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A DETAILED REVIEW ON FUNDAMENTAL OF PHARMACOVIGILANCE

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ABSTRACT

Pharmacovigilance (PV), which refers to detecting, assessing, understanding and preventing adverse drug reactions (ADRs), has progressed from being largely case-report-based in its methodology to using causality algorithms, population-level databases, risk management methodologies, audits and increasingly artificial intelligence (AI) techniques. The current narrative review summarises evidence from six recently published sources from all of these areas: a theoretical exposition of the "signal-alert-alarm-action" process and the relative strengths of case-based versus exposure-based pharmacoepidemiology designs [2]; conference-abstract evidence on the aggregation and completeness of medicine-exposure data in periodic safety update reports and reporting of additional risk-minimisation measures (aRMMs) [12]; audit-based evidence on compliance with regulatory requirements and ethical principles (beneficence, non-maleficence, autonomy and justice) for PV activities [16]; a review of the principles, challenges and reporting framework for pharmacovigilance in Ayurveda [19]; and a review of the applications, advantages and limitations of AI and machine learning (ML) - NLP, automated case processing, predictive analytics and explainable AI - in modern PV [21]. Taken together, the six recent sources reveal that PV is converging on a set of unresolved issues: inadequate and inconsistently standardised exposure denominators, inconsistent and inadequately evaluated risk-minimisation measures, persistent underreporting and reporting biases, deficiencies that consistently come up during audits and an increasing reliance on artificial intelligence tools whose data quality and regulatory acceptance remain unfinished work in progress. The review concludes with recommendations for enhancing exposure data reporting, aligning regulatory audit and ethical principles, applying PV principles to traditional medicine and implementing AI tools in an ethically responsible way along with continuous human oversight.

KEYWORDS: Pharmacovigilance; Adverse Drug Reaction; Causality Assessment; Disproportionality Analysis; Risk Minimisation Measures; Pharmacovigilance Audit; Artificial Intelligence; Signal Detection; Ayurveda.

1. INTRODUCTION

Pharmacovigilance, according to the World Health Organisation, is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem [1]. The thalidomide tragedy of the 1960s prompted the development of formal reporting of adverse drug reactions and, since then, pharmacovigilance has gone through several "chapters" of development: case-based spontaneous reporting and causality assessment; aggregated case analysis and disproportionality statistics; and, most recently, the use of population-scale electronic health records, claims databases and AI as a basis for signal detection and confirmation [2]. Each chapter has added new capacities but has not done away with the unresolved issues of previous chapters: reporting biases, insufficient exposure denominators, and resource-related oversight remain even as the number of new tools for signal detection and confirmations grows.

This review brings together evidence from five recently published sources on the key areas in pharmacovigilance – methodology, exposure and risk minimisation reporting, audits and ethics, pharmacovigilance in traditional medicine, and the use of artificial intelligence – with the well-known evidence on causality assessment and signal detection, to develop a holistic view of pharmacovigilance as a field and of its unresolved issues.

2. Foundations: Signals, Causality, and the Disproportionality Toolkit

According to Moore et al., managing the safety of drugs is like diagnosing a disease: just as disease passes through suspicion, diagnosis, evaluation, and treatment, so does a safety problem pass through the steps of signal, alert, alarm, and regulatory action [2]. A signal comes in the form of excess or unusual case report that needs to be converted into a hypothesis of causality. The French imputation model, which is based on chronological criteria (dechallenge, rechallenge), semiological criteria (laboratory confirmation), and bibliographic criteria (previous knowledge), is an algorithmic approach for causality assessment and serves as an example of what any causality assessment tool is: none of them is authoritative, as different people with different goals use the same causality assessment approach to get different results from the same case [2].

The variability of results is not specific to the French method. Naranjo Adverse Drug Reaction Probability Scale – a set of ten weighted questions designed to eliminate inter-rater disagreement in causality assessment – became one of two most widely used bedside causality assessment approaches, the other being WHO-Uppsala Monitoring Centre (WHO-UMC) categorical system [4]. Roussel Uclaf Causality Assessment Method (RUCAM) plays the same role for drug-induced liver injury [5], while DoTS classification was based on dose-relatedness, time-course, and susceptibility, instead of

causality, of ADRs [6]. Individual causality assessment approach is inherently biased: although a single case serves as a base for causality hypothesis, it cannot give population-based risk estimation [2].

Disproportionality analysis of aggregated cases solves this problem by comparing the proportion of a certain adverse event in cases of the particular drug to the same proportion in a control group and estimating the reporting odds ratio (ROR) or proportional reporting ratio (PRR) [2,8]. Bayesian approaches to disproportionality analysis – Bayesian Confidence Propagation Neural Network (BCPNN) developed at the WHO-UMC – introduced shrinkage estimators (Information Component), which stabilize signal estimates for small case counts [7], while further comparison showed that these measurements tend to converge starting from three cases despite their differences at lower case counts [9]. Disproportionality is still a measure of reporting activity and is subject to Weber effect (varying reporting intensity over time), notoriety effect (increased reporting after media alert), competition effect (interaction between co-reported drugs) and masking (interaction between correlated event-drug pairs) [2]. This makes disproportionality estimate a hypothesis generator that needs to be further analyzed for each particular case, as known for a long time that adverse drug reactions become one of the leading causes of hospitalization and in-hospital deaths, a burden that spontaneous reporting system can hardly cover [10,11].

3. From Spontaneous Reports to Population Databases: Complementary Study Designs

Moore et al. differentiate two major pharmacoepidemiological approaches that could be used to confirm a signal [2]. The event-based (case-based) designs – case-control, case-crossover, self-controlled case series and case-population approaches – start with the case of the particular outcome (e.g., acute liver injury, hospitalization for the particular event), and compare drug exposure between cases and controls or in the whole source population. Exposure-based (cohort) designs, which start with new users of a drug and track the outcomes, are used in large claim databases and electronic health record (EHR) systems, e.g. French SNDS and UK Clinical Practice Research Datalink databases; these approaches allow generating unbiased event rates for the whole population and conduct 'new-user' comparative effectiveness analyses using high-dimensional propensity score approach to adjust for indication bias [2].

An important methodological recommendation common to pharmacoepidemiology is to avoid comparison of drug users and non-users: as drugs are prescribed for a reason (indication), this indication may be associated with an outcome of interest, creating indication bias. New-user designs using active comparators (i.e., comparing one marketed drug against another drug with the similar indication) are preferred to untreated-comparator designs in almost all modern pharmacoepidemiology [2]. These population-based approaches are also complementary to disproportionality analysis: although spontaneous reporting is the most efficient source of hypotheses, especially for rare and severe events, population-based data is necessary to calculate denominators and convert alert into a quantifiable risk [2].

4. Exposure Data and Risk-Minimisation Measures: A Persistent Reporting Gap

In the ISoP conference abstracts, the denominator side of PV, which is how many patients have been exposed to a certain medicine, and if the risk-minimization measures (RMMs) managed to reach them, has been reported much less reliably than the numerator side, which is the actual case reports [12]. In a review of 62 PSURs for ATC L01 products sent to the EU regulatory network from 2012 to 2020, 87% of MAHs had reported the exposure at the world level, 13% provided no information at all, and only fewer than half of them supplemented the worldwide exposure data with exposure at the national or EU level, even though the latter is needed for distinguishing a local safety concern from the background noise [12]. This 'dilution' of the denominator could result in missing safety signals that would be country-specific, due to co-morbidity of its population, its concomitant medication practices, or prevalence of risk factors. At the same time, it makes it impossible to evaluate whether the implemented RMM really resulted in changing the behavior of prescribers and monitors [12].

A similar analysis of the effectiveness-evaluation studies for aRMM that were submitted to EU regulators also showed considerable variability in the quality of reporting, which was followed by the development of the 2017 Reporting recommendation Intended for pharmaceutical risk Minimisation Evaluation Studies (RIMES). It is a 43 item checklist across four domains (key information, intervention design, program implementation, and evaluation) that GVP 2021 revision recommends MAHs to use [12]. Another example from the same body of evidence is the before-after study of the tuberculosis screening prior to starting the therapy with infliximab and adalimumab, which illustrates what an effective RMM evaluation is capable to show: after implementation of RMM, chest X-ray screening prior to using infliximab increased from 20.9% to 37.1% of patients ($p = 0.035$) and QuantiFERON test screening increased from 17.9% to 47.4% ($p < 0.001$). Even though the post-implementation rates are still low, it shows that often the RMMs move the practice in the right direction, without reaching the full compliance [12]. Thus, exposure data quality and RMM-evaluation quality are two sides of the same problem: without reliable denominator and a standardized framework, it is impossible to assess the success of the risk-minimization intervention [12].

5. Regulatory Compliance, Audits, and the Ethics of Pharmacovigilance

5.1 The GVP audit framework

Guidelines for good pharmacovigilance practice, which were developed together by EMA and Heads of Medicines Agencies, divide the PV obligations into process-based modules (systems and quality systems, Pharmacovigilance System Master File, risk management plans, signal management, audits) and population/product-specific annexes (vaccines, biologicals, and pediatric/geriatric populations) [16,18]. The module IV of these guidelines regulates the planning, conducting, and follow-up of PV audit, which is supposed to verify the appropriateness and effectiveness of a company's PV system independent of the inspections performed by competent authorities [16,17]. The MAH is obliged to continuously monitor the risk-benefit balance of its product, evaluate all the incoming information

about it, provide timely and accurate ADR reports and preserve the integrity of the PSMF and RMP [16].

5.2 What audits actually find

In a systematic review of the PV audit findings gathered for 5 years, the non-conformances have been classified into three categories [16]. Minor non-conformances are usually connected with the quality of documentation, for example, incomplete case narratives, inconsistent data entry or under-resources of quality assurance activity. Major non-conformances include late regulatory reporting, lack of experienced Qualified Person for PV, poor processes for signal detection and literature monitoring, ineffective CAPA systems, and lack of staff training. Critical non-conformances, although the smallest one, are the most significant category: failure to maintain the PSMF, PV records falsification, signal detection/lack of action on the safety signals, and failure to report SUSAR to regulators [16]. One more important observation is that the literature screening tends to fail often: audits identified literature sources which were not being screened, and the screening itself was performed without relevant criteria being established [16]. That could be explained by the lack of resources, outsourcing of the process to external vendors without control, poor design of the search strategy and data management [16].

5.3 An ethical framework for pharmacovigilance

Using the four principles [16]. of biomedical ethics – beneficence, non-maleficence, autonomy, and justice – the audit-ethics analysis suggests evaluating the PV activities and the audits regulating them not only by the checklists but by those values: identification and mitigation of the risks proactively (beneficence); minimizing the harm through prompt identification and management of adverse events (non-maleficence); respecting patients' rights to make informed decisions, to preserve their privacy and confidentiality of safety data (autonomy); and application of PV process in an impartial way among different patient populations (justice) [16]. Conflicts of interests are also identified as one of the major ethical threats: commercial pressure for under-reporting of ADRs, internal pressure on the auditor to not jeopardize the schedule of the study, and the governance of medical registries which could be affected by outside sponsors Such conflicts, when revealed, lead to decreased public trust, which in turn results in even more under-reporting of adverse events in a vicious circle [16]. The process of rebuilding that trust after any ethical breach is described as slow and expensive, therefore, reinforcing the need for ethical safeguards not as a supplement to regulatory compliance, but as a prerequisite of it [16].

6. Pharmacovigilance Beyond Conventional Medicine: Lessons from Ayurveda

Principles of PV developed for artificial pharmaceutical drugs do not extend to the realm of traditional medicines systems automatically. According to the Rastogi's paper on the application of PV principles to the Ayurveda medicine system in India, this field should address two separate challenges: one being the need for PV in the medical system which operates on an individualised basis and relies on

the experience of the physician (yukti) and another one being the possibility of implementing PV in the context of familiarity with materia medica [19]. Those who support the 'no PV needed' perspective claim that adverse reactions to the medicine indicate the improper use of the drug or adulteration. On the other hand, according to Rastogi, Ayurvedic prescribing involves subjective clinical judgement of many modifying factors (patient's constitution, illness, location, season), and the subjectivity creates the margin for variation and possible adverse outcomes that causality analysis in the language of Ayurvedic pharmacology (rasa, guna, virya, vipaka, prabhava) can help reduce [19].

India's National Pharmacovigilance Programme for Ayurveda, Siddha and Unani (ASU) drugs started operating from 2008 with the establishment of the National Pharmacovigilance Resource Centre and regional and peripheral centres. The conventional ADR reporting form was modified to incorporate risk factors specific to the practice: the consumption of drugs in combination with other products (anupana), degradation of powder drugs containing salt or sugar because of improper storing conditions, empirical spoon measurement of dosage of drug, bulk distribution of drugs for subsequent patient's portioning at home, adverse reactions related to procedures such as Panchakarma, Ksharasutra and Rakta mokshana [19]. A survey conducted among practising physicians in Uttar Pradesh, Bihar and Maharashtra showed that practitioners acknowledge the existence of adverse reactions (the most frequent causes of which were counterfeit products and improper use of the medicine) and lack of knowledge on the principles of drug safety and ADR reporting [19]. It is worth mentioning concerns about the presence of heavy metals (such as lead and aconite) in some of the formulations of Ayurvedic drugs [19]. Thus, the general lesson is that the ADR reporting form, causality method and awareness campaign have to be derived from the clinical logic of the target medical system and not be imported 'as is'. This applies to any traditional and complementary medicine systems.

7. Artificial Intelligence in Pharmacovigilance

7.1 Why AI is entering pharmacovigilance

The volume of individual case safety reports (ICSRs) received by national and international agencies increased significantly. Shukla et al. note that it creates a 'needle in the haystack' problem which cannot be solved manually anymore; the challenge is aggravated by the fact that ADR reports are presented in handwriting, unstructured and multilingual format [21]. Accordingly, regulatory bodies became interested in the use of AI technology: the US FDA developed the roadmap for the implementation of AI into existing PV system five years before the COVID-19 pandemic intensified the demand [21].

7.2 Applications

- Automated case processing – AI systems can triage ICSRs and structurise high volume of data contained therein [21].

- Signal detection and data mining – machine learning methods help to find disproportional associations between drug and event in heterogeneous data sources that cannot be revealed with conventional statistical methods [21].
- Prediction modeling – Models trained on historical safety data can predict the probability of adverse events in certain patient sub-populations, thus allowing for more proactive risk management planning [21].
- Natural Language Processing (NLP) – NLP can extract safety information from unstructured sources such as physicians' notes, patients' reports and social-media posts, which is poorly handled by the traditional pipeline for structured reporting, as supported by evidence on social media based ADR surveillance [21,24].
- Causality and Explainable AI (XAI) – Emerging models aim at causality reasoning of the connection between a drug and an adverse event; as these judgments impact regulatory decisions and clinical trust, the review highlights the importance of explainability as much as that of prediction performance [21].

7.3 The regulatory and accountability constraints

The same review is clear in identifying the limitations of AI in this field. Performance of models is contingent upon the availability of substantial volumes of curated training data, which is scarce in a field built on historical unstructured free-text reporting [21,15]. Applying AI technologies to safety reporting data is hampered by privacy and reuse issues, as the data collected for one PV task can be reused for model training without the data owner's permission [21]. Frameworks for validation of AI-powered signal detection models are still being developed, and in its conclusions, the review argues that human expertise is indispensable and cannot be substituted by AI for the time being, with the latter being used as an additional signal detection tool, followed by clinical review of the identified signals, model retraining and traditional causality and disproportionality approaches as an extra check on machine output [16,21]. These issues resemble the problems highlighted in the audit findings of literature screening deficiencies in section 5.2: the lack of resources and data quality that undermines traditional signal detection process is the same problem that AI technology is the most vulnerable to, meaning that the use of AI without investing into the data infrastructure will do little to solve this issue.

8. Integrative Discussion

Taken all together, five sets of evidence paint the picture of a field characterized by one central unresolved tension that is relevant to all levels of analysis. PV systems are very good at reporting of suspected harms, but very poor at building up the denominators, standards, and supervision that would allow interpreting the reports with certainty. On an individual level, causality tools like the French method, Naranjo scale, and RUCAM are very useful, but give different judgments dependent on the

goal set before the assessor [2,4,5]. Aggregated report analysis is highly useful, as is disproportionality analysis; however, both of these are measures of reporting behavior rather than incidences, which are affected by the biases inherent in the reporting process [2,7,9]. On a population level, PSUR data clearly demonstrate that MAHs report only the worldwide exposure data, thus lacking the local denominators that are critical for signal detection and RMM assessment [12]. On an organizational level, audits always highlight the same few root causes of inefficiencies: under-resourcing, procedural inconsistency and poor literature screening practices irrespective of the company or geographical context [16]. On a cross-cultural level, Ayurveda proves that even the carefully designed reporting system should be adapted to the local clinical reasoning processes [19]. And on the technological edge, AI technology inherits the data quality problem rather than solves it, as its outputs depend on the quality of the structured data used for training the models [21].

The second theme that cuts across all topics discussed in this paper is the need for active and well-informed human judgement throughout the whole process. That includes the prescriber deciding on rechallenge, the auditor reviewing the CAPA plan in terms of beneficence and justice, the Ayurvedic doctor performing his/her yukti, and the PV scientist analysing an alert generated by the use of artificial intelligence – all the sources analysed above have in common that none of them see automation of the entire PV process as possible. What all of them foresee is using technological advancements (RIMES, GVP modules, NLP, structured ADR reporting) as tools that make the process of informed judgement faster, more consistent, and better documented – but not a substitute for it.

9. Future Directions

- Implement standardised procedures for the reporting of exposure data in PSURs and RMP evaluations, together with mandatory country- or region-specific denominators in addition to worldwide data, to avoid dilution of local safety information [12].
- Incorporate structured reporting as a default requirement for aRMM effectiveness studies rather than an optional recommendation [12].
- Ensure resource allocation for literature screening and signal management tasks within PV quality systems in view of audit results [16].
- Formalise causality assessment and reporting procedures for traditional and complementary medicine systems after the example of Ayurveda [19].
- Invest in structured, curated training data and explainability standards before deploying AI-based signal detection within regulatory workflows, and mandate human review of AI-generated signals [21].
- Embed the four bioethical principles into PV audit checklists, thus evaluating ethical practices together with procedural compliance, rather than separately [16].

10. CONCLUSION

The pharmacovigilance methodology had developed its own methodological arsenal - causality algorithms, disproportionality statistics, population-based cohort studies and cases, structured approaches to signal detection, and most recently, even AI-based signal detection - while not solving the underlying issues that triggered each step: the issue of incomplete exposure denominators, the inconsistency of RMM assessment, insufficient resources for signal detection, and finally, the adaptation of the Western regulatory approach to other clinical cultures. It appears that based on the material analyzed above, the next chapter of the pharmacovigilance story is less likely to be defined by another technological breakthrough, including the use of AI, but rather by the ability to solve those data quality, standardization, and ethics issues at the very basis of all the methodological developments.

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