

Adverse drug reaction monitoring: where are we?

As per the WHO definition of adverse drug reaction [ADR], this is a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for modification of physiological function. Practically speaking, no drug is absolutely safe, even when prescribed in therapeutic doses. ADR monitoring or pharmacovigilance aims to promote patient safety in relation to the use of medicines, especially with regards to prevention of unintended harm to the user. Proper pharmacovigilance also involves in provision of reliable, balanced information to avoid ADRs, and contributes to the assessment of the risk-benefit profile of medicines, thereby encouraging more effective use.

The diagnosis of an ADR is part of a broader diagnosis in a patient who is taking medicines. The differential diagnosis of a medical condition should include the possibility of an ADR. The first step is to find out what products the patient is taking, including over-the-counter formulations. The next step is to ascertain whether the observed effect could be due to any of these formulations or due to a drug-drug interaction. Problems arise when the distinction between an ADR and disease symptomatology is not clear or if the concerned patient is on several drugs concurrently. Multiple factors will have to be considered in assigning the causality of an unfortunate adverse event to the suspect drug - timing of event in relation to dosing, pattern recognition for class effects or the effects of close chemical or pharmacological congeners, and occasionally special tests such as tests for allergies or biopsies.

Rapid action in response to an ADR is important when it is of a serious nature. Emergency treatment and withdrawal of all medicines is occasionally necessary, in which case cautious reintroduction of the essential medicines should be considered. Otherwise, using clinical benefit-risk judgment, together with help from investigations, one decides which medicine should be withdrawn on trial. A problem immediately arises if one or more of such medicines is essential to the patient. A benefit-risk decision then needs to be taken considering the patient's need for the drug, the severity of reaction and the availability of appropriate treatment. If several medicines could be causative, the non-essential medicines should be withdrawn first. If the reaction is likely to be dose-related, dose reduction should be considered.

The WHO Programme for International Drug Monitoring was established in the wake of the thalidomide disaster, in 1962, when WHO was requested to study the feasibility of various measures aimed at assuring the safety of pharmaceutical products in international commerce. This resulted in the establishment of an International System for monitoring ADRs using information derived from national centers. The system started with 10 countries that had already established national systems for spontaneous ADR reporting and who agreed to contribute data. For an effective global system to become operative, a common reporting form was developed, agreed guidelines for entering information formulated, common technologies and classification prepared and compatible systems for transmitting, storing, retrieving, and disseminating the data was created. The WHO Collaborating Centre for International Drug Monitoring, the Uppsala monitoring center, holds the operational responsibility for the programme, including the maintenance of the database, which currently contains around 2 million reports of suspected ADRs. Almost 60 countries now participate in the program.

So far as India is concerned there is profound dearth of indigenous ADR data. Many factors are responsible - huge patient loads, paucity of record keeping, varying nutritional status of patients, peculiar patterns of drug usage, multiple alternative systems of medicine, inadequacy of sufficiently trained and motivated doctors and paramedical staff. These hurdles cannot be removed overnight but there is an urgent need to generate data regarding the safety profile of pharmaceutical products being marketed here. In the early 1980's, a National Programme for ADR monitoring was envisaged in the following steps; Step 1: Establishment of institution-based system where intensive monitoring would be carried out; Step 2: To be linked with class groups, such as the Central Government Health Service, Armed Forces, etc; Step 3: Involvement of general practitioners. This plan is yet to come to fruition.

Till today post-marketing surveillance of a new drug is virtually non-existent in India. It is extremely difficult to bring about withdrawal of an unsafe drug from the Indian market even after submission of serious ADR data to the Drugs Controller General of India. There is too much pressure from powerful companies not to impose ban on or stringent curbs on the sale of successful drugs, even if they are hazardous or irrational. Hardly any pharmaceutical manufacturer in India does post-marketing trials. The Union Health Ministry's recent decision to activate non-functional ADR monitoring centers in the country is a step long overdue. This has to be done without expecting support from the pharmaceutical industry. To be successful the message must reach all players in the drug use cycle - the prescriber, the dispenser and the consumer - alike. All of us must participate in the educational and capacity building effort.

Amitava Sen

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Adverse drug reactions - 1

Avijit Hazra

Introduction

Adverse drug reactions [ADRs] are inevitable consequence of pharmacotherapy. It is well known that all modern drugs carry the potential to produce undesirable effects, in addition to the desired ones. This is often paraphrased by saying that all drugs are poisons, the dose alone distinguishes the medicine from the poison. However, for rational drug use it is not sufficient to know only the correct dosing. No drug is absolutely safe under all circumstances of use or in all patients. ADRs can arise from many sources, even if a drug is correctly selected and dosed. If we believe that the first principle in treating patients is '*primum non nocere*' i.e. above all, do no harm, it follows that we should be aware to the possibility of ADRs and the ways and means to prevent or curtail them.

Formally, an adverse drug reaction is defined as an unintended and unwanted noxious effect of a drug occurring under normal conditions of use at usual doses. This excludes effects of:

- Wrong drug
- Medication errors e.g. overdose
- Defective drug i.e. product not conforming to specifications
- Therapeutic failure

The term 'adverse event' refers to an untoward occurrence during exposure to a drug. It becomes an adverse reaction only when the causality is proven or is reasonably certain. Terminologies like 'side-effect', 'adverse (drug) experience' and 'adverse (drug) effect' are now discouraged.

Magnitude of the problem

The true incidence and prevalence of ADRs is not known, largely because formalized ADR reporting systems are in place in only a few countries. Even if a very well organized ADR reporting system does exist, it is likely that reported estimates are likely to be less than true extent because mild ADRs tend to go unreported, many drug effects are highly subjective and a large fraction of the total ADR burden in the community may not be recognized as iatrogenic events but rather attributed to the underlying or a new illness.

With these limitations in mind, it has been estimated that:

- Up to 30% of hospitalized patients suffer one or more ADRs, 3% will have an ADR of

considerable severity and 0.3% may die in consequence.

- Up to 5% of hospital out-patients may require hospitalization to prevent or manage ADRs.

The development phase of a drug pays substantial attention to recognition and quantification of adverse events that may be causally attributed to the drug. Nevertheless, prior to marketing, only a fraction of all possible ADRs are detected

- During drug development, for practical reasons samples on whom trials are done, at the most, number in a few thousands. Thus uncommon ADRs are not detected.
- For technical reasons (relatively homogenous patient population studied) some ADRs go undetected.
- Some ADRs occur only after long-term exposure or only on a background of concomitant illnesses.

It must be emphasized that drug safety concerns are not confined to new chemical entities. They extend to new indications of existing products, new formulations, novel drug delivery systems and new combinations. ADR monitoring for a pharmaceutical product, thus, essentially lasts throughout its lifetime as a marketed medicine.

Classification of ADRs

ADRs may be classified in various ways. However, to understand the mechanistics of adverse reactions they have been broadly categorized into two types, A and B, as depicted in table 1.

The distinction between Type A and Type B reactions is important for multiple reasons:

- Type A reactions may be predicted from careful scrutiny of the drug's pharmacological profile. Hence they may be preventable by individualization of drug therapy,
- Type A reactions are generally more common and more readily recognized as causally related to a drug during clinical trials and post-marketing surveillance.
- Serious / persistent / recurrent Type A reactions during drug development are likely to lead to abandonment at an earlier stage.

Table 1. Salient features of the two types of adverse drug reactions

Type A [Augmented] reactions	Type B [Bizarre] reactions
Quantitative exaggeration of pharmacological / toxicological activity. Usually: <ul style="list-style-type: none"> • More common • Predictable • Dose-dependent e.g. Bleeding with heparin Hypoglycemia with glibenclamide Myelosuppression with cyclophosphamide	Qualitatively abnormal responses with no clear-cut relation to drug's activity profile. Usually: <ul style="list-style-type: none"> • Less common • Unpredictable • Dose-independent e.g. Hepatotoxicity with halothane SMON with clioquinol Aplastic anemia with chloramphenicol
Also encompasses effects not related to drug's primary (intended) pharmacologic activity, <ul style="list-style-type: none"> e.g. Anticholinergic effect of TCAs Dependence liability of opioids Withdrawal reactions 	May have genetic / immunological basis. <ul style="list-style-type: none"> e.g. Anaphylaxis due to penicillin Hemolysis due to methyl dopa Drug-induced lupus

SMON = Subacute myelo-optic neuropathy; TCAs = Tricyclic antidepressants

Organ specific toxicities may be Type A or Type B reactions. Some 'classic' examples are:

Bleomycin	—	Pulmonary fibrosis
Corticosteroids	—	Osteoporosis
Cyclophosphamide	—	Hemorrhagic cystitis
Cyclosporine	—	Nephrotoxicity
Didanosine	—	Pancreatitis
Doxorubicin	—	Cardiomyopathy
Ethacrynic acid	—	Ototoxicity
Ethambutol	—	Optic atrophy
Isoniazid	—	Hepatotoxicity
Radioiodine	—	Hypothyroidism
Statins	—	Rhabdomyolysis
Vincristine	—	Peripheral neuropathy

Occasionally, two other types of ADRs are recognized:

- Type C [Chronic] reactions e.g. Retinopathy with chloroquine, Oculomucocutaneous syndrome with practolol; and
- Type D [Delayed] reactions e.g. Clear cell adenocarcinoma of the vagina in mature women whose mothers have received stilbestrol during pregnancy, Other drug induced cancers

The term 'serious' adverse reactions usually refers to those that are:

- Fatal e.g. Anaphylaxis
- Life-threatening e.g. Bleeding
- Disabling e.g. Optic atrophy
- Incapacitating e.g. Jaundice
- Causing / prolonging hospitalization e.g. Stevens-Johnson syndrome

In addition teratogenic, mutagenic and carcinogenic events are also considered to be serious.

Diagnosis / Causality assessment of suspected ADRs

This is never an easy matter. There is always a difficult to bridge gap between 'clinical hunch' and 'scientific rigor'. It may be noted that both detection and causality assessment of ADRs:

- Requires observational powers and analytical skills.
- Diagnosis specially difficult if adverse event mimics features of underlying disease.
- Despite best efforts it is frequently not possible to deduce iatrogenicity with certainty.

The following criteria may help to decide:

- Temporal relationship of event with drug exposure.
 - But contrast Anaphylaxis and Carcinogenesis
- Nature of reaction.
 - But contrast Stevens Johnson syndrome following co-trimoxazole, breast cancer in past OCP user and sudden deaths in asthmatics on β -agonists
- Exclusion of confounding factors specially those relating to underlying illness.
- History of similar reactions to allied drugs or reports of similar events with allied drugs.
- Specific diagnostic tests. Of limited value.
 - ♦ Specific IgE antibodies in case of penicillin hypersensitivity.
 - ♦ Detection of genetic polymorphism of drug metabolizing enzymes.
 - ♦ Increased antinuclear antibody and serum complement levels in drug-induced lupus.

- Dechallenge - To assess resolution of ADR on withdrawal of drug.

Not applicable to those events that cause irreparable damage e.g. ototoxicity, hepatic fibrosis and secondary malignancy.

- Rechallenge - To assess reappearance of ADR on reinstatement of drug.

- The gold standard for assessing causality but generally not possible for ethical reasons.

Based upon the 4 principle criteria for causality - Temporal relationship / Confounding factors excluded / Dechallenge / Rechallenge - suspected ADRs have been categorized as - a) Definite / Highly probable; b) Probable; c] Possible; and, d] Unlikely / Remote.

Table 2. Examples of marketed drug withdrawals due to causally related adverse events

Product	Therapeutic category	ADR	Type
Aclofenac	NSAID	Anaphylaxis	B
Alpidem	Anxiolytic	Hepatotoxicity	B
Amineptine	Antidepressant	Dependence liability	A
Benoxaprofen	NSAID	Photosensitivity, Hepatotoxicity	A
Bromfenac	NSAID	Hepatotoxicity	B
Chlormezanon	Anti-spasticity	Stevens-Johnson syndrome	B
Fenclofenac	NSAID	Toxic epidermal necrolysis	B
Fenfluramine	Anorectic	Pulmonary hypertension, valvular heart disease	A
Metamizole	NSAID	Aggranulocytosis	B
Methysergide	Anti-migraine	Retroperitoneal fibrosis	C
Metipranolol	Anti-glaucoma	Anterior uveitis	B
Nomifensin	Antidepressant	Hemolytic anemia	B
Phenolphthalei	Laxative	Carcinogenicity	D
Proxibarbal	Sedative	Thrombocytopenia	B
Sertindole	Antipsychotic	Cardiac arrhythmias	B
Suprofen	NSAID	Nephrotoxicity	A
Terolidine	Anti-incontinence	Ventricular tachycardia	A
Tolcapone	Anti-Parkinsonism	Hepatotoxicity, Malignant neuroleptic syndrome	B
Triazolam	Hypnotic	Psychiatric reaction	A
Trovaflaxacin	Antimicrobial	Hepatotoxicity	B
Zimeldine	Antidepressant	Guillain-Barre syndrome	B

Principles of ADR prevention / minimization

1. Use drugs only if specifically indicated.
2. Avoid polypharmacy and shotgun therapeutics.
3. Leave use of specialized drugs to specialists.
4. Be extra cautious with special / high-risk clinical settings and individualize drug therapy in such situations e.g.
 - Extremes of age
 - Pregnancy
 - Breast-feeding
 - Hepatic insufficiency
 - Renal insufficiency
 - QT interval prolongation
 - Immunocompromised subject
 - Critical care patient
5. Be well acquainted with the actions and the toxicity profile of the drugs intended to be used and be particularly vigilant with drugs of low therapeutic index e.g.
 - Aminoglycosides
 - Antiarrhythmics
 - Anticonvulsants

- Cardiac glycosides
 - General anesthetics
 - Neuromuscular blockers
 - Lithium
 - Oral anticoagulants
 - Theophylline
 - Cytotoxics
 - Immunosuppressants
6. Take a careful drug history beforehand - exclude drug allergies and document all drugs already in use (including OTC products).
 7. Instruct patients carefully on nature of drug and proper mode of use and possible alerting signs-symptoms of toxicity.
 8. Unexpected deterioration of patient's condition while on drug therapy should prompt consideration of adverse drug reactions / interactions if no other cause can be found.
 9. Once ADR detected consider dose modification or drug withdrawal.
 10. Do not rechallenge unless there is diagnostic uncertainty or compelling clinical reason.

To be continued in the next issue

Making Pregnancy Safer: A Reality

Joydev Mukherji

Every year, approximately 6,00,000 women die of pregnancy related causes - 98% of these deaths occur in developing countries. Of all the health statistics monitored by the World Health Organization [WHO], the largest disparity between rich and poor nations is seen in maternal mortality levels.¹ Over 90% of maternal deaths occur in Asia and sub-Saharan Africa, with India alone accounting for 25% of such deaths worldwide, while 6 other countries - Bangladesh, Ethiopia, Nepal, Indonesia, Nigeria, and Pakistan - account for a further 30%. At present, 1 woman in 11, will die of maternal causes during the course of her lifetime in Eastern Africa, compared with 1 in 5000 in Europe.² Obstetric disorders remain the leading cause of death (in some countries one third) among women of childbearing age (15 to 45 years); this figure is much higher than that of tuberculosis, suicides, war injuries, traffic accidents, or AIDS.¹

Over the past 35 years, several major improvements in global health indicators have been achieved. Globally, mortality among under-five children was reduced by half between 1960 and 1990. Average life expectancy at birth has also increased in an unprecedented way, over the same period, from 46 to 62 years. Simultaneously, the total fertility rate has dropped from 4.9 to 2.9 and continues to fall. Maternal mortality, however, remains unchanged.

In 1987, a group of agencies (WHO, United Nation's Children's Fund [UNICEF], United Nations Fund for Population Activities [UNFPA], International Planned Parenthood Foundation [IPPF], and World Bank [WB] among them) launched the international Safe Motherhood Initiative [SMI]. The strategy adopted included 15 kinds of action.³ These ranged from mobilization of all parties (including international agencies, national governments, district administrations, and women themselves) to address the problem, to the strengthening of health care systems, including steps such as health education and improvement of women's legal status. Overall, however, only a minority of the actions recommended at the conference were strictly health related (just the last 4 of the 15 items) and, even then, the recommended approach was simultaneously too broad-based and multifaceted. These included 4 strategic objectives: a) to provide universal primary health care from infancy to adolescence (and thereafter to provide universally available family planning services) b) to provide good antenatal care (including screening for 'at risk' pregnancies); c) to ensure the presence of trained individuals at all births (including training of traditional birth

attendants); and d) to strengthen the basic obstetric care ('First Referral Unit' [FRU]) accessible to women at risk. The SMI sponsors reckoned that each of the 4 components were equally important.

In October, 1997, an international technical consultation in Sri Lanka summed up what has been learnt in 10 years of work since 1987.⁴ Much has been learnt, for example, how maternal mortality levels are under-reported, the consequences of unsafe abortion are also underestimated and, most importantly, which interventions are effective and which are not.

Socioeconomic factors (important aspect of SMI), should be considered separately, and the prevention of maternal mortality is, above all, a public health issue based on family planning and on universal accessibility to good medical care during pregnancy and childbirth.⁵ This change in view now demands a more health-related approach to safe motherhood.

The relation between gender discrimination and maternal mortality has also been questioned.⁶ The good maternal health statistics of such countries as Saudi Arabia, Iran, and Algeria, tend to disprove the tenet.

The same is true for education of women. Education more likely potentiates the effect of reproductive health interventions than to have a direct impact on maternal mortality.

Family planning has been championed to reduce maternal mortality by 30%. Recent analyses have questioned such results.⁷ Decrease in the number of pregnancies reduces the number of possible complications and thus the number of maternal deaths. Family planning does not modify a woman's risk of dying once she is pregnant. In any case, most maternal deaths (other than in unsafe abortion) occur during or after wanted pregnancies and thus could not be prevented just by giving contraceptives to women who need it.

More resources have been put into antenatal care than into delivery and postpartum care and essential care for managing complications.⁸ Yet, the vast majority of deaths occur during and immediately after delivery, because of sudden, unexpected complications, and due to unsafe abortions. Quality antenatal care improves perinatal health but without linkage to delivery care, does not greatly reduce maternal mortality. Risk screening in antenatal care cannot accurately predict which woman eventually needs emergency care, and healthcare costs cannot be saved by risk screening.⁹ It has been

estimated that around 15% of women in childbirth develop potential life-threatening complications, and 1 to 3% will die in absence of a major surgical intervention.¹⁰ Meeting this challenge of arranging for emergency obstetric care [EOC] on a global scale is therefore the problem in a nutshell.

Incidentally, the training of traditional birth attendants does not seem to have an impact on maternal mortality unless it is combined with accessible hospital settings where EOC is available.

Improving availability, accessibility and utilization of essential obstetric care

Despite the many contributory causes such as child malnutrition, too early marriage, poverty and illiteracy, harmful practices, gender discrimination, lack of family planning, etc., the causes of maternal death remain predominantly medical as summed up in Table 1.

Table 1. Proportion of maternal death by causes

Cause	Proportion
Severe bleeding	25%
Indirect: Anemia, malaria, etc.	20%
Infection	15%
Unsafe abortion	13%
Eclampsia	12%
Obstructed labor	8%
Others: Ectopic pregnancy, anesthesia accidents, etc.	8%

What can prevent maternal deaths is major obstetric interventions. Programs for preventing maternal deaths aim to centralize the essential obstetric interventions (anesthesia, Cesarean section and blood transfusion) at FRU or First Referral Level hospitals. Postpartum hemorrhage, the giant killer, can kill a mother on just 2 hours and every mother worldwide must be able to reach a FRU (with comprehensive EOC facilities) within 2 hours, even from the remotest village. Some system for providing basic EOC facilities which can be closer to the patient's home should reinforce the FRU facilities.

In guidelines jointly issued in 1997 by WHO, UNICEF and UNFPA, it is recommended that for every 5,00,000 population there should be 4 facilities offering basic EOC and 1 facility offering comprehensive EOC. Basic EOC provided in health centres includes parenteral administration of antibiotics, oxytocin, anticonvulsants, manual removal of placenta, removal of retained products and assisted vaginal delivery with forceps or vacuum extractors. Comprehensive care includes basic

EOC plus Cesarean section and blood transfusion.^{11,12}

In addition, obstetric first aid (OFA) should be available. This consists of a set of emergency measures that can be taken by qualified birth attendants at home. It includes instant uterine massage or bimanual compression to reduce bleeding, and administration of antibiotics and antipyretics orally as a temporary measure till transport is arranged. However, if OFA, is viewed as an alternative to hospitalization, this would be counter-productive and dangerous.

According to WHO a skilled attendant at birth is one of the most effective interventions to reduce maternal mortality.¹³ Professionally qualified birth attendants include midwives, doctors, and practitioners who have received at least 18 months of midwifery training and attend, on average, 5 to 10 deliveries per month. A skilled attendant will supervise, give care to and advise women during pregnancy, labor and postpartum period, and conduct deliveries with responsibility. Care includes implementation of preventive measures and detection and referral of abnormal conditions in the mother and newborn. He or she will also provide emergency measures as needed, as for example, postabortion care, and also provide education for women, their families and community members. Skilled attendants must be registered and/or legally licensed to practice. Training of traditional birth attendants has had little impact in reducing risk of maternal deaths although it has had some benefits in increasing cleanliness at birth and reducing neonatal tetanus.

The 'Making Pregnancy Safe' initiative [MPS] was launched by WHO.¹⁴ The MPS strategy builds on the lessons of SMI, existing national efforts and the consensus reached at the International Conference on Population & Development [Cairo, 1994], the Fourth World Conference on Women [Beijing, 1995] and the joint WHO – UNICEF – UNFPA – WB statement [1999]. Broadly, the goals of SMI and MPS are the same. However, the strategy of the MPS initiative is to work with the health sector, focussing on effective evidence-based interventions that target the major causes of maternal and neonatal morbidity and mortality. Strengthening the health systems and intensifying the actions needed at community level should ensure that women and their newborns have access to care they need, when they need it. The health interventions include:

- A. Prevention and management of unwanted pregnancy and unsafe abortion.
- B. Skilled care during pregnancy and childbirth.
- C. Access to referral and EOC if complications arise.

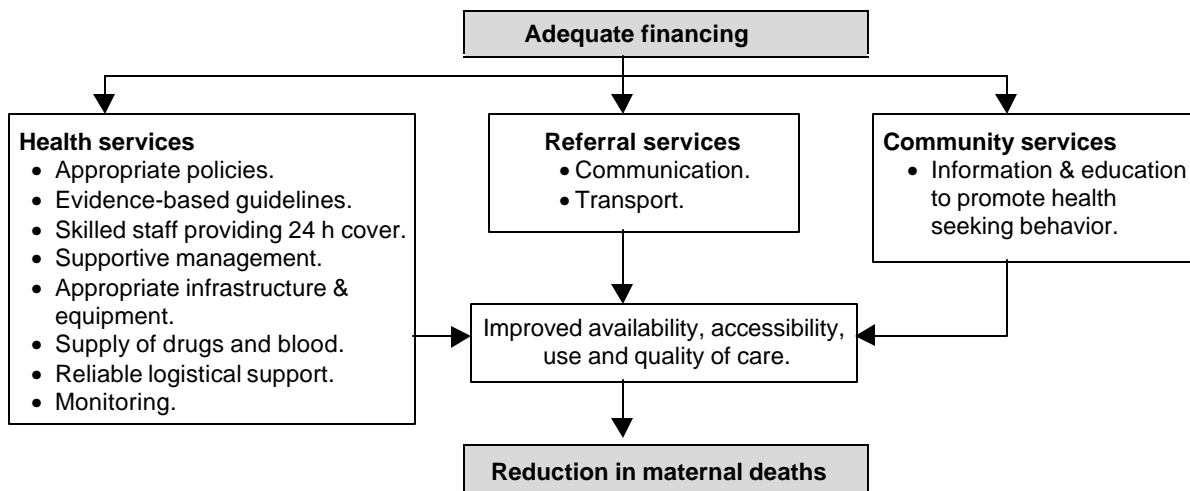


Figure 1. Resources needed to improve essential obstetric care.¹⁵

The technical interventions needed to prevent maternal deaths are well understood.¹³ What is less clear is how an environment can be created to enable interventions to be made in resource-poor settings.¹⁶ If funding agencies remain insensitive in contributing to the development of infrastructure where basic obstetric care is available, if health managers do not support the training of health professionals and their maintenance in FRUs by ensuring motivating working conditions (including an attractive compensation package), and if obstetricians do not set their chief mission to make available quality EOC, the MPS, like its predecessor, the SMI, may well remain an elusive goal.

Goals of the MPS initiative:

Reduce maternal and newborn morbidity and mortality:

- Maternal Mortality Ratio by 75% from 1990 levels by 2015.
- Infant Mortality to below 35 per 1000 live births by 2015.

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Vitamins B₁, B₆, B₁₂ combinations - banned or not banned?

Vitamins B₁, B₆, B₁₂ combinations are supposed to be banned in India by the following notification:

The Government of India, Ministry of Health & Family Welfare through its Gazette Notification no. GSR 702 (E), stated that:

'Whereas the Central Govt. is satisfied that the use of the Fixed dose combination of Vitamin B₁, Vitamin B₆, Vitamin B₁₂ dose not have the therapeutic value claimed or purported to be claimed for it. And whereas it is necessary and expedient to prohibit the manufacture, sale or distribution of the said combination of Vitamin B₁, Vitamin B₆ and Vitamin B₁₂ for human use in public interest:

Now, therefore in exercise of the powers conferred by Section 26A of Drugs and Cosmetics Act, 1940 (23 of 1940), the central Govt. hereby prohibits the manufacture, sale or distribution of fixed dose combination of Vitamin B₁, Vitamin B₆ and Vitamin B₁₂ for human use with effect from January 1, 2001.'

[F.No X-11014/6/99-DMS &PFA]
Deepak Gupta, Jt. Secy.

Rational drug activists in India have been demanding, over the past one and half decades, that this combination should be banned as it is therapeutically worthless, notwithstanding the fact that many doctors prescribe it liberally in neurological and other illnesses for want of anything better to prescribe. If you ask these prescribers, they will not be able to name a single medical condition where the recommended treatment is this combination. Vitamin B-complex and multivitamin preparations are licensed but exclusively B₁-B₆-B₁₂ combinations are not found in developed countries and there is no valid reason why they should be. It is not logical that consumers pay for a drug which has no valid indication. Pharmaceutical companies, including multinational ones like E Merck, German Remedies, Merck Sharp & Dohme, who do not market such combinations in their parent countries, contested such arguments in the Supreme Court which directed the Drug Technical Advisory Board [DTAB] to take a decision. CDMU participated in sending information to the DTAB about the therapeutic non-utility of such drugs to be used in combination. Finally the Ministry on 14th October, 1999, issued the above order.

Unfortunately the wording of the order leaves loopholes which the companies have merrily exploited and which makes the government intentions suspect. All the B₁-B₆-B₁₂ combination brands continue to be available, albeit with the addition of 1 or 2 other harmless and unnecessary vitamins such as calcium pantothenate, touting this fact that they have provided an added therapeutic punch to their brand at little extra cost. For instance, E Merck's NEUROBION, which became NEUROBION FORTE with the addition of Nicotinamide and Calcium Pantothenate, achieved sales of Rs. 35 million rupees in the year 2001. That is the kind of money that Indian consumers have paid for a drug which is mostly used for worthless indications. It is a shame. Its business as usual with the same sort of promotional catchlines. Thus NEUROBION FORTE cartons, boldly declare, without mentioning any reference as usual, that these tablets 'Help maintain structural & functional integrity of neurons.' The accompanying photographs (see figure) show an alcoholic, a senile man and a patient with cramps, implying that NEUROBION FORTE is the treatment for these conditions.

Other brands of B₁-B₆-B₁₂ combination that continue to be available taking advantage of the weak government order include:

Brand	Company
Inj ANEUDOX-12	P & B Labs
Inj ANEUDOX-12 FORTE	P & B Labs
Inj ARISTONEUROL	Aristo
Inj BETHADOXIN-12	Biological E
Inj BEVIDOX	Abbot
Inj NEUROXIN-12	Alidac
Inj PREMOBION	Prem Pharma
Tab & Inj SIONEURON	Albert David
Inj TRINEUROSOL-H	Merind
Inj VITNEURIN	Glaxo

Source: CIMS-68 [Jan-Mar, 2000] & CIMS-76 [Jan-Mar, 2002].

In addition there are countless brands of multivitamins containing these three vitamins in all sorts of combinations. The example clearly shows how 'responsible' pharmaceutical companies in India are ever ready to take advantage of weak Government orders and continue to market banned drugs freely. It is indeed a therapeutic jungle.



Rational Drug Bulletin is a member of the International Society of Drug Bulletins whose official logo is depicted alongside.

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