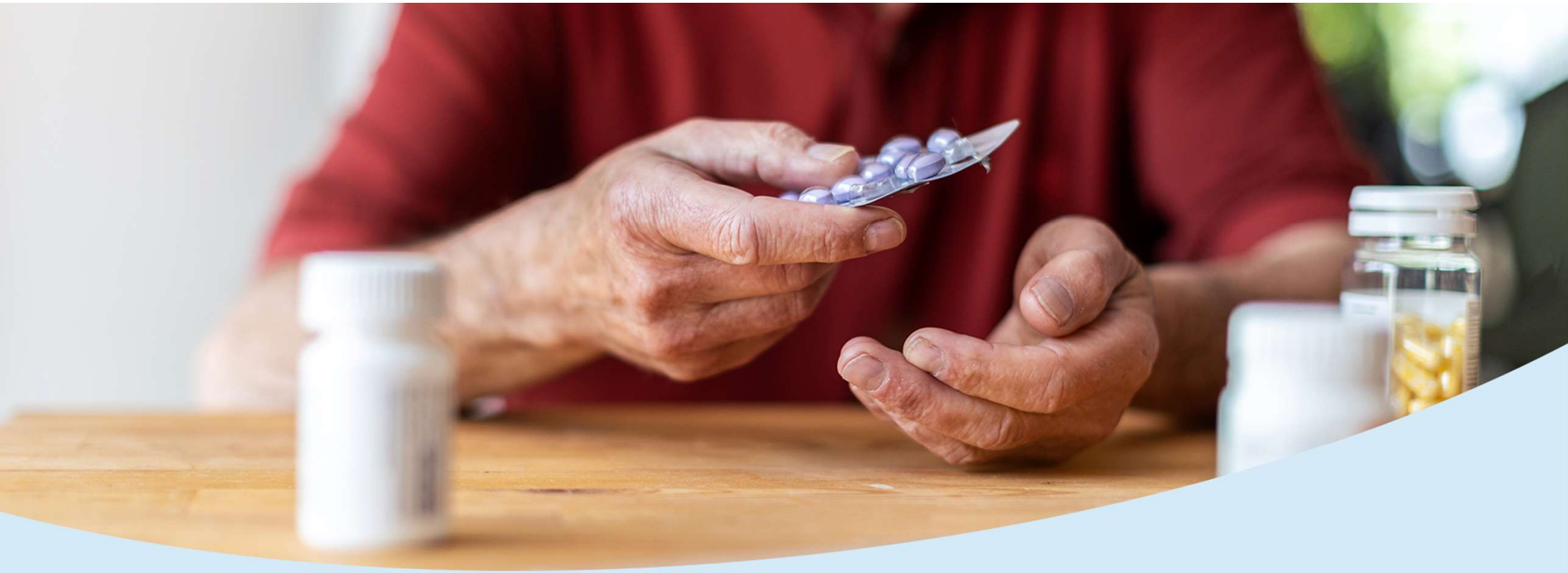

Detection of safety signals, the role of citizens report

Linda Härmark, PharmD, PhD, MBA

Deputy director

May 31 2023, Porto, Portugal

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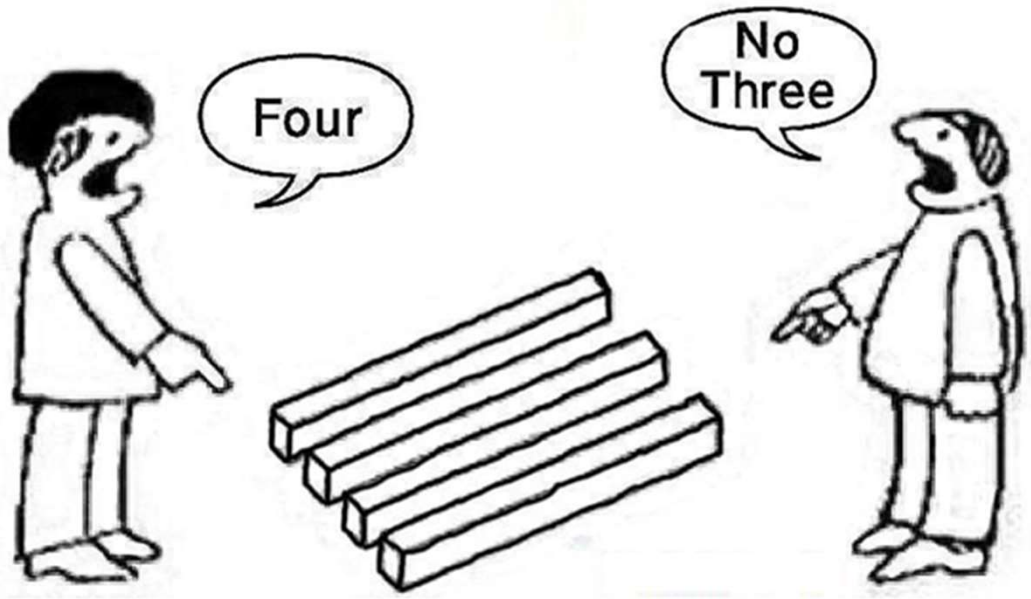

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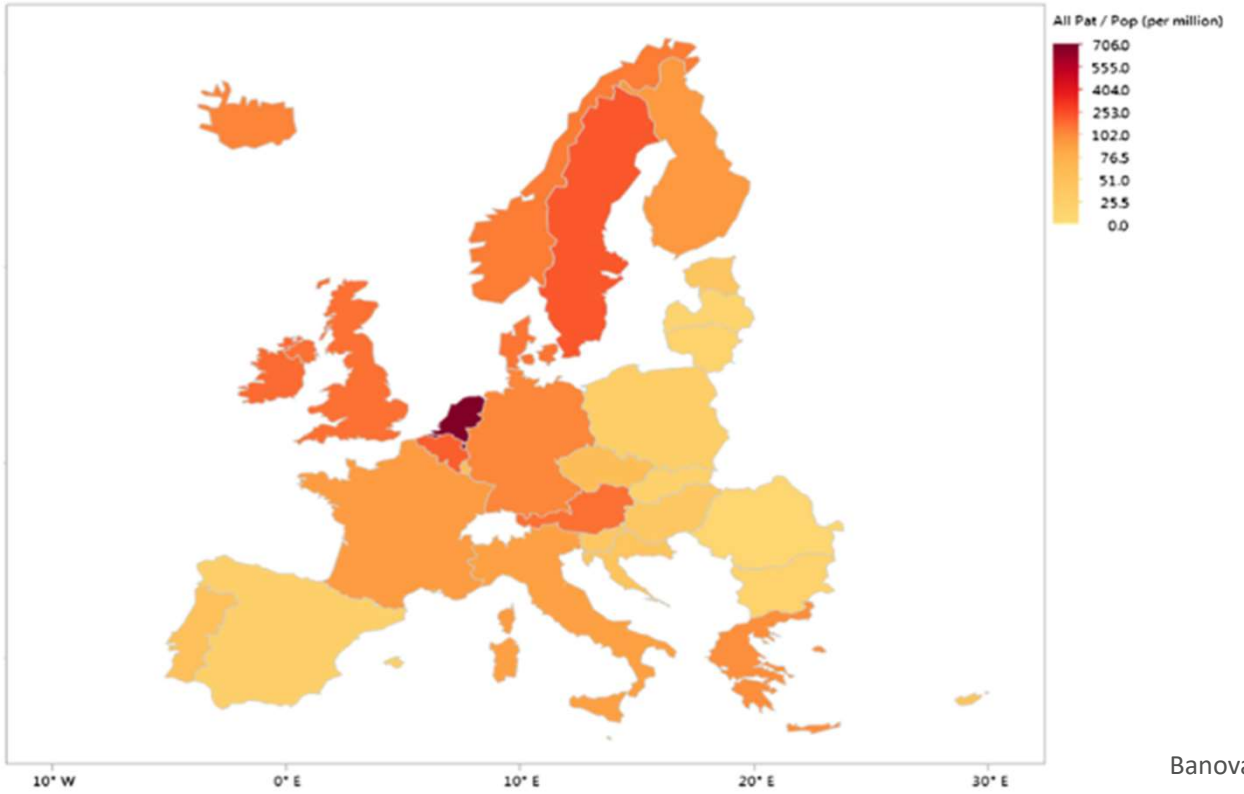
Patient reporting in the EU



Banovac, Drug Saf. (2017)

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Primary source description	MedDRA
Acne	Acne
Pain in muscles and joints, feels like I have the flu	Influenza-like symptoms
Red, allergic patches on the skin, particularly on the back. The GP suggested to place the patches on other parts of the body.	Application site reaction

Drug	ADR	No reports	No serious reactions	Disproportio-nality (ROR)
levothyroxine	sweating	8	0	2.0 (1.0-3.7)
SSRI	aggression	78	19	16 (4.23-7.66)
triamcinolon injection	Unexpected therapeutic effect	1	0	0.42 (0.38-0.46)
levocetirizine	Pruritus	9	0	22 (18.94-25.63)

SSRIs and aggression

- The Netherlands Pharmacovigilance Centre Lareb received 78 reports of aggression associated with the use of SSRIs (n=35 from consumers)
- In the literature controversy exists about whether the SSRIs have a beneficial or harmful effect on aggression
- Aggression was already mentioned in the SmPC of various SSRIs, except for fluoxetine, fluvoxamine and paroxetine

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SSRIs and agression

- Patient reports very useful in describing severity of the reaction and circumstances under which aggression occurred
- Reporters mention severely injuring others including (own) children, (attempted) murder (in 1 case followed by suicide), children being removed from home and placed in the care of someone else, aggression leading to restraining orders, initiating fights and smashing a bar

SSRI and aggression

Since stopping the drug [citalopram], due to an allergic reaction, the aggression and agitation disappeared almost instantly. I can enjoy life and I have not had any aggressive episodes again. When using citalopram I could shake my daughter back and forth, I did not have myself under control during the aggressive episodes. Often I contacted my general practitioner, crying, and telling him about this, but he did not recognize it as an adverse drug reaction and I felt he did not believe it

Definition of a signal

- “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented” (WHO 2002)

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Definition of a signal

- “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being previously unknown or incompletely documented” (WHO 2002)

- “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 and an event or set of related events, either adverse or beneficial (CIOMS VIII, Signal detection, 2010) “

What defines the value of a signal?

- Science?
  - New signal?
- Regulation?
  - Need for amendment SmPC/EPAR?
  - ‘Dear Health Care Professional letter’?
  - Suspension/withdrawal from market?
- Physician
  - Can ADR be treated?
  - Prevention of ADRs?
- Patients
  - Quality of life?
  - Which risk will I accept?

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Drug Saf (2013) 36:199–206
DOI 10.1007/s40264-013-0021-2

ORIGINAL RESEARCH ARTICLE

How Do Patients Contribute to Signal Detection?

A Retrospective Analysis of Spontaneous Reporting of Adverse Drug Reactions in the UK's Yellow Card Scheme

Lorna Hazell · Victoria Cornelius · Philip Hannaford · Saad Shakir · Anthony J. Avery · On behalf of the Yellow Card Study Collaboration

Published online: 27 February 2013

Abstract

Background In 2005, spontaneous reporting of adverse drug reactions (ADRs) to the UK's Yellow Card Scheme (YCS) was extended to include patient reports. Here, we investigate the potential pharmacovigilance impact of patient reporting.

Objectives The aim of the study was to investigate the relative contribution of patient reporting to signal detection through disproportionality analysis.

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examine how combining the patient and HCP reports may affect the SDRs identified.

Results Data were received for 5,180 patient and 20,949 HCP reports, relating to 16,566 and 28,775 drug–ADR pairs, respectively, with 4,340 (10.6 %) pairs found in both datasets. A significantly higher proportion of the SDRs identified from HCP reports involved reactions classified as serious by the Medicines and Healthcare products Regulatory Agency (MHRA), compared with patient reports

Drug Saf (2018) 41:203–212
https://doi.org/10.1007/s40264-017-0594-2

ORIGINAL RESEARCH ARTICLE

Safety Concerns Reported by Patients Identified in a Collaborative Signal Detection Workshop using VigiBase: Results and Reflections from Lareb and Uppsala Monitoring Centre

Sarah Watson[1] · Rebecca E. Chandler[1] · Henric Taavola[1] · Linda Härmark[2] · Birgitta Grundmark[1,3] · Alem Zekarias[1] · Kristina Star[1,4] · Florence van Hunsel[2]

Received: 14 December 2016 | Revised: 6 April 2017 | Accepted: 25 April 2017
DOI: 10.1002/pds.4236

WILEY

ORIGINAL REPORT

The contribution of direct patient reported ADRs to drug safety signals in the Netherlands from 2010 to 2015

Florence van Hunsel[1] | Susan de Waal[1,2] | Linda Härmark[1]

[1] Netherlands Pharmacovigilance Centre Lareb, WHO Collaborating Centre For Pharmacovigilance In Education And Patient Reporting, 's-Hertogenbosch, The Netherlands

[2] Pharmaceutical Business Administration, Institute for Allied Healthcare, Utrecht University of Applied Sciences, Utrecht, the Netherlands

Correspondence
Florence van Hunsel, Netherlands Pharmacovigilance Centre Lareb, Goudsbloemvallei 7, 5237 MH 's-Hertogenbosch, The Netherlands
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Abstract

Purpose: The purpose of this study was to investigate the contribution of patient reports to signals sent by the Netherlands Pharmacovigilance Centre Lareb to the Dutch Medicines Evaluation Board and to determine if there are certain types of signals where patient report add a distinct contribution.

Method: All signals from 2010 until 2015 were included. First, we investigated how many patient reports were present in the signals and the characteristics of these reports compared to the health care professional and marketing authorization holders' reports.
In addition to source, the analysis included ATC code of the drug, MedDRA® system organ class and preferred term for the adverse drug reaction (ADR), seriousness of the ADR, and 7 other factors like reports on over-the-counter medication, and how often an ADR listed in the important medical event terms list was present.
Secondly, we determined the proportion of reports submitted by the individual groups to signals, in a cross-sectional manner.

Results: A total of 150 signals were included, including 1691 ADR reports. Our results show that 26.3% of all ADR reports in Dutch drug safety signals were reported by patients, and 30.5% of the patient reports in the signals contained one or more terms listed as important medical events. The proportion of reports by patients which were included the signals was 2% and 3.9% for health care professional reports and 0.2% for marketing authorization holders reports.

Conclusion: Patients had an important contribution to signals overall, but especially for ADRs related to generic drug substitution and psychiatric ADRs.

KEYWORDS
ADR, patient reporting, pharmacovigilance, signal detection

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Methods

A total of 150 signals were included, including 1691 ADR reports

Signals were included if individual reports were described in the signal.

Overviews where individual cases were not described and only accumulated data were presented were excluded from the analysis.

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Contribution of patient reports to signals 2010-2015

26.3% of ICSRs in Dutch safety signals are from patients

30.5% of patient reports in the signals contained one or more terms listed as important medical event

Patients had an important contribution to signals for ADRs related to drug substitution and psychiatric ADRs

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Reporter type included in signals

Cross-sectionally: The proportion of reports by reporter type which were included in the signals was:

- 2% for consumers
- 3.9% for healthcare professionals
- 0.2% for marketing authorization holders

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Examples of Lareb signals based on patient reports

- Photosensitivity with azathioprine (help finding signal through patient-organisation!)
- High dose vitamin B6 products and neuropathy (for NVWA)
- Alitretinoine and curling hair
- Long term dermal corticosteroid use and withdrawal symptoms
- Triamcinolone injections and subcutaneous atrophy

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Signal shared with the Netherlands Food and Consumer Product Safety authority

Led to proposal from MoH to introduce a maximum limit of vitamine B6 in products on the Dutch market

Drug Saf
https://doi.org/10.1007/s40264-018-0664-0

CrossMark

ORIGINAL RESEARCH ARTICLE

Vitamin B_6 in Health Supplements and Neuropathy: Case Series Assessment of Spontaneously Reported Cases

Florence van Hunsel[1] · Sonja van de Koppel[1] · Eugène van Puijenbroek[1,2] · Agnes Kant[1]

Abstract

Introduction In the literature, vitamin B_6 has been linked to the development of polyneuropathy. Most often, these complaints were seen when taking high doses of vitamin B_6 for a long time. Evidence as to whether a lower dosage range of vitamin B_6 (< 50 mg/day) can also induce neuropathy is scarce.

Objective We aim to comprehensively describe the cases of neuropathy associated with vitamin B_6 received by the Netherlands Pharmacovigilance Centre Lareb and to assess the case series concerning the use of vitamin B_6 and neuropathic complaints.

Methods We describe the number and nature of the reported cases, including suspect product, dosage, duration of use, and vitamin B_6 serum levels. In addition, we describe the causality for the individual cases (Naranjo Probability Scale) and for the entire case series (Bradford Hill criteria).

Results In total, 90 reports on products containing vitamin B_6 included at least one adverse drug reaction in the standardized Medical Dictionary for Regulatory Activities (MedDRA®) query (SMQ; broad) 'peripheral neuropathy'. The amount of vitamin B_6 in the products varied between 1.4 and 100 mg per tablet. The serum vitamin B_6 level was known in 36 cases (88–4338 nmol/l), and the mean serum vitamin B_6 level was 907 nmol/l. However, no statistical correlation between dosage and vitamin B_6 blood levels was found.

Discussion and Conclusion Causality assessment of the case series of 90 reports to Lareb shows it is plausible for the vitamin B_6 supplements to have caused complaints such as neuropathies. This is especially the case with higher dosages and prolonged use, but dosages < 50 mg/day also cannot be excluded.

Key Points

Many vitamin supplements on the market contain a vitamin B_6 dosage higher than the maximum acceptable intake of 25 mg for adults. The literature describes neuropathic complaints with long-term use (months to years), most often for dosages from > 50 mg/daily to multiple grams daily.

A case series of 90 Dutch spontaneous reports indicates that prolonged use (mean latency 2.2 years) of vitamin B_6, most often in dosages higher than the maximum acceptable intake of 25 mg for adults, is associated with neuropathic complaints.

✉ Florence van Hunsel
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1 Introduction

1.1. Triamcinolone acetonide injection and Injection site atrophy

Introduction

Triamcinolone acetonide (Kenacort-A®) is a synthetic glucocorticosteroid with marked anti-inflammatory action. It has been approved for the Dutch market since September 1966.
The intra-articular or intrabursal administration of triamcinolone acetonide injectable suspension indicated as adjunctive therapy for short-term administration in *acute gouty arthritis, acute and subacute bursitis, acute nonspecific tenosynovitis, epicondylitis, rheumatoid arthritis, synovitis, o osteoarthritis.*
The intralesional administration of triamcinolone acetonide injectable suspension is indicated for *alopecia areata; discoid lupus erythematosus; keloids; localized hypertrophic, infiltrated, inflamm lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), and ps plaques; necrobiosis lipoidica diabeticorum.* Triamcinolone acetonide injection may also be usefu cystic tumors of an aponeurosis or tendon (ganglia) (1).

Occurrence of local atrophy after corticosteroid injection is described in the literature. It is more common with preparations with a lesser degree of water solubility. Although the condition is ofte reversible, instances of long-term disfigurement are well documented (2;3)

Case I, picture used with permission of the patient

Other sources of information

SmPC
The Dutch SmPC (1) of triamcinolone acetonide intrabursal administration and with injection of tria

Drug Saf (2018) 41:203–212
https://doi.org/10.1007/s40264-017-0594-2

ORIGINAL RESEARCH ARTICLE

Safety Concerns Reported by Patients Identified in a Collaborative Signal Detection Workshop using VigiBase: Results and Reflections from Lareb and Uppsala Monitoring Centre

Sarah Watson[1] · Rebecca E. Chandler[1] · Henric Taavola[1] · Linda Härmark[2] · Birgitta Grundmark[1,3] · Alem Zekarias[1] · Kristina Star[1,4] · Florence van Hunsel[2]

Medicines patient reports signal detection	Medicines 'normal' signal detection
Amitriptyline	Ciprofloxacine
Desloratadine	Ivermectine
Desogestrel	Natalizumab
Noscapine	(Des)loratadine
Pregabalin	Ruxolitinib
SGLT-2 inhibitors	Idelalisib
Systemic hormonal contraceptives	Chromotrypsin

Medicines patient reports signal detection	Medicines 'normal' signal detection
Dry eyes	Acute kidney injury
Depression	Serious neurological events
Panic attacks	Central nervous system lymphoma
Distorted colour vision	Weight increase in children
Genital pruritus	Perioheral neuropathy
Loss of libido	Leukoencephalopathy

Signals must be communicated

- Information can influence medicine choice at the prescribing stage
- Earlier recognition of the drug and the ADR
- Can lead to the decision to stop/change/adjust treatment to see if the ADR will disappear
- Can lead to acceptance of the ADR

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Drug Safety (2020) 43:745–749
https://doi.org/10.1007/s40264-020-00932-5

ORIGINAL RESEARCH ARTICLE

Communicating Adverse Drug Reaction Insights Through Patient Organizations: Experiences from a Pilot Study in the Netherlands

Linda Härmark[1] · Gerda Weits[1] · Rietje Meijer[2] · Federica Santoro[3] · G. Niklas Norén[3] · Florence van Hunsel[1]

Published online: 16 May 2020

Abstract

Introduction To improve therapeutic decision making, it is crucial that information regarding adverse drug reactions reaches patients. It is not enough to disseminate such findings through regulatory and scientific channels; targeted efforts to reach patients are necessary. One possible avenue is to collaborate with patient organizations.

Objectives The aim of this pilot study was to explore how adverse drug reactions can be communicated through patient organizations.

Methods A text describing a signal of levothyroxine and panic attacks was tailored to patients' needs, in terms of language, style and content, with emphasis placed on what to do when experiencing the symptoms described. The signal was communicated via the Dutch thyroid organization's digital newsletter, social media channels, website and print magazine.

Results The digital newsletter was distributed to around 5000 subscribers. On Facebook, 13,820 people viewed the message, with 2346 clicks in the message, indicating an intention to read the whole post. The interactions on social media were positive, and the tone was respectful.

Conclusion Patient organizations can help enable effective communication of adverse drug reactions to a relevant audience. The social media post generated more engagement than other communications from the patient organization, indicating a strong interest in this information. The additional patient experiences that were shared in the comments on social media further strengthened the original signal and its relevance to patients, creating an interesting feedback loop. The favourable experiences in this study support further consideration and exploration of this approach to communicate adverse drug reactions to patients.

Take home messages

- Patient reports contribute to signal detection on both on a national and global level

- Data collection
- Free text and coding
- Signal detection methodology

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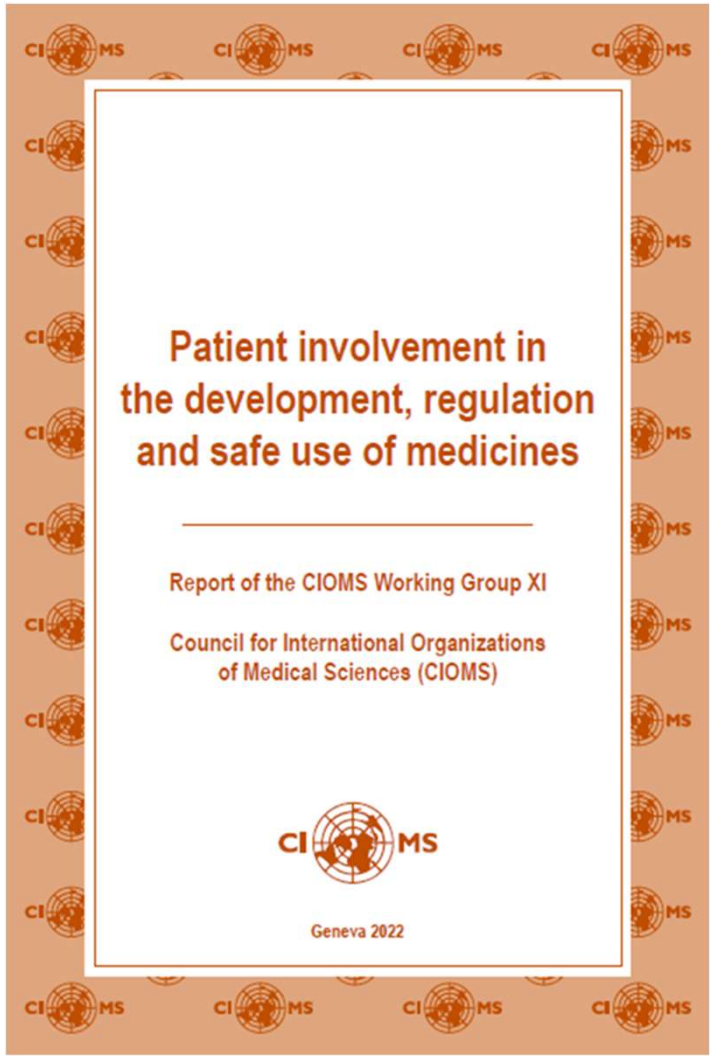
The way forward

- What is your perception of the role of patients in pharmacovigilance?
- Increase the importance of the patient perspective in your work
- Build a network op patients (organisations) that can guide you in moving forward



Free to download at:
https://cioms.ch/publications/product/patient-involvement/

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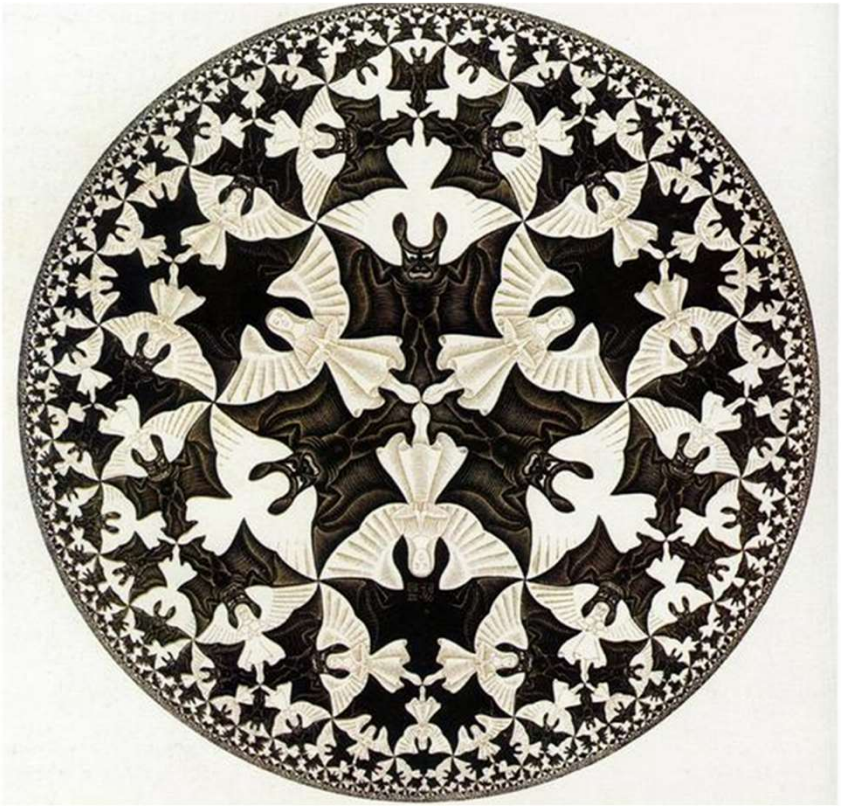
Perception is reality



Esscher, Circle of Limit

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