"A Critical analysis of Banned Drug Combinations: Insights from FDA and Government of India Decisions Through Drug Profile, Case Studies & Pharmacovigilance"

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Abstract: This study analyzed banned drug combinations in India, examining data from the FDA, CDSCO, DTAB, and other sources. It focused on fixed-dose combinations (FDCs) banned due to safety concerns and lack of therapeutic justification. The study investigated drug profiles, regulatory decisions, case studies, and pharmacovigilance data to assess public health impacts. Results showed that banned FDCs included combinations of antibiotics, NSAIDs, antihistamines, cough/cold medications. Case studies highlighted potential adverse drug reactions (ADRs) associated with these drugs, such as liver damage and gastrointestinal bleeding. It also emphasizes the crucial role of stringent regulatory oversight, including continuous evolution of FDCs, pharmacovigilance, and robust data analysis. Advancements in pharmacovigilance, stricter regulations, and increased public awareness are crucial for improving drug safety and promoting safer medication practices.

Index Terms: CDSCO, DTAB, FDA, banned drugs, Fixed-Dose Combinations (FDCs).

INTRODUCTION:

The Indian Parliament passed the 1940 Drugs and Cosmetics Act and 1945 standards to regulate the import, manufacture, sale, and distribution of drugs and cosmetics. In 1988, Schedule Y was added to the Act, outlining requirements for clinical studies. The Central Drugs Standard Control Organization (CDSCO) and the Drug Controller General of India (DCGI) oversee the process. To manufacture or import a novel drug, a firm must apply to the DCGI. Clinical trials must be conducted following Schedule Y guidelines to ensure safety and efficacy in the Indian population, with a report submitted in a specific format.

CDSCO:

The Central Drugs Standard Control Organization (CDSCO) is India's national regulatory agency, operating under the Ministry of Health and Family Welfare. Headquartered in New Delhi, it has regional and subsidiary offices across India. To obtain drug approval, companies submit a dossier to the CDSCO, which includes data formatted as a Common Technical Document (CTD).[1] The CTD is a harmonized data presentation format adopted by most countries and follows guidelines from the International Council for Harmonization (ICH).[1] The CDSCO has adopted this format for drug product registration to streamline the approval process for pharmaceutical products intended for human use.[27] The drug approval process includes submitting clinical trial applications, meeting new drug approval requirements, and documenting post-approval changes.[24] CTD consists of five modules: administrative information, summaries, quality information, non-clinical study reports, and clinical study reports.[27] The drug approval process varies globally[28].

Preclinical study:

Preclinical studies are laboratory tests conducted on animal subjects to assess the safety and efficacy of a new drug or medical device before human trials. The primary goal is to determine the product's safety profile [26].

Clinical Trials:

Clinical trials are research studies that evaluate new medical treatments. Before human trials, preclinical studies on animals and in vitro models assess safety and efficacy. The trial's aims, risks, and benefits must be carefully considered and scientifically and ethically justified.

Clinical trials have four phases:

• Phase I: Initial safety trials in healthy volunteers, focusing on dose tolerance and pharmacokinetics.
• Phase II: Exploratory trials to assess efficacy and safety in smaller patient groups, often divided into Phase IIa (pilot) and Phase IIb (more rigorous).
• Phase III: Confirmatory trials in larger patient groups to establish efficacy and safety compared to a standard treatment or placebo. Data from this phase is crucial for drug approval.
• Phase IV: Post-marketing studies to gather further information on efficacy, safety, and long-term effects in various patient populations, including different age groups and races.[24][25]

Drug Evaluation and Approval Process: The "Drug Controller General of India" is India's top authority when it comes to approving or banning drugs. [30] [[32][33] The drug approval process in India involves several steps. The applicant submits an application to the Ethical Committee, followed by filing an Investigational New Drug (IND) application with the CDSCO. The IND application is reviewed for completeness and scientific soundness. After approval, clinical trials begin and are monitored by the Ethical Committee. Upon trial completion, the IND Committee evaluates safety and efficacy, and the DCGI reviews their findings. If the drug meets standards, a license is granted for commercial production. The applicant also submits a new drug registration application. The review process typically takes 12 weeks if the application is complete [24].

FDC Authorization Process:

The Central Drugs Standard Control Organization (CDSCO) defines Fixed-Dose Combinations (FDCs) as products containing one or more active ingredients for a specific indication. According to WHO, FDCs involve at least two active ingredients in a fixed ratio.[31] Key rules for FDCs include equal plasma half-lives of combined drugs and the appropriate dose ratio based on distribution and plasma concentration. FDCs offer convenience and better patient compliance but may cause health risks, drug interactions, and ADRs.[22] FDCs are categorized into four groups, with each requiring specific data for marketing approval.[27] They are classified as rational, irrational, and categorized as good, bad, or ugly based on justification and evidence.[24]

FDCs in India are accepted when they meet dosage requirements, offer superior safety, efficacy, and compliance compared to single drugs. They are popular for better efficacy, fewer side effects, and cost-effectiveness, allowing patients to treat multiple conditions with one medication, reducing both treatment costs and drug resistance [29].

The health ministry banned certain FDCs based on the Drugs Technical Advisory Board's recommendation that they lacked therapeutic justification and posed risks. The Supreme Court ruled that the DTAB report couldn't be used to prohibit 15 out of 344 drugs in the original list, as they had been manufactured since before 1988[4]. 1988. [4] Drug regulator of India (CDSCO) came out with the policy guidelines for the approval of FDCs in 2013. CDSCO has periodically banned various FDCs due to reasons such as lack of rationale or evidence and potential safety concern.[31]

The Problems with Fixed-Dose Combination: The problems with Fixed-Dose Combinations (FDCs) include pharmacokinetic (PK) and pharmacodynamic (PD) mismatches, resulting in reduced efficacy or increased toxicity, varied peak efficacy times, chemical incompatibility reducing shelf life, drug interactions, and dose limitations. The approval process for FDCs depends on their category, drug characteristics, and disease indication. The CDSCO introduced a preliminary scrutiny system to ensure applications meet regulatory and technical requirements. If an application is inadequate, the candidate must provide sufficient information. The FDC approval timeline is 180 days. In November 2015, CDSCO launched the "SUGAM" portal for online applications.[31]

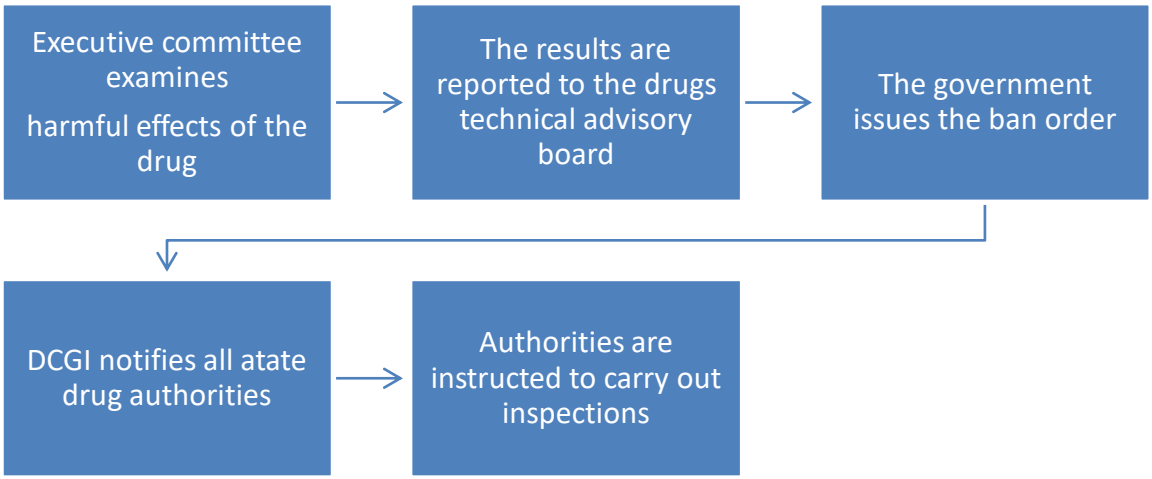
Process of Imposition of Prohibition: Banned drugs are substances prohibited due to their harmful effects, as they may cause more negative outcomes than therapeutic benefits. The Drug Controller General of India regulates drug approvals and bans. Some globally discarded harmful drugs, like Nimesulide, Phenylpropanolamine, and Furazolidone, remain available in India [30].

Reason for banning: The DTAB committee has identified four major reasons for banning drugs: pharmacokinetic and pharmacodynamic mismatches, lack of efficacy, and safety concerns.[23] The continued availability of banned drugs in India is due to factors like pharmaceutical companies' commercial interests, corruption, lack of transparency, regulatory inefficiency, poverty-driven demand, and unawareness among doctors and patients [30].

The Drug Technical Advisory Board (DTAB) in India is the final authority for imposing drug bans.[21][22][23] An executive committee reviews the harmful effects of drugs and reports to the DTAB. If a drug is deemed harmful, the

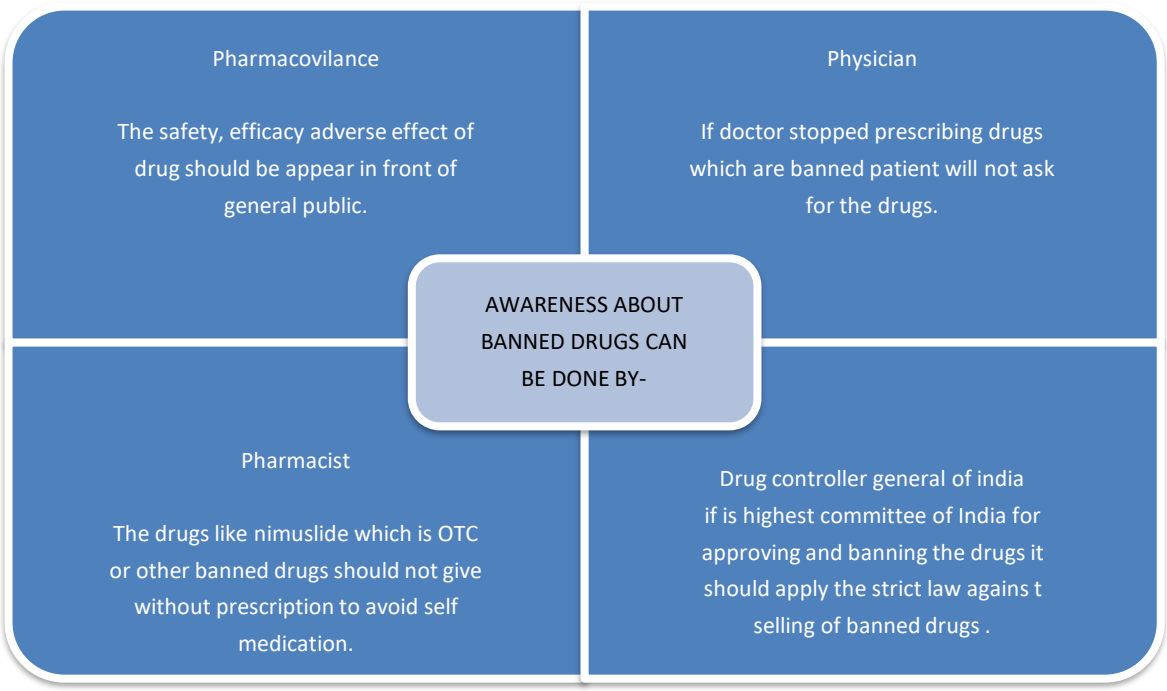
government issues a ban, notifying manufacturers and state authorities. Inspections are carried out, and pharmacists stocking banned drugs may have their licenses revoked under the Drug and Cosmetics Act.[21]

Visual Representation of the Banning Process:[21]



Pharmacovigilance:

Pharmacovigilance involves detecting, evaluating, and preventing negative outcomes of medications, including long- and short-term side effects.[30] Key elements for an effective pharmacovigilance system include government support, legislation, a national policy, a dedicated Pharmacovigilance Centre, adequate resources, drug registration systems, and post marketing surveillance. Important actions include educating healthcare providers and consumers on drug safety, monitoring the impact of activities, and ensuring continuous benefit/risk assessment by pharmaceutical companies.[2]



Name of the drug	Pharmacological classification of the drug	Drug profile	Banned formulations of this drug	Justification for the restriction	Available in India
Diclofenac	NSAIDs	Bioavailability: 55%. Half-Life: 2 hours. Clearance: 582 mL/min	Diclofenac + Paracetamol + Chlorzoxazone + Famotidine	Lack of therapeutic justification	Yes
Paracetamol	Non-opioid analgesic and antipyretic	Bioavailability: 70-90%. Half-Life: 2.5 hours Clearance: 20 L/h	Paracetamol + Mefenamic Acid+ Ranitidine + Dicyclomine	Lack of therapeutic justification	Yes
Omeprazole	PPIs	Bioavailability:	Omeprazole +	Lack of	Yes
		30-40% Half-Life: 0.5 to 1 hour. Clearance: 500-600 mL/min	Paracetamol + Diclofenac	therapeutic justification	
Chlorpheniramine	Antihistaminic	Bioavailability: 25-34% Half-Life: 20 hours. Clearance: 5-7 mL/min/kg	Chlorpheniramine + Codeine + Sodium citrate + Menthol syrup	Lack of therapeutic justification	Yes
Dextromethorphan	Anti-tussive	Bioavailability: 11% Half-Life: 2-4 hours. Clearance: 1.4 L/h/kg.	Dextromethorphan + Bromhexine + Chlorpheniramine maleate + Guaiphenesin	Lack of therapeutic justification	Yes
Phenylephrine	Decongesant	Bioavailability: 38% Half-Life: 2.5 hours. Clearance: 5-7 mL/min/kg	Phenylephrine + Pholcodine + Promethazine	Lack of therapeutic justification	Yes
Ofloxacin	Quinolone or fluoroquinolone antibiotic	Bioavailability: 95-100%. Half-Life: 4-5 hours Clearance: 500-600 mL/min	Ofloxacin + Ornidazole + Zinc bis glycinate	Lack of therapeutic justification	Yes

Ornidazole	Nitroimidazole antibiotic	Bioavailability: 90%. Half-Life: 12-14 hours. Clearance: 5-7 mL/min/kg.	Ornidazole + Doxycycline	Lack of therapeutic justification	Yes
Clotrimazole	Imidazole antibiotic	Bioavailability: Poor systemic bioavailability. Half-Life: 2 hours. Clearance: Poor systemic absorption.	Clotrimazole + Beclomethasone + Ofloxacin + Lignocaine	Lack of therapeutic justification	Yes

Table : Banned Drugs in India: A Review of Drug Names, Pharmacological Classes, Safety Profiles, and Reasons for Prohibition, and Market Status.

LITERATURE REVIEW

The studies highlight the role of CDSCO and DCGI in ensuring drug safety and banning harmful drugs. In India, challenges like weak enforcement and low awareness allow banned drugs like Nimesulide to persist. Fixed-dose combinations (FDCs) face bans due to irrational formulations and safety concerns. Strengthening regulations, public awareness, and healthcare collaboration is crucial for effective pharmacovigilance.

MATERISLS AND METHODS

This retrospective cross-sectional review study analyses banned drug combinations and evaluates FDA and Government of India regulatory decisions, focusing on fixed-dose combinations (FDCs) and other banned drugs. Data were sourced from regulatory bodies like the FDA, CDSCO, and DTAB, as well as scientific databases and government reports. Selection criteria included drugs banned due to safety and efficacy concerns, with detailed drug profiles and case studies. Case selection is mainly based on the case reports of Antibiotics, antihistaminic, NSAIDs etc. Data were analysed in Microsoft Word and Excel. The review examined drug profiles, regulatory decisions, and conducted case studies to highlight public health impacts. Pharmacovigilance data were evaluated for adverse drug reactions, analyzing trends and patterns.

RESULTS AND ANALYSIS

4.1 Drug Combinations Banned by FDA and the government of India:

Sr. no.	**Prohibited Drug Combinations**	**Combinations Brand Names**	**Year of Prohibition Implementation**	**Notifications**
1	Clotrimazole + Beclomethasone + Ofloxacin + Lignocaine	Clozotic Ear Drop.	2018	S.O.4493(E) Dated 07.09.2018
2	Ornidazole + Doxycycline	Doxyclon.	2016	S.O.245 (E) Dated 11.01. 2019
3	Phenylephrine + Pholcodine + Promethazine	Kidylinctus.	2016	S.O.4562 (E) Dated 07.09.2018

4	Dextromethorphan + Bromhexine + Chlorpheniramine maleate + Guaiphenesin	Laxin DMR.	2018	S.O.4535(E) Dated 07.09.2018
5	Paracetamol + Mefenamic Acid + Ranitidine + Dicyclomine	Meftal-Spas.	2018	S.O.4401 (E)Dated 07.09.2018
6	Diclofenac + Paracetamol + Chlorzoxazone + Famotidine	Mobizox Tablet.	2018	S.O.4387(E)Dated 07.09.2018
7	Omeprazole + Paracetamol + Diclofenac	Omezol Plus.	2018	S.O.4392(E)Dated 07.09.2018
8	Chlorpheniramine + Codeine + Sodium citrate + Menthol syrup	Sinarest AF.	2016	S.O.4543(E) Dated 07.09.2018
9	Ofloxacin + Ornidazole + Zinc bis glycinate	Zinflam-OZ.	2016	S.O.4444(E) Dated 07.09.2018

Table 4.1: List of Banned Fixed-Dose Combination (FDC) Drugs by FDA and India. [3]

4.2 Classification of drugs on their therapeutic use:

Name of drugs	**Pharmacological classification of the drug**	**Therapeutic use**
Diclofenac	NSAIDs	1. Osteoarthritis and Rheumatoid Arthritis 2. Ankylosing Spondylitis 3. Menstrual Cramps 4. Migraine Headaches 5. Musculoskeletal Pain
Paracetamol	Non-opioid analgesic and antipyretic	6. Pain Relief 7. Fever Reduction 8. Postoperative Pain 9. Osteoarthritis 10. Migraine
Omeprazole	PPIs	11. Gastroesophageal Reflux Disease (GERD) 12. Peptic Ulcers 13. Erosive Esophagitis 14. Zollinger-Ellison Syndrome 15. Helicobacter Pylori Infection

Chlorpheniramine	Antihistaminic	16. Allergic Rhinitis 17. Urticaria (Hives) 18. Common Cold 19. Other Allergic Reactions
Dextromethorphan	Antitussive	20. Cough Relief 21. Chronic Cough 22. Pseudobulbar Affect
Phenylephrine	Decongestant	23. Nasal Congestion 24. Eye Irritation 25. Haemorrhoids 26. Septic Shock
Ofloxacin	Quinolone or fluoroquinolone antibiotic	27. Respiratory Tract Infections 28. Urinary Tract Infections (UTIs) 29. Skin and Soft Tissue Infections 30. Prostate Infections 31. Sexually Transmitted Infections 32. Pelvic Inflammatory Disease 33. Eye Infections
Ornida zole	Nitroimidazole antibiotic	34. Amoebiasis 35. Giardiasis 36. Trichomoniasis
		37. Bacterial Vaginosis 38. Anaerobic Bacterial Infections 39. Surgical Site Infections
Clotrimazole	Imidazole antibiotic	40. Athlete's Foot 41. Jock Itch 42. Ringworm infections 43. Candidiasis

Table 4.2: Therapeutic Categories of Drugs and Their Uses [K.D. Tripathi essentials of pharmacology 8th edition & Micromedex]

4.3 Key reasons for regulatory bans and lack of proven efficiency:

Prohibited Drug Combinations	**Combinations Brand Names**	**Justification for the restriction**
Clotrimazole + Beclomethasone + Ofloxacin + Lignocaine	Clozotic Ear Drop.	Lack of therapeutic justification
Ornidazole + Doxycycline	Doxyclon.	Lack of therapeutic justification
Phenylephrine + Pholcodine + Promethazine	Kidylinctus.	Lack of therapeutic justification
Dextromethorphan + Bromhexine + Chlorpheniramine maleate + Guaiphenesin	Laxin DMR.	Lack of therapeutic justification

Paracetamol + Mefenamic Acid + Ranitidine + Dicyclomine	Meftal-Spas.	Lack of therapeutic justification
Diclofenac + Paracetamol + Chlorzoxazone + Famotidine	Mobizox Tablet.	Lack of therapeutic justification
Omeprazole + Paracetamol + Diclofenac	Omezol Plus.	Lack of therapeutic justification
Chlorpheniramine + Codeine + Sodium citrate + Menthol syrup	Sinarest AF.	Lack of therapeutic justification
Ofloxacin + Ornidazole + Zinc bis glycinate	Zinflam-OZ.	Lack of therapeutic justification

Table 4.3: Primary reasons for drug bans and their brand names.

4.4 Safety concern: Adverse drug reactions and toxicity:

Name of the drug	Reported ADR & Toxicity	Misuse of drug	Overuse of drug
Diclofenac	Gastrointestinal bleeding Cardiovascular problems Severe allergic reactions Hepatotoxicity	Drug Abuse and Dependence Self-Medication	Gastrointestinal Problems Cardiovascular Risks Kidney Damage Liver Damage
Paracetamol	Liver Damage Kidney Damage Allergic Reactions Blood Disorders Skin Reactions	Non-Medical Use Combining with Other Substances	Medication Overuse Headache (MOH) Liver Damage Chronic Poisoning
Omeprazole	Severe Diarrhoea Stomach Cramps Fever Blood in Stool Severe Allergic Reactions	Self-Medication Combining with Other Medications	Bone Fractures Kidney Problems Low Magnesium Levels Gastric Cancer
Chlorpheniramine	Allergic Reactions Cardiovascular Issues Neurological Effects Gastrointestinal Issues Dermatologic Reactions	Sedative use Combining with Other Substances	Central Nervous System Depression Cardiovascular Issues Gastrointestinal Issues

Dextromethorphan	Severe Drowsiness Respiratory Depression Severe Allergic Reactions Hallucinations Seizures	Recreational Use Combining with Other Substances	Central Nervous System Effects Respiratory Depression Cardiovascular Issues Psychosis
Phenylephrine	Chest Pain Difficulty Breathing Rapid or Irregular Heartbeat Severe Allergic Reactions High Blood Pressure	Stimulant use Combining with Other Substances	Cardiovascular Issues Central Nervous System Effects Gastrointestinal Issues Severe Allergic Reactions
Ofloxacin	Tendon Problems Peripheral Neuropath Central Nervous System Effects Mood or Behaviour Changes Low Blood Sugar	Inappropriate dosing Combining with Other Substances	Antibiotic Resistance Gastrointestinal Issues Central Nervous System Effect Kidney and Liver Damage
Ornidazole	Liver Impairment Blood Dyscrasia Seizures Severe Allergic Reactions	Self-Medication Combining with Other Substances	Antibiotic Resistance Gastrointestinal Issues Central Nervous System Effects Liver Impairment Blood Dyscrasia
Clotrimazole	Severe Burning or Itching Swelling, Redness, or Oozing Liver Issues Severe Allergic Reactions	Self-Medication Combining with Other Substances	Antifungal Resistance Gastrointestinal Issues Central Nervous System Effects Liver Issues

Table 4.4: Safety Issues: Adverse Reactions, Toxicity, Misuse, and Overuse of Drugs in Clinical Settings [1] [4]

4.5 Case studies of specific banned drugs:

Diclofenac-Induced Hypersensitivity:

A 29-year-old female experienced widespread skin rashes, erythematous plaques, and urticarial weals due to diclofenac use. With no significant medical history, laboratory findings confirmed drug-induced hypersensitivity. Management involved discontinuing diclofenac, administering antihistamines, and using topical treatments. The

patient was counseled on avoiding diclofenac, making lifestyle adjustments, and adhering to therapy to enhance quality of life.

Paracetamol-Induced Bullous Drug Eruption:

A 2-year-old male weighing 12 kg presented with fever, cold, severe itching, burning sensations, purplish fluid-filled lesions, and lip erosions. He had a history of paracetamol syrup use. Examination revealed purplish bullae and crusted lip erosions, with normal vital signs. Histopathology confirmed bullous fixed drug eruption. Management included prednisolone, cefotaxime, mefenamic acid, and topical treatment, along with IV fluids. Causality assessments (Naranjo score: 6) rated the reaction as probable, moderate, and preventable.

Omeprazole-Induced Liver Dysfunction:

A 53-year-old male with GERD presented with heartburn and hyperacidity. Initial liver function tests were normal but later showed elevated ALT, AST, and other markers. Medications included omeprazole, ranitidine, and a herbal product (myrrh). Discontinuing omeprazole and ranitidine, along with dietary modifications and continued herbal treatment, led to improved liver function. Serology ruled out viral hepatitis.

Chlorpheniramine-Induced Anaphylaxis:

A 54-year-old female experienced urticaria, abdominal cramping, nausea, and diarrhea immediately after chlorpheniramine administration. She was on rabeprazole, clarithromycin, amoxicillin, and dexamethasone. Laboratory findings showed elevated leukocyte count and serum tryptase. Management involved withdrawing chlorpheniramine, fluid resuscitation, and IV dexamethasone. The diagnosis confirmed chlorpheniramine-induced anaphylaxis.

Dextromethorphan-Induced Dystonia:

A 64-year-old female with ischemic heart disease, heart failure (HFrEF), diabetes, hypertension, hypothyroidism, and CKD presented with exertional breathlessness, cough, and orthopnea. While on multiple medications, including dextromethorphan, she developed dystonia (prolonged involuntary spasms). Laboratory tests were mostly normal except for elevated renal markers. Dextromethorphan was identified as the suspected cause, with a causality assessment rated as "possible" (WHO-PS and Naranjo score: 3). The reaction prolonged her hospital stay (Hartwig Level 4).

Phenylephrine-Induced Eruption:

A 19-year-old female developed skin blebs and itching after using phenylephrine for six days, along with levocetirizine, montelukast, and a nasal spray. The symptoms appeared on the sixth day of phenylephrine use. Management involved discontinuing phenylephrine, while continuing levocetirizine, montelukast, and nasal spray. The diagnosis confirmed a phenylephrine-induced eruption.

Ofloxacin-Induced Fixed Drug Eruption:

A 14-year-old male developed fever, headache, and a rash with itching, burning, and blisters on his face and trunk shortly after taking ofloxacin and paracetamol. He had a history of a similar reaction two years ago. The reaction led to the withdrawal of both medications, and supportive care with levocetirizine and IV fluids was provided. The diagnosis confirmed an ofloxacin-induced fixed drug eruption, with no reaction to paracetamol upon re-challenge.

Ornidazole-Induced Adverse Drug Reaction:

A 50-year-old female developed bilateral knee pain, swelling, skin blisters, peeling, and excoriation on her right hand and foot after starting Ofloxacin + Ornidazole and Duloxetine. The medications were discontinued, and she was treated with Clopad cream, L-Dio, Atarax, and moisturizing cream. The adverse reaction was considered probable and preventable based on causality assessments.

Clotrimazole-Induced Allergic Contact Dermatitis:

A 73-year-old male with a history of otomycosis presented with itching, redness, and dryness over his left pinna. The symptoms were diagnosed as allergic contact dermatitis caused by clotrimazole ear drops. The ear drops were discontinued, and topical emollients or corticosteroids were used, leading to complete resolution of the rash within 48 hours.

DISCUSSION:

The FDA and the Central Drugs Standard Control Organisation (CDSCO) employ strict processes to evaluate fixed-dose combinations (FDCs) for safety and efficacy, banning those with significant risks or insufficient therapeutic benefits. FDCs, such as certain opioid combinations, have been banned due to addiction risks and severe adverse effects. Both agencies prioritize public health by ensuring that only FDCs meeting safety and efficacy standards reach the market. Pharmacovigilance reports play a key role in identifying risks and aiding informed decisions about drug approvals and bans. Case studies on banned drugs highlight the importance of post-marketing surveillance in detecting adverse drug reactions (ADRs) and preventing patient harm.

The evaluation of FDCs continues to evolve with advanced pharmacovigilance tools like AI and real-time data analysis, enhancing ADR detection. Stricter regulations and global harmonization will strengthen drug safety, while public awareness and access to transparent information will empower safer medication choices. Ongoing research will focus on safer and more effective drug combinations. Despite the benefits, case studies face limitations such as causality challenges, selection bias, and underreporting of ADRs. However, the proactive approach in drug monitoring ensures continuous safety improvements and protection of public health.

CONCLUSION:

This retrospective review study analyzed banned drug combinations, focusing on FDCs, using data from regulatory bodies (FDA, CDSCO, DTAB), scientific databases, and reports. It highlights the importance of stringent regulatory oversight in ensuring public health and safety. Continuous evaluation of FDCs, supported by pharmacovigilance and case studies, aids in identifying risks, improving drug safety, and minimizing patient harm. As regulations evolve and public awareness grows, the future of drug safety looks promising, with ongoing efforts to enhance medication safety worldwide.

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