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CURRENT OPINION

Dispositions and Causality Assessment in Pharmacovigilance: Proposing the *Dx3* Approach for Assessing Causality with Small Data Sets

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Abstract
A new approach is proposed for assessing causality in pharmacovigilance. The *Dx3* approach is designed to qualitatively evaluate three types of dispositions when assessing whether a particular medicine has or could have caused a certain adverse event. These are: the drug disposition; the pre-disposition of the patient taking the drug (vulnerability) and; the disposition of the patient–drug interaction (mutuality). Each of these three types of dispositions will represent valuable causally relevant evidence for assessing a potential signal of harm. A checklist is provided to guide the assessment of causality for both single individual case safety reports (ICSRs) and case series. Different types of causal information are ranked according to how well suited they are for establishing a disposition. Two case examples are used to demonstrate how the approach can be used in practice for assessment purposes. One aim of the approach is to offer a qualitative way to assess causality and to make the reasoning of different assessors more transparent. A second aim is to encourage the collection of more qualitatively rich patient narratives in the ICSRs. Crucially, we believe this approach can support the inclusion of the single ICSR as a valid and valuable form of evidence.

1 Introduction

Pharmacovigilance experts often have to evaluate whether one or few cases can provide some evidence for a causal relationship between a medical treatment and a reported event. This has been an unsolved challenge, not only practically and methodologically, but also conceptually. We usually think about a causal relationship as something that must be observed repeatedly and ultimately generate statistical correlations. In this view, causal evidence requires statistical evidence. Typically, therefore, in order to check how plausible it is that a particular event was caused by a particular drug in a particular patient, one starts by searching for how often the drug previously provoked the same type of event in other patients. A problem in pharmacovigilance is that we often lack such information, since adverse drug reactions can be rare, rarely reported or insufficiently described, while regulatory decisions often need to be made promptly.

In this article we propose a new qualitative approach for more transparently assessing causality in individual case safety reports (ICSRs) in pharmacovigilance. The primary aim of the *Dx3* approach is to facilitate, organise and improve causal reasoning for assessing potential harms from medicines through the analysis of ICSRs databases. For this aim, we offer a systematic overview and ranking of different types of evidence.

The *Dx3* approach was developed as part of the *Cause-Health Pharmacovigilance* initiative (https://causehealthpharmacovigilance.wordpress.com/) to bring together conceptual expertise on causality with experts from pharmacovigilance. The purpose of the research collaboration was to resolve some persistent challenges within pharmacovigilance [1], informed by a specific understanding of causality [2] and its recent applications to pharmacology [3], risk assessment [4], medicine [5] and scientific methodology in general [6]. Within this conceptual framework, causality is seen as irreducibly dispositional, genuinely complex, highly context-sensitive, and particular or even unique.

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Key Points

Several methods to assess the causal link between a reported drug and a reported event are available in pharmacovigilance. Yet, causality assessment in one or more individual case safety reports is often hindered by lack of key information. In such cases, it might be difficult to get consensus among different assessors.

We propose a new causality assessment approach, Dx3, to facilitate, organise and improve causal reasoning in pharmacovigilance. The quality of available evidence is ranked according to its relevance for showing the dispositions of the drug, the patient condition, and the patient-drug interaction to generate a certain outcome.

The approach is designed to generate articulated and transparent argumentations to facilitate the discussion among assessors. An indirect aim is to encourage the collection of more qualitatively rich patient narratives in the clinical description of individual case safety reports.

We here assume that it is a necessary condition for an adverse drug reaction that it is caused by an intrinsic disposition of the drug, which in interaction with certain patients is able to produce or contribute to that effect [2, 7, 8]. This disposition could be *mainly in the drug*, *mainly in the patient* or *mainly in the mutual interaction of the drug and the patient*. The *Dx3* approach is thus designed to evaluate causality, starting already from the first ICSR containing a certain drug and a certain event or set of events. Three questions about dispositions are considered:

1. *Drug disposition:* Does this drug have the disposition to cause this adverse event?
2. *Vulnerability:* Does this patient have a pre-disposition to the adverse event?
3. *Mutuality:* Does this drug have the disposition to cause this adverse event in interaction with this particular patient?

To assess these dispositions, a checklist is provided that shows which type of evidence is causally relevant and whether it should be rated as strong, good or moderate within its category. This ranking follows from the conceptual framework of dispositions [2, 6, 7], as will be explained.

An indirect aim for developing *Dx3* is to guide the adverse event reporter in how to provide good qualitative ICSRs that include all the relevant information needed for the subsequent causality assessment and signal detection. A second indirect aim is to aid causality assessment with small case series, since causal reasoning is facilitated by spelling out in detail the dispositions at place in each single case. The idea is that once the causal evidence is both systematically and transparently evaluated for every single ICSR, it becomes easier to evaluate the hypothesis of causal relationship in the following steps of the analysis. A deep qualitative analysis is particularly well suited for small datasets, mainly because of feasibility. However, the approach is in principle helpful for causality assessment in general, also when larger case series are involved.

The *Dx3* approach can therefore contribute to three of the four stages in the pharmacovigilance process (see Fig. 1): the reporting of adverse events (stage 1); the evaluation of causality in the single ICSR (stage 3); and the evaluation of causality from a case series (stage 4).

2 Dispositions in Medicine and Pharmacovigilance

A disposition is defined as an intrinsic property that can exist unmanifested and that will tend to manifest itself when interacting with other properties. For instance, a person can have a genetic pre-disposition for diabetes type I, but its manifestation occurs because of mutual, reciprocal interaction of multiple dispositions belonging to the individual and their context [2]. The dispositional framework fits well with matters related to medicines and drug safety, since medicines are developed to have a disposition to produce a targeted effect when metabolised by a patient with the necessary disposition (e.g. of the appropriate receptor). Specifically, a medicine has a disposition to counteract an unwanted effect, either by removing a harmful disposition (subtractive interference) or by adding a curative disposition that works as a preventer or blocker (additive interference). However, all medicines will also have dispositions toward several *un*targeted effects that for most patients will remain unmanifested.

Pharmacovigilance represents a valuable opportunity for uncovering previously unknown and potentially harmful dispositions of marketed drugs when these are manifested in marginal or outlier cases [3]. However, it also represents a major challenge for establishing causality within the methodological framework of evidence-based medicine that is

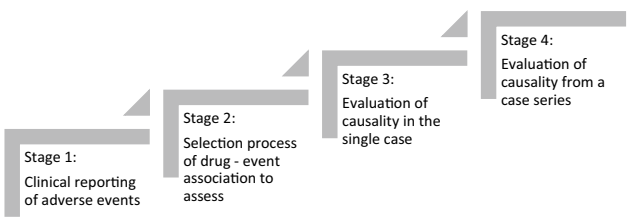

Fig. 1 The Dx3 approach can be used to inform stage 1, 3 and 4 in the pharmacovigilance process

largely unsuitable for dealing with few or single cases. Dispositional thinking offers a better foundation for qualitative causality assessment in pharmacovigilance because of its emphasis on the innate characteristics of the particular medicine (drug disposition), the single patient (vulnerability), and their unique interaction (mutuality).

The dispositional approach focuses on intrinsic properties and therefore shifts the attention from the mere identification of statistical correlations to understanding the mechanism, dynamics and interactions. Previous work has stipulated that intrinsic properties only can be identified with a plurality of different types of evidence [6]. Moreover, the identification of a plausible mechanism has been suggested as essential for the establishment of a causal disposition. Within this approach, therefore, evidence of a plausible mechanism of action is better evidence of causality than the mere identification of a correlation [9]. This view has been adopted by the medical community [10–14], including in issues of drug safety [15, 16]. The *Dx3* approach applies the same framework to causality assessment in pharmacovigilance.

3 Motivations and Novelty

The novelty of the *Dx3* approach is that it collects and reorganises elements for existing methods for causality assessment under a new conceptual framework. We have included the criteria that are common to the majority of assessment methods, in particular Lareb's CauseDoc tool [17] and the WHO-UMC method [18]. Compared to existing tools, *Dx3* emphasises the following aspects.

- *Patient pre-dispositions.* When a hypothesis of harm from a certain drug is proposed, the validity of the evidence is sometimes objected to by other experts, agencies or manufacturers. The reason for these objections is often that there is a pre-disposition in the patient or patient context for the reported event. For example, within the current WHO-UMC system for standardised case causality assessment, if the event "could also be explained by disease …", the recommended assessment would be only "possible" (the WHO-UMC guidance is available at: http://www.WHO-UMC.org/graphics/4409.pdf). However, in the *Dx3* framework, that a patient has a pre-disposition for the reported event (vulnerability) should not, contrary to common thinking and practice, automatically rule out a probable causal role of the drug in triggering the effect in the patient (mutuality). Even if the drug played only a minor role, it might still have been the tipping-point for manifestation of the event in a particular context. If there is sufficient evidence that the drug could have an intrinsic disposition to cause the adverse event (drug disposition), for instance by a known biological mechanism, then this should at least in some cases result in action (e.g. monitoring, further investigation or communication of the risk). Such a change in perspective will potentially have a significant impact on decision-making and legal issues, for instance in litigations about drug-induced harm.
- *Transparency of argumentation.* In signal detection the experiences and opinions of the pharmacovigilance assessors play a big role. Since the pharmacovigilance process involves different stages and different experts, there should be transparency about the type of evidence on which the causal conclusion is based, as well as the reasoning behind the conclusions by the individual assessor [1]. When assessors evaluate causality as 'possible', 'plausible', or 'unlikely', for instance, it is often unclear how the conclusion relates to the available evidence and which type of evidence was given more weight in the assessment. Unlike existing tools, *Dx3* does not require a classification in one causality assessment category ('possible', 'plausible', 'unlikely' or similar) at the level of ICSR causality assessment. Instead, it requires that the assessor describes the type and quality of causal evidence, providing guidance for causal reasoning at the next stages. This way, pharmacovigilance practitioners and agencies as well as decision-makers will be able to understand and compare different evidence evaluations from different assessors and experts.
- *Clinical approach and risk-management mindset.* A third motivation for the approach is its potential to influence the direction of pharmacovigilance. Clinical medicine is undergoing a shift towards personalised or precision medicine. Regulatory science, too, is moving from the "average" to appreciate the heterogeneity of responses of both benefits and harms. The *Dx3* approach encourages the consideration of individual-level risk factors that in turn can allow for the performance of finely tuned benefit risk assessments and the development of tailored risk mitigation measures. In essence, the *Dx3* approach could catalyse the transition of pharmacovigilance as a discipline from one focused on the identification of problems to one also contributing to finding solutions to such problems.

Dx3 is developed as a resource for healthcare professionals, assessors and pharmacovigilance centers to be adopted when:

1. Casuality assessment needs to be performed on the basis of few ICSRs;
2. There is a major disagreement between assessors and need for a transparent argumentation;
3. A tailored risk analysis and management at the individual level is sought.

Additionally, because of the rigorous conceptual organisation, the *Dx3* approach might be helpful for training purposes.

4 The *Dx3* Approach: A Checklist for Evaluating and Assessing Causality

The *Dx3* approach (Table 1) offers a range of assessment criteria that are organised into the three categories of dispositions (drug disposition, vulnerability, mutuality) and ranked according to their evidential strength for each of these categories (moderate, good, strong).

5 Guide for Using the *Dx3* Approach

5.1 Drug Disposition

In this part, the *Dx3* checklist is aimed at assessing whether there is available evidence of an intrinsic disposition of the drug to produce the adverse event in general. Assessing this part requires expertise and literature review.

5.1.1 Strong Evidence of Drug Disposition: Mechanistic Knowledge

Strong evidence of disposition of the drug toward the adverse event here means, in accordance with the adopted conceptual framework, that there is evidence of a plausible mechanism by which the drug could produce the event alone or together with another drug [7, 9, 19].

5.1.2 Good Evidence of Drug Disposition: Correlation Indicating Causality

Good evidence of drug disposition here means that there is statistical evidence suggesting a causal relationship between the drug and the adverse event and that temporality matches the drug's known properties.

5.1.3 Moderate Evidence of Drug Disposition: Correlation

Moderate evidence indicates that there is a correlation between the drug and the adverse event described in the literature, but there is no evidence that this is causal in the sense 'intrinsic to the drug'.

5.2 Patient Disposition (Vulnerability)

In this part, the *Dx3* checklist is aimed at assessing whether the patient has an intrinsic disposition toward the reported event that makes them particularly vulnerable to it. If so, this does not automatically rule out that the drug played a causal role in triggering that event in this specific case. It could, however, indicate that the disposition is mainly, or even only, in the patient context. In the practice of medicine, causal evaluations need to be done in the context of the specific patient, and will depend on the level of evidence of drug disposition and evidence of mutuality. Note that different assessors will still have different judgements, and here the realistic aim of this approach is not necessarily to create consensus, but rather to provide a common language for the discussion.

5.2.1 Strong Evidence of Vulnerability

Strong evidence of patient vulnerability to the reported event indicates a disposition or pre-disposition of the patient and their context (e.g. concomitant drugs) toward that event.

5.2.2 Good Evidence of Vulnerability

Good evidence of patient vulnerability indicates that, although the patient does not have a history of the reported event, they belong to a sub-population that is known to be generally more physiologically disposed or pre-disposed to that event.

5.2.3 Moderate Evidence of Vulnerability

Moderate evidence of patient vulnerability indicates that the patient belongs to a sub-population that has a correlation with the reported (or similar) events, but there is no medical understanding of such a correlation.

5.3 Patient–Drug Interaction (Mutuality)

In this part, the *Dx3* checklist is aimed at assessing whether there is evidence of an interaction between the drug and the patient that could produce the reported event in this specific case. Evidence of this type indicates a causal relationship between the drug and the event in the patient.

5.3.1 Strong Evidence of Mutuality

Strong evidence of a patient-drug interaction indicates that there is a plausible explanation of how the drug could cause the reported event in this particular patient, where the

Table 1 The Dx3 checklist for evaluating, assessing and ranking evidence of three types of dispositions

Strength of evidence	Evidence of drug disposition	Evidence of vulnerability (pre-disposition of the patient)	Evidence of mutuality (patient-drug interaction)
Strong evidence of disposition	There is evidence in the literature of a plausible mechanism by which this drug could provoke the adverse event	The medical history of the patient suggests a pre-disposition to the reported event	There is evidence of a plausible mechanism of vulnerability of the patient to this drug
	There is evidence of a mechanism for which similar drugs could provoke the adverse event	The patient uses other drugs that might have contributed to the reported event	There is evidence that this specific drug was a difference-maker (or trigger) for the reported event in this patient among concomitant drugs. For example, dechallenge and/or rechallenge is repeated
	There is evidence of a mechanism of drug-drug interaction by which the drug could provoke the adverse event when combined with some other drug(s)	The patient has experienced similar events from other drugs or confounding factors	There is evidence of dose–response There is pattern of interference with the event intensity
Good evidence of disposition	There is previous evidence of correlation suggesting a causal relationship between the drug and adverse event in the literature (ICSRs, clinical trials, etc.)	In general, the patient is in a medically vulnerable condition (e.g. age, pregnancy, chronic illness, socio-economic status, community)	Temporality is plausible with an interaction between patient's disposition and the drug's properties
	There are previous cases suggesting a causal relationship between similar drugs and adverse event in the literature (ICSR, clinical trials, etc.)		The time of onset of the reported event matches the drug's known pharmacological properties
			There is positive de-challenge once
			There is positive re-challenge once
			The intensity of the reported event matches the combination of the patient's dispositions and the drug's disposition
Moderate evidence of disposition	There are other cases of a correlation of this drug or similar drugs and adverse event	There is a correlation of similar patients and the reported event	There is a correlation of this or similar drugs and adverse events in similar patients (e.g. gender, ethnicity, socio-economic status, community)
Assessment of evidence	Strong, good, moderate	Strong, good, moderate	Strong, good, moderate

ICSR individual case safety report

event is a result of the mutual manifestation of dispositions belonging to the patient and the drug. It could also mean that the drug made a difference with respect to the event, for instance confirmed by repeated dechallenge and/or rechallenge. We will comment briefly on the entries concerning mutuality, since they might be less immediate than the other sections to pharmacovigilance professionals.

There is a plausible mechanism of vulnerability of the patient to this drug.

If an elder patient reports symptoms of liver failure from a drug that is known to be metabolised in the liver, the reported event could be caused by the combination of a disposition of liver susceptibility in the patient and a disposition of the drug's metabolic pattern.

The drug was a difference-maker, or trigger, for the reported event in this patient.

If the patient takes more than one drug, then the introduction of the suspected drug might nevertheless have worked as a trigger or tipping-point for the reported event. This means that this drug made a difference with respect to that event for this patient, among the other concomitant drugs, supported by repeated dechallenge and/or rechallenge.

There is evidence of dose–response.

If the event is reported to be more intense when the dose is increased, or weaker when decreased, this suggests that the drug has a disposition that acts in a linear, additive way in that patient toward the event. However, the event could also be caused by a confounder.

There is pattern of interference with the dose–response intensity of the reported event.

If the dose–response pattern of the adverse event is reported to change in correlation with a change in the patient's context, this suggests that there is a causal interaction between the drug and the patient, and that this interaction can be interfered with by an external element. This point might need an example. Say that a patient experiences decreasing tremor at decreased doses of lithium (dose–response). This is a strong evidence of mutuality, yet it is possible that the events are due to a confounder that is also decreasing in parallel with the decreased doses of lithium. However, if a drug is added that interferes with the metabolism of lithium (ibuprofen, for instance) and tremor increases again, this is a further evidence of a causal connection between lithium and tremor.

5.3.2 Good Evidence of Mutuality

Temporality is plausible with an interaction between patient's disposition and the drug's properties.

Temporality of the reported event should be expected to vary according to the drug's properties, but also according to the patient vulnerability.

There is positive de-challenge and/or re-challenge once.

If the reported event improves or reappears in correlation with discontinuation and re-administration of the drug in this patient, this suggests that the event is caused by an intrinsic disposition of the drug in the patient. However, the event could also be caused by a confounder.

The intensity of the event matches the combination of the patient's and the drug's dispositions.

An adverse event can be more intense than expected from previous cases or the literature, according to an increased vulnerability of this particular patient toward that event.

5.3.3 Moderate Evidence of Mutuality

Moderate evidence of a patient-drug interaction indicates that the patient belongs to a sub-population that has a correlation to adverse events from this or similar drugs, but there is no medical understanding of this correlation.

There is a correlation of this or similar drugs and adverse events in similar patients.

If the patient belongs to a sub-population that has been observed to have a higher incidence of this or a similar adverse event in concomitance with this or a similar drug(s), then this can indicate that they have a common disposition that makes them a manifestation partner for this type of event. The reason for this could be biological (e.g. gender or ethnicity), social (e.g. socio-economic status, community), or a combination of these.

5.4 Overall Conclusion

The overall conclusion for assessment of ICSRs should include an assessment of the three types of dispositions and how they relate. It is neither sufficient nor necessary to sum up the conclusion in a single word (e.g. yes, no, probable, certain, possible). The conclusion will depend on the assessor's case-specific considerations, but as a general rule, the confidence in a causal relationship based on the *Dx3* approach will be strongest in the case of the following combination of evidence:

- strong evidence of drug disposition
- moderate or no evidence of vulnerability
- strong evidence of mutuality

and weakest in the case of the following combination of evidence:

- moderate or no evidence of drug disposition
- strong evidence of vulnerability
- moderate or no evidence of mutuality.

Other important considerations for making an argument for the overall evaluations are:

– Whenever there is strong evidence of both drug disposition and mutuality, the possibility of a causal connection should be investigated further, even when there is strong evidence of vulnerability.
– Whenever there is strong evidence of drug disposition and the evidence of mutuality is good, or vice versa, a further investigation to assess causality should be seriously considered, even when there is strong evidence of vulnerability.

In both cases, the checklist might be used to formulate follow-up questions to the reporter.

6 Using the *Dx3* Checklist: Two Case Examples

We now offer two case examples to show how the checklist can be used in practice to evaluate the available evidence.

6.1 Nilotinib and Cholecystitis

An elderly patient affected by chronic myeloid leukemia was treated with nilotinib (800 mg daily). After an unspecified period of time, the patient developed abdominal pain and increase of hepatic enzymes. Abdominal ultrasonography and endoscopic retrograde cholangiopancreatography were consistent with a diagnosis of acalculous cholecystitis. Nilotinib treatment was stopped and two subsequent attempts to restart it were complicated by a return of events. Each time the nilotinib was discontinued, the patient recovered, constituting two positive rechallenges. After the final treatment episode, acalculous cholecystitis and abdominal pain were reported as completely recovered. The reporter of the case did not believe there was a causal relationship between the nilotinib and cholecystitis, without further explanation. (Clinical details were invented for illustrative purposes and patient information changed to ensure anonymity.) For case analysis and assessment using the *Dx3* checklist, see Table 2.

6.2 Ivermectin and Coma

A 13-year-old boy was admitted to the pediatric intensive care unit for impaired consciousness. He had received a single oral dose of ivermectin (0.23 mg/kg of body weight) to prevent scabies infection 2 h 30 min before the onset of impaired consciousness. His condition worsened 6 h after he received ivermectin, with persistent neurologic signs, including coma, ataxia, pyramidal signs, and binocular diplopia, as well as abdominal pain and vomiting. He was monitored for 48 h; during this period, he had a fluctuating Glasgow score and normal results on paraclinical tests. He fully recovered after 48 h [22]. For case analysis and assessment using the *Dx3* checklist, see Table 3.

Table 2 Analysis and assessment of the case of nilotinib and cholecystitis

Case analysis and assessment
Drug disposition: There is evidence for a plausible mechanism by which nilotinib can induce the symptoms here described. A number of findings related to hepatobiliary toxicity were made following repeated administration of nilotinib. Liver weight increases were observed in rats (≥ 30 mg/kg). Liver inflammation, *bile stasis, bile inspissation* and *bile duct proliferation* accompanied by increases in alanine transaminase and alkaline phosphatase were observed in dogs at ≥45 mg/kg. Findings in monkeys administered 30 mg/kg consisted of mononuclear cell infiltration, *bile duct hyperplasia*, periportal fibrosis. Additional findings made at higher doses were sinusoidal cell hyperplasia/hypertrophy, cytoplasmic aggregation of sinusoidal cells, *enlarged bile duct* and an increase in alanine transaminase [23]
Conclusion: These findings, especially the findings related to bile duct hypertrophy, amount to *strong evidence for a disposition of nilotinib to the reported events*
Patient vulnerability: Although the patient was not reported to have experienced cholecystitis before the administration of nilotinib, acalculous cholecystitis is most commonly observed in the setting of very ill patients. The condition can occur in persons of any age, although a higher frequency is reported in persons in their fourth and eighth decades of life. Acalculous cholecystitis has a slight male predominance, unlike calculous cholecystitis, which has a female predominance. However, immunosuppression and bone marrow transplant are associated with acalculous cholecystitis [21]
Conclusion: There is *good evidence of vulnerability of the patient to acalculous choleystitis*
Mutuality: The repeated dechallenge and rechallenge indicates that nilotinib was a difference-maker (or trigger) for cholecystitis in this patient among concomitant conditions (myeloid leukemia)
Conclusion: Although there is no further information about possible confounders, the repetition of challenge and de-challenge nevertheless represents *strong evidence of drug-patient interaction*
Overall assessment: Since both evidence of drug disposition and mutuality are strong, the fact that there is good evidence of patient pre-disposition to cholecystitis should not automatically be used to weaken the causal hypothesis in this case. *The evidence of causality is strong*, and the case warrants further investigations of the possibility that other patients with leukemia or similar conditions might be vulnerable to nilotinib induced cholecystitis

Table 3 Analysis and assessment of the case of ivermectin and coma

Case analysis and assessment
Drug disposition: There is some evidence of correlation between ivermectin and the neurological condition described, which indicates causality. First, the signal was detected with a measure of disproportionality in VigiBase, the WHO global database of individual case safety reports. Second, the drug is known to pass the blood brain barrier in certain types of dogs [20] Conclusion: Together, this amounts to *good evidence of ivermectin disposition to the reported event*
Patient vulnerability: There is no mention of a previous medical history of the patient, which allows us assume that the ICSR is about a healthy 13-year-old boy. However, the patient belongs to a sub-population (i.e. the case series of similar patients in Vigibase, the WHO Global Database of Individual Case Safety Reports) that has a correlation with this or similar events, but there is no medical understanding of such correlation Conclusion: This indicates *moderate evidence of the patient's vulnerability to the reported event*
Mutuality: The temporal development with resolution of the event consistent with the pharmacokinetics of ivermectin metabolism indicates that temporality matches the drug's known properties. The case offers one instance of positive dechallenge Conclusion: There is overall *good evidence for a disposition of drug-patient interaction*
Overall assessment: Since there is good evidence of ivermectin disposition to the reported event and good evidence for a disposition of drug patient interaction, *the evidence of a causal relation between ivermectin and coma in this case is strong*. The assessment is made stronger by the fact that there is only moderate evidence of the patient's vulnerability to the reported event. The case warrants further investigations of the possibility that other patients who receive ivermectin might be vulnerable to coma

7 Conclusion

Our proposed approach has some implications for the way suspected adverse events are reported clinically. Given the types of evidence required by the proposed *Dx3* approach, the ICSR will have to provide the information needed for subsequent causality assessment and signal detection, specifically about the individual event and the patient context. The pharmacovigilance process would therefore benefit greatly from qualitatively rich reports following the second and third columns of the *Dx3* checklist as a guide. This means that current reporting systems need to change to improve causality assessment, where the patient narrative is seen as vital for pharmacovigilance.

Declarations

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Code availability Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Authors' contributions RLA and ER have conceived the work. REC has provided feedback, consultancy, examples and pointed to the relevant literature. All authors contributed to writing the manuscript. ER led the CauseHealth Pharmacovigilance project which generated the paper. All authors read and approved the final manuscript and agree to be accountable for this work.

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