ORIGINAL RESEARCH ARTICLE

Drug Safety 2000 Dec; 23 (6): 533-542
0114-5916/00/0012-0533/$20.00/0

A Retrospective Evaluation of a Data Mining Approach to Aid Finding New Adverse Drug Reaction Signals in the WHO International Database

Marie Lindquist, Malin Ståhl, Andrew Bate, I. Ralph Edwards and *Ronald H.B. Meyboom*

The Uppsala Monitoring Centre, Uppsala, Sweden

Abstract

Background: The detection of new drug safety signals is of growing importance with ever more new drugs becoming available and exposure to medicines increasing. The task of evaluating information relating to safety lies with national agencies and, for international data, with the World Health Organization Programme for International Drug Monitoring.

Rationale: An established approach for identifying new drug safety signals from the international database of more than 2 million case reports depends upon clinical experts from around the world. With a very large amount of information to evaluate, such an approach is open to human error. To aid the clinical review, we have developed a new signalling process using Bayesian logic, applied to data mining, within a confidence propagation neural network (Bayesian Confidence Propagation Neural Network; BCPNN). Ultimately, this will also allow the evaluation of complex variables.

Methods: The first part of this study tested the predictive value of the BCPNN in new signal detection as compared with reference literature sources (Martindale's Extra Pharmacopoeia in 1993 and July 2000, and the Physicians Desk Reference in July 2000). In the second part of the study, results with the BCPNN method were compared with those of the former signalling procedure.

Results: In the study period (the first quarter of 1993) 107 drug–adverse reaction combinations were highlighted as new positive associations by the BCPNN, and referred to new drugs. 15 drug–adverse reaction combinations on new drugs became negative BCPNN associations in the study period. The BCPNN method detected signals with a positive predictive value of 44% and the negative predictive value was 85%. 17 as yet unconfirmed positive associations could not be dismissed with certainty as false positive signals.

Of the 10 drug–adverse reaction signals produced by the former signal detection system from data sent out for review during the study period, 6 were also identified by the BCPNN. These 6 associations have all had a more than 10-fold increase of reports and 4 of them have been included in the reference sources. The remaining 4 signals that were not identified by the BCPNN had a small, or no, increase in the number of reports, and are not listed in the reference sources.

Conclusion: Our evaluation showed that the BCPNN approach had a high and promising predictive value in identifying early signals of new adverse drug reactions.

Background

The Uppsala Monitoring Centre, as the WHO Collaborating Centre for international drug monitoring, is responsible for the technical and scientific maintenance and development of the WHO International Drug Monitoring Programme. The programme now has 56 member countries, annually contributing around 150 000 suspected adverse drug reaction (ADR) reports to the WHO database in Uppsala.

One of the main aims of the international pharmacovigilance programme is to identify early signals of safety problems related to medicines. To aid this, a new ADR signalling system has been implemented by the Uppsala Monitoring Centre. It complements the previous signal generation procedure which involved the examination of large, unwieldy amounts of sorted and tabulated material by an expert panel. We have previously published an overview of the new signalling approach, including results from an evaluation including a comparison against another signalling system.[1] The new system is based on a data mining technique, using a Bayesian Confidence Propagation Neural Network (BCPNN) to scan incoming ADR reports and compare them statistically with what is already stored in the database.[2,3]

The new quarterly output contains statistical information from the BCPNN scan. It also contains frequency counts for each drug and ADR listed, individually and occurring together. The figures from the previous quarter are also included and the data is provided in a computerised format.

Drug–adverse reaction combinations that are statistically significantly different from the background of reports ('associations') are sent to a panel of reviewers for evaluation and expert opinion. Within the WHO Programme a 'signal' concerns 'information regarding a possible relationship between a drug and an adverse event or interaction'.[4] As before, signals of possible safety problems are circulated to all national centres participating in the international pharmacovigilance programme for consideration of public health implications.

The aim of the 2 parts of this study was to evaluate the ability of the BCPNN system to:

- pick up signals early, i.e. before publication in a standard reference source (study I);
- pick up valid signals, i.e. drug–adverse reaction associations that are described in a standard reference source;
- pick up signals identified in the previous signal generation system.

Methods

BCPNN Methodology

The BCPNN methodology[2,3] uses a neural network architecture to identify unexpectedly strong dependencies between variables (e.g. drugs and adverse reactions) within the WHO database, and how dependencies change on addition of new data. The dependencies are selected using a measure of disproportionality called the Information Component (IC):

$$IC = \log_2 \frac{P_{xy}}{P_x P_y}$$

Where:

P_x = probability of a specific drug being listed on a case report;

P_y = probability of a specific ADR being listed on a case report;

P_{xy} = probability that a specific drug–adverse reaction combination is listed on a case report.

Thus the IC value is based on:

- the number of case reports with drug X (C_x)
- the number of case reports with ADR Y (C_y)
- the number of reports with the specific combination (C_{xy})
- the total number of reports (C).

Positive IC values indicate that the particular combination of variables is reported to the database more often than statistically expected from reports al-

ready in the database. The higher the value of the IC, the more the combination stands out from the background.

From the distribution of the IC, expectation and variance values are calculated using Bayesian statistics. The standard deviation for each IC provides a measure of the robustness of the value. The higher the C_x, C_y and C_{xy} levels are, the narrower the confidence interval becomes. If a positive IC value increases over time and the confidence interval narrows, this shows a likelihood of a positive quantitative association between the studied variables.

In this study we used drug as variable 'x' and adverse reaction as variable 'y'. The term 'association' denotes a drug-adverse reaction combination where the lower 95% confidence limit of the IC value is above 0.

Test of BCPNN Predictive Value in Signal Detection

A retrospective standard quarterly BCPNN database screening was made for the first quarter of 1993. We selected for analysis drug–adverse reaction combinations which in this quarter became positive 'associations' (the lower 95% confidence limit of the IC value changed from a negative to a positive value), and which included new drugs (first reported to the WHO database in 1990 or later). We also selected combinations referring to new drugs, for which the upper 95% confidence limit of the IC changed from a positive to a negative value in the study period. In this paper these are referred to as negative associations.

We then analysed if these positive and negative associations were widely known at the time. This was done by checking if they were listed in the 30th edition of Martindale[5] published in 1993. Martindale was chosen as it is a standard compendium of drug information, available worldwide and containing monographs based on published information.

We subsequently analysed if the selected associations had been strengthened or confirmed over the 7 year period from 1993 to 2000. The associations were therefore checked against Martindale, the July 2000 online edition,[6] and also against the July 2000 online version of the US Physicians' Desk Reference.[6] The latter reference source contains labelling information approved by the US Food and Drug Administration (FDA) and was used as a second reference, because of its comprehensive listing of ADRs, recognised as well as suspected.

All reports in the WHO database are coded using the WHO Adverse Reaction Terminology. This is a hierarchical classification, with the following levels:

- system organ class: a group of adverse reaction terms pertaining to the same body organ system
- high level term: a grouping term for qualitatively similar preferred terms
- preferred term: main terms for coding of adverse reactions
- included term: lower level terms, e.g. synonyms with, or more specific terms than, the preferred terms.

In the analysis we used the WHO preferred terms of the selected associations and compared those against the listed terms or descriptions used in Martindale and the Physicians' Desk Reference.

The following codes were used:

- N = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group;
- NA = not applicable, i.e. the drug was not found in the source, or was noted as being withdrawn from the market
- Y+ = a high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself
- Y = the drug was found and the same ADR, or a synonym, was listed for the drug.

Comparison of New BCPNN Approach to Previous Signalling Procedure

We made retrospective BCPNN scans to identify if, and when, drug–adverse reaction safety signals circulated to national pharmacovigilance centres fulfilled the association threshold criteria.

Before the introduction of the BCPNN, quarterly printouts at 2 threshold levels were sent to a review panel for the selection of possible signals:

- 'level 2': at least 2 case reports of the combination, with the drug being reported as suspected of having caused the reaction
- 'level 5': at least 5 case reports of the combination, with the drug being reported as suspected of having caused the reaction.

For this test, we selected all drug–adverse reaction combinations, which had been listed in the 'level 2' listing of the first quarter of 1993 and had gone on to be circulated as signals.

We checked if these were included in the 30th edition of Martindale,[5] Martindale June 1999 online version[7] and the June 1999 online version of the Physicians' Desk Reference,[7] and we analysed the increase of reports from 1993 to 1999 for the signalled combinations.

Table I. Result of an analysis of the 30th edition of Martindale (1993)[5] for positive and negative associations selected from a BCPNN retrospective screening of drug–adverse reaction combinations entered into the WHO database in the first quarter of 1993

Types of associations	Number of associations
Positive	
Associations not listed in Martindale (N or NA)	71
Association listed on high level term, or by referral to group (Y+)	29
Association listed on preferred term level (Y)	7
Total	**107**
Negative	
Associations not listed in Martindale (N or NA)	7
Association listed on high level term, or by referral to group (Y+)	4
Association listed on preferred term level (Y)	4
Total	15

ADR = adverse drug reaction; **BCPNN** = Bayesian Confidence Propagation Neural Network; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y+** = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself.

Results

Test of BCPNN Predictive Value in Signal Detection

In the first quarter of 1993, 682 drug–adverse reaction combinations fulfilled the quantitative threshold criteria for new BCPNN positive associations. 107 of these concerned new drugs. Another 32 combinations became negative associations in the study period. 15 of those referred to new drugs.

The literature reference sources (30th edition of Martindale,[5] Martindale online July 2000 and Physician's Desk Reference online July 2000[6]) were checked for references to the 107 positive and the 15 negative associations selected for analysis. The results are shown in table I and II.

As seen in table I, 71 of the positive associations were not listed at all in the 30th edition of Martindale.[5] 29 were listed by a higher level term, or indirectly, by referral to another drug in the same group, while only 7 positive associations were specifically mentioned.

For the negative associations, more than half were listed in the 30th edition of Martindale,[5] either specifically or indirectly.

Table II shows that 78 positive associations have been strengthened or confirmed in current literature, whereas 29 were not listed. Of the negative associations, 10 were now listed.

The aim of the Uppsala Monitoring Centre signalling process is to identify previously undetected adverse reactions to medicines. Thus, we consider drug–adverse reactions already known as nonsignals (in this study there were 36 positive and 8 negative such associations). In addition there were 10 positive and 2 negative associations relating to a drug withdrawn immediately before the study period, and 2 positive associations relating to a drug withdrawn during the study period. These 14 associations were excluded. Hence we obtained the results shown in table III.

From this, the positive predictive value is 44% (42 of 95) and the negative predictive value is 85% (11 of 13).

Table II. Result of an analysis of the July 2000 online versions of Martindale and Physicians Desk Reference[6] for positive and negative associations selected from a BCPNN retrospective screening of drug-ADR combinations entered into the WHO database first quarter 1993

Type of association	Number of associations
Positive	
Associations not listed in Martindale or PDR (N or NA)	29
Associations listed in Martindale or PDR (Y or Y+)	78
Total	107
Negative	
Associations not listed in Martindale or PDR (N or NA)	5
Associations listed in Martindale or PDR (Y or Y+)	10
Total	15

ADR = adverse drug reaction; **BCPNN** = Bayesian Confidence Propagation Neural Network; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y+** = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself.

Table IV lists as yet unconfirmed positive associations, excluding the 12 on withdrawn drugs. For each there is a short commentary based on a preliminary analysis.

Comparison of New BCPNN Approach to Previous Signalling Procedure

There were a total of 10 drug–adverse reaction combinations from the first quarter of 1993 'level 2' listing which were subsequently signalled in the previous procedure. The result of a BCPNN scan of these, and checks against the June 1999 online version of Martindale[7] and the June 1999 online version of Physicians' Desk Reference[7] are shown in table V. The increase in the number of reports from the first quarter of 1993, to the first quarter of 1999, is also shown in table V. On analysis, 6 of the 10 signals have fulfilled the BCPNN association criteria. The remaining 4 drug–adverse reaction combinations still had no more than 4 case reports for each at the end of the first quarter of 1999. On the other hand, the 6 signals that were BCPNN associations have all had more than a 10-fold increase in number of reports to date.

Four of the 6 signals that passed the associations threshold did so before being circulated within the WHO Programme. Two did not, and, although sumatriptan and confusion became an association in the fourth quarter of 1993, the quantitative strength of the relationship has since decreased.

Discussion

At the start of the WHO International Drug Monitoring Programme in the late 1960s quantitative and statistical methods were proposed for adverse reaction signalling purposes.[8] Because of constraints in computational power these were not realised at the time. Lately, however, there has been a renewed interest in statistical methods applied to signal generation in pharmacovigilance. We are aware of work being done in several countries based on proportional reporting ratios and odds ratios, and, in the US, a Bayesian data mining tool for signal generation has been developed for the FDA.[9]

The assessment of an ADR signalling system is difficult because there is no 'gold standard' for comparison. Also there are different definitions of the

Table III. Predictive value of the Bayesian Confidence Propagation Neural Network in new signal detection[a]

Associations	Signals[b]	Nonsignals[c]	Total
Positive	42	53	95
Negative	2	11	13

a Associations referring to withdrawn drugs are excluded.

b Listed (Y/Y+) in the July 2000 online versions of Martindale and the Physicians' Desk Reference[6] and not listed (N) in the 30th edition of Martindale.[5]

c Not listed (N) in the July 2000 online versions of Martindale or the Physicians' Desk Reference;[6] or listed (Y/Y+) in the 30th edition of Martindale.[5]

N = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y+** = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself.

Table IV. Positive associations identified by the Bayesian Confidence Propagation Neural Network from the first quarter of 1993 which are not listed in the July 2000 online versions of Martindale (MD) or the Physicians' Desk Reference (PDR)[6][a]

Drug name	WHO-ART term	MD 2000	PDR 2000	Ratio of reports (Q1 1999/Q1 1993)	Comments
Insulin ('Humulin')	Therapeutic response decreased	N	N	1.3	These reports suggest that occasionally the therapeutic effect may decrease after some time of use. A minority of reports refers to suspected interactions with other drugs
Ketorolac	Cholelithiasis	N	N	1.0	Only 3 patients, who all simultaneously had several other serious suspected adverse reactions, e.g. pancreatitis, duodenal ulcer, GI haemorrhage, ileus
Ketorolac	Hiccup	N	N	1.3	Hiccup occurred in association with, and probably secondary to, other suspected adverse reactions (e.g. vomiting, ulcer and haematemesis, abdominal pain): probably nonspecific stimulation of the phrenic nerve and not a pharmacological effect
Ketorolac	Peritonitis	N	N	2.5	In all but 1 report peritonitis occurred in patients with intestinal perforation, i.e. as a complication of another suspected adverse reaction, GI ulcer
Ketorolac	Renal tubular disorder	N	N	1.0	Concern over the high incidence of adverse reactions, including acute renal failure, has led to regulatory actions and, in some countries, withdrawal[b]
Ketorolac	Renal tubular necrosis	N	N	9.3	Concern over the high incidence of adverse reactions, including acute renal failure, has led to regulatory actions and, in some countries, withdrawal[b]
Lomefloxacin	Drug level increased	N	N	2.3	These reports refer to signs of – mainly cardiac or nervous system – toxicity. All patients simultaneously used theophylline and the term suggests that during use of lomefloxacin increased blood concentrations of theophylline were found, i.e. a suspected interaction. According to the July 2000 online version of Martindale,[6] lomefloxacin is considered not to interact significantly with theophylline or caffeine
Lomefloxacin	Tolerance increased	N	N	1.3	In these 4 reports no other drugs were recorded, and no other explanation was given
Moxonidine	Angina pectoris	N	NA	3.3	Age and concomitant illness in hypertension patients are associated with a high risk of atherosclerosis and angina pectoris. Several other groups of antihypertensive drugs are known occasionally to cause (increased) angina pectoris. These 22 reports suggest that moxonidine occasionally precipitates or aggravated angina pectoris, that the effect promptly disappears after stopping and that it may also fade when the drug is continued
Nafarelin	Lacrimation abnormal	N	N	1.0	Lacrimation disturbance and xerophthalmia have also been reported to the WHO database with the related drugs buserelin, goserelin, leuprorelin and octreotide
Nafarelin	Taste perversion	N	N	1.4	Disturbances of taste and smell have also been reported to the WHO database with the related drugs buserelin, goserelin, leurporelin and octreotide
Nicotine	Breast enlargement	N	N	2.5	Breast enlargement is reported in 11 pre- or postmenopausal women in 4 countries; 5 patients simultaneously used hormone preparations. In addition, there are 2 reports of men with gynaecomastia during the use of nicotine patches. Perhaps this is a secondary effect to decreased enzyme induction after stopping heavy smoking

Continued next page

Table IV cont.

term ‘signal’. According to the definition used in the WHO Programme a signal is essentially a hypothesis together with data and arguments, and it is not only uncertain but also preliminary in nature: the situation may change substantially over time.[4,10]

For the purpose of the paper we felt we would achieve a reasonable estimate of the predictive power of the BCPNN tool by checking historical associations identified by the BCPNN against standard reference sources. Martindale has worldwide coverage, recognition and wide availability and was used as a standard for well known, recognised ADRs. The Physicians’ Desk Reference, though not international, gives very recent information on drugs. It has a comprehensive ADR listing, generally more inclusive than that of Martindale. However, the Physicians’ Desk Reference also includes suspected adverse reactions, whether substantiated or not. We considered an ADR listed in the Physicians’ Desk Reference an indication of a possible drug–adverse reaction relationship. Table IV lists the positive associations still not mentioned in the reference sources. These cannot simply be dismissed as ‘false positives’, since at least some of them may be true signals of ADRs that are not yet established. The reader can draw some conclusions about them in addition to the comments in the table. Several of the associations in table IV raise the point that there may well be alternative explanations, relating, for example, to the way in which the drug is used, or confounding underlying disease. However, the reviewer should not dismiss the drug as causal too readily. Similarly also ‘true negatives’ might be as yet unrecognised signals.

The length of time chosen for the retrospective check against the literature was not arbitrary, but based on the assumption that 7 years would be sufficient for ADRs to be included in the reference sources, allowing for the maximum reporting for new drugs to have taken place (the Weber effect). We know however that 1 new association appeared in Martindale between 1999 and 2000, and 7 years still may not be long enough. Publishing delay must be considered in the use of these reference sources, but

Table IV. Contd.

Drug name	WHO-ART term	MD 2000	PDR 2000	Ratio of reports (Q1 1999/Q1 1993)	Comments
Nicotine	Hypercholesterolaemia	N	N	1.3	Reports in 2 countries. A follow up may be interesting
Nicotine	Libido increased	N	N	1.3	Small number of poorly documented cases from a single country
Nicotine	Penis disorder	N	N	1.0	Small number of poorly documented cases from a single country
Nicotine	Sudden death	N	N	1.8	Cause of death not specified. It is known, however, that nicotine may cause serious cardiac arrhythmia. One probable duplicate report
Technetium^{99m} sestamibi	Nausea	N	NA	4.0	Nausea usually occurred as part of a more general reaction after intravenous injection, together with urticaria, myalgia, agitation, headache

a In the study, Martindale and Physicians' Desk Reference were the standards, but for all unconfirmed associations a comprehensive literature search would be indicated.

b July 2000 online version of Martindale.[6]

GI = gastrointestinal; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **WHO-ART** = World Health Organization Adverse Reaction Terminology.

Table V. Signals circulated within the WHO Programme in 1993 to 1996 originating from the first quarter of 1993, together with the result of the Bayesian Confidence Propagation Neural Network scan of these and the subsequent check in the 30th edition of Martindale (MD 1993),[5] and the June 1999 online versions of Martindale (MD 1999) and the Physician's Desk Reference (PDR 1999).[7] The increase in the number of reports from the first quarter of 1993 to the first quarter of 1999, is also shown

Drug name	WHO-ART term	BCPNN association (quarter no. and year)	Signal circulated within th WHO Programme (month/year)	MD 1993	MD 1999	PDR 1999	Ratio of reports (Q1 1999/ Q1 1993)
Aminaphtone	Urticaria		Mar 1994	N	N	NA	0
Calcitonin	Vasculitis		Dec 1995	N	N	N	2
Finasteride	Death	Q4 1994	Dec 1993	N	N	N	174
Finasteride	Impotence	Q2 1993	Mar 1994	Y	Y	Y	130
Fludarabine	Dyspnoea	Q4 1993	Jul 1993	N	Y	Y	12
Nafarelin	Gingivitis		Feb 1995	N	N	N	1.5
Remoxipride	Convulsions		Jun 1993	Y+	N	NA	1.3
Sumatriptan	Confusion	Q4 1993	Mar 1994	N	N	Y	43
Sumatriptan	Peripheral ischaemia	Q4 1993	Jun 1994	N	N	N	24
Zolpidem	Aggressive reaction	Q4 1994	Sep 1995	N	Y+	Y	18

ADR = adverse drug reaction; **N** = the drug was found in the source but no matching ADR or corresponding high level terms were described for the drug or for the drug group; **NA** = not applicable (the drug was not found in the source, or was noted as being withdrawn from the market); **Y** = the drug was found and the same ADR, or a synonym, was listed for the drug; **Y**+ = high level term pertaining to the 'preferred term' of the ADR, but not the specific ADR, was described for the drug; or, the same ADR, or a high level term, was listed for the group to which the drug was referred to but not listed for the drug itself; **WHO-ART** = World Health Organization Adverse Reaction Terminology.

this is minimised now by their availability online using an Internet browser.

The use of our selected literature sources as a 'gold standard' is open to debate. The literature is not intended as an early signalling system, and uses many sources for its information other than the WHO database: the biases affecting inclusion and exclusion of ADR information therefore may be very different. Factors, such as those affecting the differential reporting to WHO and the inclusion of new information in the reference sources will have an effect which is independent of the performance of the BCPNN. The BCPNN is run every quarter, and we selected just one quarter: since the BCPNN is used in continuous analysis, the specificity and sensitivity are subject to necessary time-dependent changes in classification of 'positives' and 'negatives'. It is difficult to consider something as a 'nonassociation' because of this time dependency, and it is clear that there is an asymmetry in the effect of time on our results: associations cannot become nonassociations with time, whereas nonassociations can whereas nonassociations may become associations with time. To avoid this we have considered the inverse of a positive association a definite negative association in this paper. Another asymmetry is that the negative associations are a selection of all nonassociations. This assumes that definite negative associations represent all nonassociations, though it is clear that some nonassociations will became positive associations in time. This again shows the difficulty of evaluating a signalling system.

An assumption was made that a substantial increase in the number of reports of an association over the period indicated ongoing clinical interest in an association. More reports may be seen as a support for the validity of the associations, though there is often a tendency for ADRs that are becoming well known to be reported more frequently. Therefore, the associations in table IV for which the number of reports have increased are of particular interest.

Another obvious limitation is that our method for signal generation is dependent on the terminology used for recording of adverse reactions. Very little

work has been done on any of the medical terminologies in use or proposed to determine their relative value in searching for new drug signals.[11]

We found that 44% of the BCPNN signals are strengthened or confirmed in the current reference sources while not mentioned at all in the 30th edition of Martindale (1993).[5] The 84% negative predictive value indicates that combinations not highlighted for review, if not already known, are unlikely to become signals. This indicates that the BCPNN is a valuable tool in the filtering of combinations for clinical review, and that it has the ability to find early signals. The normal methods for assessing the power of a method are difficult to apply to the BCPNN, because of the reasons above.

The BCPNN associations, which are not yet reported in the current literature, are included in table IV. If these associations were to emerge in the literature in the coming years, it would increase the positive predictive value of the BCPNN.

The BCPNN has the power to analyse signals further.[3] We are developing its use for looking at complex variables to see whether parameters such as gender, age, and other drug use increase the strength of association, and whether 'syndromes' of reported terms are present. However, as with any subdivision of data, a very large amount is necessary initially, to attain statistical significance in subsets. This is a major advantage of using the large pooled WHO database, and we are trying to maximise this potential.

The BCPNN is not a panacea for drug safety monitoring. The drug–ADR combinations which reach statistical significance, do so only in comparison with the background experience of 2 million case reports. This is particularly important for commonly reported ADRs, which, however serious, would not reach significance until the quantitative experience for a drug and such an ADR is excessive. Sumatriptan and confusion is an example of this issue, passing the BCPNN association threshold after being circulated as a signal.

We have stressed[1] that although the BCPNN approach has its limitations and is not a substitute for expert review, it does have a place particularly where large volumes of data are involved. It is reassuring, however, that all signals identified in the previous system that went on to become frequently reported in the WHO database were also identified in the retrospective BCPNN analysis.

Conclusions

This retrospective evaluation of the new statistical signalling tool used at the Uppsala Monitoring Centre has shown that the BCPNN has a high predictive value, and that it can identify early signals of adverse drug reactions. It has further strengthened our view that the BCPNN will provide a useful tool in international pharmacovigilance.

To our knowledge, this is the first time an ADR-signalling method has been subjected to a rigorous performance analysis. The lack of a 'gold standard'. and the dynamic nature of signal finding with time make conventional validation methods difficult to apply.

Acknowledgements

The authors are indebted to national centres contributing data to the WHO International Drug Monitoring Programme. The opinions and conclusions, however, are not necessarily those of the various centres nor of the WHO.

Disclaimer

The WHO database contains summary reports of individual suspected adverse reactions to medicines, received from national centres in countries participating in the WHO International Drug Monitoring Programme. No causality assessment is made at the Uppsala Monitoring Centre, but if such an assessment has been made by the national centre submitting the report, this is stored in the database. Since these reports constitute suspicions of adverse drug reactions, further investigation and research is needed for a full interpretation of the data.

References

1. Lindquist M, Edwards IR, Bate A, et al. From association to alert - a revised approach to International Signal analysis. Pharmacoepidemiol Drug Saf 1999; 8: S15-25
2. Bate A, Lindquist M, Edwards IR, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54: 315-21
3. Orre R, Lansner A, Bate A, et al. Bayesian neural networks with confidence estimations applied to data mining. Computational Statistics and Data Analysis 2000; 34 (4): 473-93
4. Edwards IR, Biriell C. Harmonisation in pharmacovigilance. Drug Saf 1994; 10: 93-102

5. Reynolds JEF. 30th ed. Martindale: the extra pharmacopoeia. London: The Pharmaceutical Press, 1993
6. Micromedex vol 105. Micromedex® healthcare series vol.105 [online]. Available from URL: http://mdx.com. [Accessed 2000 July]
7. Micromedex vol 100. Micromedex® healthcare series vol.100 [online]. Available from URL: http://mdx.com. [Accessed 1999 June]
8. Finney DJ. Systematic signalling of adverse reactions to drugs. Methods Inf Med 1974; 13 (1): 1-10
9. DuMouchel W. Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat 1999; 53 (3): 177-90
10. Meyboom RH, Egberts AC, Edwards IR, et al. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16 (6): 355-65
11. Yokotsuka M, Aoyama M, Kutoba K. The use of a medical dictionary for regulatory activities terminology (MedRA) in prescription-event monitoring in Japan (J-PEM). Int J Med Inf 2000; 57 (2-3): 139-53

Correspondence and offprints: *Marie Lindquist*, Uppsala Monitoring Centre, Stora Torget 3, 753 20 Uppsala, Sweden. E-mail: marie.lindquist@who-umc.org