“A distant voice in the darkness”
The definition of a signal in pharmacovigilance

Jeff Aronson
Centre for Evidence Based Medicine,
Department of Primary Care Health Sciences,
Oxford

Honorary Consultant Physician
and Clinical Pharmacologist

Emeritus Fellow, Green-Templeton College, Oxford

President Emeritus
British Pharmacological Society
Ships that pass in the night, and speak each other in passing,
Only a signal shown, and a distant voice in the darkness;
So on the ocean of life, we pass and speak one another,
Only a look and a voice, then darkness

Tales of a Wayside Inn
About 30 percent of the world literature on adverse drug reactions is in the form of anecdotal reports (Aronson JK, g Y, Derry S. Adverse drug reactions: keeping up to date. Fundam Clin Pharmacol 2002; 16(1): 49-56.)
The numbers of publications detailing case reports of adverse drug reactions have increased faster than the numbers of all case reports and faster still than all other publications.
There are broadly speaking three types of case reports of adverse drug reactions. The first type is the between-the-eyes reaction.
This term comes from Joseph Berkson’s observation that some effects are so obvious that they do not need statistical analysis. He called that interocular traumatic impact—the effect of something hitting you between the eyes.
In this paper we detailed different types of between-the-eyes (or definitive) adverse drug reactions (Aronson JK, Hauben M. Anecdotes that provide definitive evidence. BMJ 2006; 332(7581): 1267-9.; see also Hauben M. Aronson JK. Gold standards in pharmacovigilance: the use of definitive anecdotal reports of adverse drug reactions as pure gold and high grade ore. Drug Saf 2007; 30(8): 645-55.).
There are several reasons for publishing anecdotal case reports, listed here (Aronson JK. Anecdotes as evidence. We need guidelines for reporting anecdotes of suspected adverse drug reactions. BMJ 2003; 326(7403): 1346.). Between-the-eyes reactions provide proof that the drug-event pair was causative in the individual in whom it was reported and also suggest that the drug can cause the event in general.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly recognized ADR</td>
<td>Oculomucocutaneous syndrome (practolol)</td>
</tr>
<tr>
<td>Generate hypotheses</td>
<td>Teratogenicity (antihistamines)</td>
</tr>
<tr>
<td>Test hypotheses</td>
<td>Loading dose in renal insufficiency (digoxin)</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>Lung damage (KL6) (amiodarone)</td>
</tr>
<tr>
<td>Elucidate mechanisms</td>
<td>Torsade de pointes/QT↑ (antiarrhythmics)</td>
</tr>
<tr>
<td>Methods of management</td>
<td>Self-poisoning (verapamil)</td>
</tr>
<tr>
<td>Systematic review</td>
<td>Thromboembolism (mestranol)</td>
</tr>
<tr>
<td>Remind and educate</td>
<td>Hypokalaemia (liquorice)</td>
</tr>
</tbody>
</table>
If you find the drug in a high concentration in, for example, a bile stone or a urinary stone, that is proof that the drug was causally associated with the occurrence of the stone.
This is an example of that.
Finding the drug elsewhere is similarly evidential…
…and this is an example of that.
Between-the-eyes adverse effects

1. Extrinsic or intrinsic tissue deposition of the drug or a metabolite

2. A specific anatomical location or pattern of injury
   - Cytotoxic drug extravasation
   - Intrathecal administration
   - Oral ulceration
   - Oesophageal ulceration

If the harm is associated with a particular site of administration or a pattern of damage the association with the drug may be obvious.
This is an example of that …
Lanuza García et al.  
Unsuccessful treatment with OK-432 picibanil for orbital lymphangioma.  

...as is this.
In some cases the harm can be reproduced by recreating the same condition in an \( n = 1 \) trial, which can be placebo controlled. For example, if a drug causes a phototoxic skin reaction, you can rub the drug on the back of one hand and a placebo on the back of the other and expose them both to light; a reaction on the drug-exposed hand proves the association.
Finally, if the therapeutic agent is a micro-organism you may be able to identify it at the site of harm.
...as in this case
These four types of between-the-eyes reactions can be remembered using a crime scene analogy.

<table>
<thead>
<tr>
<th>Category</th>
<th>Crime scene analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrinsic or intrinsic deposition of drug or metabolite</td>
<td>Culprit caught at the scene of the crime</td>
</tr>
<tr>
<td>Specific anatomical location or pattern of injury</td>
<td>Culprit caught at the scene of the crime and seen committing it</td>
</tr>
<tr>
<td>Physicochemical dysfunction or tissue damage</td>
<td>Culprit incriminated by recreating the crime scene</td>
</tr>
<tr>
<td>Infection-related</td>
<td>Culprit’s fingerprints found at the scene of the crime</td>
</tr>
</tbody>
</table>
The second type of anecdote is the so-called “designated medical event” (DME), an unhelpful term. A DME is an event that is often associated with a medicine, but you can’t attribute it to any medicine that the patient is taking, since it can happen spontaneously as well.
These types of harm are DMEs. They are often due to medicines, but not necessarily. They also tend to be serious events and so rechallenge with the suspected medicine may not be possible.

**Designated medical events**

Aplastic anaemia
Stevens-Johnson syndrome/TEN
Anaphylaxis
Torsade de pointes
This is Alison Lapper, who has phocomelia, but it is not due to thalidomide, as you might suppose, since she was born after thalidomide was withdrawn from the market.
She may have a genetic abnormality, such as this one, listed in OMIM (Online Mendelian Inheritance in Man; https://www.omim.org)
In such cases the suspicion that a particular medicine may have been responsible for a DME may be strengthened or weakened by considering various factors in a list attributable to Austin Bradford Hill, reorganized here for that purpose (Howick J, Glasziou P, Aronson JK. The evolution of evidence hierarchies: what can Bradford Hill’s ‘guidelines for causation’ contribute? J R Soc Med 2009: 102(5): 186-94.).
The problem of bidirectional and paradoxical drug effects can make attribution more difficult and may mislead (Smith SW, Hauben M, Aronson JK. Paradoxical and bidirectional drug effects. Drug Saf 2012; 35(3): 173-89).
Here are two examples, with different time scales. Suxamethonium first causes muscle contraction then muscle relaxation; if you observe only one or the other you might misinterpret its actions. Antibiotics can relieve fever in infection but cause it as an adverse reaction; the catch is to think that the infection has not been properly treated or has returned.
In no other instances of case reports of drug-event pairs that suggest a suspicion of an adverse drug reactions can cause be directly or even tangentially attributed. Such reports need to be amassed and analysed as a data set using specialized data mining techniques. This leads to the concept of a signal in pharmacovigilance, more accurately called a signal of suspected causality.
In crafting definitions I use a fourfold approach.
Etymology can sometimes give useful insights. Words beginning with “poly” for example, suggest “many” (polymyalgia is pain in many muscles) but may suggest “too many” (polydactyly is not many digits but too many)…
...as here
The only word of which I am aware in which “poly-” can mean either “many” or “too many” is polypharmacy (Aronson JK. In defence of polypharmacy. Br J Clin Pharmacol 2004; 57(2): 119-20.; Aronson JK. Polypharmacy, appropriate and inappropriate. Br J Gen Pract 2006; 56(528): 484-5).
The second approach to definition involves examining the ways in which usage of the word has changed. Ban, for example, from the Indo-European root BHA, to speak, gives words to do with speaking in Greek and Latin and in English originally meant to proclaim. Over the years the meaning changed, and it now means to prevent from speaking. This reminds us to avoid the etymological fallacy, namely that a word means what its origins tell us.
This approach is tempered by the fact that words generally take on meanings that people give to them. Provided that everyone, or at least a majority of interested parties, agrees with a particular meaning, that is then what the word means.
3. Using previous definitions

1. Aristotle (τὰ τόπικα): “a definition should refer to what is prior and better known”

2. Richard Chenevix Trench: “every word should be made to tell its own story”

- Examine published definitions critically
- Produce a definition that incorporates what is relevant and omits what is not

The third approach involves analysis of definitions that others have crafted before, taking what is useful, omitting what is not, and thus discovering what needs to be kept in and what needs to be left out.
The fourth approach uses operational definition, in discovering how theories and systems work and therefore how the relevant terms that describe them should be defined.
Robin Ferner and I have previously used these approaches in defining terms in pharmacovigilance (Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug Saf 2005; 28(10): 851-70)…
Clarification of Terminology in Medication Errors
Definitions and Classification

Robin E. Ferner¹ and Jeffrey K. Aronson²
1 West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, UK
2 Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford, UK

Abstract

We have previously described and analysed some terms that are used in drug safety and have proposed definitions. Here we discuss and define terms that are used in the field of medication errors, particularly terms that are sometimes misunderstood or misused. We also discuss the classification of medication errors. A medication error is a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient. Errors can be classified according to whether they are mistakes, slips or lapses. Mistakes: are errors in the planning of an action. They can be knowledge based or rule based. Slips and lapses are errors in carrying out an action – a slip through an erroneous performance and a lapse through an erroneous memory. Classification of medication errors is important because the probabilities of errors of different classes are different, as are the potential remedies.

Defining a signal

1. Etymology
2. Usage
3. Previous definitions
4. The systems approach

Taking the four approaches one by one:
Etymology suggests that a signal is a mark of something, originally a mark cut into an object.
Usage shows that by the end of the 16th century a signal was regarded as a sign of something, perhaps for action or as information or a warning; there is no indication in any of these usages that causation is implied.
We found several definitions of “signal” that had previously been published. Each has something valuable in it.
In the next slides the definitions are given in yellow and the criticisms in blue. Any useful part is highlighted. Here the useful observation is that a signal can arise from more than one case.
A signal in pharmacovigilance is more than just a statistical association. It consists of a hypothesis together with data and arguments, arguments in favor and against the hypothesis. These relate to numbers of cases, statistics, clinical medicine, pharmacology (kinetics, actions, previous knowledge) and epidemiology, and may also refer to findings with an experimental character. A description, not a definition. A signal does not consist of a hypothesis.

The information that a signal gives, which may originate in an experiment, can give rise to a hypothesis but the signal is not itself a hypothesis (i.e. causation is not implied).
Because causation is not implied by a signal, the association needs further investigation and must be validated; the events to which it relates should be potentially important.
A safety signal refers to a concern about an apparent excess of an adverse event compared to what would be expected. Signals can arise from post-marketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class.

It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event.

A description, not a definition

A signal raises concerns and, again, demands further investigation. Although multiple cases are usually required before further investigation can be justified, even a single case can be informative.
An indicator or reported information that suggests a possible causal link between an adverse event and a medicine, when the postulated link was previously unknown or poorly documented

Similar to WHO definition
Again, a single report may be informative, but the features of the case should arouse strong suspicion if they are to be regarded collectively as constituting a signal.
1. A signal can be generated by a single report, but more often requires several reports of an association between an intervention (e.g. a drug) or interventions and an event or set of related events (e.g. a syndrome)  

2. Such reports can include any types of evidence, from anecdotes to the results of randomized studies, and including animal and in vitro evidence  

3. It represents an association involving an intervention or interventions and an event or connected set of events, which, if verified, would represent a new causal association or a new aspect of a known association  

4. The event or events should have clinical and/or public health importance  

5. It may [ideally should] include a scientifically plausible hypothesis about the source of the signal (i.e. mechanism), as part of the subjective processes that elevate a collection of messages to a signal of suspected causality  

6. It incites to action, which could be verification plus remedial action, or (if verification is not necessary) remedial action alone  

7. Signals of unanticipated potential therapeutic benefits as well as harms should be explicitly accommodated

This slide summarizes the important features of a signal that have come out of this analysis, also showing the texts in which each feature is covered.
The next three slides show the processes that are followed when amalgamations of individual case reports are analysed to determine whether signals have emerged, from the original message …
Defining a signal—Evaluating the system

Subjective evaluation

Scientific validity/novelty/importance/absence of obvious confounders?

N
(\textit{any})

Not a signal of suspected causality

Y (\textit{all})

Unverified signal of suspected causality

Attempted verification

Y

Subjective evaluation
…to final decisions about whether a signal has been detected and if so what needs to be done.
Definition of a signal of suspected causality

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention or interventions and an event or set of related events, either adverse or beneficial, which would command regulatory, societal, or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions.

This led us to develop this definition of a signal of suspected causality…
…which CIOMS VIII shortened. This definition has been adopted internationally.