



## Practical addenda

### Addendum 3: Screening ADE databases

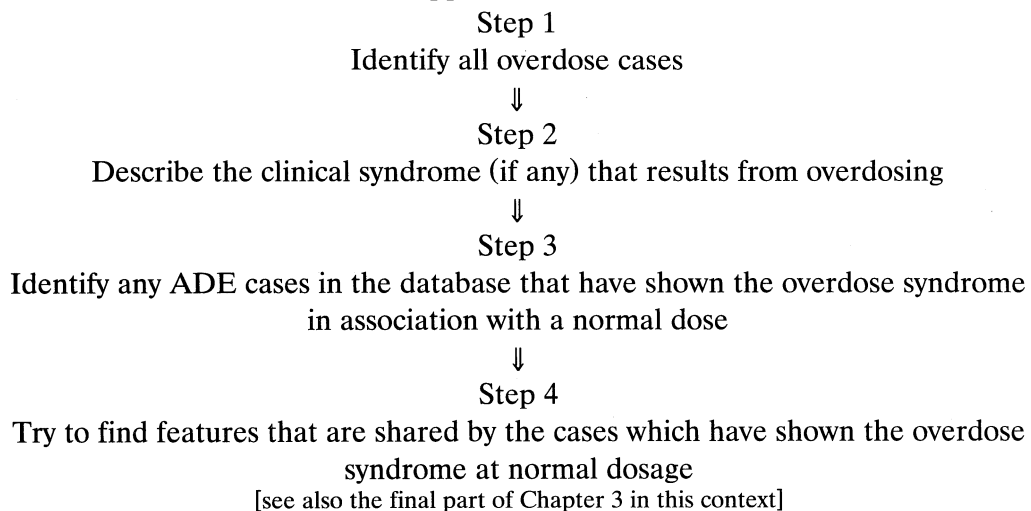
This Addendum displays screening techniques described in Chapter 3. These are semi-automated techniques that search for signals in an ADE database.

#### 1. The relative ADE profile

This illustration is also given in Chapter 3. It is repeated here for the sake of completeness (Fig. 1). Bars that extend beyond the upper confidence interval, which is represented by the right vertical line, are considered signals.

#### 2. The overdose approach

This scheme summarizes the approach:



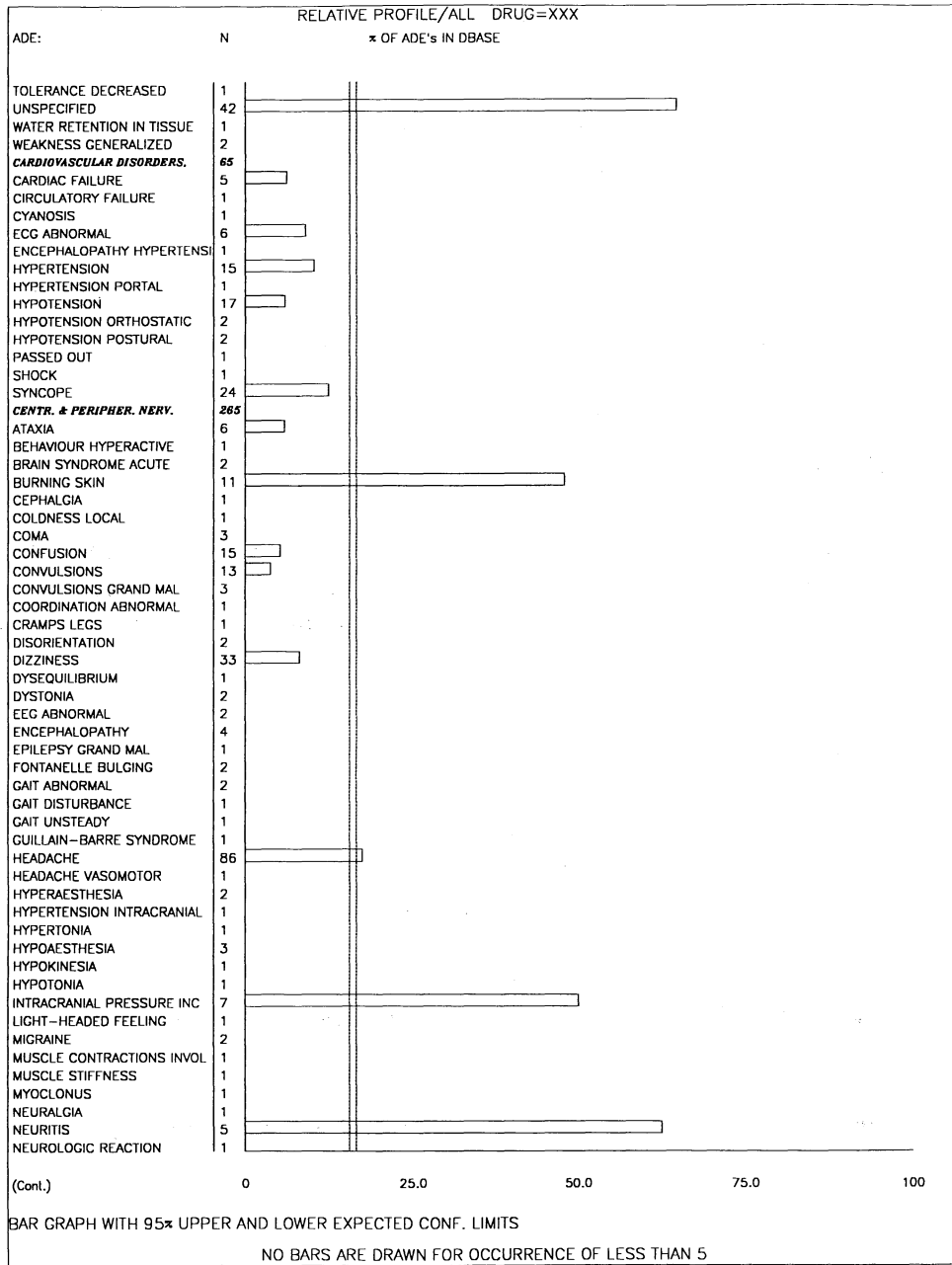


Fig. 1.

### 3. A search for drug-specific syndromes

The result of this exercise is shown in Figs. 2 and 3.

DRUG SPECIFIC SYNDROME		DRUG: A, NUMBER OF COMBINATION OCCURRENCES GE 5		
ADE COMBINATION		=EXPECTED FREQ (%) IN D.BASE	# COMBIN. VS TOT. # PTS CONF.LIM (+ %)	OCCUR. OF COMBINATIONS
Akathisia	Dyskinesia	0.25	0.17-0.82 (0.38%)	6
Akathisia	Dyskinesia tardive	0.28	0.17-0.82 (0.38%)	6
Akathisia	Extrapyramidal disorder	0.46	0.26-0.99 (0.5%)	8
Akathisia	Hypokinesia	0.11	0.13-0.73 (0.31%)	5
Akathisia	Muscle rigidity	0.26	0.17-0.82 (0.38%)	6
Akathisia	Parkinson's syndrome	0.54	1.12-2.39 (1.64%)	26
Akathisia	Suicide attempt	0.03	0.13-0.73 (0.31%)	5
Akathisia	Tremor	0.27	0.17-0.82 (0.38%)	6
Confusion	Muscle rigidity	0.06	0.13-0.73 (0.31%)	5
Confusion	Urinary incontinence	0.01	0.13-0.73 (0.31%)	5
Death	Pneumonia	0.07	0.17-0.82 (0.38%)	6
Depression	Parkinson's syndrome	0.08	0.13-0.73 (0.31%)	5
Drug interaction	Extrapyramidal disorder	0.12	0.21-0.91 (0.44%)	7
Dyskinesia	Extrapyramidal disorder	0.23	0.17-0.82 (0.38%)	6
Dyskinesia	Muscle rigidity	0.13	0.26-0.99 (0.5%)	8
Dyskinesia	Parkinson's syndrome	0.28	0.13-0.73 (0.31%)	5
Dyskinesia	Tremor	0.14	0.17-0.82 (0.38%)	6
Dystonia	Extrapyramidal disorder	0.40	0.13-0.73 (0.31%)	5
Dystonia	Laryngospasm	0.03	0.13-0.73 (0.31%)	5
Dystonia	Muscle rigidity	0.23	0.17-0.82 (0.38%)	6
Dystonia	Parkinson's syndrome	0.48	0.26-0.99 (0.5%)	8
Dystonia	Tongue protusion spastic involun	0.05	0.21-0.91 (0.44%)	7
Dystonia	Torticollis	0.08	0.3-1.07 (0.57%)	9
Dystonia	Trismus	0.04	0.21-0.91 (0.44%)	7
Extrapyramidal disorder	Fever	0.16	0.13-0.73 (0.31%)	5
Extrapyramidal disorder	Muscle rigidity	0.24	0.77-1.86 (1.2%)	19
Extrapyramidal disorder	Saliva increased	0.06	0.13-0.73 (0.31%)	5
Extrapyramidal disorder	Speech disorder	0.12	0.21-0.91 (0.44%)	7
Extrapyramidal disorder	Tremor	0.26	0.39-1.24 (0.69%)	11
Extrapyramidal disorder	Weight decrease	0.04	0.13-0.73 (0.31%)	5
Extrapyramidal disorder	Hypertonia	0.02	0.13-0.73 (0.31%)	5
Fever	Tremor	0.10	0.13-0.73 (0.31%)	5
Hypertonia	Hypokinesia	0.01	0.21-0.91 (0.44%)	7
Hypokinesia	Muscle rigidity	0.06	0.26-0.99 (0.5%)	8
Hypokinesia	Parkinson's syndrome	0.12	0.3-1.07 (0.57%)	9
Hypokinesia	Tremor	0.06	0.3-1.07 (0.57%)	9
Hyponatraemia	Thirst	0.01	0.17-0.82 (0.38%)	6
Muscle rigidity	Parkinson's syndrome	0.29	0.26-0.99 (0.5%)	8
Muscle rigidity	Speech disorder	0.07	0.21-0.91 (0.44%)	7
Muscle rigidity	Tremor	0.14	0.48-1.39 (0.82%)	13
Parkinson's syndrome	Tremor	0.30	0.34-1.15 (0.63%)	10

Fig. 2.

PATIENTS WITH MORE THAN 2 ADEs ONLY, OVERDOSES EXCLUDED  
 DRUG SPECIFIC SYNDROME  
 PREVIOUS ITEM SELECTION: TRIPLET OCCURENCES >= 2

ADE COMBINATION		NUMBER OF OCCURENCES	
Akathisia	Depression	Parkinson's syndrome	2
Akathisia	Dyskinesia	Parkinson's syndrome	2
Akathisia	Extrapyramidal disorder	Extrapyramidal disorder	2
Akathisia	Dystonia	Parkinson's syndrome	2
Akathisia	Extrapyramidal disorder	Hypokinesia	2
Akathisia	Extrapyramidal disorder	Muscle rigidity	2
Akathisia	Extrapyramidal disorder	Weight decrease	2
Akathisia	Hypokinesia	Muscle rigidity	3
Akathisia	Hypokinesia	Parkinson's syndrome	2
Akathisia	Muscle rigidity	Tremor	2
Confusion	Convulsion	Urinary incontinence	2
Confusion	Drug interaction	Extrapyramidal disorder	2
Confusion	Hyponatraemia	Urinary incontinence	2
Convulsions	Hyponatraemia	Thirst	2
Convulsions	Hyponatraemia	Urinary incontinence	2
Death	Pneumonia	Weight decrease	2
Drug interaction	Extrapyramidal disorder	Muscle rigidity	3
Drug interaction	Extrapyramidal disorder	Tremor	2
Drug interaction	Muscle rigidity	Tremor	2
Dyskinesia	Extrapyramidal disorder	Muscle rigidity	3
Dyskinesia	Hypokinesia	Parkinson's syndrome	2
Dyskinesia	Muscle rigidity	Tremor	3
Dyskinesia tardive	Extrapyramidal disorder	Hypokinesia	2
Dyskinesia tardive	Extrapyramidal disorder	Weight decrease	2
Dystonia	Extrapyramidal disorder	Tremor	2
Dystonia	Muscle rigidity	Parkinson's syndrome	3
Dystonia	Muscle rigidity	Tremor	2
Dystonia	Tongue protrusion spastic involun	Trismus	3
Extrapyramidal disorder	Fever	Tremor	2
Extrapyramidal disorder	Hypokinesia	Saliva increased	2
Extrapyramidal disorder	Hypokinesia	Tremor	2
Extrapyramidal disorder	Hypokinesia	Weight decrease	2
Extrapyramidal disorder	Muscle rigidity	Saliva increased	2
Extrapyramidal disorder	Muscle rigidity	Speech disorder	3
Extrapyramidal disorder	Muscle rigidity	Tongue protrusion spastic involun	2
Extrapyramidal disorder	Muscle rigidity	Tremor	3
Extrapyramidal disorder	Saliva increased	Tremor	3
Hypertonia	Hypokinesia	Parkinson's syndrome	2
Hypertonia	Hypokinesia	Tremor	2
Hypokinesia	Muscle rigidity	Parkinson's syndrome	4
Hypokinesia	Muscle rigidity	Tremor	4
Hypokinesia	Parkinson's syndrome	Tremor	3
Muscle rigidity	Parkinson's syndrome	Tremor	5
Muscle rigidity	Saliva increased	Speech disorder	2
Muscle rigidity	Speech disorder	Tremor	2

Fig. 3.

#### 4. Screening for drug interactions

This result is shown in Fig. 4.

DRUG A, "ADE CONC.MED" FOR # >= 5 ARE RETAINED ONLY 14:54 Thursday, November 4, 1993

OBS	ADE	CONC. MEDICATION	(1)	CONF. LIMIT FOR (1)	CONF. LIMIT FOR (2)	(2)	ALERT
			# A PTS WITH ADE			# COMB. PTS WITH ADE	
1	Akathisia	AMITRIPTYLINE	7.03%(115/1637)	[5.88, 8.37]	[9.22, 33.42]	18.42% (7/38)	X
2	Akathisia	BIPERIDEN	7.03%(115/1637)	[5.88, 8.37]	[13.22, 27.72]	19.47%(22/113)	X
3	Akathisia	DIAZEPAM	7.03%(115/1637)	[5.88, 8.37]	[4.44, 19.26]	9.52% (6/63)	
4	Akathisia	LITHIUM	7.03%(115/1637)	[5.88, 8.37]	[2.51, 12.9]	5.81% (5/86)	
5	Akathisia	LORAZEPAM	7.03%(115/1637)	[5.88, 8.37]	[6.47, 22.77]	12.5% (8/64)	
6	Anuria	AMITRIPTYLINE	0.49%(8/1637)	[0.25, 0.96]	[5.75, 27.33]	13.16% (5/38)	X
7	Confusion	LITHIUM	1.71%(28/1637)	[1.19, 2.46]	[2.51, 12.9]	5.81% (5/86)	X
8	Death	FUROSEMIDE	7.57%(124/1637)	[6.39, 8.96]	[11.19, 46.87]	25% (5/20)	X
9	Drug interaction	LITHIUM	1.71%(28/1637)	[1.19, 2.46]	[4.79, 17.3]	9.3% (8/86)	X
10	Dyskinesia	BIPERIDEN	3.6%(59/1637)	[2.8, 4.62]	[1.9, 9.94]	4.42% (5/113)	
11	Dystonia	BENZTROPINE	6.17%(101/1637)	[5.1, 7.44]	[2.7, 10.94]	5.51% (7/127)	
12	Extrapyramidal D	BENZTROPINE	6.96%(114/1637)	[5.83, 8.3]	[3.23, 11.94]	6.3% (8/127)	
13	Extrapyramidal D	BIPERIDEN	6.96%(114/1637)	[5.83, 8.3]	[2.46, 11.1]	5.31% (6/113)	
14	Extrapyramidal D	LITHIUM	6.96%(114/1637)	[5.83, 8.3]	[2.51, 12.9]	5.81% (5/86)	
15	Extrapyramidal D	TRIHENXYPHENIDYL	6.96%(114/1637)	[5.83, 8.3]	[6.26, 29.38]	14.29% (5/35)	
16	Fever	BENZTROPINE	2.5%(41/1637)	[1.85, 3.38]	[3.23, 11.94]	6.3% (8/127)	
17	Muscle rigidity	LITHIUM	3.97%(65/1637)	[3.13, 5.03]	[2.51, 12.9]	5.81% (5/86)	
18	Overdose effect	BENZTROPINE	2.93%(48/1637)	[2.22, 3.87]	[1.69, 8.89]	3.94% (5/127)	
19	Parkinson's synd	BIPERIDEN	7.64%(125/1637)	[6.45, 9.02]	[12.49, 26.75]	18.58%(21/113)	X
20	Parkinson's synd	CLOZAPAM	7.64%(125/1637)	[6.45, 9.02]	[12.5, 50.87]	27.78% (5/18)	X
21	Parkinson's synd	DIAZEPAM	7.64%(125/1637)	[6.45, 9.02]	[7.7, 24.97]	14.29% (9/63)	
22	Parkinson's synd	LITHIUM	7.64%(125/1637)	[6.45, 9.02]	[4.79, 17.3]	9.3% (8/86)	
23	Parkinson's synd	PERAZINE	7.64%(125/1637)	[6.45, 9.02]	[21.16, 57.29]	37.5% (9/24)	X
24	QT increased	LORAZEPAM	0.67%(11/1637)	[0.38, 1.2]	[3.38, 17.02]	7.81% (5/64)	X
25	Sudden death	CHLORPROMAZINE	3.12%(51/1637)	[2.38, 4.07]	[5.5, 19.66]	10.67% (8/75)	X
26	Tremor	BENZTROPINE	4.15%(68/1637)	[3.29, 5.23]	[1.69, 8.89]	3.94% (5/127)	
27	Tremor	BIPERIDEN	4.15%(68/1637)	[3.29, 5.23]	[4.88, 15.53]	8.85%(10/113)	
28	Tremor	LITHIUM	4.15%(68/1637)	[3.29, 5.23]	[2.51, 12.9]	5.81% (5/86)	

Fig. 4.

FOR EVERY DRUG AND FORMULATION TWO RATIOS (A AND B) ARE COMPARED 14:57 Thursday, November 4, 1993

A: NUMBER OF PATIENTS/AE IN A SPECIFIC COUNTRY

DIVIDED BY ALL REPORTED PATIENTS IN THIS COUNTRY

B: NUMBER OF PATIENTS/AE (WITHOUT THE SPEC. COUNTRY)

DIVIDED BY ALL REPORTED PATIENTS (WITHOUT THE SPEC. CNTRY)

----- DRUG=A -----

OBS	FORM	COUNTRY	ADE	A: SPECIFIC COUNTRY		B: OTHER COUNTRIES		WRN
108	Ampoule	United Sta	Cardiac arrest	2/23	8.7 (2.42-26.8) %	0/1	0 (0-79.35) %	
109	Ampoule	United Sta	Muscle rigidity	2/23	8.7 (2.42-26.8) %	0/1	0 (0-79.35) %	
110	Ampoule	United Sta	Nausea	6/23	26.09 (12.55-46.47) %	0/1	0 (0-79.35) %	
111	Ampoule	United Sta	Pruritus	12/23	52.17 (32.96-70.76) %	0/1	0 (0-79.35) %	
112	Ampoule	United Sta	Vomiting	6/23	26.09 (12.55-46.47) %	0/1	0 (0-79.35) %	
113	Topical	United Sta	Agitation	17/306	5.56 (3.5-8.72) %	1/28	3.57 (0.63-17.71) %	
114	Topical	United Sta	Anorexia	3/306	0.98 (0.33-2.84) %	1/28	3.57 (0.63-17.71) %	
115	Topical	United Sta	Application site reaction	70/306	22.88 (18.52-27.9) %	0/28	0 (0-12.06) %	X
116	Topical	United Sta	Constipation	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
117	Topical	Germany	Death	9/12	75 (46.77-91.11) %	18/322	5.59 (3.56-8.66) %	X
118	Topical	Netherlands	Death	2/5	40 (11.76-76.93) %	25/329	7.6 (5.2-10.98) %	X
119	Topical	United Sta	Depression	2/306	0.65 (0.18-2.35) %	1/28	3.57 (0.63-17.71) %	
120	Topical	United Sta	Diarrhoea	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
121	Topical	United Sta	Dyspepsia	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
122	Topical	United Sta	Efficacy, lack of	3/306	0.98 (0.33-2.84) %	0/28	0 (0-12.06) %	
123	Topical	United Sta	Fatigue	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
124	Topical	United Sta	Fever	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
125	Topical	United Sta	Headache	9/306	2.94 (1.55-5.49) %	0/28	0 (0-12.06) %	
126	Topical	United Sta	Hypertension	3/306	0.98 (0.33-2.84) %	0/28	0 (0-12.06) %	
127	Topical	United Sta	Influenza-like symptoms	3/306	0.98 (0.33-2.84) %	0/28	0 (0-12.06) %	
128	Topical	United Sta	Malaise	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
129	Topical	United Sta	Mouth dry	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
130	Topical	United Sta	Nausea	38/306	12.42 (9.18-16.59) %	1/28	3.57 (0.63-17.71) %	
131	Topical	Portugal	Neoplasm malignant aggrav	2/3	66.67 (20.77-93.85) %	2/331	0.6 (0.17-2.18) %	X
132	Topical	United Sta	Nervousness	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
133	Topical	United Sta	Oedema legs	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
134	Topical	United Sta	Pruritus	10/306	3.27 (1.78-5.91) %	0/28	0 (0-12.06) %	
135	Topical	United Sta	Rash	4/306	1.31 (0.51-3.31) %	0/28	0 (0-12.06) %	
136	Topical	United Sta	Rigors	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
137	Topical	United Sta	Sleep disorder	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
138	Topical	United Sta	Therapeutic response decreased	88/306	28.76 (23.97-34.07) %	0/28	0 (0-12.06) %	X
139	Topical	United Sta	Therapeutic response increased	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
140	Topical	United Sta	Twitching	3/306	0.98 (0.33-2.84) %	0/28	0 (0-12.06) %	
141	Topical	United Sta	Urinary retention	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
142	Topical	United Sta	Vertigo	2/306	0.65 (0.18-2.35) %	0/28	0 (0-12.06) %	
143	Topical	United Sta	Vomiting	24/306	7.84 (5.33-11.4) %	1/28	3.57 (0.63-17.71) %	
144	Vial	Switzerland	Efficacy, lack of	4/4	100 (-) %	0/0	(-) %	

----- DRUG=B -----

OBS	FORM	COUNTRY	REACTION	A: SPECIFIC COUNTRY		B: OTHER COUNTRIES		WRN
145	Ampoule	Germany	Dyskinesia	2/11	18.18 (-) %	0/0	(-) %	

----- DRUG=C -----

OBS	FORM	COUNTRY	REACTION	A: SPECIFIC COUNTRY		B: OTHER COUNTRIES		WRN
146	Tablet	Great Brit	Collapse transient	2/10	20 (5.67-50.98) %	0/3	0 (0-56.15) %	
147	Tablet	Great Brit	Epistaxis	2/10	20 (5.67-50.98) %	0/3	0 (0-56.15) %	

----- DRUG=D -----

OBS	FORM	COUNTRY	REACTION	A: SPECIFIC COUNTRY		B: OTHER COUNTRIES		WRN
148	Ampoule	Great Brit	Extrapyramidal disorder	3/17	17.65 (6.19-41.03) %	0/3	0 (0-56.15) %	
149	Ampoule	Great Brit	Injection site mass	7/17	41.18 (21.61-63.99) %	0/3	0 (0-56.15) %	

AN X IS SHOWN IF THE SPECIFIC COUNTRY LOWER LIMIT  
EXCEEDS THE OVERALL(/DRUG/FORM) UPPER LIMIT  
COUNTRIES WITH # REPORTS <= 1 ARE EXCLUDED

Fig. 5.

WEEKLY STATUS, DATA FROM PERIOD: 28OCT93 TO 04NOV93 08:30 Thursday, November 4, 1993 25  
 WITH RETROSPECTIVE VIEW OF FREQUENCIES FOR S.EXP. CASES & DEATHS  
 (# S+NS+DTHS PRIM. TERMS/PROD./PERIOD)/(# PATIENTS/PRODUCT/PERIOD)(%)  
 SORT KEY=MEDICATION AND ASSESSMENT

----- DRUG=A -----									
ASSES	REFNO	PRIMTERM	6 MNTS CONF. LIM.	6 MTHS YR BEFORE	DOSE	DOSEFREQ	SCHED	AGE	CTRY
NS	22274	Agitation Agitation Insomnia Speech disorder						43.00	GER
SE	20078	Hypotension	3.01-56.35 (16.67 %)	0-39.03 (0 %)				45.00	USA
----- DRUG=B -----									
ASSES	REFNO	PRIMTERM	6 MNTS CONF. LIM.	6 MTHS YR BEFORE	DOSE	DOSEFREQ	SCHED	AGE	CTRY
NS	22346	Somnolence			10		single	70.00	USA
NS	22379	Gamma-GT increas			5		daily	unk.	GER
----- DRUG=C -----									
ASSES	REFNO	PRIMTERM	6 MNTS CONF. LIM.	6 MTHS YR BEFORE	DOSE	DOSEFREQ	SCHED	AGE	CTRY
NS	18857	Nausea					daily	unk.	USA
NS	18858	Vomiting					daily	unk.	USA
NS	18859	Nausea					daily	unk.	USA
NS	22332	Vomiting					daily	unk.	USA
NS	22332	Nervousness			40		daily	63.00	GER
NS	22332	Tongue oedema					daily	63.00	GER
SE	19615	Hypotension	2.32-25.85 (8.33 %)	0-25.88 (0 %)			daily	65.00	USA
SE	22275	Angioedema	2.32-25.85 (8.33 %)	0-25.88 (0 %)	60		daily	56.00	GER
SE	22422	Extrapramidal D	0.74-20.24 (4.17 %)	1.62-37.74 (9.09 %)			daily	76.00	GBR
SU	19110	Neuroleptic mali	2.32-25.85 (8.33 %)	0-25.88 (0 %)	5		daily	36.00	USA
SU	22378	Apnoea			1		total	51.00	GER
SU	22378	Hepatic function			5		total	51.00	GER

Fig. 6.

### 5. Screening for batch problems

As explained in Chapter 3, the batch number usually remains unknown. Fig. 5 is, therefore, rather theoretical. However, in this display, one can replace the batch number by a country or a group of countries to which specific batches have been shipped, as an approximation to the problem under study.

### 6. Detecting increased frequency of a known adverse effect

See Fig. 6. For background information pertaining to this display, the reader is referred to Chapter 3.