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DRUG DILEMMAS

Drug Dilemmas

Adverse Reactions & Interactions

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For Shrenik

Foreword To The First Edition

I am proud to have been given the privilege of writing the Foreword for the first publication of the General Practitioners' Association titled 'Drug Dilemmas—Adverse Reactions and Interactions'.

Since its inception more than 6 years ago, this very enterprising Body has organised a number of scientific meetings on wide range of subjects covering various aspects of general practice and these have been of immense value to the medical fraternity. With this very timely publication, the Association has served to fulfil the long-felt need to highlight one of the most intellectually stimulating problems confronting medicine, that is, the adverse drug reactions and drug interactions.

The enormous range of potent and valuable drugs has transformed the face of therapeutics in the last three decades. This has undoubtedly conferred a benefit on patients suffering from a wide variety of diseases. But, in the wake of the benefits, potent therapeutic agents have brought undesirable or adverse effects. The balancing of the benefits against the risks involved presents a very burning topic.

Polypharmacy, which is a centuries-old practice, till fairly recently mattered little because a great majority of drugs were not very potent pharmacologically. With the introduction of potent therapeutic agents, the pharmacological action of drug may be quantitatively altered in patients receiving other drugs, thus leading to drug interactions. Drug interaction is an important cause of both unexpected and toxic therapeutic effects. Adverse drug reactions due to drug interactions are proportional to the number of drugs given and the duration of administration. The frequency of adverse drug interactions in clinical practice makes it mandatory for the physician to know the drug and mechanism involved in the drug interaction. I believe that awareness of possible hazards of medication and possible interactions between drugs on the part of those who use them, can only result in better therapeutics with benefit to the patient in terms of both safety and efficacy.

This book has been prepared with the objective to make available a clinically useful guide to drug—drug interactions. An attempt has been made to present the material in an easily accessible form, assisted by an extensive index and numerous clear sub-headings so that the busy physicians can obtain the information re-

quired in the shortest possible time. I hope this volume will serve as a convenient desk reference and will receive a warm welcome amongst prescribing physicians. I have no doubt that its contribution in strengthening the understanding of therapeutics will be greatly appreciated by the medical profession.

The concise but comprehensive practical information given in the publication has made me realise the importance of reinforcement required to keep abreast of medical knowledge in relation to day-to-day medical problems encountered by general practitioners and I congratulate Dr. Ambalal Shah and Dr. Nitin Shah for their unstinted efforts in providing such excellent material. Dr. Ramnik H. Parekh, with his usual creative ability, has done a slick job in designing this book and I am sure the readers will join me in congratulating him.

Adverse drug reactions and drug interactions are problems which we have got to learn to solve. Therefore, it is particularly befitting that the General Practitioners' Association has taken a worthwhile step in this direction by bringing out an invaluable guide for the physician's desk. I hope the Association will publish many such books of use to the professional colleagues in day-to-day practice and wish them every success in their efforts towards fulfilling this aim.

3 February, 1977

Dev R. Chadha

Preface

The aim of therapy is to induce the desired and, if possible, harmless effect with the use of drugs (as available) to alleviate human suffering; on the other hand, "Drug Dilemmas" may affect the doctor-patient relationship, often leading the doctor to feel guilty and the patient to become aggressive.

Iatrogenesis is an added dimension in the causation of disease. Sometimes drugs are used excessively or indiscriminately, in combination with one another, giving rise to new kinds of toxicity resulting from such combinations; toxicity is a kind of pharmacodynamics.

As Louis Lasagna said, "The mind of man has removed the stopper from the medicine jar. The chemical genie, formerly imprisoned within, now stands before us. He is a spirit known to work miracles, but also to wreak havoc. It is not clear that we are yet sufficiently wise to control the genie adequately. It is quite clear that we can never wish to put him back in the jar." The total picture of adverse reactions to medicines prescribed compared to the benefits derived from them appears to have gone out of hand; those who clamour for 'immediate and completely safe' therapeutic agents without knowing their interactions would only bring about confusion.

The knowledge of Pharmacology and Pharmacodynamics is ever expanding and hence a greater understanding of short and long term adverse reactions of drug therapy is desirable. Scientific exchanges between pharmacologists and clinicians have enlarged our knowledge of drug interactions. On the other hand, inadequate attention has been paid to the strides that have taken place in the field of drug interactions. This attitude is best explained by paraphrasing William Shakespeare: "The evil that drugs do lives after them; the good is oft interred with their recall."

This book is meant for simple-minded clinicians. It does not attempt to be an encyclopaedia. We have laid emphasis on the commonly encountered adverse reactions and interactions of drugs. Information has been gathered from various text books, papers and articles published in the literature; it is however difficult to cite all references. Any suggestion or criticism to improve upon this effort would be most welcome.

Acknowledgements

In a way, this book is Dr. Praful Dalal's and Dr. Ramnik Parekh's 'baby'—the former conceived it and the latter nourished and nurtured it—both 'God-fathered' it from the first draft to this edition. In that respect, we are only it's foster parents.

Although several chapters were reviewed by physicians who are authorities in their respective fields, we alone are responsible for any errors or omissions which exist in the following pages.

The following have been particularly helpful: Dr. Kishor Shah, Dr. Krishnakumar Shah, Dr. Ashit Sheth, Dr. (Mrs.) Rekha Sheth and Dr. (Mrs.) Jyoti Parekh.

Thanks are due to Miss Shilpa Dalal for the cover design and Mr. K. Ramdas who patiently typed and retyped the manuscript. Thanks also to the staff of the Popular Press (Bombay) Pvt. Ltd. for their patience, as deadline after deadline was missed.

We are grateful to Dr. Dev R. Chadha for having consented to write the Foreword—we feel honoured to have his name adorn the book.

We are indebted to the Managing Committee of the General Practitioners' Association, Greater Bombay. It would be true to say that this book would not have been possible but for their sponsorship and help.

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Contents

	Foreword		vii
	Preface		ix
	Acknowledgements		xi
Chapter 1	**Anticonvulsant Drugs**		1
Chapter 2	**Analgesic, Antipyretic & Anti-inflammatory Agents**		11
Chapter 3	**Narcotics**		21
Chapter 4	**Corticosteroids**		27
Chapter 5	**Uricosuric Agents**		31
Chapter 6	**Antimicrobials**		37
	Part One	The Penicillin Groups of Antibiotics	38
	Part Two	Sulphonamides and Urinary Antiseptics	47
	Part Three	The Aminoglycosides	53
	Part Four	Drugs Used in Tuberculosis	57
	Part Five	Antifungal Agents	64
Chapter 7	**Diuretics**		67
Chapter 8	**Antihypertensives**		79
Chapter 9	**Drugs Used in Angina Pectoris**		91
Chapter 10	**Anticoagulants**		95
Chapter 11	**Drugs Used in Cardiac Arrhythmias**		99
Chapter 12	**Cholesterol Lowering Agents**		111
Chapter 13	**Hypoglycaemic Agents**		119
Chapter 14	**Psychotropic Agents**		125
	Index		139

CHAPTER ONE

Anticonvulsant Drugs

The Lord may forgive us our sins—but the nervous system never does.
William James

1. Regular medical care is one of the most important aspects of the treatment. The physician should see the patient at regular intervals, in order to regulate the dosage of his medication and examine him for adverse drug reactions. Periodic physical examinations and blood, renal and liver function tests should be performed on all patients receiving drugs such as Primidone, Paramethadione, Trimethadione and Ethosuximide
2. Treatment should be instituted as soon as the diagnosis has been established
3. The selection of the drug of first choice for the treatment of any case of epilepsy should be based on the type of seizures and the toxicity of the drug
4. Treatment should begin with one drug. Other drugs should be prescribed, if necessary, only after it has been determined that the maximum tolerated dosage of the starting drug failed to produce a satisfactory clinical response
5. The medication should be taken daily, in divided doses, at times of the day which do not interfere with the patient's routine activities
6. The dose of anticonvulsant medication varies from patient to patient
7. The medication should be taken for a prolonged period
8. The medication should be discontinued very gradually. A sudden withdrawal of anticonvulsant medication is a frequent cause of recurrence of seizure or status epilepticus
9. The physician should investigate precipitatory factors of epileptic seizures and direct his treatment accordingly.

Phenobarbitone:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
PHENOBARBITONE (Gardenal): **Dose:** **Children:** I.M. or I.V. 3-5 mg./kg. 0-1 year: 30-60 mg. 1-5 years: 90 mg. 6-12 years: 120 mg. **Adults:** 1-5 mg./kg. body weight. When given thrice daily there is a cumulative effect. Dose is 100-300 mg. in divided doses per day. **Uses:** Major anticonvulsant used in all types of epilepsy. To be used with caution in children, as it tends to produce idiosyncratic reaction.	**Skin:** Rash (erythematous, urticarial, purpuric, scarlatiniform or morbilliform) with pruritus; exfoliative dermatitis **Gastro-intestinal:** Anorexia, constipation, halitosis, coated tongue. **Renal:** Albuminuria, casts, hematoporphyrinuria. **Haematological:** Anaemia. **Mental:** Drowsiness, irritability, hyperexcitability, poor memory, emotional lability, paranoic, suicidal tendency, confusion, hallucinations, sedation. **Central Nervous System:** Dysarthria, ataxia, nystagmus, diplopia. **Pregnancy:** Interferes with Folic acid metabolism and vit. K. metabolism.	**Anticonvulsants:** Phenytoin Primidone Mysoline **Antimicrobials:** Griseofulvin **Anticoagulants:** **Psychotropic agents:** Tricyclic antidepressants Phenothiazines MAO inhibitors **Central Nervous System Depressants:** Alcohol, sedative, hypnotics, tranquillisers, narcotics, antiemetics, antihistaminics. **Miscellaneous:** Corticosteroids Oral contraceptives Folic Acid	Complex situation. Withdrawal of Phenobarbitone may cause Phenytoin toxicity. Reduce the dose of Phenobarbitone. Accentuates the untoward effects of barbiturates. Reduced effect of the drug. Reduced anticoagulant effect. Reduced antidepressants effect; enhanced CNS depression; lowers epileptic threshold. In lower dosages, raises the epileptic threshold, while in higher dosages, lowers. Potentiates the sedative properties of barbiturates. Enhanced barbiturate effect, hypotension and shock. Additive CNS depressant effect. Anticonvulsants may induce the metabolism of these steroids. ? Phenobarbitone increases the metabolism of the oestrogens in animals. ? Reduced anticonvulsant effect.

Diphenylhydantoin:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
DIPHENYLHYDANTOIN (PHENYTOIN) (Dilantin): **Dose:** **Children:** upto 5 years, 30-60 mg. 6-12 yrs., 90 mg. **Adults:** 100 mg. t.d.s. **Maximum dose:** 800 mg. Strong alkalinity may cause gastric irritation unless each dose is taken after meals. More effective if taken before meals. I.M. or I.V. 250 mg. as 5% solution slowly (upto 500 mg.) Prophylactic control with ECG.	**Skin:** Rash (erythematous, scarlatiniform, morbilliform), exfoliative dermatitis, haemorrhagic erythema multiforme, hirsutism. **Gastro-intestinal:** Anorexia, nausea, vomiting, epigastric pain, haematemesis. **Hepatic:** Hepatitis, jaundice. **Renal:** Albuminuria, hematoporphyrinuria. **Haematological:** Leucocytosis, eosinophilia, lymphadenopathy. **Mental:** Apathy, confusion, drowsiness, insomnia, irritability, hallucinations, delusions. **Central Nervous System:** Ataxia, nystagmus, vertigo, tremor, diplopia, blurred vision, ptosis, ocular pain, dysphagia, headache, peripheral neuritis, toxic amblyopia, choreoathetosis, dystonia, withdrawal seizues, worsening of petit mal. **Miscellaneous:** Gum hyperplasia, fever, bronchial irritation, dyspnoea, periarteritis nodosa, oedema of face, increased libido, cardiac arrhythmias, ECG changes, low PBI. Teratogenic effect.	**Anaesthetic:** Halothane **Analgesics—anti-inflammatory agents:** Phenylbutazone Corticosteroids **Antimicrobials:** Isoniazid, PAS Chloramphenicol Sulphaphenazole **Antihypertensives:** Reserpine **Cardiac glycosides:** Digoxin, Digitoxin **Anticoagulant:** **Hypoglycaemic agents:** **Central Nervous System Depressants:** Alcohol **Miscellaneous:** Folic acid	Phenytoin toxicity. Phenytoin toxicity. Reduced corticosteroid effect. Phenytoin toxicity. Phenytoin toxicity. Phenytoin toxicity. Decreases anticonvulsant effect. Phenytoin toxicity. Phenytoin toxicity. Reduced anticoagulant effect of Coumarin. Enhanced hyperglycaemia Reduces Phenytoin effect with heavy drinking. Decreases anticonvulsant effect.

Primidone:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
PRIMIDONE (Mysoline): **Dose:** Children: 5-20 mg./kg. body weight Adults: 15-25 mg./kg. body weight 125 mg. daily, and then increase upto 250 mg., three times a day. Maximum dose: 2 g. **Uses:** Same as Phenobarbitone. Drug of choice in psychomotor epilepsy and akinetic minor seizures.	**Gastrointestinal, Skin, Mental** and **Neurological:** Similar to Phenobarbitone. **Haematological:** Megaloblastic anaemia. **Miscellaneous:** Oedema of legs and eye-lids, painful gums, goiter, hypothyroidism (?)	This is a Pyrimidine derivative related to Phenobarbitone, but with different chemical and pharmacological properties. **Interacting drugs and interactions are similar to Phenobarbitone**	Similar to Phenobarbitone.

Precautions:

1. Patients with porphyuria.
2. Patients who are hypersensitive to Phenobarbitone.

Pregnancy:

Reports suggest an association between the use of ant convulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Reference has been made to Primidone in several cases in which it was used with other anticonvulsants, but no conclusive effects of teratogenicity were demonstrated. The data also indicates that the great majority of mothers receiving anticonvulsant medication deliver normally.

Anticonvulsant drugs should not be discontinued in patients to whom the drug is administered to prevent major seizures because of the strong possibility of precipitating **status epilepticus** with attendant hypoxia and risk to both the mother and the unborn child.

When the nature, frequency and severity of the seizure does not pose a clear threat to the patient, the physician should weigh the expected therapeutic benefits of anticonvulsant therapy against possible risks, on an individual basis. Pregnant women under anticonvulsant therapy should receive prophylactic vitamin K therapy for one month prior to and during delivery.

Nursing mothers:

It is suggested that the presence of undue somnolence and drowsiness in nursing newborns of Primidone-treated mothers be taken as an indication that nursing should be discontinued.

In patients already receiving other anticonvulsants, Primidone should be gradually increased, as dosage of the other drugs is maintained or gradually decreased. This regimen should be continued until a satisfactory dosage level is achieved for combination or the other medication is completely withdrawn. When therapy with this product alone is the objective, the transition should not be completed in less than two weeks.

Troxidone, Paramethadione and Ethosuximide:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
TROXIDONE (Tridione): **Dose:** Children: 20-60 mg./kg. body weight Adults: 10-25 mg./kg. body weight Clinical improvement is seen in 1-4 weeks. Requires frequent blood and urine examination.	**Gastro-intestinal, Skin and Mental:** Same as Phenobarbitone. **Hepatic:** Hepatitis. **Renal:** Nephrotic syndrome, microscopic haematuria. **Haematological:** Leucopenia, agranulocytosis, thrombocytopenia, aplastic anemia. **Central Nervous System:** Hemeralopia, photophobia, dizziness, tremor, worsening of grand mal.	Same as Phenobarbitone	Same as Phenobarbitone.
PARAMETHADIONE (Paradione): **Dose:** Children: 10-25 mg./kg. body weight Adults: 10-25 mg./kg. body weight	Same as Troxidone, but less frequent.	Same as Troxidone	Same as Troxidone.
ETHOSUXIMIDE (Zarontin): **Dose:** Children: 20-60 mg./kg. body weight Adults: 20-30 mg./kg. body weight Increase dose every 7 days upto 2 g. Complete blood count, liver function tests; urine to be checked regularly.	**Skin:** Dermatitis, hirsutism (?) **Gastro-intestinal:** Anorexia, nausea, vomiting, epigastric pain. **Hepatic:** Hepatitis (?) **Haematological:** Leucopenia, agranulocytosis, aplastic anemia, pancytopenia. **Mental:** Drowsiness, euphoria, insomnia, night terrors, hyperactivity, agitation, aggressiveness, paranoia. **Central Nervous System:** Headache, dizziness. **Miscellaneous:** Hiccup, increased libido, myopia, swollen tongue, vaginal bleeding.	**Psychotropic agents:** Tricyclic antidepressants **Antihypertensives:** Reserpine **Miscellaneous:** Oral contraceptives	Reduced anticonvulsant effects. Can produce seizures. Reduced anticonvulsant effect. Change in response to anticonvulsant is a possibility.

Acetazolamide and Carbamazepine:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
ACETAZOLAMIDE (Diamox): **Dose:** Children 12-35 mg./kg. body weight Adults: 5-15 mg./kg. body weight **Uses:** Given with Primidone and Diazepam, it is of value in the control of infantile spasms, akinetic seizures and major epilepsies refractory to other drugs. It is of value as an adjuvant therapy.	**Skin:** Pallor, dermatitis **Gastro-intestinal:** Anorexia, nausea, vomiting, diarrhoea. **Renal:** Polyuria, nocturnal enuresis, crystalluria, renal calculi. **Haematological:** Leukopenia. **Mental:** Drowsiness, lethargy, excitement disorientation. **Central Nervous System:** Ataxia, withdrawal seizures, paresthesias.	**Antimicrobials:** Methenamine Mandelate Nitrofurantoin Quinidine **Hypoglycaemic agents:** **Psychotropic agents:** Amphetamines Lithium carbonate	 Acetozolamide renders urine alkaline, so the drug is less effective. Acetozolamide renders urine alkaline; serum level increased. Increases blood glucose level in diabetics and also those being treated with hypoglycaemic agents. Enhanced effect. Increased excretion of Lithium. Impairs therapeutic response.
CARBAMAZEPINE (Tegretol): **Dose:** 100-200 mg. Can be increased upto 800-1200 mg. **Uses:** 1. Grand mal and psychomotor epilepsy. 2. Trigeminal Neuralgia. **Precautions:** 1. Glaucoma. 2. Cardio-vascular disease. 3. Elderly patients with confusion and agitation. 4. Check blood count and liver function tests frequently.	**Skin:** Rash (erythematous, morbilliform, urticarial), light sensitivity dermatitis. **Gastro-intestinal:** Nausea, dry mouth, diarrhoea. **Hepatic:** Jaundice, disturbance of liver function. **Respiratory System:** Dyspnoea. **Cardio-vascular System:** Bradycardia, Oedema, raised or lowered blood pressure. **Genito-urinary:** Oliguria. **Mental:** Confusion. **C.N.S.:** Ataxia, depression, psychosis, dizziness, drowsiness, headache, nystagmus, tremor, vertigo, diplopia, neuritis, blurring of vision, difficulty of accommodation. **Haematological:** Leucopenia, aplastic anaemia, agranulocytosis, eosinophilia, pancytopenia.	**Psychotropic agents:** MAO inhibitors **Anticonvulsants:** Phenytoin	 Anticonvulsant effect. (To stop MAO inhibitors two weeks before this therapy). Elimination of Phenytoin delayed but Carbamazepine elimination is unaffected.

Diazepam, Nitrazepam and Sodium Valproate:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
DIAZEPAM (Valium): **Dose:** Children: 0.1-1 mg./kg. body weight Adults: 0.1-2 mg./kg. body weight I.V. Valium is useful in Status Epilepticus.	**Skin:** Dermatitis. **Gastrointestinal:** Nausea. **Mental:** Drowsiness, lethargy, excitability. **Central Nervous System:** Ataxia, withdrawal seizures.	**Central Nervous System Depressants:** Alcohol	Potentiates the effect of other drugs, which depress C.N.S.
NITRAZEPAM (Hypnotex): **Dose:** Children: 0.6-1 mg./kg. body weight	**Mental:** Drowsiness, fatigue. **Central Nervous System:** Confusion in elderly patients. **Overdose:** Course sustained, bilateral nystagmus with a rotatory element elicited on lateral gaze; incoordination of lower limbs and ataxia.	**Psychotropic agents:** MAO **Central Nervous System Depressants:** Alcohol	Same as Diazepam. Additive effect.
SODIUM VALPROATE* (Epilim): New epileptic drug. **Dose:** The daily maintenance dosage is 800-1600 mg. In children, 30 mg./kg. should be taken 3-4 times a day. In most of the clinical trials, Sodium Valproate was added to the patient's regimen. No double-blind trial was done.	**Gastro-intestinal:** Anorexia and nausea occur on an empty stomach. Teratogenicity has been found in animals, but in humans, the results are not known. Drowsiness is profound when given with Phenobarbitone but not so when given with Phenytoin. A reduction in the dose of Phenobarbitone or Primidone may be necessary.	Authors have no confirmed notes on interaction.	

* Not available in our country.

Sulthiame and Clonazepam:

Drug and Dosage	Adverse Reactions	Interacting Drug	Interaction
SULTHIAME* **(Ospolot):** Is a weak carbonic anhydrase inhibitor and has a mild diuretic effect. It has a mild tranquillising action but no hypnotic effect. New anticonvulsant for mentally subnormal epileptics refractory to other drugs. **Uses:** Temporal lobe epilepsy, Grand Mal. **Dose:** Average 600 mg. per day. 1 tablet (0.2 g.), daily; increase to 2 tablets after 3 days. Other drugs of the same group: (i) Methsuximide (ii) Phensuximide (iii) Pheneturide (i) & (ii) are used in Psychomotor epilepsy.	**Skin:** Rash papular. **Gastrointestinal:** Nausea. **Cardio-Vascular System:** Dyspnoea, ? angina on effort; ? hypotension. **Mental:** Tiredness, lassitude, drowsiness, psychotic reactions of paranoid features in those who had suffered in the past from such episodes; insomnia, development of incontinence with mental confusion. Initial period of aggressiveness. **Central Nervous System:** Headache, dysarthralgia, ataxia, vertigo, ptosis, diplopia, papilloedema, status epilepticus, paresthesia of face and upper extremity. **Miscellaneous:** Tiredness and lassitude.	**Anticonvulsants:** Phenytoin	May elevate serum concentration of Phenytoin.
CLONAZEPAM* **(Rivotril, Roche):** New antiepileptic drug. **Dose:** Infants : 0.5-1 mg. Small children: 1.5-3 mg. School children: 3-6 mg. Adults : 6-8 mg. **Uses:** Myoclonus, petit mal, absences and myoclonic, focal and psychomotor epilepsies. Maximum effect observed in 3 weeks.	**Mental:** Fatigue, somnolence, aggressiveness, irritability or agitation. **Central nervous system:** Occasionally, muscular hypotonia. **Respiratory system:** Salivary or bronchial hypersecretions.	Alcohol	Alcohol can provoke epileptic seizures, irrespective of therapy. It may modify the action of 'Rivotril', compromise the success of therapy or give rise to unpredictable side-effects when ingested concurrently.

* Not available in our country.