different drugs. If enough number of patients who have taken no drug for reasonably long period are available, the comparison may be also made between patients with a drug or a class of drugs and those without any drug[16]

Original idea to use concurrent or contemporary control in PEM

At least in the early stage of PEM, the between-drug comparison was thought to be the major means to analyse the data irrespective of whether a likely conclusion was negative or positive[100,101]. When designing PEM, Inman wrote in an article "Postmarketing surveillance of adverse drug reactions in general practice" published in BMJ in 1981 as follows[101].

Each "test" drug will be matched with a "control drug", the test drug being one that has recently been granted a product license and the control drug will usually be a chemically or pharmacologically similar drug already marketed for the same indications.

For example, the first two PEM studies conducted in January 1982 were those on two NSAIDs, benoxaprofen and fenbufen[1]. In the study on the relationship between jaundice and erythromycin conducted also in 1982, the estolate and stearate of erythromycin were compared with each other[105]. The conclusion of this study was, as mentioned earlier, negative rejecting a hypothesis raised by VRS.

On the contrary, a positive results was obtained (i.e., a "warning signal" was raised) by the between-drug comparison in the PEM study on terodiline as follows.

Torsades de pointes and terodiline: PEM study where the between-drug comparison was used as a major tool to generate a "warning signal"[131,118]

I the PEM study on terodiline, many events associated with the use of terodiline were reported and analysed. However, one of the most important issues addressed in the study was the relation between terodiline and torsades de pointes published as a letter from the DSRU to BMJ[118] preceding to the full report on the study[31]. In the letter, the between-drug comparison was used as a tool of hypothesis strengthening rather than hypothesis generating because the hypothesis had been already raised somewhere else. In 1991, McLeod and co-workers reported a case who developed torsades de pointes (one type of potentially fatal ventricular arrhythmias) allegedly due to terodiline[119] and other possible cases had been reported to the CSM[120]. In the letter from the DSRU, instead of analysing torsades de pointes itself which could be diagnosed only when a patient was on ECG monitoring, several events which might be associated with this arrhythmia were studied and compared between terodiline and an NSAID, nabumetone. Two studies on terodiline and nabumetone were conducted approximately at the same time and two groups of patients were said to be similar in terms of distribution of age and co-prescribed drugs. Several events such as confusion, syncope, cerebrovascular accident, transient ischaemic attack and falls/fractures were considered to have a close relationship with torsades de pointes and used in the comparison between two drugs. The rates of these events with terodiline were several times higher than those with nabumetone. In addition, six classes of drugs potentially causative of those events and co-prescribed with terodiline were examined later in a special project leading to a negative conclusion where any co-prescribed drug was judged not to have been relevant to the events examined[31]. Those drugs were diuretics, beta-blockers, digitalis, nitrates, ACE-inhibitors and calcium-antagonists. Within some days after the letter from the DSRU was published in BMJ, the drug was withdrawn voluntarily by the manufacturers[31]. Though it was stressed, in the letter, that the results were by no means conclusive[118], this letter from the DSRU was

probably one of the major driving forces to have led to the withdrawal of terodiline.

When the results of the PEM study on terodiline were analysed and the letter was sent to BMJ in 1991[118], the original idea to use the concurrent control had been already abandoned by the DSRU. For instance, the PEM study on nabumetone was conducted as one of the routine PEM studies on the newly marketed drugs independently of the study of terodiline[66]. Therefore, nabumetone did not have features to be possessed by the control drug as originally conceived in 1981; i.e., a chemically or pharmacologically similar drug with the same indications[101] Though not a lot of criticisms by the authors outside the DSRU were addressed to this letter[118], the use of nabumetone as a control drug might have some problems.

Major indication of terodiline was urinary incontinence while that of nabumetone was various including osteoarthritis, joint pain, unspecified 'arthritis', back pain or rheumatoid arthritis. The rates of some events directly associated with the indication of one drug but not with that of the other may differ considerably even if they are by no means associated with either drug. For instance, the rate of urinary tract infection with terodiline coded in the first six months irrespective of whether the patient continued the drug was 3.9 per 1000 patients per month and three times higher than that with nabumetone, 1.4 per 1000 patients per month. On the contrary, the rate of orthopaedic surgery with terodiline and that with nabumetone were 0.2 and 0.8 per 1000 patients per month, respectively. The mechanism to have caused these differences is known as confounding by the indication[102]. For instance, urinary tract infection may have occurred in association with neoplasm of urinary tract rather than the drug itself and neoplasm in turn may have been underlying urinary incontinence. Some of other possible diseases or pathological conditions underlying urinary incontinence (e.g., autonomic dysfunction) may have caused some events such as confusion, syncope, and falls/fractures by a mechanism other than torsades de points (e.g., orthopaedic hypotension).

The discussion on the possible relationship between terodiline and torsades de points would be clearer if more information on the underlying diseases had been available for individual patients who had confusion, syncope and

falls/fractures etc. During the developing phase of PEM, the DSRU has revised the questionnaire (green form) several times to improve it but the question on complications has not been included in the form. An important information for the underlying diseases might be obtained just by a simple additional question on the complications and/or concurrent abnormal conditions which may or may not have a relationship with the indication of the drug. If the information could provide a likely alternative explanation, this would help distinguish the event likely caused by the underlying diseases from that caused by the drug. In the opposite case, non-existence of the alternative explanation may or may not support the possibility that the event in question is an ADR. For example, if the patient has been otherwise healthy until the occurrence of an acute disease (e.g., acute infection) for which the drug is prescribed, there may be no way to distinguish whether the event is caused by the drug or by the acute disease itself provided that both scenarios are equally likely.

Reasons why the DSRU gave up the use of the concurrent control drug in PEM

Probably, the experience with 'Indocid' gave the most important driving force to make the DSRU give up the use of control group in PEM. In 1983 the study of two NSAIDs, benoxaprofen and fenbufen was extended and later in the same year zomepirac, piroxicam and 'Osmosin' (indomethacin slow-release) were added[121,122]. Though not included in the report of the PEM studies on 5 NSAIDs in 1985[84], the DSRU has also conducted, at the same time, a study of 'Indocid' (old preparation of indomethacin). The original intention was to explore the possibility that 'Osmosin' and 'Indocid' might show different rates of gastrointestinal disorder. According to Inman[6],

> The results of this experiment were very instructive from the methodological point of view. Many patients in the 'Indocid' group had been using the drug for very long periods, sometimes as long as 20 years. The number of events recorded was much lower than with the other five preparations and the data are considered not to be comparable. Many doctors complained that it took too much

of their time to record events in patients who had used 'Indocid' often for many years and asked us not to embark on other studies of well-established drugs.

In addition to an extraordinary burden to doctors who were asked to record events which occurred during the preceding several years in the patients with 'Indocid', there seemed to be another problem associated with 'survival cohorts'. True cohort studies should be distinguished from studies of 'survival cohorts' or 'available patient cohorts'[123]. Many of the current users of the old drug, particularly the old drug used for a chronic condition, are often 'survivors' who have not had any serious adverse events. On the other hand, those having experienced serious events during the use of the drug are likely to have stopped it and unlikely to be found in the current users.

A policy not to employ a 'control' group seemed to have been already established before the PEM study of terodiline was conducted. For example the PEM study on ranitidine conducted in 1985 did not use a control group as follows[8]:

For a number of reasons, we did not initiate a green form exercise for cimetidine. The drug had been marketed several years earlier, and although many ranitidine-treated patients had been using cimetidine (some were cimetidine failures), the reverse could no be true. It was clear that the two groups would not be comparable in other respects. Our subsequent experience with 'Indocid', already referred to, suggest that our decision not to attempt a study of cimetidine was probably correct. The main value of the ranitidine data will be for comparison with any new H_2-receptor antagonist which may be marketed in the future.

The problem of historical control

To avoid the problem associated with 'survival cohorts', a historical control may be employed where the current data of the new drug are compared with those

of the old drug obtained by the study conducted in the past when the drug was marketed for the first time. However, it is known that choosing concurrent controls (i.e., patients treated during the same period of time) is, in general, a better way of avoiding bias[115]. One example of biases associated with the use of a historical control is publicity of the adverse drug reaction common to the class which may increase with time. For example, the rate of cough recorded in the PEM studies on lisinopril, ramipril and perindopril were three times higher than the PEM study on enalapril conducted years earlier when this ADR was not widely known[77].

In this regard, it may be worth trying to come back to the original idea of PEM when it was designed in 1981 as follows[101]:

> An unknown proportion of the patients receiving the control drug will have been taking it for some time, though this will not be apparent from the prescription. Others will be "new" patients who have recently started treatment. The first task will be to process prescriptions for the control drug in such a way that *contemporary treatments* may be selected for comparison with the new product. In practice this will be done by monitoring the prescriptions for the control drug for several months until patients who are "new to the system" start to appear. These will be put on one side for further study and the remainder discarded. There would be little point, for example, in comparing patients starting treatment with a β-blocking agent marketed for the first time in 1981 with controls who might have been taking propranolol for ten or more years.

If all of the prescriptions to cover the whole country are monitored for several months to identify and exclude the current users of the control drugs who have used that control drug already for years, patients who are "new to the system" could be selected. Most of those patients may be the "new" users of the control drug. Unfortunately, it seemed that in the study of 'Indocid', the use of this technique was not considered seriously so that the control group identified

was judged to be not suitable for the comparison with other five NSAIDs[8]. In addition, after receiving complaints from doctors involved in the 'Indocid' study, the idea to try to identify the concurrent control seems to have been completely abandoned.

It may be however emphasized that a proper control drug was not available any way in the PEM study of terodiline because terodiline was a unique drug and no drug with similar indication existed when terodiline was monitored by PEM. In addition, the use of the concurrent control, even if possible, will not solve all of the problems inherent to the observational study. The observational studies, including cohort studies, are in general subject to a great many more potential biases than are clinical trials where patients are randomised. If it takes very long time to identify enough number of the 'new' users of the control drug, the use of the concurrent control may be impractical. With these limitations, however, a concurrent (or contemporary) control may be seriously considered whenever there is any possibility to use it.

Appendix 4

Hypothesis generating and strengthening by the methods other than the between-drug comparison in PEM

Renal failure with enalapril[76,78]

The PEM study on enalapril was conducted between 1985 and 1986. Similar to the ranitidine study, no information for the patients using captopril was collected in the enalapril study. When the results of the enalapril study were available, the main concern was a large number of fatal cases of which a considerable proportion was associated with renal failure occurring with a frequency much higher than expected. In 1988 a series of two reports on the PEM study of enalapril were published in BMJ[76,78] and the subtitle of the latter of the two was "investigation of the potential role of enalapril in deaths with renal failure" which obviously signalled a possible relationship between enalapril and death from renal failure. In the PEM study of enalapril, 1098 of 15169 green forms recorded patients as having died. The patient notes for 913 of 1098 fatal cases were retrieved and examined for any abnormality of renal function. 178 cases were found to have had a creatinine concentration of more than 250 μmol/l or a urea concentration of more than 20 mmol/l at any time or have been mentioned of renal abnormality. Excluding 36 cases where serial measurements clearly showed no further rise after enalapril and 30 cases who were unassessable, 112 cases were judged to be assessable. In 75 of the 112 cases, enalapril had been associated with a rise in the creatinine or urea concentration of 50% or more and in 10 patients enalapril was thought to have contributed to a deterioration in renal function sufficient to be a factor in the subsequent deaths. Those 10 patients were characterised by the old age, use of high dose, concomitant use of potassium sparing diuretics or NSAIDs and pre-existing renal disease[78].

The report on the PEM study of enalapril forms a striking contrast to many recent papers which report on 'reno-protective' effects of ACE inhibitor in the patients with diabetic nephropathy[124-128]. ACE inhibitors may be 'reno-protective' also in the patients with other renal impairment[129,130]. On the other

hand, it is also known that in patients with severe bilateral renal artery stenosis, ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure[131]. Progressive renal failure was recorded in about 5 % of patients with documented renovascular hypertension treated with ACE inhibitors[132]. The observation in PEM that the combination of potassium-sparing diuretics and ACE inhibitors is especially undesirable has been also obtained in another study[132]. In this regard, it is interesting to see that the change in the description on ACE inhibitors has occurred in the British National Formulary (BNF)[61]. For instance, in the BNF No. 12 (September 1986) issued around when the PEM study of enalapril was finished, the description on indications of enalapril was given as

Indications: all grades of essential hypertension and renovascular hypertension (where standard therapy is ineffective or inappropriate); congestive heart failure (adjunct)

However, in the BNF No. 31 (March 1996), 'renovascular hypertension' is deleted from 'indications' of ACE inhibitors including enalapril. In the note for all ACE inhibitors, it is given that ACE inhibitors may be avoided in all patients with known or suspected renovascular disease. The findings about the risk associated with the concomitant use of potassium sparing diuretics or NSAIDs obtained in the PEM study[78] are also noted in this BNF. The note on renal effects of ACE inhibitors given in the BNF No. 31 reads as follows (type in capital, italic or bold in the BNF No. 31 is reproduced below):

RENAL EFFECTS. In patients with severe *bilateral renal artery stenosis* (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are thus **contra-indicated** in patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with *severe unilateral renal artery stenosis and a normal*

contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

In general, ACE inhibitors are therefore best avoided in **all** patients with *known or suspected renovascular disease*, unless the blood pressure cannot be controlled by other drugs. If they are used in these circumstances renal function needs to be monitored with great care.

---- Although ACE inhibitors now have a specialised role in some forms of renal disease they also occasionally cause *impairment of renal function* which may progress and become severe in other circumstances (at particular risk are the elderly).

Concomitant treatment with NSAIDs increases the risk of renal damage, and *potassium-sparing diuretics* (or *potassium-containing salt substitutes*) increase the risk of hyperkalaemia.

There may be a need to resolve an apparent discrepancy between the report on 'potential role of enalapril in deaths with renal failure' from the DSRU[76,78] and those on 'renoprotective' effect of ACE inhibitors including enalapril[124-130]. Noteworthily, the rate of renal failure has dramatically decreased in the sequential manner with time when compared among the PEM studies of four ACE inhibitors conducted between 1985 and 1995. Figure 19 shows the rate of renal failure reported in green forms (including both fatal and nonfatal cases) in the first 6 months irrespective of whether or not the patient continued one of four ACE inhibitors. Four ACE inhibitors in Figure 19 (year of study) are enalapril (1985 to 1986), lisinopril (1988 to 1989), ramipril (1990 to 1991) and perindopril (1990 to 1995). The decrease in the rate of renal failure with time is remarkable even when the rate is compared in the patients who had an indication of hypertension only, i.e., when the rate is estimated after excluding those with other indications such as cardiac failure as well as those with unknown indication (Figure 20). The difference of the rates of renal failure between ACE inhibitors was probably due to the selection bias and this point was appreciated already when the results of the lisinopril study became available. Mentioning the lisinopril study, Inman wrote[12]:

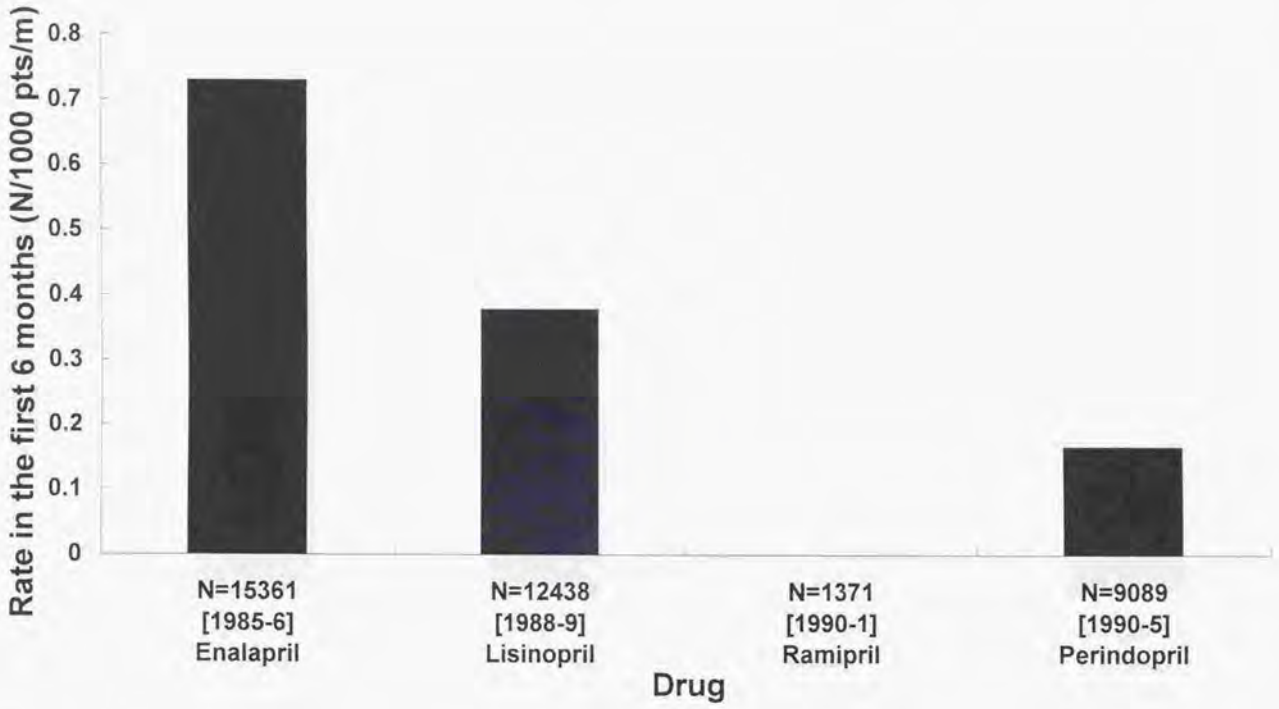


Figure 19 Rate in the first 6 months of renal failure in patients (of all indications) with ACE inhibitors

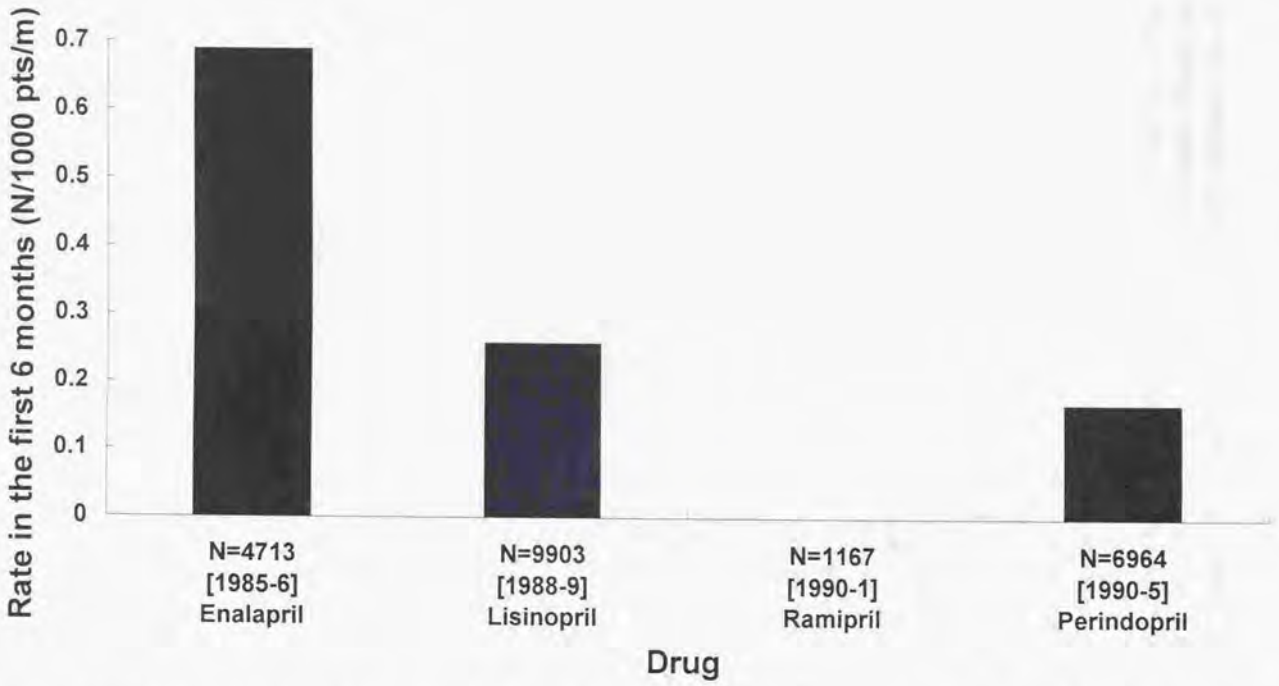


Figure 20 Rate in the first 6 months of renal failure in hypertensive patients with ACE inhibitors

The rate of renal failure during treatment with enalapril was calculated to be 6.5 per thousand patient-years of use of the drug. The corresponding rate for lisinopril is 3.9 per thousand patient-years. We believe that this may reflect a difference in the selection of patients, the newer drug being used in patients with less advanced cardiovascular disease. This is suggested by the fact that, during the first six months' treatment with enalapril there were 403 deaths (2.9 %) compared with 157 (1.3 %) in the lisinopril group during the same period.

However, the scenario seems to be a little more complicated. If the newer drug was used in patients with less advanced cardiovascular disease, the rates of other cardiovascular conditions (e.g., ischaemic heart disease) as well as that of renal failure might be expected to be higher with the older drug. However, when the rate of myocardial infarction, for example, recorded in green forms in the first 6 months irrespective of whether or not the patient continued the drug is compared between four ACE inhibitors, the decrease in the rate with time is not so remarkable (Figure 21) as compared to the decrease in the rate of renal failure (Figures 19 and 20). The rate of myocardial infarction is similar between four ACE-inhibitors except for perindopril where the rate is approximately half of that with other ACE-inhibitors. The same trend can be seen even when the rate is compared between selected patients with an indication of hypertension (Figure 22). The discrepancy of the pattern of the rates between renal failure (Figures 19 and 20) and myocardial infarction (Figures 21 and 22) suggests that the selection might be more specific than conceived by Inman when the lisinopril study was compared with the enalapril study[12]. One of the likely scenarios was that patients who had already had renal dysfunction rather than those who had in general advanced cardiovascular disease were specifically selected when enalapril was prescribed to the patients.

Captopril was the first ACE inhibitor marketed in the UK and it was known in as early as 1980 that this drug could cause proteinuria presumably through an autoimmune mechanism[133]. Enalapril was the second ACE inhibitor in the UK

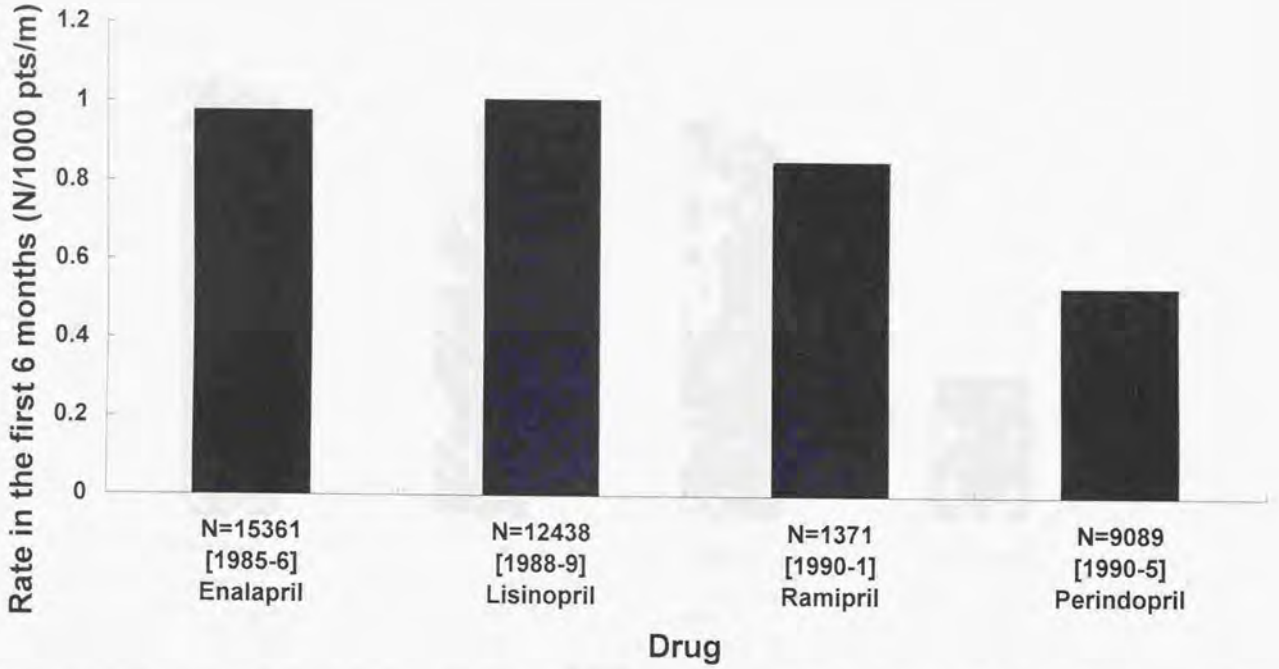


Figure 21 Rate in the first 6 months of myocardial infarction in patients (of all indications) with ACE inhibitors

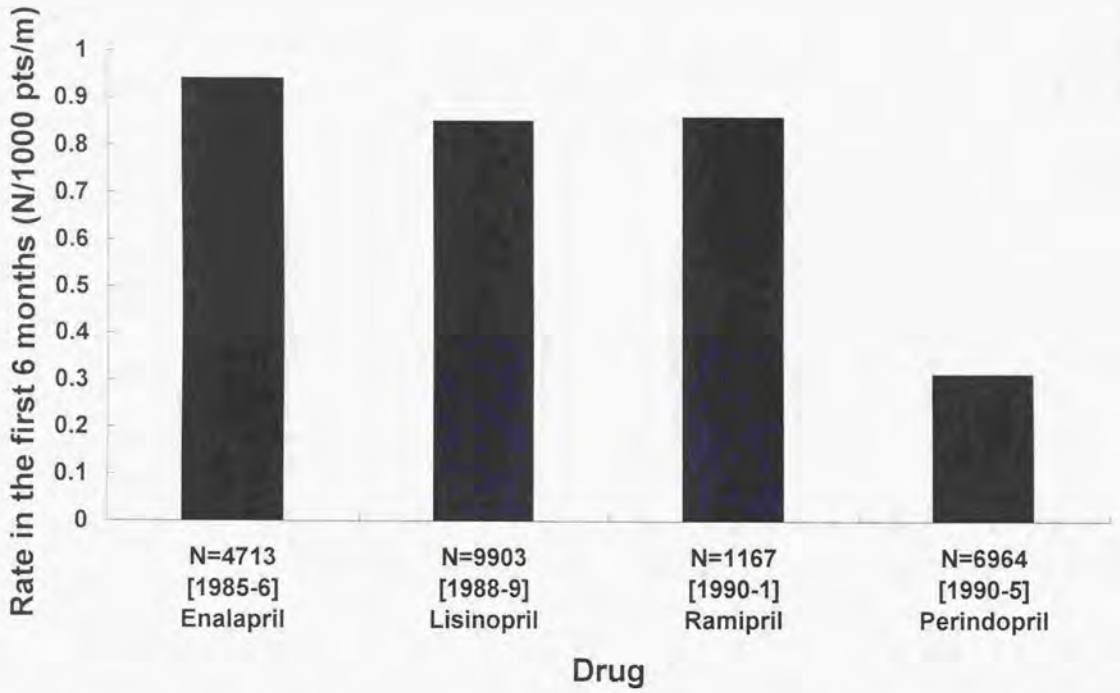


Figure 22 Rate in the first 6 months of renal failure in hypertensive patients with ACE inhibitors

and thought to be devoid of this side effect with captopril[134]. In addition, being different from captopril, 'renovascular hypertension' was one of the indications shown in the datasheet of enalapril when it was marketed in the UK for the first time as well as in the BNF available during the PEM study of enalapril as shown above. It might be not impossible that many doctors, as a result, thought enalapril was relatively safe for patients with renal dysfunction and preferentially prescribed enalapril to the patients who had already had renal dysfunction. Unfortunately, no direct evidence to support or deny this hypothesis can be obtained from the PEM study of enalapril.

No PEM study was conducted on captopril. Therefore, it is very difficult to guess what would have happened and whether the selection bias would have been easier to recognise if captopril had been studied as a concurrent control along with enalapril. However, even when no control was used or unable to use, if a simple question on the concomitant disease or concurrent abnormal condition was added to the green form, it might be not very difficult to recognise that the fraction of patients who had already had renal dysfunction was higher than expected. Another interesting measure would be obtained by the question on the duration of hypertension in case it was the indication of the drug in the individual patients. If the proportion of the patients who had already had renal dysfunction was higher than expected from the average duration of hypertension, this information might be used as an evidence suggesting that enalapril was selectively prescribed to the patients with renal impairment. In any case, however, the fraction of patients who already had renal dysfunction or who suffered from hypertension for certain years should be measured in the whole population. In other words, this kind of information is able to obtain only when it is included in all of the questionnaires used in the study unless the second questionnaire enquiring additional questions is sent to all of the doctors who have sent back the first questionnaire.

Even if more direct information on the selection bias had been available, the conclusion of the enalapril study, (i.e., enalapril had been associated with a deterioration in renal function in 75 cases and might contribute to the 10 deaths) would not have been largely altered. However, mentioning the selection bias, if possible, would have made the report more informative.

Logic behind signalling renal failure associated with enalapril

Even if the control drug was not used in the PEM study of enalapril, the first clue leading to signalling renal failure associated with enalapril was probably brought by an intuitive perception that the rate of renal failure was much higher than expected though the detailed follow-up study was done only for the patients who died. This perception was proven to be correct as shown in Figure 23. In Figure 23, the rate of renal failure with enalapril including both of the fatal and non-fatal cases is measured in hypertensive patients with enalapril and other drugs. The rate with enalapril is more than twice higher than any other drugs among nine cardiovascular drugs.

According to Strom and Melmon, there may be no need to randomise all studies of beneficial drug effects even if beneficial drug effects are often confounded by the indication[135]. According to them, there are three major categories where a randomised clinical trial (RCT) is not necessarily requisite. (1) If the course of a patient's disease is sufficiently predictable, the beneficial drug effects may be studied even in a single patient. (2) If the decision about whether to treat is based on some factor that may not be related to the outcome variable under study such as vaccination in healthy individuals, an RCT may be also not necessary. In addition, (3) if the indication can be sufficiently characterised, an RCT may be not necessary, though confounding by the indication may exist. A similar argument may hold true for the adverse effect. If confounding by the indication does not exist, the adverse effect may be studied without randomised control or even without any control. On the other hand, If the adverse effect is confounded by the indication, the study may be very difficult by the observational research unless the indication is sufficiently characterised.

Unfortunately, renal failure in the PEM study of enalapril was in fact heavily confounded by the indication and the magnitude of confounding was probably much bigger than that assumed when the report on the PEM study of enalapril was published[76,78]. In addition, the indication was not sufficiently characterised. For instance, in most patients with hypertension, no additional information on the indication was available so that whether or not the patients

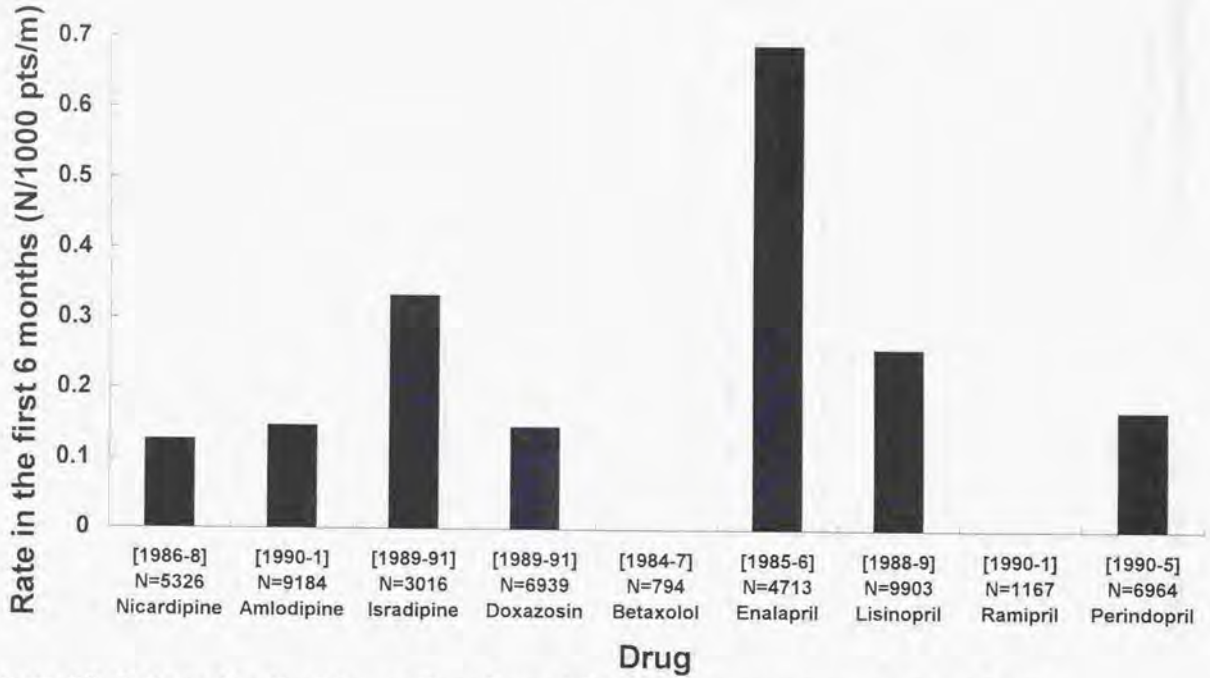


Figure 23 Rate in the first 6 months of renal failure in hypertensive patiens with antihypertensive drugs

with pre-existing renal dysfunction were selected could not be clarified.

Cough with enalapril

As detailed in a paper published in 1996 from the DSRU, cough induced by ACE-inhibitors had been unrecognised for several years since the first introduction of captopril in the late 1970s[77]. In 1982 two papers by Havelka et al. reported dry cough as an ADR to captopril[136,137] but cough induced by captopril described in these two papers and another paper published in 1983[138] was not widely accepted. A letter by Soseko and Kaneko from Japan[139] led a series of reports on dry persistent cough induced by captopril and enalapril from Australia[140], Canada[141], France[142] and UK[143,144] including one from the DSRU[78].

The letter on cough induced by enalapril from the DSRU[145] was based on the PEM study of enalapril and the signal strengthened the hypothesis raised by other authors[139-144]. In the letter, it was emphasised that cough recurred by rechallenge in 4 cases, two with enalapril and the other two with captopril[145]. In the full paper on the PEM study of enalapril published in 1988, it was described as a feature characterising enalapril-induced cough that cough persisted during treatment and disappeared after stopping enalapril[76]. In either of the two publications from the DSRU[76,145], the signal was raised by the comparison of cough between different periods of the same patient (e.g., while using the drug, after stopping the drug, and after rechallenge) but not by the comparison of the rate with other drug(s) nor with the magnitude of the rate expected. The logic used in those publications are not new at all. Rather, it has been repeated in the papers on a method for estimating the probability of ADR that rechallenge is normally regarded to be more informative than dechallenge and if the same event occurs by rechallenge, the probability of ADR is considered to be high[22,24]. However, in the daily clinical practice, the possibility of an ADR is rarely tested by rechallenge. Therefore, the 'on' vs. 'off' comparison may have a bigger chance to be used as a general method employed in various PEM studies. The method is classifiable as one of the 'within-drug' comparisons where a signal is raised from the feature observed within a single PEM study rather than a comparison between different PEM studies.

Appendix 5

Comparison of crude rates between drugs in PEM

The problems associated with the comparison of crude rates between drugs in PEM

In general, the comparison between groups is much more difficult in epidemiology than in clinical studies where the patients are randomised. In PEM, this point has been repeatedly emphasised. For example, in the front page preceding 'Contents' of some PEM reports prepared in house by the DSRU, the following warning is given in italic[81,146].

WARNING. *Seemingly large (e.g., more than threefold) differences in rates of events with apparently similar drugs may sometimes occur in a variety of circumstances, for example when there are differences in age or sex distribution, indication, dose, concurrent treatment, or timing of studies in relation to alterations in perception associated with publicity.*

For example, age and sex distribution differs between drugs. In Figures 24 and 25, 'Psychotropic' includes 7 psychotropic drugs (fluvoxamine, fluoxetine, paroxetine, sertraline, buspirone, flunitrazepam and zopiclone), 'CV' includes 10 cardiovascular drugs (diltiazem, nicardipine, amlodipine, isradipine, doxazosin, betaxolol, xamoterol, enalapril, lisinopril and ramipril), 'NSAIDs' include 3 NSAIDs (etodolac, nabumetone, tenoxicam), 'GI' includes 5 gastro-intestinal drugs (nizatidine, famotidine, omeprazole, cisapride and misoprostol), 'Antihistamines' include 3 antihistamines (acrivastine, cetirizine and loratadine), 'Asthma' includes 2 anti-asthmatics (nedocromil and salmeterol) and 'Anti-infectives' include 9 anti-infectives (acyclovir, cefixime, ciprofloxacin, enoxacin, norfloxacin, ofloxacin, azithromycin, fluconazole and itraconazole). Figure 24 shows that approximately the same number of female and male patients use cardiovascular, gastrointestinal and anti-asthmatic drugs but the number of female patients is bigger than that of male patients with other classes of drugs.

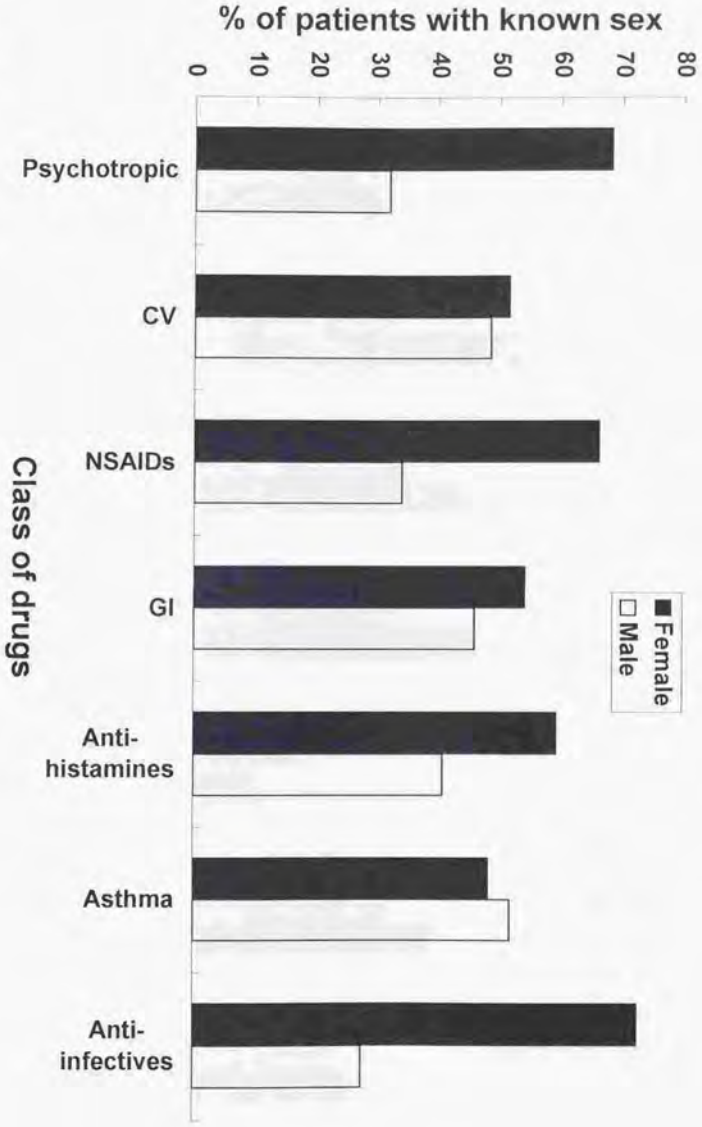


Figure 24 Sex distribution

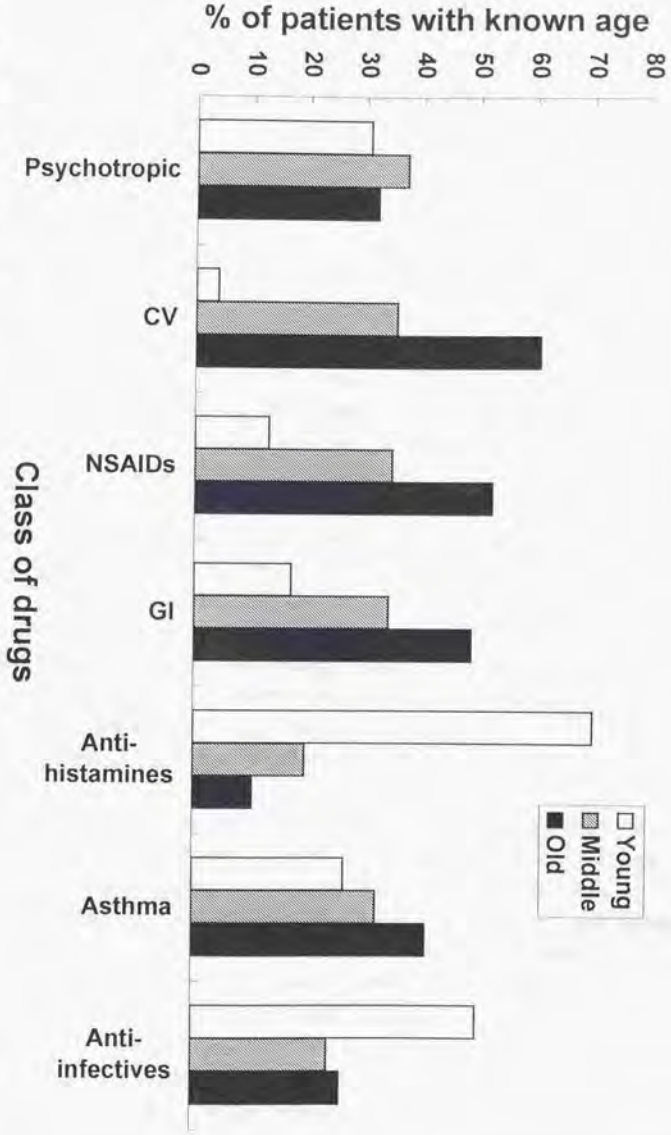


Figure 25 Distribution of age

Figure 25 shows that approximately the same number of young (less than 40 years old), middle (40 to 59 years old) and old (60 years or more) patients use psychotropic drugs, but more young patients are found with anti-histamines and anti-infectives. With other drugs (particularly, with cardiovascular drugs), old patients predominate.

The information on distribution of age and sex can be obtained relatively easily and reliably. It is possible to adjust the difference of age-sex distribution (and other known factors) between two or more drugs by some means (e.g., stratification, matching and the use of multivariate models[52-54]). However, in order to make such means work efficiently, the information on all of the major critical explanatory factors must be available. If it is likely that the information on some of major critical explanatory factors are lacking, the use of those methods including the use of the mathematical model is misleading[147]. As stressed earlier, in the analysis of the PEM data, it is very critical to make an allowance for factors other than age and sex. The factors critical in the analysis of the PEM data include indication (and its seriousness) of drug and concurrent illnesses and PEM may be improved in collecting more information on the indication and concurrent illnesses. However, if the indication is totally different between two drugs, any strategy to adjust the explanatory factors may not discriminate whether the difference of the rates between two drugs is due to the difference of the indication or that of the drug effect. Where two drugs share major indications, those two drugs may be in fact the members of the same class of drugs. In such a case, the publicity of an ADR common to the class may change with time as stressed in the 'warning' shown above while the publicity of an ADR is difficult to quantify. Figure 26 shows the first monthly rate of cough coded irrespective of whether the patient still uses the drug. The highest rates are observed with two ACE inhibitors (lisinipril, LPT, and ramipril, RMP) but the rate with enalapril (ELP) is small. The difference of the rate of cough between ACE inhibitors is almost certainly due to the change in the publicity of this ADR to the ACE inhibitors[77]. Figure 26 also shows that the rate of cough is high with nedocromil (NCM) used in patients with asthma and an antibiotic, cefixime (CXM), where one of major indications is chest infection. Cough with those two drugs are probably associated with their indications, asthma and chest infection, respectively, which are not shared by ACE-inhibitors where hypertension and cardiac failure are major indications.

Figure 26 The first monthly rate of cough with 41 PEM drugs

PEM may have some other limitations when obtaining the information on the explanatory factors. In PEM, study subjects are only those who have used one particular drug, and therefore, no information is available on the patients with no drug. Figure 27 shows the first monthly rates of headache with 41 PEM drugs. Headache is a common ADR and with 35 of 41 drugs (shown by closed columns), headache is described as an ADR to the drug in the BNF[61]. In such a case, the comparison of the rates (e.g., whether the rate is above or below the average) may be not useful in distinguishing whether or not 'headache' is an ADR to the drug.

Some of those weaknesses inherent to PEM may be not a big problem in other observational studies based on hospital-based or regional database such as GPRD[4,5]. In such database, it may be easier to obtain the information on the concurrent control and patients with no drug.

Opinions on the between-comparison of the crude rates within the DSRU

The between-drug comparison of crude rates with various drugs seems to have been used rather routinely in these two to three years in the DSRU. For example, in the editorial of an issue of *Pharmacoepidemiology and Drug Safety* presenting 10 PEM studies on various drugs, Dr. R.D. Mann, the editor of the journal and the director of the DSRU since January 1994 listed the rates of cough for top 5 drugs among 39 drugs to indicate the relationship between ACE-inhibitors and cough[148]. Five drugs include three ACE-inhibitors (enalapril, lisinopril and ramipril), cefixime and nedocromil (see Figure 26 as well). Similarly, ranking (top five drugs) is shown for many events in the PEM report on salmeterol prepared in July 1994[86] which is also published in *Journal of Clinical Epidemiology* in 1996[97]. In a recent paper on 5 antibiotics, the highest event rates among the 5 drugs are highlighted for several events[51].

Between-drug comparison is mentioned as a potentially effective method to identify possible ADRs also by Professor Inman in some PEM reports[30,81].

Experience with previously recognised acute adverse reactions

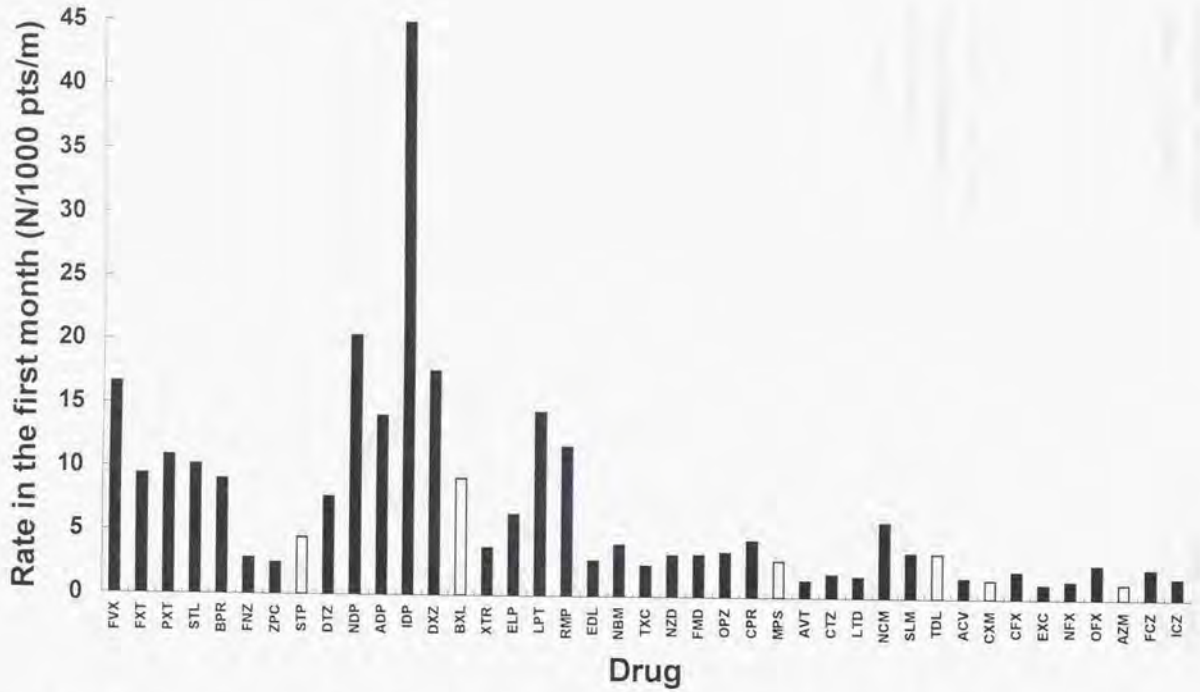


Figure 27 The first monthly rate of headache (closed column: known ADR)

has shown that there is usually at least a threefold difference between the first month rate and the rate in subsequent months of continued treatment with the same drug. This is also usually true when the first month rate is three or more times higher than the pooled rate for the same event with other drugs.

It seems that the opinion on the role of the between-drug comparison in the analysis of the PEM data has been not fixed within the DSRU. The opinion may have been altered within the individual researchers of the DSRU as well. However, the point that the between-drug comparison is sometimes very difficult so that one must be careful to employ this comparison to reach any reliable conclusion seems to have been eventually shared by all researchers in the DSRU. For instance, in the recent paper published from the DSRU more than 2 years after Dr. Mann has taken over directorship, the following point is stressed by the current researchers of the DSRU[51].

The limitations of PEM are that the statistical methods relevant to studies involving randomized allocation to treatment are inappropriate and comparisons between drugs have, therefore, to be made with care.

Role of the between-drug comparison in PEM

Between-drug comparison needs a great care in PEM particularly when generating 'signals'. If the event is a known ADR to a drug, that drug may be excluded from the comparison, but the drugs to be excluded by this reason will differ between events analysed. The dependence of the incidence on age or sex may also differ between events. Cardiovascular events are in general closely associated with cardiovascular drugs while psychological events are associated with psychotropic drugs. Therefore, drugs which are associated with the indication may differ between events. Many factors produce various influences with a different pattern among drugs compared being dependent on the nature of the event analysed. Therefore, the between-drug comparison may not be regarded as a good means of screening a lot events to pick up possible ADRs. It seems that in the DSRU the within-drug comparison has been

recognised as a better tool of screening a lot of events than the between-drug comparison though the issue is still under debate. The between-drug comparison may be more useful in scrutinising the possible ADRs pre-selected by the within-drug comparison or any other means. This will be particularly true if more information is available on the possible explanatory factors including concomitant diseases and severity of the indication.

Appendix 6

Within-drug comparison as a method for the initial screening in PEM

ADRs expected to be detected by PEM

In some textbook[3], PEM is evaluated as a system suitable for hypothesis-testing or strengthening rather than that for hypothesis-generating. It is true that the limitation exists in hypothesis-generating function of PEM. For instance, the green form is not sent to doctors until some fixed period (usually 6 to 12 months) after the patient begins to use the drug. Many of frequent ADRs are expected to be detected in the pre-marketing stage. If a doctor suspects an ADR so far unrecognised and reports it immediately to VRS in early postmarketing phase, this action will precede the date when the first questionnaire on that drug is sent back to the DSRU.

Nevertheless, PEM does have a hypothesis-generating function and is expected to exert this function particularly under some specific situation where an ADR which is not rare is not observed and/or missed in both of the pre-marketing studies and VRS in the early postmarketing phase. Although the amount of the information on the individual patients is relatively small in PEM as compared to that in GPRD[4,5] or databases in HMOs in the US[6,7], PEM has a unique feature that it can identify large number of patients relatively quickly so that more than 10,000 valid answers can be obtained on average within 2 years after the drug is marketed. Before the results are published, a preliminary report is made and circulated to relevant bodies such as the regulatory agency or pharmaceutical company within the first 6 months or even within shorter time period (e.g., 3 months) after receiving questionnaires sent back from GPs, though it depends on the magnitude of the drug use in the market. What PEM can do and is expected to do is, first of all, to overview or screen events reported from general practitioners carefully but quickly and not to miss any serious problems particularly those problems not having been identified or confirmed in the pre-marketing stage as well as early postmarketing phase. Before mentioning the method of screening events used in PEM, it may be important to consider what

type of ADRs are expected to be detected by PEM

There are at least five factors relevant to the problem when and by which means an ADR is suspected for the first time. The first factor is the magnitude of the rate. According to Jick[149], the rate of drug-induced illness may be classified as 'high' which is > 1/200/year (0.5 % per year), 'intermediate', and 'low' which is < 1/10,000/year (0.01 % per year). Most ADRs with the high rate is expected to be detected in the pre-marketing stage. If PEM detects new ADRs, the rate will be 'intermediate' or 'high' because a study on around 10,000 patients is usually unabale to detect an ADR with the rate which is 'low'. On the other hand, the rate of serious 'type B' ADRs are often 'low'[99]. This problem has been illuminated by Venning already in 1983 as follows in a paper where how 18 ADRs considered 'important' at that time are detected is addressed[150]:

--- it seems that this (a cohort approach) would almost certainly have been ineffective for these serious adverse reactions unless cohort sizes in excess of 100 000 users had been followed up, including long term observation in some instances.

However, this conclusion may be oversimplified. Of 18 'important' ADRs which Venning selected in his paper[150], at least three reactions (dermatitis due to practolol and keratoconjunctivitis due to practolol and SMON due to clioquinol) were not so rare that generating hypotheses on those ADRs would have required a cohort study with a size in excess of 100,000 users. The rate of these 3 may be classified as 'intermediate' or even 'high'. For instance, it is described in his paper that some of practolol-associated problems might have been detected if adverse events as distinct from suspected adverse reactions during the clinical trials had been recorded as there was a significant increase in eye complaints during practolol treatment established by a later study of just 71 patients[151].

The second factor may be the timing of onset of ADRs. Most pre-marketing clinical trials are conducted for short period only and therefore, late-onset ADRs may be not observed even if the rate is 'high'. The late-onset ADR has another problem that the relationship with the drug may be missed by doctors even if such a late-onset ADR does take place in individual patients as the drugs which

have been administered without problems for months are often excluded from the list of possible causative agents or mechanisms. Therefore, the chance is fair that a late-onset ADR is missed by VRS.

The third factor is whether an ADR occurs in some specific risk groups. If patients with some specific risk factors (age, sex, concomitant disease, use of co-medications which may interact with the drug of interest, etc.) are excluded from the pre-marketing clinical trials, this ADR may be observed only in the postmarketing phase where the rate of such ADRs may be 'high'.

The fourth factor is whether or not an ADR is unique. If an ADR is difficult to be distinguished from commonplace illnesses as with psoriasis-like eruption and dry eye induced by practolol[5-11], the reaction may be easily missed.

The fifth factor is whether or not an ADR is difficult to be distinguished from events occurring often as a consequence of the indication of the drug. For instance, cough induced by an ACE inhibitor is difficult to be distinguished from that due to heart failure which is one of the major indications of the drug[77].

ADRs expected to be detected by PEM may therefore include: a) ADRs with the 'intermediate' rate particularly when the reaction is difficult to recognise (e.g., mimicking commonplace illnesses or occurring often as a consequence of the indication), b) ADRs occurring in specific risk groups particularly when the reaction is difficult to recognise and c) late-onset ADRs. Some comments may be added to the late-onset ADRs. As discussed above, the late-onset ADR has a fair chance not to be observed in the pre-marketing stage and missed in early postmarketing phase even if the rate is high. When a late-onset ADR which is not trivial nor rare is missed for long, it may result in a disaster as with practolol syndrome or SMON. Nevertheless, as shown in the 'results' section in the text, all known ADRs with the rate more than 1.8 % per six months to 24 drugs examined in this thesis have a feature that the rate in the first month is larger than the monthly rate in the subsequent 5 months. This indicates that the late-onset ADR, particularly that with a high rate, is rather an exceptional phenomenon. It is of note that whether or not the method of comparing the first monthly rate with that in the subsequent 5 months examined in this thesis is effective in picking up the late-onset ADRs has been unknown

because the DSRU has not encountered many late-onset ADRs. In any case, the DSRU must be always alert to the possibility that any event coded preferentially in the late months is in fact a late-onset ADR.

Screening possible ADRs

To detect ADRs or generate a hypothesis, an examination by the experienced persons' eye is very important. However, various kinds of events are reported in one PEM study so that some algorithm or mechanical procedure may be helpful if it can pick up possible ADRs which will be then further examined to clarify whether there is any possibility that the event is an ADR. For instance, events which are by nature serious and often caused by a drug (e.g., some haematological events such as aplastic anaemia or agranulocytosis) may require further examination and follow-up even if just one case is reported. This procedure has been employed since early PEM studies though not systematically. For instance, particular attention has been paid to some important events (aplastic anaemia, leucopenia and thrombocytopenia, etc.) in early PEM studies[71,86]. However, it is since 1994 to 1995 that the list of 'serious events' used in the 'Yellow Card Scheme' operated by the CSM has been also used in PEM where those who code events in the DSRU watch whether any of reported events is one of the terms in the list so that serious events are immediately forwarded to researchers to urge a prompt and proper action (e.g., further enquiry).

However, the follow-up study is expensive and time-consuming. In addition, the extent of extra work accepted by doctors is limited. Therefore, the detailed examination of individual cases is possible only for a restricted number of patients with selected events. There is a need to develop other means which efficiently pick up possible ADRs irrespective of whether the event is serious or whether it is thought to be an ADR by doctors.

'On' vs 'off' comparison in PEM

One of the oldest ways used in PEM to find possible ADRs was to compare the

rate during the 'on' period when the patient continued the drug with the rate during the 'off' period when the patient had no longer taken the drug. The basic logic is similar to that in a cross-over study where each patient serves as his own control. The comparison was used for example in the early PEM studies on 5 NSAIDs, benoxaprofen, fenbufen, zomepirac, piroxicam and 'Osmosin' (indomethasin)[109]. Some ADRs were illuminated as those with the high 'on' rate as compared with the 'off' rate. For instance, when expressed as 'per 1000 patient-years', benoxaprofen showed the 'on' rate of 109 and 'off' rate of 2 for photosensitivity while both of the 'on' and 'off' rates with other 4 drugs were 5 or less[109]. Similarly, indomethacin had the 'on' rate of 71 and 'off' rate of 20 per 1000 patient-years for headache while both 'on' and 'off' rates for other 4 drugs were 18 per 1000 patient-years or less. Similar comparisons between the rates during 'on' and 'off' periods were employed in two other papers on the PEM studies of diltiazem[71] and nabumetone[86] published in 1990 where the ratio of the 'on' to 'off' rates was also shown for selected events though no criterion about what ratio would be critical was presented.

The method of 'on' vs 'off' comparison has been however abandoned at least because of two major reasons. One is described in a paper on PEM study of fluvoxamine as follows[40]:

> In previous studies we compared the frequency of events occurring during treatment with the frequency of events during the follow-up period. A limitation of this comparison is that, after treatment, patients attend their GPs less often and there are therefore fewer opportunities for the doctors to ask about their health and to record events.

The problem addressed here is that of reporting bias. Soon after a newly marketed drug is prescribed to a patient, both the doctor and patient will watch carefully what happens to the patient and there could be a large chance that every problem including minor one is recorded in the patient's notes. After the drug is stopped, attention may be not paid particularly to minor events and a chance that the event is recorded is decreased. In other words, the 'off' rate can be much smaller than the 'on' rate even if there is no real decrease in the rate and too many events which are in fact not associated with the drug may be

picked up if the ratio of the 'on' rate to 'off' rate is used. As long as I know, this problem was the major direct reason making Professor Inman give up the use of the 'on' vs. 'off' comparison. I believe that another reason raised later was not the direct driving force to make him abandon the 'on' vs 'off' comparison. Another reason is described in a PEM report prepared in house in the DSRU in January 1995 after he has retired from the DSRU in January 1994 as follows[152]:

> In the past we have attempted to signal possible adverse reactions by comparing the frequency of events that occur during treatment with the frequency in the same patients after they have stopped treatment. A major flaw in this comparison is that the treatment group includes patients who remain on treatment throughout the study period. They contribute no untreated or 'control' experience and they are the least likely to have experienced side-effects. A better comparison might be to compare the 'on' and 'off' treatment period only in those who had contributed roughly equal periods of event experience during ('on') and after stopping ('off') the drug.

The patients who continue to use the drug for the whole observation period are likely to differ from those who stopped the drug during the early period of treatment. The diagnosis would be likely to be correct in the patients who can benefit from the long use of the drug. The patients who use the drug for long period may be also characterised as those having experienced no serious or troublesome ADRs during the treatment. If the diagnosis was incorrect and the use of the drug was proven to be inappropriate, the patient might stop the drug early. Those who experienced ADRs may also stop the drug early. Therefore, the two rates to be compared cannot be considered to have been measured in the same population.

Though the 'on' vs 'off' comparison has been no longer employed since 1993, the use of this comparison could be reasonable and efficient particularly for the drug which is used normally for short period only (for example just 7 days) such as antibiotics. For such drugs, two mechanisms given above which may become obstacles to the use of 'on' vs 'off' comparison may be not problematic. When the drug is used just for days, both the doctor and patient may still

carefully watch what happens even after stopping the drug and the information during the 'off' period may be more reliable. In addition, the information can be obtained for both 'on' and 'off' periods for almost all patients when the drug is used only for short period. However, if the drug is used for a short period only, some days after stopping the drug may be included into the 'on' period. This is because some ADR may appear only certain period (days or even weeks) after starting the drug and if the drug is used for few days, a chance is high that the ADR appears after the drug is stopped.

Comparison between the rate in the first month (T1) and that in the subsequent months (T2)

The idea of the use of the comparison between the event rate in the first month after the first prescription of the drug and that measured in subsequent months is probably not very new. For instance, in a paper on the methodology of PEM published in 1990, Rawson, Pearce and Inman wrote as follows mentioning the PEM study on enalapril[41].

Trends across the 12 months can also be assessed on a month-by-month basis. For example, the high rates of dizziness and headache occurring during the first month after the initial prescription as compared with those recorded during the subsequent 11 months are illustrated in ---

In this description, it is emphasised that some ADRs have the pattern that the first monthly rate is much higher than the monthly rate in subsequent months. In fact, the difference between these two rates (i.e., the first monthly rate and the monthly rate in subsequent 11 months) and 99 % confidence interval for the difference were already given in the paper on enalapril published in BMJ in 1988[76].

To compare the rate in the first month with that in the succeeding months, it is of critical importance to know when the prescription has been issued for the first time. In PEM, this information is relatively reliable because of several reasons. Each PEM study is conducted soon after a new drug is marketed. The first

prescription cannot be issued before the date of marketing. An effort is made to identify the first prescription prescribed to each patient. In the questionnaire sent to doctors, they are asked to give the date of the first prescription and if the date reported is earlier than the date of the first prescription already confirmed in the DSRU, the date is corrected as that reported. If the date reported by the doctor is later than the date of the first prescription already confirmed in the DSRU, the latter is used because it is likely that the date reported by the doctor is by some reason incorrect in such a case. In addition, the date of the first prescription is known for all of the patients because at least one prescription, where the date is an essential feature, should have been found before a patient is identified.

The first of the series of reports on PEM studies where the comparison between the rates in two periods is used as a main method to pick up possible ADRs is that reporting the results of the PEM study of fluvoxamine[40]. Though this paper is published in 1994 apparently later than a series of 10 papers on other PEM studies published in *Pharmacoepidemiology and Drug Safety* in 1993[30-39], the method used may be rated as the 'first version' of the method. In the report on the PEM study of fluvoxamine, Edwards, Inman, Wilton and Pearce wrote[40]:

--- we have progressed in this study to the method of comparing the rates of events during the first month of treatment with the mean rates for the second to sixth month of treatment. Practical experience of more than 20 drugs has shown that, provided the rate during the first month is 1 or more per 1000 patients and the month 1:2-6 rate ratio is 3 or more, almost all recognised adverse reactions are signalled. Some events that are probably drug-related have been signalled by ratios of 2.5 or more, but with lower ratio it is generally not possible to confirm a cause and effect relationship.

In this report, both of the first monthly rate (T1) and the monthly rate in subsequent months (T2) were estimated in the patients treated by the drug. In other words after the patient stopped the drug, the event was not counted and the duration under observation was not included in the denominator to estimate the event rate. When translated into the wording used in the statistics, the

patient is regarded 'censored'[153,154] when the patient stops the drug even if the patient is still observed.

It may be of note that the rate during the second period (T2) was calculated using the data during the five months (i.e., from the second to sixth month) in this report[40] but not during the 11 months (i.e., from the second to twelfth month) as in the report on the PEM study of enalapril[76]. The reason why the method of calculation has been altered is not mentioned explicitly in any publication, but, the reason is probably the same as the first of the two reasons why the 'on' vs 'off' comparison has been abandoned as given above; i.e., the information long after the first prescription is issued to the patient will become less reliable.

The way of calculating the first monthly rate (T1) and the monthly rate in subsequent months (T2) has been further altered soon. In the 'second version' of the method, similar to the 'first version' of the method, the rate during the first month (T1) and the monthly rate during the subsequent 5 months (T2) were estimated but done so irrespective of whether or not treatment had been continued[30]. In other words, the patient is 'censored' only when the patient is lost to follow-up or no longer under observation by the doctor. During the first six months, the patient is normally not 'censored' because the questionnaire is sent 6 to 12 months after the first prescription of the drug so that in almost all PEM studies, every patient is observed at least for 6 months. Therefore, if the rates are compared between the patients irrespective of whether or not treatment has been continued, the comparison is done within the same population. The reason why the definition of denominator has been changed is also not given explicitly in any publication but there seem to be at least two major reasons. The first reason is the same as that give as the second of the two reasons why the 'on' vs 'off' comparison has been abandoned. The profiles of the population who continue to use the drug will change with time (because patients may stop the drug early when they have some specific reasons such as misdiagnosis) so that the two rates (T1 and T2) may be estimated in the populations with different profiles. The second reason is associated with the estimation of the background rate. If the event is not associated with either of the drug or indication, the event rate may be used to estimate the 'background' rate. In such a case, there is no reason to exclude those not treated by the drug. Particularly when the population who continue to use the drug shrink

rapidly, the rate may be less reliable when estimated in the population treated by the drug.

Some confusion about the estimation of the rate ratio

After the 'second version' of the method of comparison of the two rates (T1 and T2) is used, the method has been explained in the PEM reports as follows[30]:

Adverse reactions tend to occur early, most commonly during the first month after the initial prescription. Although many different comparisons are possible, one of the most useful is the comparison of the rates of events during the first month of treatment with the rates for the same events during the subsequent follow-up period, irrespective of whether or not treatment is continued. ---- Experience has shown that, where the rate ratios exceed 3.0, the events are either the result of a reaction to the drug, or a sign or symptom of the disorder being treated. Sometimes, the rate during the period T2 is reduced as a result of successful treatment. For Example the frequency of headache may diminish as a response to an analgesic.

At least during some days of the first period where the first monthly rate (T1) is estimated, the patient used the drug, and particularly when the drug is normally used for a long period, the decrease in the population who continue to use the drug is not remarkable during the first month. When the rate estimated in the subsequent months (T2) estimated irrespective of whether the treatment is continued is smaller than T1, there could be two main mechanisms accounting for this reduction. The rates of some events including acute ADRs may decrease as time elapses even if all of the patients continue to use the drug until the last day of the second period. However, other mechanism can underlie the decrease in the event rate. Even if the rate of the event does not change with time provided that the patient continues the drug , T2 could be smaller than T1 if the event does not occur after stopping the drug and if the substantial fraction of the patients have stopped the drug during the early period. In this case, the magnitude of the decrease in the rate would be dependent on the fraction of the

patients who stopped the drug early during treatment. If the second mechanism prevails, the rate ratio of T1 to T2 is determined by factors which are not necessarily inherent to the drug effect. The duration of drug treatment may be dependent on how the patients were selected. For instance, average years of the disease before treatment, severity of disease and/or concurrent illnesses may affect the average duration of treatment and those factors may be in tern determined by other issues such as whether other drugs of the same class have been already available in the market. The duration of treatment may be also dependent on some ADRs of the drug unrelated to the event of interest if one of such ADRs could make many patients stop the drug early during the treatment.

In many cases, it is likely that the rate ratio of T1 to T2 is in fact determined by both of the above two mechanisms, the rate ratio inherent to the drug which would be observed in the population where all patients use the drug till the last day of observation, and, the duration of treatment. However, at least when the method was advocated for the first time, it was probably assumed that the method would apply to the rate ratio inherent to the drug only and the method was not employed unless it was found that certain fraction of patients continued the drug for long period. For instance, of the 10 PEM reports published in 1993 in *Pharmacoepidemiology and Drug Safety*[30-39], the rate ratio method is used only in the six reports while in the three reports on antiinfectives (fluconazole, itraconazole and ciprofloxacin)[32,33,36] and one on a hypnotic, zopiclone[38] which may be used intermittently by the patients, the method is not employed.

Later, after Professor Inman retired, the method was modified and used for antiinfectives[51]. For most antiinfectives studied and analysed in PEM, the duration of treatment was 7 days or less. The comparison has been done using the rate in the first week rather than first month and that in the subsequent 5 weeks rather than 5 months. This new method divides the period of study into the first period which includes almost all patients treated by the drug and the second period where almost all patients are not treated by the drug. The results of the comparison between this new method of analysing weekly rates and the 'conventional' method of analysing monthly rates are shown in Tables 34-36 in this thesis.

Appendix 7

Comparison between T1 and T2: A guidepost but not a proof

Statistical test and rate ratio method

In 1990 Rawson, Pearce and Inman wrote[41]:

> Classical statistical significance tests do not have a major role to play in such analyses (comparison between T1 and T2) because due to the nature of PEM (the DSRU cannot decide which patients are to take which drugs or for how long) there are, as discussed above, several potential biases (e.g., surgery attendance, non-response and recording biases) and confounders (e.g., different indications for treatment and substitute or concomitant therapy) which may affect the quality of the data. In such situations, frequentist statistical methods are inappropriate because the underlying assumptions made about the procedures used to collect the data are invalid. --- The medical significance and interpretation of PEM data are more important than statistical significance. --- if false alarms are not to be raised, an examination of statistical significance alone is insufficient.

Not just in PEM but in epidemiology in general the indiscriminate use of statistical significance test has been warned. For example, Clayton and Hills described[52]:

> In epidemiology, which is not an experimental sciences the usefulness of the idea (of statistical significance test) has been particularly questioned. Undoubtedly the idea of statistical significance testing has been overused, at the expense of the more useful procedures for estimation of parameters ---.

Indeed in the PEM report of enalapril[76] and in the recent report by Rawson[155], the confidence interval of the difference of the rates (T1 and T2) are shown but no statistical significance test has been employed.

However, it seems that the problem encountered in the analysis of the PEM study is not so simple that every difficulty is settled just by precluding the statistical significance test. If one or a few events have been already selected as those to be studied more in depth and if the statistical significant test is inappropriate, the test may be simply avoided. However, in the first step of analysis, some events which are possible ADRs need to be selected for further study. When the number of the PEM studies to be analysed is increased to make the researchers very busy while a lot of events have been coded in each study, the use of some algorithm or mechanical procedure to select possible ADRs is mandatory as manual handling of large amount of data is mistakable and some automatic method will be, if used judiciously as an adjunct to other methods, of great help not to miss any serious problems. Indeed 10 PEM reports published in *Pharmacoepidemiology and Drug Safety* in 1993[30-39] would be impossible without a computer calculation scheme to select events which have the rate ratio of 2.5 or more. Nevertheless, in exactly the same context as that which warns the use of the statistical significant test in PEM[41], the use of 2.5 or 3.0 as critical value could be criticised to be one which is dangerous. Due to the nature of PEM, the medical significance and interpretation of PEM data are more important than the rule of '3.0' and the overuse of such criteria may be misleading.

The empirical rule of thumb of critical rate ratio '3.0' (or '2.5') and the statistical test share some common features. Both are used for judgement and the critical criteria conventionally used (e.g., rate ratio 3.0 or p value 0.01) are arbitrary. In fact the rate ratio method and statistical significant test is mutually translatable as shown in the 'methodology' and 'results' sections. If some fixed value of '3.0' or '2.5' is used, the criterion of '3.0' or '2.5' corresponds to the statistical test using various p values. If a fixed p value is used such as $p \leq 0.01$, this test corresponds to the various critical values of the rate ratio. Both can pick up events for further study and events selected by one method may overlap with those by the other method but both suffer from the problems inherent to the nature of PEM. One must be very careful to examine the possibility that events

not picked up by any method are in fact an ADR. In this regard, both methods may be used simultaneously as one method may pick up the event which may be not picked up by the other method as shown in the 'results' section. It is of note that some of frequent known ADRs are missed when only the rate ratio method is used (see the 'results' section).

Comparison between T1 and T2 is a guidepost but not a proof of an ADR

The comparison between T1 and T2 is an index to be used to find possible ADRs but it does not serve as evidence to support any causal relationship between the drug and event. The comparison between T1 and T2 is associated with time-lag or 'incubation period' between the start of exposure and occurrence of the event which is however not an essential aspect of the causal relationship. For instance, Fletcher et al raise 1) temporality, 2) strength, 3) dose-response, 4) reversibility, 5) consistency, 6) plausibility, 7) specificity and 8) analogy as aspects important in evaluating the causal relationship[156]. Though different authors raise somewhat different aspects as important ones[21,117,157-159], time-lag or 'incubation period' is never considered to be essential for the evaluation of the causal relationship. The between-drug comparison (related to 'strength' above) and the 'on' vs 'off' comparison (related to 'reversibility' above) may serve as a piece of evidence to support the relationship. For instance, if an event occurs in the patients who take a particular drug while no event occurs in the patients who do not take that drug, this may be raised as evidence to support a possible causal relationship. This is particularly so if factors other than the drug are controlled. Even if they are not controlled, the magnitude of the possibility that the event is an ADR will be increased when there is plenty of evidence showing that any other factors are unlikely to explain such difference observed between drugs. Similarly, if the event occurs only during patients take the drug but no event occurs during they do not, this may be also widely recognised to be some evidence to support the relationship between the drug and event particularly if other explanation is hard to exist. The dependence of the rate with dose is another evidence to support a causal relationship (i.e., 'dose-response' above).

As shown in the 'results' section, the comparison of T1 and T2 does pick up

events which have been proven to be an ADR effectively. However, It may be realised that once events are selected as possible ADRs by the comparison between T1 and T2 irrespective of whether the method used is the rule of thumb of '3.0' or statistical test, this possibility should be further examined by one or more of the other methods which provide more direct evidence to support the causal relationship.

	A	B	C
1	EVENT	Original Description	
2	**Skin**		
3	Acne		
4	Acne@	ACNE	G
5	Acne rosacea	ACNE ROSACEA	G
6	Alopecia	ALOPECIA	F
7	Atrophy skin	ATROPHY SKIN	F
8	Cyst sebaceous	CYST SEBACEOUS	F
9	Darier's disease	DARIERS DISEASE	F
10	Dermatitis	DERMATITIS	F
11	Dermatitis contact	DERMATITIS CONTACT	F
12	Dry skin	DRY SKIN	F
13	Eczema		
14	Eczema@	ECZEMA	G
15	Eczema atopic	ECZEMA ATOPIC	G
16	Intertrigo	INTERTRIGO	G
17	Neurodermatitis	NEURODERMATITIS	G
18	Pompholyx	POMPHOLYX	G
19	Eczema varicose	ECZEMA VARICOSE	F
20	Eruption bullous		
21	Blister	BLISTER	G
22	Dermatitis herpetiformis	DERMATITIS HERPETIFO	G
23	Eruption bullous@	BULLOUS ERUPTION	G
24	Pemphigoid	PEMPHIGOID	G
25	Pemphigus	PEMPHIGUS	G
26	Erythema	ERYTHEMA	F
27	Erythema multiforme	ERYTHEMA MULTIFORME	F
28	Erythema nodosum	ERYTHEMA NODOSUM	F
29	Erythroderma		
30	Dermatitis exfoliative	DERMATITIS EXFOL	G
31	Erythroderma@	ERYTHRODERMA	G
32	Erythromelalgia	ERYTHROMELALGIA	F
33	Fixed eruption	FIXED ERUPTION	F
34	Folliculitis	FOLLICULITIS	F
35	Granuloma	GRANULOMA	F
36	Granuloma annulare	GRANULOMA ANNULARE	F
37	Granuloma pyogenic	GRANULOMA PYOGENIC	F
38	Granulomatosis	GRANULOMATOSIS	F
39	Haematoma nail	HAEMATOMA NAIL	F
40	Hair change	HAIR CHANGE	F
41	Hair ingrown	HAIR INGROWING	F
42	Hair loss	HAIR LOSS	F
43	Henoch-Schonlein purpura	HENOCH-SCH PURPURA	F
44	Herpes simplex, skin	HERPES SIMPLEX 1	F
45	Herpes zoster	HERPES ZOSTER	F
46	Hirsutism	HIRSUTISM	F
47	Hyperkeratosis		
48	Hyperkeratosis@	HYPERKERATOSIS	G
49	Ichthyosis	ICHTHYOSIS	G
50	Pityriasis	PITYRIASIS	G
51	Infection skin, unspecified/local bacterial		
52	Abscess skin	ABSCESS SKIN	G
53	Cellulitis	CELLULITIS	G
54	Erysipelas	ERYSIPELAS	G
55	Impetigo	IMPETIGO	G
56	Infection skin	INFECTION SKIN	G
57	Paronychia	PARONYCHIA	G
58	Sycosis barbae	SYCOSIS BARBAI	G
59	Leprosy	LEPROSY	F
60	Lice	LICE	F
61	Lichen planus	LICHEN PLANUS	F
62	Lichen sclerosus	LICHEN SCLEROSIS	F
63	Lupus discoid	LUPUS DISCOID	F
64	Molluscum contagiosum	MOLLUSCUM CONTAG	F
65	Nail change		
66	Koilonychia	KOILONYCHIA	G
67	Nail change@	NAIL CHANGE	G
68	Nail ingrown	NAIL INGROWING	G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
69	Onychia	ONYCHIA	G
70	Onychogryphosis	ONYCHOGRYPHOSIS	G
71	Onycholysis	ONYCHOLYSIS	G
72	Onychomycosis	ONYCHOMYCOSIS	F
73	Photosensitivity	PHOTOSENS	F
74	Pigmentation	PIGMENTATION	F
75	Pressure sore	PRESSURE SORE	F
76	Pruritus		
77	Pruritus@	PRURITUS	G
78	Pruritus ani	PRURITUS ANI	G
79	Pruritus vulvae	PRURITUS VULVAE	G
80	Psoriasis	PSORIASIS	F
81	Purpura	PURPURA	F
82	Pyoderma gangrenosum	PYODERMA GANGRENOSUM	F
83	Rash	RASH	F
84	Rhinophyma	RHINOPHYMA	F
85	Scabies	SCABIES	F
86	Scarlet fever	SCARLATINA	F
87	Scleroderma		F
88	Scleroderma@	SCLERODERMA	
89	Scleroderma [F]	SCLERODERMA[F]	
90	Seborrhoea		
91	Dandruff	DANDRUFF	G
92	Seborrhoea@	SEBORRHOEA	G
93	Sezary syndrome	SEZARY	F
94	Sinus pilonidal	SINUS PILONIDAL	F
95	Sore skin	SORE SKIN	F
96	Stevens-Johnson syndrome	STEVENS JOHNSON	F
97	Tinea	TINEA	F
98	Ulcer skin	ULCER SKIN	F
99	Ulcer varicose	ULCER VARICOSE	F
100	Ulcer varicose haemorrhagic	ULCER VARICOSE HAEM	F
101	Urticaria	URTICARIA	F
102	Vitiligo	VITILIGO	F
103	Weber-Christian disease	WEBER-CHRISTIAN	F
104	**Musculoskeletal**		
105	Abscess muscle	ABSCESS MUSCLE	F
106	Amyotrophy diabetic	AMYOTROPHY DIABETIC	F
107	Arthritis	ARTHRITIS	F
108	Arthritis psoriatic	ARTHRITIS PSORIATIC	F
109	Arthritis rheumatoid		
110	Arthritis rheumatoid*		G
111	Arthritis rheumatoid@	ARTHRITIS RHEUM	
112	Arthritis rheumatoid[F]	ARTHRITIS RHEUM[F]	
113	Felty's syndrome	FELTYS	G
114	Still's disease	STILLS	G
115	Atrophy muscle	ATROPHY MUSCLE	F
116	Bone abnormal	BONE ABNORMAL	F
117	Bursitis		
118	Bursitis @	BURSITIS	G
119	Bursitis knee	BURSITIS KNEE	G
120	Bursitis olecranon	BURSITIS OLECRANON	G
121	Bursitis toe	BURSITIS TOE	G
122	Calcaneal spur	CALCANEAL SPUR	F
123	Capsulitis	CAPSULITIS	F
124	Chondrocalcinosis	CHONDROCALCINOSIS	F
125	Chondromalacia	CHONDROMALACIA	F
126	Cramp	CRAMP	F
127	Cyst Baker's	CYST BAKERS	F
128	Disc prolapsed	DISC PROLAPSED	F
129	Dupuytren's contracture	DUPUYTRENS	F
130	Effusion joint	EFFUSION JOINT	F
131	Ehlers-Danlos syndrome	EHLERS-DANLOS	F
132	Exostosis heel	EXOSTOSIS HEEL	F
133	Fracture spontaneous	FRACTURE SPONT	F
134	Frozen shoulder	FROZEN SHOULDER	F
135	Ganglion	GANGLION	F
136	Haemarthrosis	HAEMARTHROSIS	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
137	Infection bone	INFECTION BONE	F
138	Lumbago	LUMBAGO	F
139	Muscle weakness	MUSCLE WEAKNESS	F
140	Muscular dystrophy		F
141	Muscular dystrophy@	MUSCULAR DYSTROPHY	
142	Muscular dystrophy[F]	MUSCULAR DYSTROPH[F]	
143	Myalgia	MYALGIA	F
144	Myasthenia gravis	MYASTHENIA GRAVIS	F
145	Myopathy	MYOPATHY	F
146	Myositis	MYOSITIS	F
147	Necrosis bone	NECROSIS BONE	F
148	Nerve entrapment		
149	Carpal tunnel syndrome	CARPAL TUNNEL	G
150	Nerve entrapment@	NERVE ENTRAPMENT	G
151	Tarsal tunnel syndrome	TARSAL TUNNEL	G
152	Osgood-Schlatter disease	OSGOOD-SCHLATTER	F
153	Osteoarthritis	ARTHRITIS OSTEO	F
154	Osteochondritis	OSTEOCHONDRITIS	F
155	Osteochondrosis	OSTEOCHONDROSIS	F
156	Osteomyelitis		F
157	Osteomyelitis@	OSTEOMYELITIS	
158	Osteomyelitis[F]	OSTEOMYELITIS[F]	
159	Osteoporosis		F
160	Osteoporosis@	OSTEOPOROSIS	
161	Osteoporosis[F]	OSTEOPOROSIS[F]	
162	Paget's disease	PAGETS	F
163	Pain back	PAIN BACK	F
164	Pain bone	PAIN BONE	F
165	Pain groin	PAIN GROIN	F
166	Pain joint		
167	Pain joint@	PAIN JOINT	G
168	Rheumatism	RHEUMATISM	G
169	Pain limb	PAIN LIMB	F
170	Pain neck	PAIN NECK	F
171	Plantar fasciitis	PLANTAR FASCIITIS	F
172	Polymyalgia rheumatica	POLYMYALGIA RHEUM	F
173	Reiter's syndrome	REITERS SYNDROME	F
174	Rotator cuff	ROTATOR CUFF	F
175	Sciatica	SCIATICA	F
176	Scoliosis	SCOLIOSIS	F
177	Spasm muscular	SPASM MUSCULAR	F
178	Spondylitis	SPONDYLITIS	F
179	Spondylitis ankylosing	SPONDYLITIS ANKYL	F
180	Spondylitis cervical	SPONDYLITIS CERVICAL	F
181	Spondylolisthesis	SPONDYLOLISTHESIS	F
182	Spondylosis	SPONDYLOSIS	F
183	Spondylosis cervical	SPONDYLOSIS CERVICAL	F
184	Swelling joint	SWELLING JOINT	F
185	Synovitis	SYNOVITIS	F
186	Tendinitis	TENDINITIS	F
187	Tennis elbow	TENNIS ELBOW	F
188	Tenosynovitis	TENOSYNOVITIS	F
189	Tietze's syndrome	TIETZES	F
190	Torticollis	TORTICOLLIS	F
191	Trigger finger	TRIGGER FINGER	F
192	Tuberculosis bone	TB BONE	F
193	**Psychiatric**		
194	Aggression	AGGRESSION	F
195	Agitation	AGITATION	F
196	Alcoholism		
197	Alcoholism#[F]		
198	Alcohol withdrawal	ALCOHOL WITHDRAWAL	G
199	Alcoholism *		G
200	Alcoholism@	ALCOHOLISM	
201	Alcoholism[F]	ALCOHOLISM[F]	
202	Alcoholism acute	ALCOHOLISM ACUTE	G
203	Alcoholism chronic*		G
204	Alcoholism chronic@	ALCOHOLISM CHRONIC	

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
205	Alcoholism chronic[F]	ALCOHOLISM CHRON[F]	
206	Anxiety		
207	Aerophagia	AEROPHAGIA	G
208	Anxiety@	ANXIETY	G
209	Da Costa's syndrome	DA COSTAS	G
210	Hyperventilation hysterical	HYPERVENT HYSTERICAL	G
211	Anxiety/depression	ANXIETY/DEPRESSION	F
212	Behaviour abnormal	BEHAVIOUR ABNORMAL	F
213	Cachexia		F
214	Cachexia@	CACHEXIA	
215	Cachexia[F]	CACHEXIA[F]	
216	Confusion	CONFUSION	F
217	Delusion	DELUSIONS	F
218	Dementia		
219	Dementia#[F]		
220	Alzheimer's disease*		G
221	Alzheimer's disease@	ALZHEIMERS	
222	Alzheimer's disease[F]	ALZHEIMERS[F]	
223	Dementia@	DEMENTIA	G
224	Dementia presenile	DEMENTIA PRESENILE	G
225	Dementia senile*		G
226	Dementia senile@	DEMENTIA SENILE	
227	Dementia senile[F]	DEMENTIA SENILE[F]	
228	Depersonalization	DEPERSONALIZATION	F
229	Depression		
230	Depression@	DEPRESSION	G
231	Depression manic	DEPRESSION MANIC	G
232	Depression menopausal	DEPRESSION MENOPAUSE	G
233	Depression postnatal	DEPRESSION POSTNATAL	G
234	Dermatitis artefacta	DERMATITIS ARTEFACTA	F
235	Dreams abnormal	DREAMS ABNORMAL	F
236	Eating disorder		
237	Anorexia nervosa	ANOREXIA NERVOSA	G
238	Bulimia nervosa	BULIMIA NERVOSA	G
239	Euphoria	EUPHORIA	F
240	Formication	FORMICATION	F
241	Globus hystericus	GLOBUS HYSTERICUS	F
242	Grief reaction	GRIEF REACTION	F
243	Hallucination	HALLUCINATIONS	F
244	Homicide	HOMICIDE	F
245	Hyperactive	HYPERACTIVE	F
246	Hypochondriasis	HYPOCHONDRIASIS	F
247	Hypomania	HYPOMANIA	F
248	Hysteria	HYSTERIA	F
249	Insomnia	INSOMNIA	F
250	Irritability	IRRITABILITY	F
251	Libido decreased	LIBIDO DECREASED	F
252	Malaise, lassitude		
253	Lassitude	LASSITUDE	G
254	Malaise	MALAISE	G
255	Mania	MANIA	F
256	Mood change		
257	Mood change@	MOOD CHANGE	G
258	Mood swings	MOOD SWINGS	G
259	Neurosis	NEUROSIS	F
260	Obsession/compulsive	OBSESSION/COMPULSIVE	F
261	Panic attack	PANIC ATTACK	F
262	Paranoia	PARANOIA	F
263	Phobia		
264	Agoraphobia	AGORAPHOBIA	G
265	Cancer phobia	CANCER PHOBIA	G
266	Claustrophobia	CLAUSTROPHOBIA	G
267	Phobia@	PHOBIA	G
268	Pseudocyesis	PSEUDOCYESIS	F
269	Psychosis	PSYCHOSIS	F
270	Schizophrenia	SCHIZOPHRENIA	F
271	Self injury	SELF INJURY	F
272	Senility		F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
273	Senility@	SENILITY	
274	Senility[F]	SENILITY[F]	
275	Solvent abuse	SOLVENT ABUSE	F
276	Somnambulism	SOMNAMBULISM	F
277	Suicidal thought	SUICIDAL THOUGHTS	F
278	Suicide attempt, drug overdose		
279	Suicide attempt, drug overdose#[F]		
280	Overdose*		G
281	Overdose@	OVERDOSE	
282	Overdose[F]	OVERDOSE[F]	
283	Overdose other drug*		G
284	Overdose other drug@	OVERDOSE OTHER DRUG	
285	Overdose other drug[F]	OVERDOSE OTHER DRUG[F]	
286	Overdose unknown drug*		G
287	Overdose unknown drug@	OVERDOSE UNKNOWN DRUG	
288	Overdose unknown drug[F]	OVERDOSE UNKNOWN DRUG[F]	
289	Suicide attempt*		G
290	Suicide attempt@	SUICIDE ATTEMPT	
291	Suicide attempt[F]	SUICIDE ATTEMPT[F]	
292	Suicide threat	SUICIDE THREAT	G
293	Tics	TICS	F
294	**Central and Peripheral Nervous System**		
295	Abscess brain	ABSCESS BRAIN	F
296	Amnesia	AMNESIA	F
297	Aphasia, dysphasia		
298	Aphasia	APHASIA	G
299	Dysphasia	DYSPHASIA	G
300	Ataxia	ATAXIA	F
301	Atrophy brain	ATROPHY BRAIN	F
302	Bell's palsy	BELLS PALSY	F
303	Brown-Sequard syndrome	BROWN-SEQUARD	F
304	Burning sensation	BURNING SENSATION	F
305	Catalepsy	CATALEPSY	F
306	Cerebral palsy	CEREBRAL PALSY	F
307	Coma	COMA	F
308	Convulsion, epilepsy		
309	Convulsion, epilepsy#[F]		
310	Convulsion*		G
311	Convulsion@	CONVULSION	
312	Convulsion[F]	CONVULSION[F]	
313	Epilepsy *		G
314	Epilepsy@	EPILEPSY	
315	Epilepsy[F]	EPILEPSY[F]	
316	Epilepsy grand mal	EPILEPSY GRAND MAL	G
317	Epilepsy petit mal	EPILEPSY PETIT MAL	G
318	Status epilepticus*		G
319	Status epilepticus@	STATUS EPILEPTICUS	
320	Status epilepticus[F]	STATUS EPILEPTICUS[F]	
321	Disorientation	DISORIENTATION	F
322	Dizziness	DIZZINESS	F
323	Drop attack	DROP ATTACK	F
324	Drowsiness, sedation		
325	Drowsiness	DROWSINESS	G
326	Sedation	SEDATION	G
327	Dysphonia	DYSPHONIA	F
328	Electroencephalogram abnormal	EEG ABNORMAL	F
329	Encephalitis	ENCEPHALITIS	F
330	Encephalopathy		F
331	Encephalopathy@	ENCEPHALOPATHY	
332	Encephalopathy[F]	ENCEPHALOPATHY[F]	
333	Extrapyramidal disease		
334	Extrapyramidal disease#[F]		
335	Akinesia	AKINESIA	G
336	Dystonia	DYSTONIA	G
337	Extrapyramidal disease@	EXTRAPYRAMIDAL	G
338	Huntington's chorea	HUNTINGTONS CHOREA	G
339	Movement involuntary	MOVEMENT INVOL	G
340	Parkinson's disease*		G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
341	Parkinson's disease@	PARKINSONS	
342	Parkinson's disease[F]	PARKINSONS[F]	
343	Shy-Drager syndrome*		G
344	Shy-Drager syndrome@	SHY-DRAGER	
345	Shy-Drager syndrome[F]	SHY-DRAGER[F]	
346	Feeling cold	FEELING COLD	F
347	Feeling hot	FEELING HOT	F
348	Flushing	FLUSHING	F
349	Foot drop	FOOT DROP	F
350	Guillain-Barre syndrome		F
351	Guillain-Barre syndrome@	GUILLAIN-BARRE	
352	Guillain-Barre syndrome[F]	GUILLAIN-BARRE[F]	
353	Haematoma subdural	HAEMATOMA SUBDURAL	F
354	Headache, migraine		
355	Headache	HEADACHE	G
356	Migraine	MIGRAINE	G
357	Hemiparesis		F
358	Hemiparesis@	HEMIPARESIS	
359	Hemiparesis[F]	HEMIPARESIS[F]	
360	Hemiplegia		F
361	Hemiplegia@	HEMIPLEGIA	
362	Hemiplegia[F]	HEMIPLEGIA[F]	
363	Hydrocephalus		F
364	Hydrocephalus@	HYDROCEPHALUS	
365	Hydrocephalus[F]	HYDROCEPHALUS[F]	
366	Lost consciousness	LOST CONSCIOUSNESS	F
367	Meningism	MENINGISM	F
368	Meningitis		
369	Meningitis *		G
370	Meningitis@	MENINGITIS	
371	Meningitis[F]	MENINGITIS[F]	
372	Meningitis viral	MENINGITIS VIRAL	G
373	Motion sickness	MOTION SICK	F
374	Motor neurone disease		F
375	Motor neurone disease@	MOTOR NEURONE	
376	Motor neurone disease[F]	MOTOR NEURONE[F]	
377	Multiple sclerosis		F
378	Multiple sclerosis@	MULTIPLE SCLEROSIS	
379	Multiple sclerosis[F]	MULTIPLE SCLERO[F]	
380	Myelitis	MYELITIS	F
381	Myelopathy	MYELOPATHY	F
382	Narcolepsy	NARCOLEPSY	F
383	Neuralgia	NEURALGIA	F
384	Neuralgia postherpetic	NEURALGIA P HERPETIC	F
385	Neuralgia trigeminal	NEURALGIA TRIGEM	F
386	Neuropathy		
387	Neuropathy#[F]		
388	Miller Fisher syndrome	MILLER FISHER	G
389	Neuritis peripheral	NEURITIS PERIPH	G
390	Neuritis*		G
391	Neuritis@	NEURITIS	
392	Neuritis[F]	NEURITIS[F]	
393	Neuropathy peripheral	NEUROPATHY PERIPH	G
394	Neuropathy@	NEUROPATHY	G
395	Paralysis diaphragmatic	PARALYSIS DIAPHRAGM	F
396	Paralysis facial	PARALYSIS FACIAL	F
397	Paralysis ocular	PARALYSIS OCULAR	F
398	Paralysis pseudobulbar	PARALYSIS PSEUDOBULB	F
399	Paraplegia	PARAPLEGIA	F
400	Paresis	PARESIS	F
401	Post viral syndrome	POST VIRAL SYND	F
402	Ptosis	PTOSIS	F
403	Quadriplegia	QUADRIPLEGIA	F
404	Sensation abnormal		
405	Anaesthesia	ANAESTHESIA	G
406	Hyperaesthesia	HYPERAESTHESIA	G
407	Hypoaesthesia	HYPOAESTHESIA	G
408	Paraesthesia	PARAESTHESIA	G

	A	B	C
409	Sleep paralysis	SLEEP PARALYSIS	F
410	Smell, taste abnormal		
411	Anosmia	ANOSMIA	G
412	Smell abnormal	SMELL ABNORMAL	G
413	Taste abnormal	TASTE ABNORMAL	G
414	Syncope	SYNCOPE	F
415	Syringomyelia	SYRINGOMYELIA	F
416	Tremor	TREMOR	F
417	**Eye**		
418	Amaurosis		
419	Amaurosis@	AMAUROSIS	G
420	Amaurosis fugax	AMAUROSIS FUGAX	G
421	Blepharitis	BLEPHARITIS	F
422	Blepharospasm	BLEPHAROSPASM	F
423	Cataract	CATARACT	F
424	Choroiditis	CHOROIDITIS	F
425	Conjunctivitis	CONJUNCTIVITIS	F
426	Corneal dystrophy	CORNEAL DYSTROPHY	F
427	Cyst Meibomian	CYST MEIBOMIAN	F
428	Dacryocystitis	DACRYOCYSTITIS	F
429	Dry eye	DRY EYE	F
430	Ectropion	ECTROPION	F
431	Entropion	ENTROPION	F
432	Episcleritis	EPISCLERITIS	F
433	Exophthalmos	EXOPHTHALMOS	F
434	Floaters	FLOATERS	F
435	Glaucoma	GLAUCOMA	F
436	Haemorrhage retinal	HAEM RETINAL	F
437	Haemorrhage subconjunctival	HAEM SUBCONJ	F
438	Haemorrhage vitreous	HAEM VITREOUS	F
439	Herpes ophthalmic	HERPES OPHTHALMIC	F
440	Horner's syndrome	HORNERS	F
441	Infection corneal	INFECTION CORNEAL	F
442	Iridocyclitis	IRIDOCYCLITIS	F
443	Iritis	IRITIS	F
444	Irritation eye	IRRITATION EYE	F
445	Keratitis	KERATITIS	F
446	Keratoconjunctivitis phlyctenular	CONJUNCT PHLYCTENUL	F
447	Keratopathy	KERATOPATHY	F
448	Lacrimal block	LACRIMAL BLOCK	F
449	Lacrimal swelling	LACRIMAL SWELLING	F
450	Lacrimation	LACRIMATION	F
451	Macular degeneration	MACULAR DEGEN	F
452	Neuritis optic	NEURITIS OPTIC	F
453	Nystagmus	NYSTAGMUS	F
454	Optic atrophy	OPTIC ATROPHY	F
455	Pain eye	PAIN EYE	F
456	Papilloedema	PAPILLOEDEMA	F
457	Photophobia	PHOTOPHOBIA	F
458	Pigment corneal	PIGMENT CORNEAL	F
459	Pinguecula	PINGUECULA	F
460	Pterygium	PTERYGIUM	F
461	Retinal detachment	RETINAL DETACH	F
462	Retinal thrombosis artery	RETINAL THROMB ART	F
463	Retinal thrombosis vein	RETINAL THROMB VEIN	F
464	Retinopathy	RETINOPATHY	F
465	Scleritis	SCLERITIS	F
466	Scotoma	SCOTOMA	F
467	Sore eye	SORE EYE	F
468	Stye	STYE	F
469	Ulcer corneal	ULCER CORNEAL	F
470	Uveitis	UVEITIS	F
471	Visual defect		
472	Diplopia	DIPLOPIA	G
473	Hemianopia	HEMIANOPIA	G
474	Vision deteriorated	VISION DETERIORATED	G
475	Vision field defect	VISION FIELD DEFECT	G
476	Visual disturbance	VISUAL DISTURBANCE	G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
477	Xanthelasma	XANTHELASMA	F
478	Xanthopsia	XANTHOPSIA	F
479	**Ear**		
480	Deafness	DEAFNESS	F
481	Earache	EARACHE	F
482	Eardrum perforation	EARDRUM PERF	F
483	Earwax	EARWAX	F
484	Herpes zoster oticus	HERPES ZOSTER OTICUS	F
485	Hyperacusis	HYPERACUSIS	F
486	Labyrinthitis	LABYRINTHITIS	F
487	Mastoiditis	MASTOIDITIS	F
488	Meniere's disease	MENIERES	F
489	Otitis externa	OTITIS EXTERNA	F
490	Otitis media	OTITIS MEDIA	F
491	Otorrhoea	OTORRHOEA	F
492	Otosclerosis	OTOSCLEROSIS	F
493	Tinnitus	TINNITUS	F
494	Vertigo	VERTIGO	F
495	**Cardiovascular**		
496	Aneurysm		
497	Aneurysm#[F]		
498	Aneurysm aortic*		G
499	Aneurysm aortic@	ANEURYSM AORTIC	
500	Aneurysm aortic[F]	ANEURYSM AORTIC[F]	
501	Aneurysm dissecting*		G
502	Aneurysm dissecting@	ANEURYSM DISSECTING	
503	Aneurysm dissecting[F]	ANEURYSM DISSECT[F]	
504	Aneurysm arterial*		G
505	Aneurysm arterial@	ANEURYSM ARTERY	
506	Aneurysm arterial[F]	ANEURYSM ARTERY[F]	
507	Aneurysm ventricular*		G
508	Aneurysm ventricular@	ANEURYSM VENTRIC	
509	Aneurysm ventricular[F]	ANEURYSM VENTRIC[F]	
510	Aneurysm cerebral		F
511	Aneurysm cerebral@	ANEURYSM CEREBRAL	
512	Aneurysm cerebral[F]	ANEURYSM CEREBRAL[F]	
513	Arteriosclerosis		
514	Arteriosclerosis[F]		
515	Arteriosclerosis@	ARTERIOSCLER	G
516	Atherosclerosis*		G
517	Atherosclerosis@	ATHEROSCLEROSIS	
518	Atherosclerosis[F]	ATHEROSCLEROSIS[F]	
519	Arteriosclerosis cerebral		
520	Arteriosclerosis cerebral#[F]		
521	Arteriosclerosis cerebral@	ARTERIOSCLER CEREB	G
522	Atherosclerosis cerebral*		G
523	Atherosclerosis cerebral@	ATHEROSCLER CEREB	
524	Atherosclerosis cerebral[F]	ATHEROSCLER CEREB[F]	
525	Arteritis	ARTERITIS	F
526	Arteritis temporal	ARTERITIS TEMPORAL	F
527	Cardiac arrest		F
528	Cardiac arrest@	CARDIAC ARREST	
529	Cardiac arrest[F]	CARDIAC ARREST[F]	
530	Cardiac failure		
531	Cardiac failure#[F]		
532	Cardiac failure*		G
533	Cardiac failure@	CARDIAC FAILURE	
534	Cardiac failure[F]	CARDIAC FAILURE[F]	
535	Congestive cardiac failure*		G
536	Congestive cardiac failure@	CCF	
537	Congestive cardiac failure[F]	CCF[F]	
538	Left ventricular failure*		G
539	Left ventricular failure@	LVF	
540	Left ventricular failure[F]	LVF[F]	
541	Cardiogenic shock		F
542	Cardiogenic shock@	CARDIOGENIC SHOCK	
543	Cardiogenic shock[F]	CARDIOGENIC SHOCK[F]	
544	Cardiomegaly	CARDIOMEGALY	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
545	Cardiomyopathy		
546	Cardiomyopathy#[F]		
547	Cardiomyopathy*		G
548	Cardiomyopathy@	CARDIOMYOPATHY	
549	Cardiomyopathy[F]	CARDIOMYOPATHY[F]	
550	Fibrosis myocardial*		G
551	Fibrosis myocardial@	FIBROSIS MYOCARDIAL	
552	Fibrosis myocardial[F]	FIBROSIS MYOCARD[F]	
553	Myocardial degeneration*		G
554	Myocardial degeneration[F]	MYOCARDIAL DEGEN[F]	
555	Myocarditis*		G
556	Myocarditis@	MYOCARDITIS	
557	Myocarditis[F]	MYOCARDITIS[F]	
558	Cerebrovascular accident		
559	Cerebrovascular accident#[F]		
560	Cerebro-vascular accident*		G
561	Cerebrovascular accident@	CVA	
562	Cerebrovascular accident[F]	CVA[F]	
563	Embolus cerebral	EMBOLUS CEREBRAL	G
564	Haemorrhage cerebral*		G
565	Haemorrhage cerebral@	HAEM CEREBRAL	
566	Haemorrhage cerebral[F]	HAEM CEREBRAL[F]	
567	Haemorrhage subarachnoid*		G
568	Haemorrhage subarachnoid@	HAEM SUBARACH	
569	Haemorrhage subarachnoid[F]	HAEM SUBARACH[F]	
570	Stenosis artery cerebral	STENOSIS ART CEREB	G
571	Thrombosis cerebral*		G
572	Thrombosis cerebral@	THROMBOSIS CEREBRAL	
573	Thrombosis cerebral[F]	THROMBOSIS CEREB[F]	
574	Vertebrobasilar syndrome	VBS	G
575	Chilblain	CHILBLAINS	F
576	Clubbing	CLUBBING	F
577	Cold extremities	COLD EXTREMITIES	F
578	Cor pulmonale, hypertension pulmonary		
579	Cor pulmonale, hypertension pulmonary#[F]		
580	Cor pulmonale*		G
581	Cor pulmonale@	COR PULMONALE	
582	Cor pulmonale[F]	COR PULMONALE[F]	
583	Hypertension pulmonary*		G
584	Hypertension pulmonary@	HYPERTENSION PULMON	
585	Hypertension pulmonary[F]	HYPERTENSION PULM[F]	
586	Cyanosis	CYANOSIS	F
587	Cyst pericardial	CYST PERICARDIAL	F
588	Deep vein thrombosis		F
589	Deep vein thrombosis@	DVT	
590	Deep vein thrombosis[F]	DVT[F]	
591	Disorders of heart rate		
592	Bradycardia	BRADYCARDIA	G
593	Tachycardia	TACHYCARDIA	G
594	Disorders of rhythm		
595	Disorders of rhythm#[F]		
596	Arrhythmia	ARRHYTHMIA	G
597	Extrasystoles	EXTRASYSTOLES	G
598	Fibrillation atrial*		G
599	Fibrillation atrial@	FIBRILLATION ATRIAL	
600	Fibrillation atrial[F]	FIBRILL ATRIAL[F]	
601	Fibrillation ventricular	FIBRILLATION VENTRIC	G
602	Sick-sinus syndrome	SICK SINUS	G
603	Wolff-Parkinson-White syndrome	WOLFF-PARKINS WHITE	G
604	Dressler's syndrome	DRESSLERS SYNDROME	F
605	Effusion pericardial		F
606	Effusion pericardial@	EFFUSION PERICARDIAL	
607	Effusion pericardial[F]	EFFUSION PERICARD[F]	
608	Embolus pulmonary		F
609	Embolus pulmonary@	EMBOLUS PULMONARY	
610	Embolus pulmonary[F]	EMBOLUS PULMONARY[F]	
611	Endocarditis		
612	Endocarditis*		G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
613	Endocarditis@	ENDOCARDITIS	
614	Endocarditis[F]	ENDOCARDITIS[F]	
615	Subacute bacterial endocarditis	SBE	G
616	Faintness	FAINTNESS	F
617	Goodpasture's syndrome	GOODPASTURES SYNDROME	F
618	Heart block		
619	Bundle branch block	BUNDLE BRANCH BLOCK	G
620	Heart block*		G
621	Heart block@	HEART BLOCK	
622	Heart block[F]	HEART BLOCK[F]	
623	Heart sounds abnormal		
624	Heart sounds abnormal@	HEART SOUNDS ABNORM	G
625	Triple rhythm	TRIPLE RHYTHM	G
626	Hypertension		
627	Encephalopathy hypertensive	ENCEPHALOPATHY H/T	G
628	Hypertension*		G
629	Hypertension@	HYPERTENSION	
630	Hypertension[F]	HYPERTENSION[F]	
631	Hypertension/angina	HYPERTENSION/ANGINA	F
632	Hypertension/congestive cardiac failure	HYPERTENSION/CCF	F
633	Hypotension	HYPOTENSION	F
634	Ischaemia mesenteric		
635	Ischaemia mesenteric#[F]		
636	Embolus mesenteric*		G
637	Embolus mesenteric@	EMBOLUS MESENTERIC	
638	Embolus mesenteric[F]	EMBOLUS MESENTER[F]	
639	Infarction gastrointestinal*		G
640	Infarction gastrointestinal@	INFARCTION GI	
641	Infarction gastrointestinal[F]	INFARCTION GI[F]	
642	Thrombosis mesenteric*		G
643	Thrombosis mesenteric@	THROMBOSIS MESENTER	
644	Thrombosis mesenteric[F]	THROMBOSIS MESENT[F]	
645	Ischaemia peripheral		
646	Ischaemia peripheral#[F]		
647	Claudication	CLAUDICATION	G
648	Embolus artery*		G
649	Embolus artery@	EMBOLUS ARTERY	
650	Embolus artery[F]	EMBOLUS ARTERY[F]	
651	Gangrene*		G
652	Gangrene@	GANGRENE	
653	Gangrene[F]	GANGRENE[F]	
654	Ischaemia peripheral@	ISCHAEMIA PERIPHERAL	G
655	Stenosis artery*		G
656	Stenosis artery@	STENOSIS ARTERY	
657	Stenosis artery[F]	STENOSIS ARTERY[F]	
658	Thrombosis artery*		G
659	Thrombosis artery@	THROMBOSIS ARTERY	
660	Thrombosis artery[F]	THROMBOSIS ARTERY[F]	
661	Ischaemic heart disease		
662	Ischaemic heart disease#[F]		
663	Angina	ANGINA	G
664	Ischaemic heart disease*		G
665	Ischaemic heart disease@	IHD	
666	Ischaemic heart disease[F]	IHD[F]	
667	Myocardial infarction*		G
668	Myocardial infarction@	MI	
669	Myocardial infarction[F]	MI[F]	
670	Oedema		
671	Fluid retention	FLUID RETENTION	G
672	Oedema face	OEDEMA FACE	G
673	Oedema@	OEDEMA	G
674	Swollen ankles	SWOLLEN ANKLES	G
675	Swollen limb	SWOLLEN LIMB	G
676	Pain chest, tight chest		
677	Pain chest	PAIN CHEST	G
678	Tight chest	TIGHT CHEST	G
679	Palpitation	PALPITATIONS	F
680	Pericarditis	PERICARDITIS	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
681	Phlebitis	PHLEBITIS	F
682	Polyarteritis	POLYARTERITIS	F
683	Polyarteritis nodosa	POLYARTERITIS NODOSA	F
684	Raynaud's phenomenon	RAYNAUDS	F
685	Restless legs	RESTLESS LEGS	F
686	Rheumatic heart disease		F
687	Rheumatic heart disease@	RHEUMATIC HEART	
688	Rheumatic heart disease[F]	RHEUMATIC HEART[F]	
689	Stenosis artery renal	STENOSIS ART RENAL	F
690	Superficial venous thrombosis	SVT	F
691	Thrombophlebitis	THROMBOPHLEBITIS	F
692	Thrombosis spinal	THROMBOSIS SPINAL	F
693	Transient ischaemic attack	TIA	F
694	Valvular disease		
695	Valvular disease#[F]		
696	Stenosis aortic*		G
697	Stenosis aortic@	STENOSIS AORTIC	
698	Stenosis aortic[F]	STENOSIS AORTIC[F]	
699	Stenosis mitral*		G
700	Stenosis mitral@	STENOSIS MITRAL	
701	Stenosis mitral[F]	STENOSIS MITRAL[F]	
702	Valve incompetence*		G
703	Valve incompetence@	VALVE INCOMP	
704	Valve incompetence[F]	VALVE INCOMP[F]	
705	Vasculitis		F
706	Vasculitis@	VASCULITIS	
707	Vasculitis[F]	VASCULITIS[F]	
708	Veins varicose	VEINS VARICOSE	F
709	**Respiratory**		
710	Asphyxia, fatal[F]	ASPHYXIA[F]	F
711	Asthma, wheezing		
712	Asthma, wheezing#[F]		
713	Asthma*		G
714	Asthma@	ASTHMA	
715	Asthma[F]	ASTHMA[F]	
716	Asthma/bronchitis	ASTHMA/BRONCHITIS	G
717	Bronchospasm	BRONCHOSPASM	G
718	Wheezing	WHEEZING	G
719	Choking sensation	CHOKING SENSATION	F
720	Churg-Strauss syndrome	CHURG-STRAUSS	F
721	COAD (Chronic Obstructive Airways Disease)		
722	COAD#[F](Chronic Obstructive Airways Disease#[F])		
723	Bronchiectasis*		G
724	Bronchiectasis@	BRONCHIECTASIS	
725	Bronchiectasis[F]	BRONCHIECTASIS[F]	
726	Bronchitis chronic*		G
727	Bronchitis chronic@	BRONCHITIS CHRONIC	
728	Bronchitis chronic[F]	BRONCHITIS CHRON[F]	
729	COAD*(Chronic Obstructive Airways Disease)		G
730	COAD@(Chronic Obstructive Airways Disease)	COAD	
731	COAD[F](Chronic Obstructive Airways Disease[F])	COAD[F]	
732	Emphysema*		G
733	Emphysema@	EMPHYSEMA	
734	Emphysema[F]	EMPHYSEMA[F]	
735	Cough	COUGH	F
736	Cyst bronchogenic	CYST BRONCHOGENIC	F
737	Cystic fibrosis		F
738	Cystic fibrosis@	CYSTIC FIBROSIS	
739	Cystic fibrosis[F]	CYSTIC FIBROSIS[F]	
740	Dyspnoea	DYSPNOEA	F
741	Effusion pleural	EFFUSION PLEURAL	F
742	Epistaxis	EPISTAXIS	F
743	Fibrosis lung		
744	Fibrosis lung#[F]		
745	Alveolitis fibrosing*		G
746	Alveolitis fibrosing@	ALVEOLITIS FIBROSING	
747	Alveolitis fibrosing[F]	ALVEOLITIS FIBROS[F]	
748	Fibrosis lung*		G

G low-level term to be grouped under high-level term F freestanding low-level term

	A	B	C
749	Fibrosis lung@	FIBROSIS LUNG	
750	Fibrosis lung[F]	FIBROSIS LUNG[F]	
751	Haemoptysis		F
752	Haemoptysis	HAEMOPTYSIS	
753	Haemoptysis[F]	HAEMOPTYSIS[F]	
754	Haemosiderosis pulmonary		F
755	Haemosiderosis pulmonary@	H SIDEROSIS PULMONARY	
756	Haemosiderosis pulmonary[F]	H SIDEROSIS PULM[F]	
757	Hoarseness	HOARSENESS	F
758	Hyperventilation	HYPERVENT	F
759	Oedema pulmonary		F
760	Oedema pulmonary@	OEDEMA PULMONARY	
761	Oedema pulmonary[F]	OEDEMA PULMONARY[F]	
762	Pleurisy	PLEURISY	F
763	Pleurodynia	PLEURODYNIA	F
764	Pneumoconiosis		
765	Pneumoconiosis*		G
766	Pneumoconiosis@	PNEUMOCONIOSIS	
767	Pneumoconiosis[F]	PNEUMOCONIOSIS[F]	
768	Silicosis	SILICOSIS	G
769	Pneumothorax	PNEUMOTHORAX	F
770	Respiratory Failure		F
771	Respiratory failure@	RESP FAILURE	
772	Respiratory failure[F]	RESP FAILURE[F]	
773	Respiratory tract infection		
774	Respiratory tract infection#[F]		
775	Abscess lung	ABSCESS LUNG	G
776	Aspergillosis*		G
777	Aspergillosis@	ASPERGILLOSIS	
778	Aspergillosis[F]	ASPERGILLOSIS[F]	
779	Bronchitis acute	BRONCHITIS ACUTE	G
780	Bronchitis*		G
781	Bronchitis@	BRONCHITIS	
782	Bronchitis[F]	BRONCHITIS[F]	
783	Bronchopneumonia*		G
784	Bronchopneumonia@	BRONCHOPNEUMONIA	
785	Bronchopneumonia[F]	BRONCHOPNEUMONIA[F]	
786	Catarrh	CATARRH	G
787	Coryza	CORYZA	G
788	Croup	CROUP	G
789	Empyema*		G
790	Empyema@	EMPYEMA	
791	Empyema[F]	EMPYEMA[F]	
792	Haemophilus influenzae infection	HAEMOPHILUS	G
793	Infection chest*		G
794	Infection chest@	INFECTION CHEST	
795	Infection chest[F]	INFECTION CHEST[F]	
796	Influenza*		G
797	Influenza@	INFLUENZA	
798	Influenza[F]	INFLUENZA[F]	
799	Laryngitis	LARYNGITIS	G
800	Legionnaires' disease	LEGIONNAIRES	G
801	Mycoplasmosis	MYCOPLASMOSIS	G
802	Pertussis	PERTUSSIS	G
803	Pharyngitis	PHARYNGITIS	G
804	Pneumocystis	PNEUMOCYSTIS	G
805	Pneumonia*		G
806	Pneumonia@	PNEUMONIA	
807	Pneumonia[F]	PNEUMONIA[F]	
808	Pneumonitis	PNEUMONITIS	G
809	Psittacosis	PSITTACOSIS	G
810	Rhinitis	RHINITIS	G
811	Rhinorrhea	RHINORRHEA	G
812	Sinusitis	SINUSITIS	G
813	Tonsillitis	TONSILLITIS	G
814	Tracheitis	TRACHEITIS	G
815	Tuberculosis pulmonary*		G
816	Tuberculosis pulmonary@	TB PULMONARY	

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
817	Tuberculosis pulmonary[F]	TB PULMONARY[F]	
818	Upper respiratory tract infection	URTI	G
819	Rhinitis allergic	RHINITIS ALLERGIC	F
820	Ulcer pharynx	ULCER PHARYNX	F
821	Wegener's granulomatosis	WEGENERS	F
822	**Alimentary**		
823	Abscess anorectal	ABSCESS ANORECTAL	F
824	Abscess dental	ABSCESS DENTAL	F
825	Abscess liver	ABSCESS LIVER	F
826	Angiodysplasia colon	ANGIODYSPLASIA	F
827	Anorexia		F
828	Anorexia@	ANOREXIA	
829	Anorexia[F]	ANOREXIA[F]	
830	Appendicitis		
831	Appendicitis#[F]		
832	Appendicitis@	APPENDICITIS	G
833	Appendix perforated*		G
834	Appendix perforated@	APPENDIX PERF	
835	Appendix perforated[F]	APPENDIX PERF[F]	
836	Ascites	ASCITES	F
837	Bowel obstruction		
838	Bowel obstruction#[F]		
839	Bowel obstruction*		G
840	Bowel obstruction@	BOWEL OBSTRUCTION	
841	Bowel obstruction[F]	BOWEL OBSTRUCTION[F]	
842	Hernia strangulated*		G
843	Hernia strangulated@	HERNIA STRANGULATED	
844	Hernia strangulated[F]	HERNIA STRANG[F]	
845	Ileus	ILEUS	G
846	Bulimia	BULIMIA	F
847	Calculus salivary	CALCULUS SALIVARY	F
848	Campylobacter	CAMPYLOBACTER	F
849	Candidiasis oral	MONILIA ORAL	F
850	Cardiac achalasia	CARDIAC ACHALASIA	F
851	Cardiospasm	CARDIOSPASM	F
852	Cheilitis	CHEILITIS	F
853	Cholelithiasis, cholecystitis		
854	Cholelithiasis, cholecystitis#[F]		
855	Cholangitis	CHOLANGITIS	G
856	Cholecystitis	CHOLECYSTITIS	G
857	Cholelithiasis*		G
858	Cholelithiasis@	CHOLELITHIASIS	
859	Cholelithiasis[F]	CHOLELITHIASIS[F]	
860	Colic biliary	COLIC BILIARY	G
861	Gall bladder perforated*		G
862	Gall bladder perforated@	GALL BLADDER PERF	
863	Gall bladder perforated[F]	GALL BLADDER PERF[F]	
864	Cirrhosis		
865	Cirrhosis*		G
866	Cirrhosis@	CIRRHOSIS	
867	Cirrhosis[F]	CIRRHOSIS[F]	
868	Oesophageal varices	OESOPH VARICES	G
869	Coeliac disease	COELIAC	F
870	Constipation	CONSTIPATION	F
871	Cyst pancreas	CYST PANCREAS	F
872	Cyst peritonsillar	CYST PERITONSILLAR	F
873	Diarrhoea	DIARRHOEA	F
874	Distension abdominal	DISTENSION ABDO	F
875	Dry mouth	DRY MOUTH	F
876	Dumping syndrome	DUMPING SYNDROME	F
877	Dysentery		
878	Dysentery#[F]		
879	Dysentery@	DYSENTERY	G
880	Salmonellosis*		G
881	Salmonellosis@	SALMONELLA	
882	Salmonellosis[F]	SALMONELLA[F]	
883	Shigellosis	SHIGELLOSIS	G
884	Typhoid fever	TYPHOID	G

G low-level term to be grouped under high-level term F freestanding low-level term

	A	B	D
885	Dyspepsia		
886	Barrett's syndrome	BARRETTS	G
887	Duodenitis	DUODENITIS	G
888	Dyspepsia@	DYSPEPSIA	G
889	Gastritis	GASTRITIS	G
890	Heartburn	HEARTBURN	G
891	Oesophageal reflux	OESOPH REFLUX	G
892	Oesophagitis	OESOPHAGITIS	G
893	Dysphagia	DYSPHAGIA	F
894	Enterocele	ENTEROCELE	F
895	Faecal impaction	FAECAL IMPACTION	F
896	Faecal incontinence	FAECAL INCONTINENCE	F
897	Fissure anorectal	FISSURE ANORECTAL	F
898	Fistula colo-vaginal	FISTULA COLO-VAGINAL	F
899	Fistula colo-vesical	FISTULA COLO-VESICAL	F
900	Fistula gastro-pulmonary	FISTULA GASTRO PULM	F
901	Flatulence	FLATULENCE	F
902	Gastroenteritis	GASTROENTERITIS	F
903	Giardiasis	GIARDIA	F
904	Gilbert's syndrome	GILBERTS	F
905	Gingivitis	GINGIVITIS	F
906	Glossitis	GLOSSITIS	F
907	Gum hypertrophy	HYPERTROPHY GUM	F
908	Haemorrhage gastrointestinal		F
909	Haemorrhage gastrointestinal@	HAEM GI	
910	Haemorrhage gastrointestinal[F]	HAEM GI[F]	
911	Haemorrhage gastrointestinal upper		
912	Haemorrhage gastrointestinal upper#[F]		
913	Haematemesis*		G
914	Haematemesis@	HAEMATEMESIS	
915	Haematemesis[F]	HAEMATEMESIS[F]	
916	Hernia hiatus haemorrhage*		G
917	Hernia hiatus haemorrhagic@	HERNIA HIATUS HAEM	
918	Hernia hiatus haemorrhagic[F]	HERNIA HIAT HAEM[F]	
919	Mallory-Weiss syndrome	MALLORY-WEISS	G
920	Melena	MELAENA	G
921	Oesophageal haemorrhage*		G
922	Oesophageal haemorrhage@	OESOPH HAEM	
923	Oesophageal haemorrhage[F]	OESOPH HAEM[F]	
924	Ulcer duodenal haemorrhage*		G
925	Ulcer duodenal haemorrhage@	ULCER DUODENAL HAEM	
926	Ulcer duodenal haemorrhage[F]	ULCER DUO HAEM[F]	
927	Ulcer gastric haemorrhage*		G
928	Ulcer gastric haemorrhage@	ULCER GASTRIC HAEM	
929	Ulcer gastric haemorrhage[F]	ULCER GASTR HAEM[F]	
930	Ulcer oesophageal haemorrahge	ULCER OESOPH HAEM	G
931	Ulcer peptic haemorrhage*		G
932	Ulcer peptic haemorrhage@	ULCER PEPTIC HAEM	
933	Ulcer peptic haemorrhage[F]	ULCER PEPTIC HAEM[F]	
934	Haemorrhage oral	HAEM ORAL	F
935	Haemorrhage rectal	HAEM RECTAL	F
936	Haemorrhagic diarrhoea	HAEM DIARRHOEA	F
937	Haemorrhoids	HAEMORRHOIDS	F
938	Halitosis	HALITOSIS	F
939	Hepatic failure		
940	Encephalopathy hepatic	ENCEPHALOP HEPATIC	G
941	Hepatic Failure*		G
942	Hepatic failure@	HEPATIC FAILURE	
943	Hepatic failure[F]	HEPATIC FAILURE[F]	
944	Hepatitis, jaundice		
945	Hepatitis, jaundice#[F]		
946	Bilirubinuria	BILIRUBINURIA	G
947	Hepatitis infectious	HEPATITIS INFECT	G
948	Hepatitis infectious A	HEPATITIS INFECT A	G
949	Hepatitis infectious B	HEPATITIS INFECT B	G
950	Hepatitis*		G
951	Hepatitis@	HEPATITIS	
952	Hepatitis[F]	HEPATITIS[F]	

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
953	Jaundice	JAUNDICE	G
954	Jaundice cholestatic	JAUNDICE CHOLESTATIC	G
955	Jaundice obstructive*		G
956	Jaundice obstructive@	JAUNDICE OBSTRUCTIVE	
957	Jaundice obstructive[F]	JAUNDICE OBSTRUCT[F]	
958	Hepatomegaly	HEPATOMEGALY	F
959	Hernia	HERNIA	F
960	Hernia hiatus	HERNIA HIATUS	F
961	Hiccough	HICCOUGH	F
962	Ileum perforated	ILEUM PERF	F
963	Inflammatory disease colon		
964	Inflammatory disease colon#[F]		
965	Colitis	COLITIS	G
966	Colitis pseudomembranous*		G
967	Colitis pseudomembranous@	COLITIS PSEUDOMEMBRANOUS	
968	Colitis pseudomembranous[F]	COLITIS PSEUDOMEM[F]	
969	Colitis ulcerative	COLITIS ULCERATIVE	G
970	Colon perforated*		G
971	Colon perforated@	COLON PERF	
972	Colon perforated[F]	COLON PERF[F]	
973	Crohn's disease*		G
974	Crohn's disease@	CROHNS	
975	Crohn's disease[F]	CROHNS[F]	
976	Diverticulitis	DIVERTICULITIS	G
977	Diverticulosis*		G
978	Diverticulosis@	DIVERTICULOSIS	
979	Diverticulosis[F]	DIVERTICULOSIS[F]	
980	Diverticulum perforated*		G
981	Diverticulum perforated@	DIVERTICULUM PERF	
982	Diverticulum perforated[F]	DIVERTICULUM PERF[F]	
983	Irritable bowel syndrome	IBS	F
984	Leukoplakia oral	LEUKOPLAKIA MOUTH	F
985	Lichen planus oral	LICHEN PLANUS MOUTH	F
986	Liver function test abnormal	LFT ABNORMAL	F
987	Lymphangiectasia gastro-intestinal	LYMPHANGIECTASIA GI	F
988	Menetrier's disease	MENETRIERS	F
989	Mumps	MUMPS	F
990	Nausea, vomiting		
991	Nausea	NAUSEA	G
992	Vomiting	VOMITING	G
993	Oesophageal spasm	OESOPH SPASM	F
994	Oesophageal stricture		
995	Oesophageal stricture*		G
996	Oesophageal stricture@	OESOPH STRICTURE	
997	Oesophageal stricture[F]	OESOPH STRICTURE[F]	
998	Stenosis oesophageal	STENOSIS OESOPH	G
999	Oesophagus perforated	OESOPH PERF	F
1000	Pain abdomen	PAIN ABDOMEN	F
1001	Pancreatitis		
1002	Pancreatitis*		G
1003	Pancreatitis@	PANCREATITIS	
1004	Pancreatitis[F]	PANCREATITIS[F]	
1005	Pseudocyst	PSEUDOCYST	G
1006	Pancreatolithiasis	PANCREATOLITHIASIS	F
1007	Parotid enlarged	PAROTID ENLARGED	F
1008	Parotitis	PAROTITIS	F
1009	Peritonitis		F
1010	Peritonitis@	PERITONITIS	
1011	Peritonitis[F]	PERITONITIS[F]	
1012	Pharynx irritation	PHARYNX IRRITATION	F
1013	Proctalgia	PROCTALGIA	F
1014	Proctitis	PROCTITIS	F
1015	Prolapse rectal	PROLAPSE RECTAL	F
1016	Rectal discharge	RECTAL DISCHARGE	F
1017	Rectal stricture	RECTAL STRICTURE	F
1018	Saliva increased	SALIVA INCREASED	F
1019	Sialadenitis	SIALADENITIS	F
1020	Sore mouth	SORE MOUTH	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1021	Steatorrhoea	STEATORRHOEA	F
1022	Stenosis pyloric	STENOSIS PYLORIC	F
1023	Stomatitis	STOMATITIS	F
1024	Swollen tongue	SWOLLEN TONGUE	F
1025	Tenesmus	TENESMUS	F
1026	Threadworms	THREADWORMS	F
1027	Toothache	TOOTHACHE	F
1028	Ulcer mouth	ULCER MOUTH	F
1029	Ulcer oesophageal	ULCER OESOPH	F
1030	Ulcer peptic		
1031	Ulcer peptic#[F]		
1032	Ulcer duodenal perforated*		G
1033	Ulcer duodenal perforated@	ULCER DUODENAL PERF	
1034	Ulcer duodenal perforated[F]	ULCER DUO PERF[F]	
1035	Ulcer duodenal*		G
1036	Ulcer duodenal@	ULCER DUODENAL	
1037	Ulcer duodenal[F]	ULCER DUODENAL[F]	
1038	Ulcer gastric	ULCER GASTRIC	G
1039	Ulcer gastric perforated*		G
1040	Ulcer gastric perforated@	ULCER GASTRIC PERF	
1041	Ulcer gastric perforated[F]	ULCER GASTR PERF[F]	
1042	Ulcer peptic perforated*		G
1043	Ulcer peptic perforated@	ULCER PEPTIC PERF	
1044	Ulcer peptic perforated[F]	ULCER PEPTIC PERF[F]	
1045	Ulcer peptic*		G
1046	Ulcer peptic@	ULCER PEPTIC	
1047	Ulcer peptic[F]	ULCER PEPTIC[F]	
1048	Ulcer rectal	ULCER RECTAL	F
1049	Volvulus colon	VOLVULUS COLON	F
1050	Volvulus gastric	VOLVULUS GASTRIC	F
1051	Zollinger-Ellison syndrome	ZOLLINGER-ELLISON	F
1052	**Metabolic and Endocrine**		
1053	Acidosis		
1054	Acidosis@	ACIDOSIS	G
1055	Acidosis lactic	ACIDOSIS LACTIC	G
1056	Acromegaly	ACROMEGALY	F
1057	Addison's disease	ADDISONS	F
1058	Amyloidosis		F
1059	Amyloidosis@	AMYLOIDOSIS	
1060	Amyloidosis[F]	AMYLOIDOSIS[F]	
1061	Carotenaemia	CAROTENAEMIA	F
1062	Cushing's syndrome	CUSHINGS	F
1063	Cyst thyroid	CYST THYROID	F
1064	Dehydration	DEHYDRATION	F
1065	Diabetes mellitus improved	DIABETES IMPROVED	F
1066	Diabetes mellitus, hyperglycaemia		
1067	Diabetes mellitus, hyperglycaemia#[F]		
1068	Diabetes mellitus worsened	DIABETES WORSE	G
1069	Diabetes mellitus*		G
1070	Diabetes mellitus@	DIABETES MELLITUS	
1071	Diabetes mellitus[F]	DIABETES MELLITUS[F]	
1072	Encephalopathy diabetic*		G
1073	Encephalopathy diabetic[F]	ENCEPHALOP DIABET[F]	
1074	Glycosuria	GLYCOSURIA	G
1075	Hyperglycaemia	HYPERGLYCAEMIA	G
1076	Ketoacidosis diabetic*		G
1077	Ketoacidosis diabetic@	KETOSIS DIABETIC	
1078	Ketoacidosis diabetic[F]	KETOSIS DIABETIC[F[	
1079	Nephropathy diabetic*		G
1080	Nephropathy diabetic@	NEPHROPATHY DIABETIC	
1081	Nephropathy diabetic[F]	NEPHROPATHY DIAB[F]	
1082	Neuropathy diabetic	NEUROPATHY DIABETIC	G
1083	Retinopathy diabetic	RETINOPATHY DIABETIC	G
1084	Ulcer diabetic	ULCER DIABETIC	G
1085	Electrolyte abnormal		
1086	Electrolyte abnormal@	ELECTROLYTE ABNORMAL	G
1087	Hypercalcaemia	HYPERCALCAEMIA	G
1088	Hyperkalaemia	HYPERKALAEMIA	G

	A	B	C
1089	Hypernatraemia	HYPERNATRAEMIA	G
1090	Hypocalcaemia	HYPOCALCAEMIA	G
1091	Hypokalaemia	HYPOKALAEMIA	G
1092	Hyponatraemia	HYPONATRAEMIA	G
1093	Excessive thirst	EXCESSIVE THIRST	F
1094	Globulin abnormal	GLOBULIN ABNORMAL	F
1095	Goitre	GOITRE	F
1096	Gout	GOUT	F
1097	Haemochromatosis	HAEMOCHROMATOSIS	F
1098	Hyperaldosteronism		
1099	Bartter's syndrome	BARTTERS	G
1100	Conn's syndrome	CONNS SYNDROME	G
1101	Hyperaldosteronism@	HYPERALDOSTERONISM	G
1102	Hyperlipidaemia		
1103	Hypercholesterolaemia	HYPERCHOLESTEROL	G
1104	Hyperlipidaemia familial	FAMILIAL HYPERLIPID	G
1105	Hyperlipidaemia@	HYPERLIPAEMIA	G
1106	Hyperparathyroidism	HYPERPARATHYROID	F
1107	Hyperprolactinaemia	HYPERPROLACTIN	F
1108	Hyperthermia	HYPERTHERMIA	F
1109	Hyperthyroidism	HYPERTHYROID	F
1110	Hyperuricaemia	HYPERURICAEMIA	F
1111	Hypoalbuminaemia	HYPOALBUMINAEMIA	F
1112	Hypoglycaemia	HYPOGLYCAEMIA	F
1113	Hypogonadism	HYPOGONADISM	F
1114	Hypoparathyroidism	HYPOPARATHYROID	F
1115	Hypothermia		F
1116	Hypothermia@	HYPOTHERMIA	
1117	Hypothermia[F]	HYPOTHERMIA[F]	
1118	Hypothyroidism	HYPOTHYROID	F
1119	Obesity		
1120	Obesity#[F]		
1121	Obesity@	OBESITY	G
1122	Pickwickian syndrome*		G
1123	Pickwickian syndrome@	PICKWICKIAN	
1124	Pickwickian syndrome[F]	PICKWICKIAN[F]	
1125	Osteomalacia	OSTEOMALACIA	F
1126	Porphyria		F
1127	Porphyria@	PORPHYRIA	
1128	Porphyria[F]	PORPHYRIA[F]	
1129	Refsum's syndrome	REFSUMS SYND	F
1130	Scurvy	SCURVY	F
1131	Sweating	SWEATING	F
1132	Tetany	TETANY	F
1133	Thyroiditis	THYROIDITIS	F
1134	Water Intoxication	WATER INTOX	F
1135	Weight gain	WEIGHT GAIN	F
1136	Weight loss	WEIGHT LOSS	F
1137	**Urologic**		
1138	Abscess renal	ABSCESS RENAL	F
1139	Albuminuria	ALBUMINURIA	F
1140	Bladder irritability	BLADDER IRRITABILITY	F
1141	Calculus renal	CALCULUS RENAL	F
1142	Caruncle urethral	CARUNCLE URETHRAL	F
1143	Colic renal		
1144	Colic renal@	COLIC RENAL	G
1145	Pain renal	PAIN RENAL	G
1146	Cyst renal	CYST RENAL	F
1147	Enuresis	ENURESIS	F
1148	Fibrosis retroperitoneal	FIBROSIS RETROPERIT	F
1149	Haematuria	HAEMATURIA	F
1150	Hydronephrosis	HYDRONEPHROSIS	F
1151	Micturition disorder		
1152	Dysuria	DYSURIA	G
1153	Frequency	FREQUENCY	G
1154	Incontinence	INCONTINENCE	G
1155	Nocturia	NOCTURIA	G
1156	Urgency	URGENCY	G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1157	Necrosis papillary	NECROSIS PAPILLARY	F
1158	Nephritis, nephropathy		
1159	Nephritis, nephropathy#[F]		
1160	Nephritis	NEPHRITIS	G
1161	Nephropathy	NEPHROPATHY	G
1162	Nephrotic syndrome*		G
1163	Nephrotic syndrome@	NEPHROTIC SYNDROME	
1164	Nephrotic syndrome[F]	NEPHROTIC SYND[F]	
1165	Oxaluria	OXALURIA	F
1166	Polyuria	POLYURIA	F
1167	Pyuria	PYURIA	F
1168	Renal failure		
1169	Renal failure#[F]		
1170	Renal failure acute	RENAL FAILURE ACUTE	G
1171	Renal failure chronic*		G
1172	Renal failure chronic@	RENAL FAILURE CHRON	
1173	Renal failure chronic[F]	RENAL FAILURE CH[F]	
1174	Renal failure*		G
1175	Renal failure@	RENAL FAILURE	
1176	Renal failure[F]	RENAL FAILURE[F]	
1177	Uraemia*		G
1178	Uraemia@	URAEMIA	
1179	Uraemia[F]	URAEMIA[F]	
1180	Renal function test abnormal	RFT ABNORMAL	F
1181	Retention	RETENTION	F
1182	Stenosis ureteric	STENOSIS URETERIC	F
1183	Tuberculosis renal	TB RENAL	F
1184	Urea raised	UREA RAISED	F
1185	Urinary tract infection		
1186	Urinary tract infection#[F]		
1187	Cystitis	CYSTITIS	G
1188	Pyelitis	PYELITIS	G
1189	Pyelonephritis*		G
1190	Pyelonephritis@	PYELONEPHRITIS	
1191	Pyelonephritis[F]	PYELONEPHRITIS[F]	
1192	Stenosis urethral	STENOSIS URETHRAL	G
1193	Urethral stricture	URETHRAL STRICTURE	G
1194	Urethritis	URETHRITIS	G
1195	Urinary tract infection*		G
1196	Urinary tract infection@	UTI	
1197	Urinary tract infection[F]	UTI[F]	
1198	**Male Reproductive and Gynaecomastia**		
1199	Balanitis	BALANITIS	F
1200	Cyst epididymis	CYST EPIDIDYMIS	F
1201	Ejaculation premature	EJACULATION PREM	F
1202	Ejaculation retrograde	EJACULATION RETRO	F
1203	Epididymitis	EPIDIDYMITIS	F
1204	Fertility restored	FERTILITY RESTORED	F
1205	Gynaecomastia	GYNAECOMASTIA	F
1206	Haemospermia	HAEMOSPERMIA	F
1207	Hydrocele	HYDROCELE	F
1208	Impotence, ejaculation failure		
1209	Ejaculation failure	EJACULATION FAILURE	G
1210	Impotence	IMPOTENCE	G
1211	Oligospermia	OLIGOSPERMIA	F
1212	Orchitis	ORCHITIS	F
1213	Peyronie's disease	PEYRONIES	F
1214	Phimosis	PHIMOSIS	F
1215	Priapism	PRIAPISM	F
1216	Prostatism	PROSTATISM	F
1217	Prostatitis	PROSTATITIS	F
1218	Spermatocele	SPERMATOCELE	F
1219	Testicle enlarged	TESTICLE ENLARGED	F
1220	Varicocele	VARICOCELE	F
1221	**Female Reproductive**		
1222	Abscess Bartholin's gland	ABSCESS BARTHOLIN	F
1223	Abscess pelvic	ABSCESS PELVIC	F
1224	Bartholinitis	BARTHOLINITIS	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1225	Cervical erosion	CERVICAL EROSION	F
1226	Cervical smear abnormal	CERVICAL SMEAR ABN	F
1227	Cervicitis	CERVICITIS	F
1228	Cyst Bartholin's	CYST BARTHOLIN	F
1229	Cyst ovarian	CYST OVARIAN	F
1230	Cyst vaginal	CYST VAGINAL	F
1231	Cystocele	CYSTOCELE	F
1232	Dyskaryosis	DYSKARYOSIS	F
1233	Dyspareunia	DYSPAREUNIA	F
1234	Endometriosis	ENDOMETRIOSIS	F
1235	Endometritis	ENDOMETRITIS	F
1236	Haemorrhage postcoital	HAEM POST COITAL	F
1237	Haemorrhage postmenopausal	HAEM POST MENOPAUSE	F
1238	Haemorrhage vaginal	HAEM VAGINAL	F
1239	Hydrosalpinx	HYDROSALPINX	F
1240	Infertility female	INFERTILITY FEMALE	F
1241	Leukoplakia vaginal	LEUKOPLAKIA VAGINAL	F
1242	Menopausal symptoms	MENOPAUSAL	F
1243	Menstrual disorder		
1244	Amenorrhoea	AMENORRHOEA	G
1245	Dysmenorrhoea	DYSMENORRHOEA	G
1246	Irregular periods	IRREGULAR PERIODS	G
1247	Menorrhagia	MENORRHAGIA	G
1248	Oligomenorrhoea	OLIGOMENORRHOEA	G
1249	Polymenorrhoea	POLYMENORRHOEA	G
1250	Metrorrhagia	METRORRHAGIA	F
1251	Mittelschmerz	MITTELSCHMERZ	F
1252	Pelvic inflammatory disease		
1253	Oophoritis	OOPHORITIS	G
1254	Pelvic inflammatory disease@	PELVIC INFLAM	G
1255	Salpingitis	SALPINGITIS	G
1256	Premenstrual tension	PMT	F
1257	Prolapse uterine	PROLAPSE UTERINE	F
1258	Pyometra	PYOMETRA	F
1259	Rectocele	RECTOCELE	F
1260	Stenosis vaginal	STENOSIS VAGINAL	F
1261	Urethrocele	URETHROCELE	F
1262	Vaginal soreness	VAGINAL SORENESS	F
1263	Vaginitis, vulvitis		
1264	Infection vaginal bacterial	INFECTION VAG BACT	G
1265	Vaginal candidiasis	MONILIA VAGINAL	G
1266	Vaginal discharge	VAGINAL DISCHARGE	G
1267	Vaginitis	VAGINITIS	G
1268	Vaginitis trichomonas	VAGINITIS TRICHOMON	G
1269	Vulvitis	VULVITIS	G
1270	**Breast Disorder**		
1271	Abscess breast	ABSCESS BREAST	F
1272	Breast discharge	BREAST DISCHARGE	F
1273	Breast disorder	BREAST DISORDER	F
1274	Breast enlarged	BREAST ENLARGED	F
1275	Galactorrhoea	GALACTORRHOEA	F
1276	Mastalgia	MASTALGIA	F
1277	Mastitis	MASTITIS	F
1278	**Obstetric**		
1279	Abortion threatened	ABORTION THREAT	F
1280	Hyperemesis gravidarum	HYPEREMESIS GRAVIDA	F
1281	Placenta praevia	PLACENTA PREVIA	F
1282	Pregnancy ectopic	PREGNANCY ECTOPIC	F
1283	Pregnancy toxaemia	PREGNANCY TOXAEMIA	F
1284	**Haemopoietic**		
1285	Anaemia	ANAEMIA	F
1286	Anaemia haemolytic	ANAEMIA HAEMOLYTIC	F
1287	Anaemia iron deficiency		
1288	Anaemia iron deficiency@	ANAEMIA FE DEF	G
1289	Anaemia microcytic	ANAEMIA MICROCYTIC	G
1290	Anaemia macrocytic		
1291	Anaemia folic acid deficiency	ANAEMIA FOLATE	G

	A	B	C
1292	Anaemia macrocytic@	ANAEMIA MACROCYTIC	G
1293	Anaemia vitamin B12 deficiency	ANAEMIA B12 DEF	G
1294	Anaemia sickle cell	ANAEMIA SICKLE CELL	F
1295	Anaemia sideroblastic	ANAEMIA SIDEROBLAST	F
1296	Bone marrow abnormal	BONE MARROW ABNORMAL	F
1297	Coagulation disorder	COAGULATION DISORDER	F
1298	Cyst spleen	CYST SPLEEN	F
1299	Eosinophilia		
1300	Eosinophilia@	EOSINOPHILIA	G
1301	Hypereosinophilic syndrome	HYPEREOSINOPHILIA	G
1302	Erythrocyte sedimentation rate raised	ESR RAISED	F
1303	Haematoma spontaneous	HAEMATOMA SPONTANEOUS	F
1304	Haemophilia		F
1305	Haemophilia@	HAEMOPHILIA	
1306	Haemophilia[F]	HAEMOPHILIA[F]	
1307	Hyperbilirubinaemia	HYPERBILIRUBINAEMIA	F
1308	Hypergammaglobulinaemia		
1309	Hypergammaglobulinaemia#[F]		G
1310	Hypergammaglobulinaemia@	HYPERGAMMAGLOBULIN	G
1311	Waldenstrom's macroglobulinaemia*		G
1312	Waldenstrom's macroglobulinaemia@	WALDENSTROM	
1313	Waldenstrom's macroglobulinaemia[F]	WALDENSTROM[F]	
1314	Hypogammaglobulinaemia	HYPOGAMMAGLOBULIN	F
1315	Jaundice haemolytic	JAUNDICE HAEMOLYTIC	F
1316	Leucocytosis		
1317	Leucocytosis@	LEUCOCYTOSIS	G
1318	Lymphocytosis	LYMPHOCYTOSIS	G
1319	Neutrophilia	NEUTROPHILIA	G
1320	Leucopenia		
1321	Leucopenia@	LEUCOPENIA	G
1322	Neutropenia	NEUTROPENIA	G
1323	Lymphadenopathy		
1324	Glands swollen	GLANDS SWOLLEN	G
1325	Lymphadenitis	LYMPHADENITIS	G
1326	Lymphadenopathy@	LYMPHADENOPATHY	G
1327	Myelodysplastic syndrome		F
1328	Myelodysplastic syndrome@	MYELODYSPLASIA	
1329	Myelodysplastic syndrome[F]	MYELODYSPLASIA[F]	
1330	Myelofibrosis		F
1331	Myelofibrosis@	MYELOFIBROSIS	
1332	Myelofibrosis[F]	MYELOFIBROSIS[F]	
1333	Pancytopenia		
1334	Pancytopenia#[F]		G
1335	Anaemia aplastic*		G
1336	Anaemia aplastic@	ANAEMIA APLASTIC	
1337	Anaemia aplastic[F]	ANAEMIA APLASTIC[F]	
1338	Anaemia hypoplastic	ANAEMIA HYPOPLASTIC	G
1339	Pancytopenia@	PANCYTOPENIA	G
1340	Polycythaemia	POLYCYTHAEMIA	F
1341	Red cell abnormal	RED CELL ABNORMAL	F
1342	Splenomegaly	SPLENOMEGALY	F
1343	Thalassaemia	THALASSAEMIA	F
1344	Thrombocytopenia	THROMBOCYTOPENIA	F
1345	Thrombocytosis	THROMBOCYTOSIS	F
1346	Tuberculosis adenitis	TB ADENITIS	F
1347	Wiskott-Aldrich syndrome	WISKOTT-ALDRICH	F
1348	**Neoplasm**		
1349	Malignancies		
1350	Malignancies#[F]		
1351	Astrocytoma*		G
1352	Astrocytoma@	ASTROCYTOMA	
1353	Astrocytoma[F]	ASTROCYTOMA[F]	
1354	Cancer*		G
1355	Cancer@	CANCER	
1356	Cancer[F]	CANCER[F]	
1357	Carcinoma adrenal gland*		G
1358	Carcinoma adrenal gland@	CA ADRENAL GLAND	
1359	Carcinoma adrenal gland[F]	CA ADRENAL GLAND[F]	

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1360	Carcinoma bile duct*		G
1361	Carcinoma bile duct@	CA BILE DUCT	
1362	Carcinoma bile duct[F]	CA BILE DUCT[F]	
1363	Carcinoma bladder*		G
1364	Carcinoma bladder@	CA BLADDER	
1365	Carcinoma bladder[F]	CA BLADDER[F]	
1366	Carcinoma bone*		G
1367	Carcinoma bone@	CA BONE	
1368	Carcinoma bone[F]	CA BONE[F]	
1369	Carcinoma brain*		G
1370	Carcinoma brain@	CA BRAIN	
1371	Carcinoma brain[F]	CA BRAIN[F]	
1372	Carcinoma breast*		G
1373	Carcinoma breast@	CA BREAST	
1374	Carcinoma breast[F]	CA BREAST[F]	
1375	Carcinoma bronchus*		G
1376	Carcinoma bronchus[F]	CA BRONCHUS	
1377	Carcinoma broncus@	CA BRONCHUS[F]	
1378	Carcinoma caecum*		G
1379	Carcinoma caecum@	CA CAECUM	
1380	Carcinoma caecum[F]	CA CAECUM[F]	
1381	Carcinoma cervix*		G
1382	Carcinoma cervix@	CA CERVIX	
1383	Carcinoma cervix[F]	CA CERVIX[F]	
1384	Carcinoma colon*		G
1385	Carcinoma colon@	CA COLON	
1386	Carcinoma colon[F]	CA COLON[F]	
1387	Carcinoma duodenum*		G
1388	Carcinoma duodenum@	CA DUODENUM	
1389	Carcinoma duodenum[F]	CA DUODENUM[F]	
1390	Carcinoma epiglottis	CA EPIGLOTTIS	G
1391	Carcinoma gall bladder*		G
1392	Carcinoma gall bladder@	CA GALL BLADDER	
1393	Carcinoma gall bladder[F]	CA GALL BLADDER[F]	
1394	Carcinoma gastrointestinal*		G
1395	Carcinoma gastrointestinal@	CA GASTRO INTESTINAL	
1396	Carcinoma gastrointestinal[F]	CA GI[F]	
1397	Carcinoma ileum*		G
1398	Carcinoma ileum@	CA ILEUM	
1399	Carcinoma ileum[F]	CA ILEUM[F]	
1400	Carcinoma jejunum	CA JEJUNUM	G
1401	Carcinoma kidney*		G
1402	Carcinoma kidney@	CA KIDNEY	
1403	Carcinoma kidney[F]	CA KIDNEY[F]	
1404	Carcinoma larynx*		G
1405	Carcinoma larynx@	CA LARYNX	
1406	Carcinoma larynx[F]	CA LARYNX[F]	
1407	Carcinoma liver*		G
1408	Carcinoma liver@	CA LIVER	
1409	Carcinoma liver[F]	CA LIVER[F]	
1410	Carcinoma lung*		G
1411	Carcinoma lung@	CA LUNG	
1412	Carcinoma lung[F]	CA LUNG[F]	
1413	Carcinoma nasopharynx*		G
1414	Carcinoma nasopharynx@	CA NASOPHARYNX	
1415	Carcinoma nasopharynx[F]	CA NASOPHARYNX[F]	
1416	Carcinoma oesophagus*		G
1417	Carcinoma oesophagus@	CA OESOPHAGUS	
1418	Carcinoma oesophagus[F]	CA OESOPHAGUS[F]	
1419	Carcinoma ovary*		G
1420	Carcinoma ovary@	CA OVARY	
1421	Carcinoma ovary[F]	CA OVARY[F]	
1422	Carcinoma palate	CA PALATE	G
1423	Carcinoma pancreas*		G
1424	Carcinoma pancreas@	CA PANCREAS	
1425	Carcinoma pancreas[F]	CA PANCREAS[F]	
1426	Carcinoma parotid	CA PAROTID	G
1427	Carcinoma penis	CA PENIS	G

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1428	Carcinoma pharynx*		G
1429	Carcinoma pharynx@	CA PHARYNX	
1430	Carcinoma pharynx[F]	CA PHARYNX[F]	
1431	Carcinoma prostate*		G
1432	Carcinoma prostate@	CA PROSTATE	
1433	Carcinoma prostate[F]	CA PROSTATE[F]	
1434	Carcinoma rectum*		G
1435	Carcinoma rectum@	CA RECTUM	
1436	Carcinoma rectum[F]	CA RECTUM[F]	
1437	Carcinoma salivary gland	CA SALIVARY GLAND	G
1438	Carcinoma skin*		G
1439	Carcinoma skin@	CA SKIN	
1440	Carcinoma skin[F]	CA SKIN[F]	
1441	Carcinoma spine*		G
1442	Carcinoma spine@	CA SPINE	
1443	Carcinoma spine[F]	CA SPINE[F]	
1444	Carcinoma stomach*		G
1445	Carcinoma stomach@	CA STOMACH	
1446	Carcinoma stomach[F]	CA STOMACH[F]	
1447	Carcinoma testis*		G
1448	Carcinoma testis@	CA TESTIS	
1449	Carcinoma testis[F]	CA TESTIS[F]	
1450	Carcinoma thyroid*		G
1451	Carcinoma thyroid@	CA THYROID	
1452	Carcinoma thyroid[F]	CA THYROID[F]	
1453	Carcinoma tongue*		G
1454	Carcinoma tongue@	CA TONGUE	
1455	Carcinoma tongue[F]	CA TONGUE[F]	
1456	Carcinoma tonsil*		G
1457	Carcinoma tonsil@	CA TONSIL	
1458	Carcinoma tonsil[F]	CA TONSIL[F]	
1459	Carcinoma trachea	CA TRACHEA	G
1460	Carcinoma ureter*		G
1461	Carcinoma ureter@	CA URETER	
1462	Carcinoma ureter[F]	CA URETER[F]	
1463	Carcinoma urethra*		G
1464	Carcinoma urethra@	CA URETHRA	
1465	Carcinoma urethra[F]	CA URETHRA[F]	
1466	Carcinoma uterus*		G
1467	Carcinoma uterus@	CA UTERUS	
1468	Carcinoma uterus[F]	CA UTERUS[F]	
1469	Carcinoma vagina*		G
1470	Carcinoma vagina@	CA VAGINA	
1471	Carcinoma vagina[F]	CA VAGINA[F]	
1472	Carcinoma vulva*		G
1473	Carcinoma vulva@	CA VULVA	
1474	Carcinoma vulva[F]	CA VULVA[F]	
1475	Carcinomatosis*		G
1476	Carcinomatosis@	CARCINOMATOSIS	
1477	Carcinomatosis[F]	CARCINOMATOSIS[F]	
1478	Ependymoma*		G
1479	Ependymoma@	EPENDYMOMA	
1480	Ependymoma[F]	EPENDYMOMA[F]	
1481	Fibrosarcoma	FIBROSARCOMA	G
1482	Glioma*		G
1483	Glioma@	GLIOMA	
1484	Glioma[F]	GLIOMA[F]	
1485	Hodgkin's disease*		G
1486	Hodgkin's disease@	HODGKINS	
1487	Hodgkin's disease[F]	HODGKINS[F]	
1488	Kaposi's sarcoma	KAPOSI SARCOMA	G
1489	Lentigo maligna	LENTIGO MALIGNA	G
1490	Leukaemia acute*		G
1491	Leukaemia acute@	LEUKAEMIA ACUTE	
1492	Leukaemia acute[F]	LEUKAEMIA ACUTE[F]	
1493	Leukaemia chronic	LEUKAEMIA CHRONIC	G
1494	Leukaemia lymphocytic acute*		G
1495	Leukaemia lymphocytic acute@	LEUKAEMIA LYMPH AC	

G low-level term to be grouped under high-level term F freestanding low-level term

	A	B	C
1496	Leukaemia lymphocytic acute[F]	LEUKAEMIA LYMP AC[F]	
1497	Leukaemia lymphocytic chronic*		G
1498	Leukaemia lymphocytic chronic@	LEUKAEMIA LYMPH CH	
1499	Leukaemia lymphocytic chronic[F]	LEUKAEMIA LYMP CH[F]	
1500	Leukaemia myeloid acute*		G
1501	Leukaemia myeloid acute@	LEUKAEMIA MYELOID AC	
1502	Leukaemia myeloid acute[F]	LEUKAEMIA MYEL AC[F]	
1503	Leukaemia myeloid chronic*		G
1504	Leukaemia myeloid chronic@	LEUKAEMIA MYELOID CH	
1505	Leukaemia myeloid chronic[F]	LEUKAEMIA MYEL CH[F]	
1506	Leukaemia*		G
1507	Leukaemia@	LEUKAEMIA	
1508	Leukaemia[F]	LEUKAEMIA[F]	
1509	Liposarcoma*		G
1510	Liposarcoma@	LIPOSARCOMA	
1511	Liposarcoma[F]	LIPOSARCOMA[F]	
1512	Lymphoma malignant*		G
1513	Lymphoma malignant@	LYMPHOMA MALIGNANT	
1514	Lymphoma malignant[F]	LYMPHOMA MALIG[F]	
1515	Mastocytosis	MASTOCYTOSIS	G
1516	Melanoma*		G
1517	Melanoma@	MELANOMA	
1518	Melanoma[F]	MELANOMA[F]	
1519	Mesothelioma*		G
1520	Mesothelioma@	MESOTHELIOMA	
1521	Mesothelioma[F]	MESOTHELIOMA[F]	
1522	Mycosis fungoides*		G
1523	Mycosis fungoides@	MYCOSIS FUNGOIDES	
1524	Mycosis fungoides[F]	MYCOSIS FUNGOIDES[F]	
1525	Myeloma*		G
1526	Myeloma@	MYELOMA	
1527	Myeloma[F]	MYELOMA[F]	
1528	Osteosarcoma	OSTEOSARCOMA	G
1529	Sarcoma*		G
1530	Sarcoma@	SARCOMA	
1531	Sarcoma[F]	SARCOMA[F]	
1532	Teratoma	TERATOMA	G
1533	Non-malignant tumours		
1534	Non-malignant tumours#[F]		
1535	Adenoma adrenal	ADENOMA ADRENAL	G
1536	Adenoma colon	ADENOMA COLON	G
1537	Adenoma endocrine	ADENOMA ENDOCRINE	G
1538	Adenoma rectum	ADENOMA RECTUM	G
1539	Cholesteatoma	CHOLESTEATOMA	G
1540	Chondroma	CHONDROMA	G
1541	Cyst dermoid	CYST DERMOID	G
1542	Fibroids	FIBROIDS	G
1543	Fibroma	FIBROMA	G
1544	Leiomyoma	LEIOMYOMA	G
1545	Lipoma	LIPOMA	G
1546	Lymphoma	LYMPHOMA	G
1547	Meigs' syndrome	MEIGS	G
1548	Meningioma*		G
1549	Meningioma@	MENINGIOMA	
1550	Meningioma[F]	MENINGIOMA[F]	
1551	Myoblastoma	MYOBLASTOMA	G
1552	Neuroma	NEUROMA	G
1553	Non-malignant tumour bladder	NMT BLADDER	G
1554	Non-malignant tumour brain	NMT BRAIN	G
1555	Non-malignant tumour breast	NMT BREAST	G
1556	Non-malignant tumour gastrointestinal	NMT GASTROINTESTINAL	G
1557	Non-malignant tumour kidney	NMT KIDNEY	G
1558	Non-malignant tumour larynx	NMT LARYNX	G
1559	Non-malignant tumour liver	NMT LIVER	G
1560	Non-malignant tumour parathyroid	NMT PARATHYROID	G
1561	Non-malignant tumour parotid	NMT PAROTID	G
1562	Non-malignant tumour pharynx	NMT PHARYNX	G
1563	Non-malignant tumour pituitary	NMT PITUITARY	G

	A	B	C
1564	Non-malignant tumour prostate	NMT PROSTATE	G
1565	Non-malignant tumour salivary	NMT SALIVARY	G
1566	Non-malignant tumour skin	NMT SKIN	G
1567	Non-malignant tumour spine	NMT SPINE	G
1568	Non-malignant tumour stomach	NMT STOMACH	G
1569	Non-malignant tumour thyroid	NMT THYROID	G
1570	Non-malignant tumour tongue	NMT TONGUE	G
1571	Osteoma	OSTEOMA	G
1572	Papilloma	PAPILLOMA	G
1573	Phaeochromocytoma	PHAEOCHROMOCYTOMA	G
1574	Polyp	POLYP	G
1575	Polyp gastrointestinal	POLYP GI	G
1576	Polyp nasal	POLYP NASAL	G
1577	Polyp rectal	POLYP RECTAL	G
1578	Polyp uterine	POLYP UTERINE	G
1579	Others		
1580	Neoplasm	NEOPLASM	G
1581	**Miscellaneous Infection**		
1582	Abscess	ABSCESS	F
1583	Abscess subphrenic	ABSCESS SUBPHRENIC	F
1584	Actinomycosis	ACTINOMYCOSIS	F
1585	Bacteraemia	BACTERAEMIA	F
1586	Candidiasis	MONILIA	F
1587	Chlamydial infection	CHLAMYDIA	F
1588	Fungal infection	MYCOSIS	F
1589	Gardnerella infection	GARDNERELLA	F
1590	Glandular fever	GLANDULAR FEVER	F
1591	Gonorrhoea	GONORRHOEA	F
1592	Herpangina	HERPANGINA	F
1593	Herpes		
1594	Herpes@	HERPES	G
1595	Herpes simplex	HERPES SIMPLEX	G
1596	Herpes simplex genital	HERPES SIMPLEX 2	G
1597	HIV positive and AIDS		
1598	AIDS*(Acquired immunodeficiency syndrome*)		G
1599	AIDS@(Acquired immunodeficiency syndrome@)	AIDS	
1600	AIDS[F](Acquired immunodeficiency syndrome)	AIDS[F]	
1601	HIV (Human immunodeficiency virus) positive	HIV POSITIVE	G
1602	Infection	INFECTION	F
1603	Infection postoperative		F
1604	Infection postoperative@	INFECTION POST OP	
1605	Infection postoperative[F]	INFECTION POST OP[F]	
1606	Infection viral	INFECTION VIRAL	F
1607	Malaria	MALARIA	F
1608	Measles	MEASLES	F
1609	Poliomyelitis	POLIOMYELITIS	F
1610	Pyrexia of unknown origin	PYREXIA OF UNKNOWN ORIGIN	F
1611	Q fever	Q FEVER	F
1612	Rheumatic fever	RHEUMATIC FEVER	F
1613	Rigor	RIGOR	F
1614	Rubella	RUBELLA	F
1615	Septicaemia		F
1616	Septicaemia@	SEPTICAEMIA	
1617	Septicaemia[F]	SEPTICAEMIA[F]	
1618	Syphilis	SYPHILIS	F
1619	Tetanus		F
1620	Tetanus@	TETANUS	
1621	Tetanus[F]	TETANUS[F]	
1622	Varicella	VARICELLA	F
1623	Viraemia	VIRAEMIA	F
1624	Wart	WART	F
1625	Wart genital	WARTS GENITAL	F
1626	**Immunological**		
1627	Allergy	ALLERGY	F
1628	Anaphylaxis	ANAPHYLAXIS	F
1629	Angioneurotic oedema	ANGIONEUROTIC OEDEMA	F
1630	Antinuclear antibody positive	ANF POSITIVE	F
1631	Behcet's syndrome	BEHCETS	F

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1632	Drug interaction	DRUG INTERACTION	F
1633	Sarcoidosis		F
1634	Sarcoidosis@	SARCOIDOSIS	
1635	Sarcoidosis[F]	SARCOIDOSIS[F]	
1636	Sjogren's syndrome	SJOGRENS SYNDROME	F
1637	Systemic lupus erythematosus		F
1638	Systemic lupus erythematosus@	SLE	
1639	Systemic lupus erythematosus[F]	SLE[F]	
1640	Transplantation rejection	TRANSPLANT REJECTION	F
1641	Unspecified side effects	UNSPECIFIED SIDE EFFECTS	F
1642	Vaccination reaction	VACCINATION REACTION	F
1643	**Adverse Reaction to Specific Drug**		
1644	Adverse reaction to other drug		
1645	Adverse reaction to other drug@	ADR TO OTHER DRUG	
1646	Adverse reaction to other drug[F]	ADR TO OTHER DRUG[F]	
1647	Dependence	DEPENDENCE	
1648	Withdrawal symptoms	WITHDRAWAL SYMPTOMS	
1649	**Accident and Injury**		
1650	Animal bite	ANIMAL BITE	
1651	Assault	ASSAULT	
1652	Burn		
1653	Burn@	BURN	
1654	Burn[F]	BURN[F]	
1655	Choking		
1656	Choking@	CHOKING	
1657	Choking[F]	CHOKING[F]	
1658	Drowning		
1659	Drowning@	DROWNING	
1660	Drowning[F]	DROWNING[F]	
1661	Drug overdose accidental	DRUG OD ACCIDENTAL	
1662	Electroshock		
1663	Electroshock@	ELECTROSHOCK	
1664	Electroshock[F]	ELECTROSHOCK[F]	
1665	Erythema ab igne	ERYTHEMA AB IGNE	
1666	Fall		
1667	Fall#[F]		
1668	Fall*		
1669	Fall@	FALL	
1670	Fall[F]	FALL[F]	
1671	Fall major injury*		
1672	Fall major injury@	FALL MAJOR INJURY	
1673	Fall major injury[F]	FALL MAJOR INJURY[F]	
1674	Fall minor injury	FALL MINOR INJURY	
1675	Fall no injury	FALL NO INJURY	
1676	Fracture		
1677	Fracture@	FRACTURE	
1678	Fracture[F]	FRACTURE[F]	
1679	Frostbite	FROSTBITE	
1680	Haematoma	HAEMATOMA	
1681	Hyperkeratosis solar	HYPERKERATOSIS SOLAR	
1682	Injury		
1683	Injury@	INJURY	
1684	Injury[F]	INJURY[F]	
1685	Insect bite & sting		
1686	Bee sting	BEE STING	
1687	Insect bite	INSECT BITE	
1688	Wasp sting	WASP STING	
1689	Murder	MURDERED[F]	
1690	Poisoning nonmedicinal	POISONING NON MED	
1691	Raped	RAPED	
1692	Road traffic accident		
1693	Road traffic accident@	RTA	
1694	Road traffic accident[F]	RTA[F]	
1695	Shooting	SHOOTING	
1696	Stabbing	STABBING	
1697	Sunburn	SUNBURN	
1698	**Death**		
1699	DEATH GROUP01 SKIN		

G: low-level term to be grouped under high-level term F: freestanding low-level term

	A	B	C
1700	DEATH GROUP02 MSK		
1701	DEATH GROUP03 PSYCHIATRIC		
1702	DEATH GROUP04 CNS		
1703	DEATH GROUP07 CVS		
1704	DEATH GROUP08 RESPIRATORY		
1705	DEATH GROUP09 ALIMENTARY		
1706	DEATH GROUP10 METABOLIC		
1707	DEATH GROUP11 URINARY		
1708	DEATH GROUP17 HAEMOPOIETIC		
1709	DEATH GROUP18 MALIGNANCIES		
1710	DEATH GROUP19 NMT		
1711	DEATH GROUP21 INFECTION		
1712	DEATH GROUP22 IMMUNOLOGICAL		
1713	DEATH GROUP45 ADR		
1714	DEATH GROUP23 ACC & INJ		
1715	DEATH GROUP25 SURGERY		
1716	Death cause uncertain	DEATH CAUSE UNCERTAIN	
1717	**Grand Total**		
1718	**Surgery**		
1719	Abdominal surgery		
1720	Abdominal surgery#[F]		
1721	Appendicectomy	APPENDICECTOMY	
1722	Cholecystectomy	CHOLECYSTECTOMY	
1723	Gastrectomy	GASTRECTOMY	
1724	Gastrointestinal surgery	GI SURG	
1725	Hernia surgery	HERNIA SURG	
1726	Liver transplantation*		
1727	Liver transplantation@	LIVER TRANSPLANT	
1728	Liver transplantation[F]	LIVER TRANSPLANT[F]	
1729	Peptic ulcer surgery	PEPTIC ULCER SURG	
1730	Splenectomy	SPLENECTOMY	
1731	Vagotomy	VAGOTOMY	
1732	Acupuncture	ACUPUNCTURE	
1733	Adrenalectomy	ADRENALECTOMY	
1734	Blood transfusion	BLOOD TRANSFUSION	
1735	Bone marrow transplantation	BONE MARROW TRANSPL	
1736	Catheterisation	CATHETERISE	
1737	Chemotherapy	CHEMOTHERAPY	
1738	Dental surgery	DENTAL SURG	
1739	Dialysis renal	DIALYSIS RENAL	
1740	Ear nose and throat surgery	ENT SURG	
1741	Electroconvulsive therapy	ECT THERAPY	
1742	Endoscopy	ENDOSCOPY	
1743	Gastroscopy	GASTROSCOPY	
1744	Genitourinary surgery		
1745	Genitourinary surgery#[F]		
1746	Circumcision	CIRCUMCISION	
1747	Cystoscopy	CYSTOSCOPY	
1748	Genitourinary surgery@	GU SURG	
1749	Nephrectomy	NEPHRECTOMY	
1750	Orchidectomy	ORCHIDECTOMY	
1751	Prostatectomy*		
1752	Prostatectomy@	PROSTATECTOMY	
1753	Prostatectomy[F]	PROSTATECTOMY[F]	
1754	Renal transplantation	RENAL TRANSPLANT	
1755	Transurethral resection of prostate	TUR	
1756	Vasectomy	VASECTOMY	
1757	Gynaecological surgery		
1758	Abortion therapeutic	ABORTION THERAP	
1759	Caesarean section	CAESAREAN SECTION	
1760	Gynaecological surgery@	GYNAE SURG	
1761	Hysterectomy	HYSTERECTOMY	
1762	Lumpectomy	LUMPECTOMY	
1763	Mastectomy	MASTECTOMY	
1764	Minor surgery	MINOR SURG	
1765	Neurological surgery	NEURO SURG	
1766	Oesophageal dilatation	OESOPH DILATION	
1767	Ophthalmic surgery		

G low-level term to be grouped under high-level term F freestanding low-level term

	A	B	C
1768	Cataract extraction	CATARACT EXTRACTION	
1769	Corneal graft	CORNEAL GRAFT	
1770	Eye surgery	EYE SURG	
1771	Orthopaedic surgery		
1772	Orthopaedic surgery#[F]		
1773	Amputation	AMPUTATION	
1774	Orthopaedic surgery@	ORTHO SURG	
1775	Total hip replacement*		
1776	Total hip replacement@	THR	
1777	Total hip replacement[F]	THR[F]	
1778	Plastic surgery	PLASTIC SURG	
1779	Radiotherapy	RADIOTHERAPY	
1780	Sex change	SEX CHANGE	
1781	Surgery	SURG	
1782	Thoracic surgery		
1783	Thoracic surgery#[F]		
1784	Cardiac catheter	CARDIAC CATHETER	
1785	Cardiac surgery*		
1786	Cardiac surgery@	CARDIAC SURG	
1787	Cardiac surgery[F]	CARDIAC SURG[F]	
1788	Heart transplantation*		
1789	Heart transplantation@	HEART TRANSPLANT	
1790	Heart transplantation[F]	HEART TRANSPLANT[F]	
1791	Heart valve surgery	HEART VALVE SURG	
1792	Heart-lung transplantation*		
1793	Heart-lung transplantation@	HEARTLUNG TRANSPLANT	
1794	Heart-lung transplantation[F]	HEARTLUNG TRANSP[F]	
1795	Lung transplantation*		
1796	Lung transplantation@	LUNG TRANSPLANT	
1797	Lung transplantation[F]	LUNG TRANSPLANT[F]	
1798	Pacemaker	PACEMAKER	
1799	Thoracic surgery*		
1800	Thoracic surgery@	THORACIC SURG	
1801	Thoracic surgery[F]	THORACIC SURG[F]	
1802	Thyroid surgery	THYROID SURG	
1803	Tracheostomy	TRACHEOSTOMY	
1804	Vascular surgery		
1805	Endarterectomy	ENDARTERECTOMY	
1806	Vascular surgery@	VASCULAR SURG	
1807	Vascular surgery[F]	VASCULAR SURG[F]	
1808	**Referrals**		
1809	Hospital referrals no admission		
1810	Hospital referrals: Cardiology	HOSP REF CVS	
1811	Hospital referrals: Dermatology	HOSP REF SKIN	
1812	Hospital referrals: Ear, nose and throat	HOSP REF ENT	
1813	Hospital referrals: Gastroenterology	HOSP REF GI	
1814	Hospital referrals: General medicine	HOSP REF GEN MED	
1815	Hospital referrals: Gynaecology	HOSP REF GYNAE	
1816	Hospital referrals: Haematology	HOSP REF HAEMATOLOGY	
1817	Hospital referrals: Neurology	HOSP REF NEURO	
1818	Hospital referrals: Ophthalmology	HOSP REF EYE	
1819	Hospital referrals: Orthopaedics	HOSP REF ORTHO	
1820	Hospital referrals: Plastic surgery	HOSP REF PLASTIC	
1821	Hospital referrals: Psychiatry	HOSP REF PSYCH	
1822	Hospital referrals: Respiratory	HOSP REF RESP	
1823	Hospital referrals: Rheumatology	HOSP REF RHEUM	
1824	Hospital referrals: Urology	HOSP REF GU	
1825	Hospital referrals@	HOSP REF	
1826	Non-surgical admissions	HOSP ADM	
1827	**Social**		
1828	Arson	ARSON	
1829	Bereavement	BEREAVEMENT	
1830	Burgled	BURGLED	
1831	Domestic	DOMESTIC	
1832	Incest	INCEST	
1833	Loneliness	LONELINESS	
1834	Marital	MARITAL	
1835	Prison admission	PRISON ADM	

G low-level term to be grouped under high-level term F freestanding low-level term

	A	B	C
1836	Redundancy	REDUNDANCY	
1837	Shop lifting	SHOP LIFTING	
1838	**Events Ignored**		
1839	Events ignored		
1840	Blood unspecified	BLOOD NOS	
1841	Cardiovascular system unspecified	CVS NOS	
1842	Central nervous system unspecified	CNS NOS	
1843	Congenital unspecified	CONGENITAL NOS	
1844	Dehiscence	DEHISCENCE	
1845	Died abroad	DIED ABROAD	
1846	Drug unpalatable	UNPALATABLE	
1847	Ear unspecified	EAR NOS	
1848	Event not coded	EVENT NOT CODED	
1849	Eye unspecified	EYE NOS	
1850	Fatal outcome	FATAL OUTCOME	
1851	Gastrointestinal unspecified	GI NOS	
1852	Generic drug problem	GENERIC DRUG PROBLEM	
1853	Gynaecology unspecified	GYNAE NOS	
1854	Haemorrhage postoperative	HAEMORRHAGE NOS	
1855	Haemorrhage unspecified	HAEM POST OP	
1856	Hereditary unspecified	HEREDITARY NOS	
1857	Ischaemia	ISCHAEMIA	
1858	Laboratory test abnormal	LAB TEST ABNORMAL	
1859	Liver unspecified	HEPATIC NOS	
1860	Male reproductive system unspecified	MALE REPRO NOS	
1861	Metabolic unspecified	METABOLIC NOS	
1862	Microcephaly	MICROCEPHALY	
1863	Multiple congenital	MULTIPLE CONGENITAL	
1864	Musculoskeletal unspecified	MSK NOS	
1865	Nodule	NODULE	
1866	Non-malignant tumour unspecified	NMT NOS	
1867	Pain	PAIN	
1868	Pain postoperative	PAIN POST OP	
1869	Prophylaxis	PROPHYLAXIS	
1870	Psychiatric unspecified	PSYCHIATRIC NOS	
1871	Psychosomatic unspecified	PSYCHOSOMATIC NOS	
1872	Respiratory unspecified	RESP NOS	
1873	Skin unspecified	SKIN NOS	
1874	Urinary unspecified	URINARY NOS	
1875	Pregnancy		
1876	Abortion	ABORTION	
1877	Abortion spontaneous	ABORTION SPONT	
1878	Birth normal	BIRTH NORMAL	
1879	Pregnancy@	PREGNANCY	
1880	Substitute	SUB	
1881	Voids		
1882	Doctor died	DR DIED	
1883	Doctor moved	DR MOVED	
1884	Doctor retired	DR RETIRED	
1885	Drug not taken	DRUG NOT TAKEN	
1886	IMS (Intercontinental medical statistics) study	IMS STUDY	
1887	No record of drug	NO RECORD OF DRUG	
1888	No reply from FHSA**	NO REPLY FROM FPC	
1889	No reply from general practitioner	NO REPLY FROM GP	
1890	Patient emigrated	PT EMIGRATED	
1891	Patient moved	PT MOVED	
1892	Patient not registered	PT NOT REG	
1893	Records incomplete	RECORDS INCOMPLETE	
1894	Records not traced	RECORDS NOT TRACED	
1895	Records returned to FHSA**	RECORDS RET TO FPC	
1896	Returned unopened	RET UNOPENED	
1897	Struck off register	STRUCK OFF REGISTER	
1898	Void@	VOID	
1899	Wrong drug dispensed	WRONG DRUG DISPENSED	
1900	**FHSA (Family health service authority), formally FPC (Family practitioner committee)		

Appendix 9

Maximum likelihood estimators for two rates during two periods of observation in PEM

Exponential model for PEM

The statistical theory presented in this thesis is based on a Poisson model as in the previous paper published from the DSRU[59]. In the model, the occurrence of an episode is assumed to be independent of another episode of the same event in an individual patient. When the number of episodes of an event for individual i in the time interval [0, t] is defined as $N_i(t)$, the probability that $N_i(t) = n$ is given as

$$Pr(N_i(t) = n) = \frac{\exp(-\lambda t)(\lambda t)^n}{n!} \quad , n = 0, 1, 2. \text{ ----} \qquad (1)$$

where λ is the event rate. As only the first episode of the event is coded in PEM, particular attention is paid to the probability that the first episode occurs at time t or no episode occurs in [0, t] (i.e., $N_i(t) = 0$). The model may be reduced to the exponential model such that[59]

$$Pr(\text{no episode before time } t) = \exp(-\lambda t) \qquad (2)$$

Estimation of rates

Two rates during two periods may be estimated as maximum likelihood estimators (mles) based on the exponential model (equation 2) for two periods of observation.

For the first period (Penod 1)

$$Pr(\text{no episode in } [0,t] \text{ during Period 1}) = \exp(-\lambda_1 t) \quad (0 \leq t \leq t_1) \qquad (3)$$

where λ_1 is the event rate during the first period given in 'per patient per day', t is time after the first prescription of the drug given in days and t_I is the last day of the first period (t_I = 30 in this thesis).

For the second period (Period 2)

$$\Pr(\text{no episode in } [t_I, t] \text{ during Period 2}) = \exp(-\lambda_2(t-t_I)) \quad (t_I \leqq t \leqq t_{II}) \tag{4}$$

where λ_2 is the event rate during the second period given in 'per patient per day' and t_{II} is the last day of the second period (t_{II} = 180 in this thesis). The event rate is measured irrespective of whether the patient has had one or more episodes of the event during the first period. In other words, equation 4 describes events during the second period not only in the patients with no episode during the first period but also in the patients who have already had one or more episodes during the first period. As given in the 'method' section, in PEM once the patient has one or more episodes during the first period, any episode during the second period is not coded even if it does occur. However, this problem is settled in what follows. It is assumed that episodes of the event during the first period and those during the second period occur independently. For example, the probability that no episode of the event occurs in [0, t] where $t_I < t \leqq t_{II}$ is given as

$$\begin{aligned}\Pr(\text{no episode in } [0,t]) &= \Pr(\text{no episode in } [0, t_I] \text{ and in } [t_I,t]) \\ &= \Pr(\text{no episode in } [0, t_I])\Pr(\text{no episode in } [t_I,t]) \\ &= \exp(-\lambda_1 t_I)\exp(-\lambda_2(t- t_I)) \quad (t_I < t \leqq t_{II})\end{aligned} \tag{5}$$

For the patient i (i = 1, 2, ---, N), the following three quantities of time are defined. Time when the patient i has the first episode of an event is defined as t_i. The observation time during the first period is defined as the censored time during Period 1, c_{1i}. When the patient is observed beyond t_I, $c_{1i} = t_I$. If the patient is lost to follow-up during Period 1, $c_{1i} \leqq t_I$. For the patients observed beyond t_I, the censored time during Period 2, c_{2i}, is defined. When the patient is observed until the last day of the second period, $c_{2i} = t_{II}$. If the patient is lost to

follow-up during Period 2, $t_i < c_{2i} \leqq t_{II}$.

If the patient does not have any episode during observation, it is assumed that the patient has the first episode of the event after the observation is terminated: i.e., $t_i > c_{2i}$ for the patients who are observed beyond t_I and $t_i > c_{1i}$ for the patients who are lost to follow-up during Period 1.

For N_1 patients who have the first episode during Period 1, the contribution of the likelihood is its density function, $f_1(t_i)$, given as

$$f_1(t_i) = \lambda_1 \exp(-\lambda_1 t_i) \quad (0 \leqq t_i \leqq t_I) \tag{6}$$

For N_{1c} patients who have no episode during Period 1 but are lost to follow-up at c_{1i} $(0 \leqq c_{1i} \leqq t_I)$, the contribution of the likelihood is its survivor function, $S_1(c_{1i})$

$$S_1(c_{1i}) = \exp(-\lambda_1 c_{1i}) \quad (0 \leqq c_{1i} \leqq t_I) \tag{7}$$

The probability that a patient has no episode during $[0,t]$ where $t_I < t \leqq t_{II}$ is given in equation 5. Therefore, for N_2 patients who have the first episode during Period 2, the contribution of the likelihood is its density function, $f_2(t_i)$

$$\begin{aligned} f_2(t_i) &= \exp(-\lambda_1 t_I)\, \lambda_2 \exp(-\lambda_2 (t_i - t_I)) \\ &= \exp(-\lambda_1 c_{1i})\, \lambda_2 \exp(-\lambda_2 (t_i - t_I)) \qquad (t_I < t_i \leqq t_{II}) \end{aligned} \tag{8}$$

For N_{2c} patients who have no episode during Period 1 as well as during $[t_i, c_{2i}]$ of Period 2, the contribution of the likelihood is its survivor function, $S_2(c_{2i})$

$$S_2(c_{2i}) = \exp(-\lambda_1 c_{1i}) \exp(-\lambda_2 (c_{2i} - t_I)) \quad (t_I < c_{2i} \leqq t_{II}) \tag{9}$$

The number of whole patients, N, is given as $N = N_1 + N_{1c} + N_2 + N_{2c}$. The likelihood, $L(\lambda_1, \lambda_2)$ is given as

$$L(\lambda_1, \lambda_2) = \prod_{N1} f_1(t_i) \prod_{N1c} S_1(c_{1i}) \prod_{N2} f_2(t_i) \prod_{N2c} S_2(c_{2i}) \tag{10}$$

and

$$l(\lambda_1, \lambda_2) = \log L(\lambda_1, \lambda_2)$$

$$= \sum_{N1} \log f_1(t_i) + \sum_{N1c} \log S_1(c_{1i}) + \sum_{N2} \log f_2(t_i) \sum_{N2c} \log S_2(c_{2i})$$

$$= N_1 \log \lambda_1 - \lambda_1[\sum_{N1} t_i + \sum_{N-N1} c_{1i}] + N_2 \log \lambda_2 - \lambda_2[\sum_{N2} (t_i - t_i) + \sum_{N2c} (c_{2i} - t_i)] \quad (11)$$

If two quantities x_{1i} and x_{2i} are defined as

$$x_{1i} = \min(t_i, c_{1i})$$

$$x_{2i} = 0 \quad \text{if } t_i < t_i \text{ or } c_{1i} < t_i$$
$$= \min((t_i - t_i), c_{2i} - t_i)) \quad (12)$$

equation 11 is rewritten as

$$l(\lambda_1, \lambda_2) = \log L(\lambda_1, \lambda_2)$$

$$= N_1 \log \lambda_1 - \lambda_1 \Sigma x_{1i} + N_2 \log \lambda_2 - \lambda_2 \Sigma x_{2i} \quad (13)$$

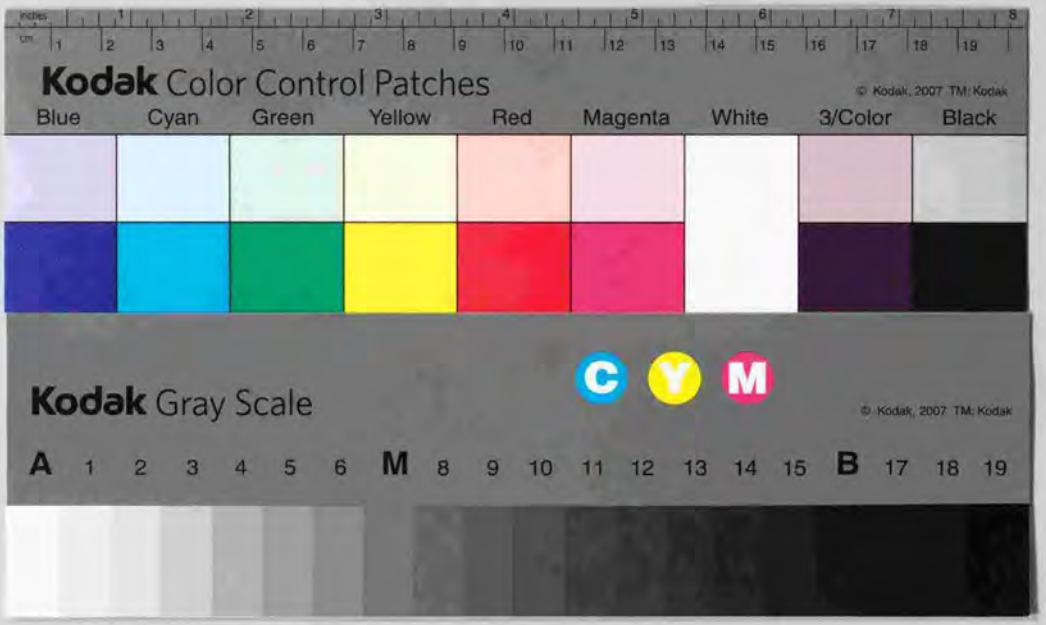
The mles are obtained by solving

$$\partial l / \partial \lambda_1 = 0 \text{ and } \partial l / \partial \lambda_2 = 0 \quad (14)$$

leading to mles of

$$\hat{\lambda}1 = N_1/\Sigma x_{1i} \quad \text{and} \quad \hat{\lambda}2 = N_2/\Sigma x_{2i} \quad (15)$$

It may be noted that two rates estimated according to equation 15 are free from the 'skewing effect' mentioned in some PEM reports[30-39]. In addition, the estimates are independent of each other to allow the use of the standard statisitical test on the difference of two rates[52-58]. These points are further discussed in the text.


Kodak Color Control Patches
© Kodak, 2007 TM: Kodak
Blue
Cyan
Green
Yellow
Red
Magenta
White
3/Color
Black
Kodak Gray Scale
C
Y
M
© Kodak, 2007 TM: Kodak
A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19