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Vinodkumar Mugada[1], Vidyadhara Suryadevara[2], Manasa Cheekurumilli[3], Srinivasa Rao Yarguntla[4]

SIGNAL DETECTION IN PHARMACOVIGILANCE: METHODS, TOOLS, AND WORKFLOWS FROM CASE IDENTIFICATION TO ADVERSE DRUG REACTION DATABASE ENTRY

[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Vignan Institute of Pharmaceutical Technology, Duvvada, AP, India
[2]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, AP, India
[3]Department of Pharmacy Practice, Vignan Institute of Pharmaceutical Technology, Duvvada, AP, India
[4]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Vignan Institute of Pharmaceutical Technology, Duvvada, AP, India

ABSTRACT

Adverse drug reactions (ADRs) remain a major, yet largely preventable, global public health challenge, causing significant morbidity, mortality, and healthcare costs. This review synthesises evidence on the global burden, pharmacovigilance systems, and prevention strategies for ADRs, integrating data from multiple regions, healthcare settings, and drug classes. Epidemiological findings reveal wide variability in incidence and mortality, with older adults, low-resource settings, and exposure to high-risk medicines – such as antibiotics, antiretrovirals, and cardiovascular agents – representing key vulnerabilities. Despite advances in surveillance, underreporting, data quality issues, and methodological biases persist, particularly in low- and middle-income countries. Comparative analyses of pharmacovigilance platforms, including World Health Organization's (WHO's) VigiBase, EudraVigilance, and EU-ADR, highlight complementary strengths and the value of integrating spontaneous reporting with electronic health record analytics. Emerging statistical methods, including machine learning and federated analytics, offer improved signal detection timeliness and precision. Prevention strategies span prescriber-level, system-level, and patient engagement interventions. These include clinical decision support systems, pharmacogenomic-guided therapy, deprescribing protocols, mobile reporting applications, and wearable biosensors. Evidence shows that active surveillance and automated alerts outperform voluntary reporting, while digital tools can enhance detection and risk communication. However, implementation remains uneven due to infrastructure, workforce, and policy gaps. Looking forward, achieving the World Health Organization's goal of halving severe medication-related harm by 2030 will require embedding ADR surveillance and prevention into universal health coverage frameworks. Policy priorities include mandating interoperable safety systems, harmonising international safety indicators, investing in capacity building for resource-limited settings, and aligning incentives with safer prescribing. Coordinated global action can bridge surveillance gaps, strengthen prevention, and build resilient, equitable pharmacovigilance systems, advancing both patient safety and sustainable health systems worldwide.

Keywords: *adverse drug reactions, pharmacovigilance, medication errors, patient safety, computer assisted signal detection*

STRESZCZENIE

Niepożądane działania leków (ADR) pozostają poważnym, choć w dużej mierze możliwym do uniknięcia, globalnym wyzwaniem dla zdrowia publicznego, generując znaczną zachorowalność, śmiertelność i koszty opieki zdrowotnej. Niniejszy przegląd syntetyzuje dowody dotyczące globalnego obciążenia, systemów nadzoru nad bezpieczeństwem farmakoterapii oraz strategii zapobiegania ADR, integrując dane z wielu regionów, placówek opieki zdrowotnej i klas leków. Wyniki epidemiologiczne ujawniają dużą zmienność zapadalności i śmiertelności, przy czym osoby starsze, placówki o niskich zasobach oraz osoby narażone na leki wysokiego ryzyka – ta-

kie jak antybiotyki, leki antyretrowirusowe i leki stosowane w chorobach układu krążenia – stanowią kluczowe obszary podatności. Pomimo postępów w nadzorze, nadal utrzymują się niedoszacowania, problemy z jakością danych i błędy metodologiczne, szczególnie w krajach o niskich i średnich dochodach. Analizy porównawcze platform nadzoru nad bezpieczeństwem farmakoterapii, w tym VigiBase, EudraVigilance i EU-ADR Światowej Organizacji Zdrowia (WHO), podkreślają uzupełniające się mocne strony i wartość integracji spontanicznego zgłaszania z analizą elektronicznej dokumentacji medycznej. Nowe metody statystyczne, w tym uczenie maszynowe i analityka federacyjna, oferują lepszą terminowość i precyzję wykrywania sygnałów. Strategie prewencyjne obejmują interwencje na poziomie lekarza przepisującego leki, systemu oraz zaangażowania pacjenta. Należą do nich systemy wspomagania decyzji klinicznych, terapia oparta na farmakogenomice, protokoły odstawiania leków, mobilne aplikacje raportujące oraz biosensory noszone na ciele. Dowody wskazują, że aktywny nadzór i automatyczne alerty przewyższają dobrowolne raportowanie, a narzędzia cyfrowe mogą usprawnić wykrywanie i komunikację dotyczącą ryzyka. Jednak wdrażanie pozostaje nierównomierne ze względu na luki w infrastrukturze, kadrze pracowniczej i polityce. W przyszłości osiągnięcie celu Światowej Organizacji Zdrowia, jakim jest zmniejszenie o połowę poważnych szkód związanych z lekami do 2030 roku, będzie wymagało włączenia nadzoru nad działaniami niepożądanymi leków i profilaktyki ADR do powszechnych ram opieki zdrowotnej. Priorytety polityczne obejmują wprowadzenie interoperacyjnych systemów bezpieczeństwa, harmonizację międzynarodowych wskaźników bezpieczeństwa, inwestowanie w budowanie potencjału w środowiskach o ograniczonych zasobach oraz dostosowanie zachęt do bezpieczniejszego przepisywania leków. Skoordynowane działania na skalę globalną mogą zniwelować luki w nadzorze, wzmocnić profilaktykę i zbudować odporne, sprawiedliwe systemy nadzoru nad bezpieczeństwem farmakoterapii, zwiększając zarówno bezpieczeństwo pacjentów, jak i stabilność systemów opieki zdrowotnej na całym świecie.

Słowa kluczowe: *niepożądane działania leków, nadzór farmaceutyczny, błędy w stosowaniu leków, bezpieczeństwo pacjenta, komputerowe wspomaganie wykrywania sygnałów*

INTRODUCTION

Adverse drug reactions (ADRs) are harmful and unintended responses to medications administered at normal therapeutic doses and are a significant concern in both clinical practice and public health. The World Health Organization defines an ADR as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man" (1). The European Union broadens this definition to include reactions arising from medication errors, misuse, or off-label use, thereby expanding the remit of pharmacovigilance (2). On the other hand, an adverse event is "Any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment" (3). ADRs account for approximately 6% of hospital admissions, rank among the top six causes of mortality in high-income countries, and contribute to over 100,000 deaths annually in the United States (4). The Global Burden of Disease Study reports a decline in the disability-adjusted life year (DALY) rate attributable to ADRs, from 84.93 to 62.79 per 100,000 between 1990 and 2017, yet substantial regional disparities remain (5). Compared to healthcare-associated infections (HCAIs), up to 87.1% of ADRs in hospitalized patients are preventable (6,7), and this highlights ADRs as a preventable global public health threat (8). In response, the World Health Organization launched the Medication Without Harm initiative to achieve a 50% reduction in severe medication-related harm by 2027. This objective aligns with Sustainable Development Goal (SDG) 3.8, which promotes universal access to safe, effective, and affordable medicines, and SDG 3.b addresses treatment gaps through improved medication safety practices (9,10).

The current review aimed to quantify the global impact of ADRs by assessing incidence, mortality, and DALY metrics and by identifying vulnerable populations and high-risk drug classes (11,12), to evaluate pharmacovigilance systems, including WHO's VigiBase and the EU-ADR network, as essential mechanisms for early safety signal detection and validation (13,14), and to examine how validated safety signals inform targeted interventions, such as prescriber decision-support tools, deprescribing protocols, and public engagement strategies, to mitigate harm at both clinical and population levels (10,15).

EPIDEMIOLOGY OF ADRS FACTORS INFLUENCING INCIDENCE OF ADRS

Multiple factors influence the incidence of ADRs. Studies report several factors that influence the occurrence of ADRs including: older age, female gender, higher number of co-morbidities, increased number of drugs, receiving potentially inappropriate medication (PIM), use of herbal remedy in previous

4 weeks, renal diseases, hepatic conditions, and previous ADRs (16-24).

GLOBAL BURDEN

The incidence and mortality rates of ADRs vary markedly across healthcare settings due to differences in pharmacovigilance capacity, drug utilisation patterns, and population characteristics. Prospective hospital-based studies illustrate this heterogeneity: in Ethiopia, the incidence was 27.4 ADRs per 100 admissions (95% CI: 19.8–30.4); in Uganda, 48.9% of elderly inpatients experienced at least one ADR, corresponding to 78 ADRs per 1000 person-days; in Korea, prevalence reached 10.2%; and in Italian medical wards, 3.2% (7, 25-27).

Older adults are consistently at higher risk. In the Ugandan cohort, nearly half of patients experienced an ADR during six months of follow-up, echoing findings from a seminal U.S. meta-analysis estimating an overall ADR incidence of 6.7% and fatal ADRs at 0.32% (25,28). Mortality data further highlight this impact: in South African medical wards, ADRs contributed to 2.9% of all deaths and 16% of in-hospital mortality (29). A recent meta-analysis confirmed a significant association between suspected ADRs and mortality (OR: 1.50; 95% CI: 1.21–1.86) (30).

Consistent patterns emerge across regions. In Ethiopia, antibiotics accounted for 26.2% of ADRs, followed by cardiovascular medicines at 24.7% (25). South African reports implicated antiretrovirals (notably tenofovir), anti-tuberculosis drugs (e.g., rifampicin), and co-trimoxazole as leading causes of fatal ADRs (31). In Korea, opioids were most frequently associated overall, while antibiotics dominated serious ADR categories (27). In Eritrea, 64% of patients receiving combination ART required regimen changes – incidence 12.3 per 1000 person-months – most often due to toxicity, treatment failure, or shortages (32). Despite widespread NSAID use in Southeast Asia, region-specific evidence linking these agents to renal injury or hospitalisation is limited, representing a notable surveillance gap.

REGIONAL AND HIGH-RISK PATTERNS

In Europe, ADR-related hospitalisations are disproportionately common among older adults. A large-scale review reported that 3.5% of admissions in those ≥65 years were ADR-related, with 10.1% experiencing an ADR during hospitalisation (33). The Irish ADAPT study found a 10.0% incidence of ADR-related admissions (95% CI: 9.1%–11.0%), 71.1% of which were potentially preventable (34). A broader review estimated a pooled prevalence of 11.0% (95% CI: 5.1%–16.8%), with individual cohorts reporting rates as high as 46.3% (35). A meta-analysis estimated ADR-related hospitalisation at 8.3% (95% CI: 6.4%–10.7%) in elderly populations (36). Sex-based differences are also evident. Italian pharmacovigilance data from over 300,000 reports showed higher overall ADR reporting in women (55.6% vs. 43.1%), but greater ADR-related mortality in men (37). In Sweden, women reported more ADRs (57% vs. 42%), yet severe ADRs were more frequent in men after adjustment (37).

DATA GAPS AND BIASES IN GLOBAL ADR SURVEILLANCE

Capture-recapture analyses consistently highlight substantial underreporting in hospital pharmacovigilance. The median underreporting rate in Iran was 76.0% (IQR: 64.32–81.35) (38). In France, notification rates for drug-induced acute kidney injury were as low as 6.1%, suggesting approximately 94% of events go unreported (39); another French study found rates of 12.9% (95% CI: 10.0–15.8) for similar outcomes (40). Low- and middle-income countries face recurring challenges, including low reporting rates, fragmented national systems, poor coordination, and reliance on short-term educational interventions (41). Additional barriers such as limited infrastructure, language constraints, stigma, and workforce shortages are reported across Africa and Southeast Asia (42). Studies in India reveal a gap between theoretical pharmacovigilance knowledge and reporting behaviours (43-46). In Rwanda, targeted education programmes improved ADR awareness and reporting (47).

Estimating true ADR incidence is complicated by unreliable denominators in spontaneous reporting systems, introducing bias into prevalence and risk calculations. A systematic review of signal detection algorithms reaffirmed these methodological limitations (48). Multi-source capture–recapture methods address under-ascertainment and confirm that no single source, such as spontaneous reports or administrative databases, offers complete coverage (39,40,49). Triangulation remains essential for accurate epidemiological estimates.

PHARMACOVIGILANCE AND SIGNAL DETECTION

VigiBase, the WHO global repository for post-marketing surveillance, collects ADR reports on medicines and vaccines from national pharmacovigilance centres across member states of the WHO Programme for International Drug Monitoring (50). Submitted reports undergo

standardised processing before integration (51). The database encompasses data from 36 countries, with region-specific analyses such as those involving the UN Asia region between 2016 and 2021 (52,53). Continuous updates and rigorous quality checks maintain harmonisation across reporting centres (51).

EudraVigilance serves as the pharmacovigilance infrastructure for the European Economic Area, capturing suspected ADRs for all authorised medicines (54). It records both serious and non-serious ADRs from marketing authorisation onwards. Examples include opioid safety analyses in Germany and longitudinal fosfomycin safety surveillance from initial approval to October 2021 (55,56).

The EU-ADR Web Platform links longitudinal EHR data from multiple European nations, using distributed analytics to identify drug-event associations (57). Integration of clinical datasets enables scalable, near-real-time signal detection that complements spontaneous reporting systems. Studies show that integrating spontaneous reporting systems with EHR-based databases can improve detection timeliness and accuracy. Cost-effectiveness analyses recommend tailoring system selection to the event type and data resource availability (58).

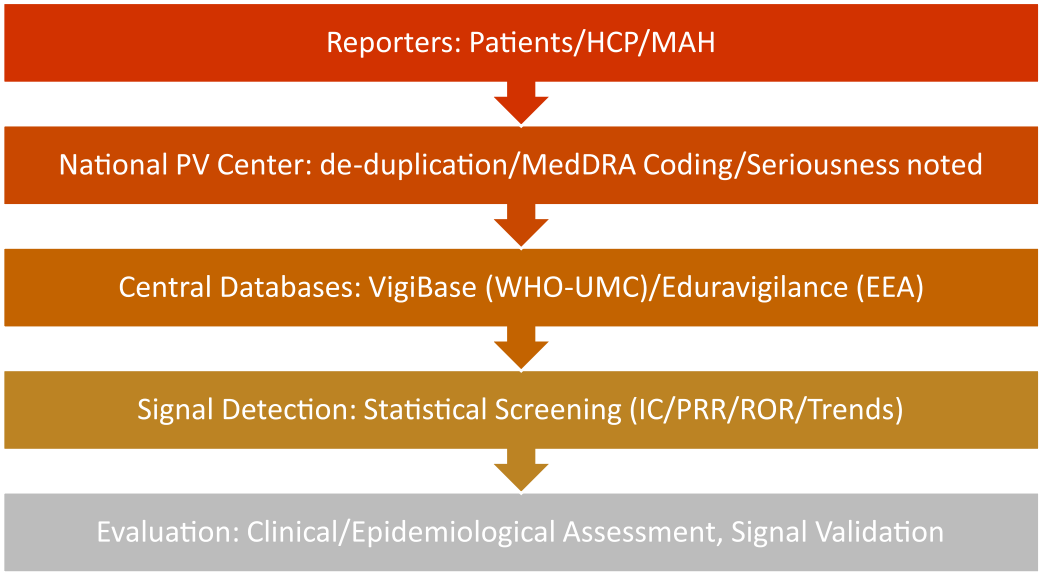
DATA QUALITY AND PREPROCESSING

The **VigiMatch algorithm** applies probabilistic matching to identify likely duplicate records by rewarding matched fields and penalising discrepancies (59,60). Validation studies report positive predictive values from 86% in the UK to 33% in Spain, with most false positives representing related rather than unrelated cases (60). VigiMatch has detected duplicates overlooked by rule-based systems. However, 2025 evaluations show newer models outperform VigiMatch across precision, recall, and false positive rates (61).

Accurate denominator estimation is essential for metrics such as the Proportional Reporting Ratio (PRR). The ATC/DDD (Anatomical Therapeutic Chemical / Defined Daily Dose) methodology standardises usage rates by calculating drug consumption per 1000 inhabitants per day, incorporating prescription volume (N), dose (M), pack size (Q), the assigned WHO *DDD*, population (P), and time period (T) (62,63). This harmonised approach corrects for variations in prescribing patterns and enables cross-country comparability.

CORE STATISTICAL ENGINES

Signal detection relies on robust statistical methodologies. Traditional disproportionality measures – Information Component (IC), PRR, and Reporting Odds Ratio (ROR) – remain widely used, while machine learning techniques increasingly supplement or replace them, offering improved sensitivity, specificity, and timeliness. In an analysis of immune checkpoint inhibitor-related ADRs in



HCP – Healthcare Professional; MAH – Marketing Authorisation Holder; NPC – National Pharmacovigilance Centre; MedDRA – Medical Dictionary for Regulatory Activities; IC/PRR/ROR – Information Component /Proportional Reporting Ratio/Reporting Odds Ratio; SmPC – Summary of Product Characteristics; RMP – Risk-Minimisation Plan

Figure 1. Signal detection and evaluation process in pharmacovigilance. Spontaneous reports from patients, HCPs, and MAH are verified by the NPC and forwarded to VigiBase/EudraVigilance for standardisation and quality control; statistical screening and clinical evaluation inform regulatory actions (SmPC updates, RMP) and safety communications.

paediatric oncology using VigiBase and Food and Drug Administration Adverse Drug Event Reporting System (FAERS), IC achieved the highest sensitivity (100%), followed by ROR (60%) and PRR (40%) (64). ROR demonstrated superior timeliness, detecting signals approximately one quarter earlier than PRR and IC (65,66). Gradient Boosting Machines (GBM) have achieved higher sensitivity (79%) and specificity (79%) than ROR (18%) and IC (21%) (67). Hybrid frameworks combining pharmacological network modelling with Bayesian algorithms have further improved performance, with an AUC of 0.8291 versus IC (0.7343), ROR (0.6828), and PRR (0.6721) (68).

PERFORMANCE AND IMPACT

Analysis of 4,520 safety signals in VigiBase revealed a median time to communication (TTC) of 9 years from first report to regulatory action (69). This delay was consistent for both designated medical events (DMEs) and other signals, with intermediate timelines showing 7 years from the accumulation of three cases and 6 years from disproportionality detection to communication. Over time, TTC has lengthened – rising from 5 to 9 years for DMEs and from 4 to 10 years for non-DMEs (59). Evidence on the positive predictive value (PPV) of VigiBase signals validated by regulators between 2015 and 2024 is limited, with most research focusing on cross-database signal consistency rather than downstream clinical or regulatory outcomes (70).

EMERGING INNOVATIONS: FEDERATED ANALYTICS FOR DISTRIBUTED SURVEILLANCE

The Sentinel System enables participating institutions to execute standardised queries locally, sharing anonymised aggregate data for central analysis (71). This model accelerates processing while maintaining data privacy. The Observational Health Data Science and Informatics (OHDSI) initiative advances global collaboration by developing open-source tools and a Common Evidence Model for real-world data analytics complementing the traditional and EHR-based systems described earlier (72).

PREVENTION AND MITIGATION STRATEGIES PRESCRIBER-LEVEL INTERVENTIONS

In the AF-ALERT randomized controlled trial of 458 hospitalized atrial fibrillation patients, alert-based CDSS significantly increased anticoagulation prescription rates (25.8% vs. 9.5%, $P < 0.0001$) and reduced composite adverse outcomes at 90 days (11.3% vs. 21.9%, $P = 0.002$) (73). The CODES pragmatic trials in Italian hospitals, involving over 10,000 patients, demonstrated progressive acceptance of EBMeDS-MediDSS as a reliable clinical tool (74).

The OPERAM multicenter trial applied CDSS-assisted STOPP/START criteria in 819 older inpatients with polypharmacy, generating 5,080 medication-related signals with 39% acceptance by pharmacotherapy teams (75). Large multicenter trials such as SENATOR and OPERAM, however, did not show significant reductions in ADRs, mortality, or drug-related readmissions, contrasting with positive single-center results (76). A meta-analysis of eight randomized controlled trials ($n = 6,708$) found that CYP2C19 genotype-guided antiplatelet therapy reduced major adverse cardiovascular events (RR 0.71, 95% CI 0.51–0.98, $p = 0.04$) and myocardial infarction risk (RR 0.56, 95% CI 0.40–0.78, $p < 0.01$) without increasing bleeding risk (77). CYP2C19 loss-of-function carriers on clopidogrel had a 62% higher MACE risk than those on alternative P2Y12 antagonists (RR 1.62, 95% CI 1.42–1.86, $p < 0.00001$), with pronounced effects in Asian populations (78).

SYSTEM-LEVEL APPROACHES

WHO's "Medication Without Harm" challenge has been implemented using varied strategies, though measurable reductions in harm remain sparsely documented. In one evaluation, 83% of participants rated the "Five Moments for Medication Safety" materials as useful (79). Active surveillance methods consistently outperform voluntary reporting in ADR detection. In Ahmedabad, a Preliminary Trigger Tool List identified 66 ADRs in 327 patients (PPV 19.27%, sensitivity 100%, specificity 21.66%); its modified version detected 23 ADRs compared to 16 via spontaneous reporting, capturing more moderately severe and preventable cases (80). In oncology, the Global Trigger Tool identified 0.90 adverse events per patient compared to 0.24 via voluntary reporting, with only 2% overlap between the two methods (81).

Electronic health record–embedded alerts have achieved significant prescribing improvements. DOAC alerts prompted prescription modification in 34.2% of inappropriate cases (82). Surgical opioid alerts reduced inappropriate prescribing from 48% to 3% and lowered mean opioid supply from 92 to 57 oral morphine milligram equivalents (Rizk et al., 2024). Acute kidney injury alerts improved physician awareness, increasing creatinine follow-up rates (56.6% to 65.8%) and nephrotoxic drug discontinuation (59.2% to 63.2%) (83).

PATIENT & PUBLIC ENGAGEMENT

The Med Safety mobile application, adapted for eight national pharmacovigilance systems, has enhanced ADR reporting capacity (84). Post-implementation surveys indicated increased case safety reports and positive user experiences, though active reporting remained limited in some contexts. In Ghana, 64.7% of healthcare professionals continued using the app post-installation, yet only 27.3% submitted ADR reports (85). In Uganda, strong acceptability was reported, with offline functionality and two-way risk communication cited as facilitators; training significantly improved adoption rates (86). An app-based reporting can strengthen communication between national pharmacovigilance centres and healthcare professionals, with potential to enhance signal detection (85,86).

FUTURE PRIORITIES

Pilot studies highlight the potential of wearable biosensors for early detection of drug-induced complications. QTNet, a deep learning model, detected dofetilide-induced QT prolongation with 87% sensitivity and 77% specificity using single-lead ECG from wearable devices (87). The BodyGuardian™ system reliably measured QT intervals with <15 ms disagreement compared to manual assessment (88). For hypoglycaemia, the VitalConnect HealthPatch MD identified 28 of 39 events via heart rate variability changes (89), and smartwatch-based monitoring achieved an AUC of 0.76 ± 0.07 using multiple physiological indicators (90).

Digital twin models offer personalised dosing by integrating individual physiological and clinical parameters. For example, a fentanyl protocol in advanced cancer optimised transdermal delivery and reduced ADR risk (91). Structured implementation frameworks can enhance deprescribing. Focus groups with 54 geriatricians and pharmacists identified five priority domains for hospital-based interventions, yielding 44 evidence-based components (91). In Swiss nursing homes, interprofessional quality circles supported deprescribing but were difficult to sustain after trial completion (92).

CONCLUSION

Adverse drug reactions remain a preventable global burden. Pharmacovigilance approaches, namely spontaneous reporting, EHR surveillance, and federated analytics, are complementary but constrained by under-reporting, uneven data quality, and delayed validation. Machine-learning advances improve detection; preventive strategies such as clinical decision support, pharmacogenomics, and deprescribing, show impact yet face uneven implementation. Embedding medication safety in universal coverage, enabling interoperable data sharing, and building capacity, especially in LMICs, are essential to sustainably reduce ADR-related morbidity and mortality.

– Embed medication safety in universal coverage and national patient-safety agendas
– Mandate interoperable pharmacovigilance, real-time data sharing, and streamlined reporting systems
– Prioritize LMIC capacity building and adoption of preventive genomic-guided interventions

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Address for correspondence:
Vinodkumar Mugada
Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Vignan Institute of Pharmaceutical Technology, Duvvada, AP, Visakhapatnam, India,
email: mugadavinodkumar18@vignanpharma.com