

**Lareb**  
Nederlands Bijwerkingen Centrum  
Netherlands Pharmacovigilance Centre

## Causality assessment

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Biomedical sciences, Nijmegen

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www.lareb.nl

## Contents

- Introduction
- Causality assessment
- Cases
- Conclusions

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## Adverse drug reactions (ADRs)

<p>Type A (augmented)</p> <ul style="list-style-type: none"> <li>• Pharmacological effect</li> <li>• Dose dependent</li> <li>• Frequent</li> <li>• Recognizable in clinical trials</li> </ul>	<p>Type B (izarre)</p> <ul style="list-style-type: none"> <li>• Idiosyncratic</li> <li>• Rare</li> <li>• Serious</li> <li>• Not detectable in clinical trials</li> </ul>
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Source: Talbot J, Waller P. Stephen's detection of new adverse drug reactions. 5th edition, 2004. John Wiley & Sons Ltd: Chichester. p.92

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## Gap between trial and practice differences in population

Drug for chronic use, for non-lifethreatening diseases

<b>Total 1500 patients</b>	
600 patients minimally 6 months	phase 1-3
300 patients minimally 1 year	
<hr/>	
> 100.000 patients	post-marketing surveillance

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## Gap between trial and practice differences in population




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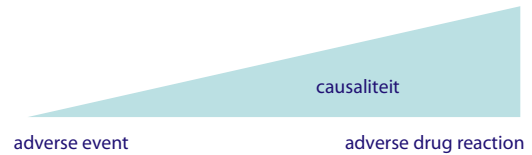
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## Spontaneous reporting system

- Type A in uncontrolled situation
- Type B
- Causality assessment

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## Causality



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## WHO causality definitions

	time relationship	attribution to other factors
certain	dechallenge and rechallenge	absent
probable	dechallenge	possible
possible	not improbable	possible
unlikely	improbable	plausible

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## Naranjo algorithm

- Systematic causality assessment
- 10 questions
- Sum score
- 63 case reports
- Algorithm: 3 authors
- Niet gevalideerd

Naranjo et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;239-245

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## Naranjo algorithm

$\geq 9$       certain  
 $5-8$       probable  
 $1-4$       possible  
 $\leq 0$       unlikely

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		Yes	No	?
1	Are there previous <i>conclusive</i> reports on this reaction?	1	0	0
2	Did the event <u>appear after</u> the suspected drug was administered?	2	-1	0
3	Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	1	0	0
4	Did the adverse reaction <u>reappear</u> when the drug was readministered?	2	-1	0
5	Are there <u>alternative causes</u> (other than the drug) that could on their own have caused the reaction?	-1	2	0
6	Did the reaction reappear when a placebo was given?	-1	1	0
7	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	1	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0
9	Did the patient have a similar reaction to the same or similar drugs in <i>any</i> previous exposure?	1	0	0
10	Was the adverse event confirmed by any objective evidence?	1	0	0

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## Causality assessment in reporting systems

- Health professional report
  - concerned reporting
  - under-reporting: a problem?
- Assessment by Lareb
  - Causality assessment
    - intrinsic
    - extrinsic



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## Intrinsic

- Pharmacological plausibility
  - kinetics, dynamics, chemical structure
  - latency, de-/rechallenge
  - concomitant medication
- Patient characteristics
  - confounding by indication, co morbidity
  - drug metabolism

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## Extrinsic

- Literature
  - See next slide
- Background incidence
- Databases
  - disproportionality

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## Extrinsic

[www.cvzkompassen.nl/fk](http://www.cvzkompassen.nl/fk) (in Dutch)  
[www.cbg-meb.nl](http://www.cbg-meb.nl) (SmPC in Dutch)  
[www.emea.eu.int/index/indexh1.htm](http://www.emea.eu.int/index/indexh1.htm)  
[www.lareb.nl](http://www.lareb.nl)  
[www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DB=PubMed](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DB=PubMed)  
 Micromedex  
 Meylers  
 Informatorium Medicamentorum (in Dutch)  
 MICROMEDEX Healthcare Series

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## Disproportionality

In the database the association between a certain drug and a certain ADR is significantly more frequent than other associations

$$ROR = \frac{axd}{bxc}$$

Disproportionality is statistically significant if CI-95% > 1

	ADR	Other ADRs
Drug	a	b
Other drugs	c	d

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## Cases

1. Epistaxis and pipamperone
2. Pergolide and gambling
3. Statins en impotence

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## Case

- Girl, 8 years
- pipamperone 10 mg TID
- Indication: aggression
- Reported ADR: epistaxis
- Latency: 3 months
- Recovered after cessation
- Concomitant medication: not reported

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## Details

- Psychiatry resident reports:
  - ADR appeared more often
  - This time during the night, it appeared more serious than before according to mother
  - Seen before in other patients

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## Extrinsic causality

- Literature
  - Kompas/SmPC: -
  - Micromedex: -
  - Pubmed: -
- Background incidence
  - High

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## Databases

	drug	reports	ROR (95%CI)
Lareb database			
	pipamperone	12	27.6 (15.0-51.0)
	risperidone	13	5.0 (2.9-8.8)
WHO database			
	pipamperone	14	5.8 (3.4-9.9)
	risperidone	76	1.3 (1.1-1.7)

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	Sex	Age category		Sex	Age category	
pipamperone	Male	11 - 20	risperidone	Female	11 - 20	
	Male	8 - 10		Male	8 - 10	
	Female	8 - 10		Male	41 - 50	
	Male	8 - 10		Male	31 - 40	
	Female	31 - 40		Female	2 - 4	
	Female	8 - 10		Female	51 - 60	
	Male	8 - 10		Male	11 - 20	
	Male	8 - 10		Male	8 - 10	
	Female	11 - 20		Female	61 - 70	
	Male	5 - 7		Male	70 and older	
	Male	8 - 10		Male	11 - 20	
	Male	8 - 10		Female	11 - 20	
	Male	5 - 7		Male	8 - 10	

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## Risperidone and epistaxis

Micromedex:  
"..During pre-marketing (n=2607) evaluation of risperidone, purpura, and epistaxis were reported in 1 in 100 to 1 in 1000 patients."



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## Intrinsic causality

- Pharmacological plausibility
  - Trombocytopenia and antipsychotics
  - Risperidone serotonin-receptor antagonist
  - Pipamperone anticholinergic effects
- Patient characteristics
  - Nose-picking
  - Kiesselbach plexus

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## Causality assessment

PRO	CON

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## Cases

1. Epistaxis and pipamperone
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## Gambling addiction

- A • Female, 50 years
  - Pergolide dose increase
  - "Hypersexuality" and gambling addiction
- B • Male, 58 years
  - Levodopa/carbidopa, pergolide and entacapone
  - Gambling addiction
  - Dechallenge +

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## Gambling addiction by pergolide?



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## Extrinsic causality

- Literature

- Kompas/SmPC:

Zoals bij andere dopamine agonisten is bij patiënten die pergolide behandeling ondergaan zeer zeldzaam ( $<1/1000$  gevallen) dwangmatig zelfbeloninggedrag (ziekelijke gokverslaving) en libido toename gemiddeld.

- Pubmed: several publications

- Background incidence

Low

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## Intrinsic causality

- Pharmacological plausibility

- Known ADR of pramipexole (Sifrol®)

- Known ADR of ropinirole (Requip®)

- Also other impulse control disorders

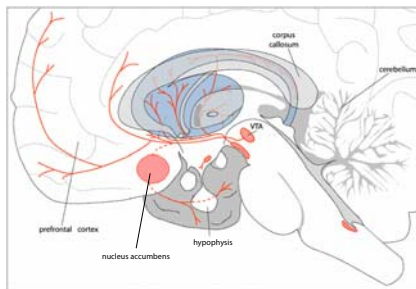
- Mechanism: see next slide

- Patient characteristics

- Disease deterioration

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## Reward system



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## Causality assessment

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## Cases

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## Impotence

- Male, 48 years  
familiar hypercholesterolemia
- Medication:
  - statin since 3 months
  - metoprolol since years
- At GP patient reports impotence
  - since 2-3 months erectile dysfunction

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## Course

- Patient is convinced of causal relationship
- Statin use is ended

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## Extrinsic causality

- Literature
  - Kompas/SmPC:-
  - Micromedex:  
Five men developed impotence within 1 week of starting or increasing the dose of simvastatin; normal sexual function returned within 1 week after simvastatin was stopped. All of the men had coronary artery disease; however, 2 men received only aspirin. Drug therapy was not mentioned for the other men. Two men were **rechallenged** with simvastatin and developed impotence again which resolved 1 week after stopping the drug. The Australian Adverse Drug Reactions Committee has received 42 reports of impotence associated with simvastatin; in 35 cases, simvastatin was the only drug implicated. The onset of impotence occurred between 48 hours and 27 months after starting simvastatin.
- Background incidence  
Quite high

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## Erectile dysfunction

geneesmiddel	Lareb	WHO	ROR (95%CI)
C10AA	73		3.5 (2.8-4.5)
atorvastatine		231	2.8 (2.5-3.2)
fluvastatine		38	3.1 (2.2-4.2)
lovastatine		137	3.5 (3.0-4.1)
pravastatine		86	2.5 (2.0-3.1)
rosuvastatine		26	1.2 (0.8-1.7)
simvastatine		327	3.5 (3.2-3.9)

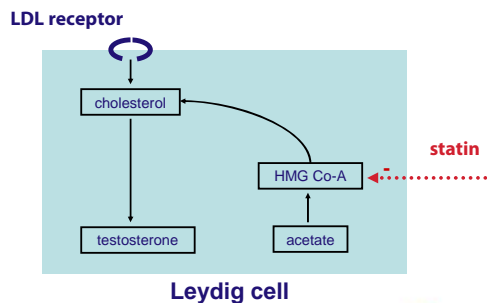
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## Intrinsic causality

- Pharmacological plausibility
  - Mechanism: see next slide
- Patient characteristics
  - Confounding by indication
  - Comorbidity
  - Concomitant medication

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## Hypothesis



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## Causality assessment

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## Conclusions

- Causality assessment is a multidisciplinary process:
  - Clinical
  - Pharmacological
  - Epidemiological

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## Conclusions

- Intrinsic and extrinsic causality always play a role
- The causality in a single report doesn't have to be strong

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