

POSSIBLE TOXIC EFFECTS OF BENZODIAZEPINES;

At therapeutic doses due to drug-drug interactions in hospitalized patients

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ABSTRACT... Introduction: Benzodiazepines and its derivatives are used widely as anxiolytics, hypnotics, seizure control and as muscle relaxants. **Design:** The prescriptions of 270 patients were evaluated for moderate to severe drug interactions using drug interaction detection software. **Setting:** Teaching hospital in Gujrat, Pakistan. **Objective:** This study is used to evaluate the possible toxic effects of benzodiazepine related drug-drug interactions in prescriptions of indoor patients. **Material & Methods:** The prescriptions were processed through a software program named, The Medical Letter Adverse Drug Interaction program. The randomly collected patient chart profiles included both male and female patients ranging from age of few months old children to old aged patients. **Result:** Out of 270 patients medication charts 210 medication charts were having at least one or more drug interactions ranging from moderate to severe. Out of 80 interacting drug combinations found, 15 were benzodiazepine related drug interactions. So, percentage of benzodiazepines related drug interactions was 18.75%. Moreover, the data also showed that the percentage of DDIs increases as the prescription size increases. Our results indicate that hospitalized patients in Pakistan are at risk of ADRs caused by potential DDIs. Moreover, there are chances that the safe therapeutic doses of benzodiazepines may become toxic or ineffective due to drug-drug interactions and polypharmacy. **Conclusions:** So, the use of DDIs detection software programs in hospitals and pharmacies should be promoted in order to minimize drugs especially benzodiazepines related injuries and to ensure patient safety.

Key words: Benzodiazepines, Drug-drug interactions, Prescriptions, Pakistan.

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INTRODUCTION

Benzodiazepines shares parallel neuropharmacologic characteristics together with sedation, sleep induction, anxiety reduction, muscle relaxation and anticonvulsant effects¹.

In medical and psychiatric practice benzodiazepines and its derivatives are used widely as anxiolytics, hypnotics, seizure control and as muscle relaxants. During past two decades, the use of benzodiazepines has been widely increased. Whenever a patient is treated with two or more than two drugs at the same time, there are chances that the drugs may interact in such way that can alter their pharmacokinetic and pharmacodynamic parameters. This can result in increased or decreased drug concentrations resulting in drug toxicity or ineffective treatment^{1,2}. There may be multiple drug interactions in a single prescription but only few are clinically important to be considered and monitored^{3,5}. Polypharmacy is associated with multiple DDIs, prescription errors, ADRs and

sometimes ineffective treatment^{6, 7}. The more pronounced adverse effects of this class of drugs reaction has become a great matter of discussion for the clinical studies. The etiology of unnecessary medicine good effects has concerned assessment of drug pharmacokinetics and pharmacodynamics⁴. Blood loss owing to oral anticoagulants, gastropathy and hypoglycemia from diabetes treatment linked with non-steroidal anti-inflammatory drugs have been recognized in epidemiological studies as recurrent unpleasant drug reactions in aged persons^{8,9}. As polypharmacy is widespread, the possible for unpleasant drug reactions has amplified for each drug group¹⁰⁻¹².

Only 3% of all hospital admissions are the risk of DDIs⁸⁻¹². When physicians cannot avoid the use of multiple drugs in case of serious patients then risk benefit ratios are considered, also considering the availability of alternatives. Drug-drug interactions are important to consider while using the drugs with narrow

therapeutic ratios and especially when patient is renally or hepatically compromised, too young or too old and when multiple drugs are being administered at the same time to the same patient. As the number of drugs increases in prescriptions, it is more suitable to use drug interaction detection software programs to ensure the patient safety^{13,14}.

In Pakistan and many other countries, there is no trend to evaluate the prescriptions for drug interactions either manually or by screening programs for DDIs detection. Almost all patient medication charts are hand written. Patients are at great risk of ADRs due to DDIs. Although issues like primary health care and pharmaceutical care are always in talk but the area of study like drug interactions has not been given any importance in Pakistan and many other countries until now¹⁵⁻¹⁸.

OBJECTIVE OF STUDY

The objective of the study was to evaluate the toxic effects of benzodiazepines related potential drug-drug interactions in indoor patients in a teaching hospital in Pakistan. The secondary objective was to evaluate the frequency of benzodiazepine related drug-drug interactions in hospitalized patients.

METHODS

Patient medication charts hospitalized in different wards including male medical ward, female medical ward, gynae ward, children ward, emergency ward and TB ward of a teaching hospital in Gujrat, Pakistan were collected over a period of 3 months. The medication charts were picked randomly including male, female, young and old patients. The prescriptions were processed in THE MEDICAL LETTER ADVERSE DRUG INTERACTION PROGRAM. The drug interactions found related to benzodiazepines were separated and their percentage was calculated in relation to total number of interacting combinations found using Microsoft excel. The information was collected with the consent of hospital authorities and it

included name, age, sex, diagnosis, patient history, list of medications and doses. The detected DDIs were cross-over checked manually for enough published scientific data to support our results¹⁹. Major DDIs include those which can cause serious harm to the patient if goes unchecked while moderate include those which are documented DDIs but are not of serious nature and can be minimized by just monitoring the patient for ADRs²⁰. The insignificant drug interactions were not considered. Only major and moderate DDIs were further analyzed in Microsoft Excel.

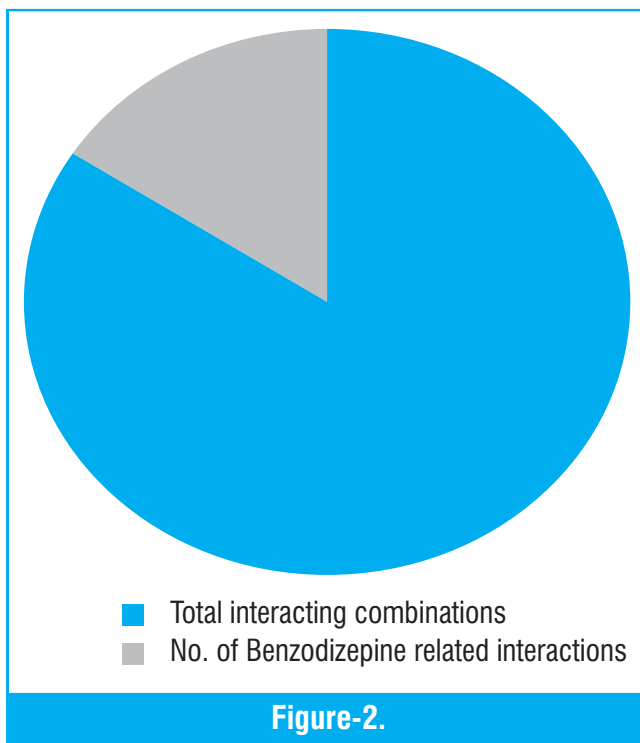
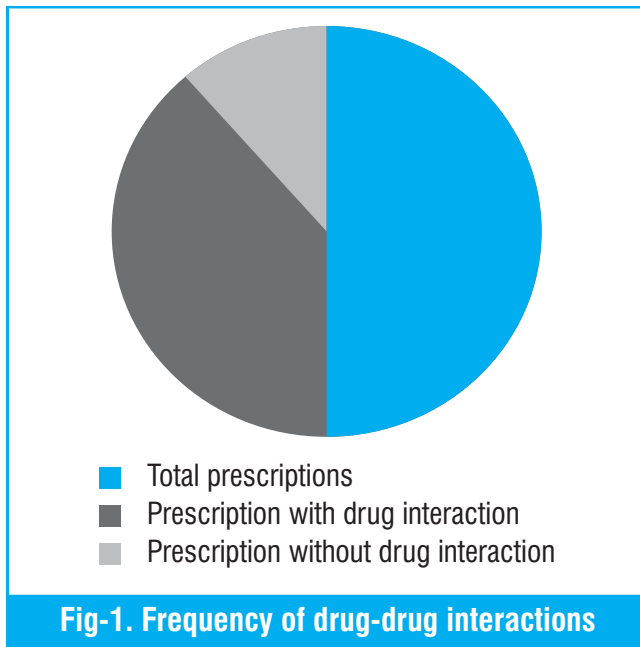
RESULTS & DISCUSSION

Each prescription on average contains 5 to 6 medications. Out of these 270 prescriptions 210 i.e. 77% prescriptions were containing one or more drug interactions while 60 i.e. 23% prescriptions were having not even a single minor drug interaction. (Figure-1). Total 80 interacting combinations were found in 270 prescriptions. Out of these 80 interacting combinations 15 combinations were benzodiazepine related i.e. 18.75% (Figure-2). The results also showed that as the number of drugs in a prescription increases, the frequency of drug interactions increases. Drug interactions related to benzodiazepines are also shown in table-I. The results indicate benzodiazepine toxicity problems that can result due to potential drug-drug interactions and lack of prescription monitoring programs. If this study is conducted on large scale, more reliable results can be obtained. Medications when used in combination with other drugs like benzodiazepines must be selected carefully to avoid resulting toxicity and prescription errors²¹⁻²⁷.

This indicates that the indoor patients in Pakistan hospitals who are under treatment with more than 4 or 5 drugs are at the risk of moderate to severe drug interactions. These interactions may be life threatening and require close monitoring in order to ensure patient safety, or they may be moderate and can exacerbate

DRUG COMBINATION	TYPE/MECHANISM OF INTERACTION	POTENTIAL ADVERSE EFFECTS	RECOMMENDATION
Ranitidine (Antihistamines, H2-blockers) Valium (Benzodiazepines)	Pharmakokinetic (decreased metabolism) (altered absorption)	Possible benzodiazepine toxicity	Monitor clinical status; oxazepam, lorazepam, and temazepam do not interact; famotidine, and possibly nizatidine, may be used instead, Monitor benzodiazepine effect or concentration
Dexamethasone (Corticosteroids) Valium (Benzodiazepines)	Pharmakokinetic (increased metabolism) CYP3A4	Possible decreased midazolam effect	-
Alprazolam (Benzodiazepines) Omeprazole	Pharmakokinetic (decreased metabolism)	Possible diazepam, flurazepam, clorazepate and triazolam toxicity	Monitor response to diazepam
Acetaminophen Alprazolam (Benzodiazepines)	(mechanism not established)	Possible diazepam toxicity	Monitor clinical status
Alprazolam (Benzodiazepines) Isoniazid	(decreased metabolism)	Possible IV diazepam toxicity Possible triazolam toxicity	Decrease dosage, but in combined anti-tuberculosis therapy, suppression of diazepam effect by rifampicin tends to predominate Oxazepam metabolism not affected
Alprazolam (Benzodiazepines) Piroxicam (Nonsteroidal anti-inflammatory drugs)	(delayed absorption) (displacement from binding)	Possible delayed onset of action of naproxen with diazepam Shortened induction with midazolam anesthesia after aspirin	Monitor closely
Alprazolam (Benzodiazepines) Rifampicin (Rifampin)	(increased metabolism)	Possible decreased oral and IV diazepam, triazolam or nitrazepam effect and oral midazolam effect	Increased dosage of benzodiazepine, in combined anti-tuberculosis therapy with isoniazid, effect of rifampicin predominates; triazolam and oral midazolam may be ineffective in patients on rifampicin
Alprazolam (Benzodiazepines) Dexamethasone (Corticosteroids)	(probably increased metabolism; CYP3A4)	Effect relatively small	Dose adjustment
Diazepam (Benzodiazepines) Valium (Benzodiazepines)	Additive effects	Possible toxicity	Beaware of additive effects
Acetaminophen Diazepam (Benzodiazepines)	(mechanism not established)	Possible diazepam toxicity	Monitor clinical status
Diazepam (Benzodiazepines) Zantac (Antihistamines, H2-blockers)	(decreased metabolism) (altered absorption)	Possible benzodiazepine toxicity with cimetidine Altered benzodiazepine effect with ranitidine	Monitor clinical status Monitor benzodiazepine effect or concentration
Cipro (Fluoroquinolones) Diazepam (Benzodiazepines)	(decreased metabolism)	Possible diazepam toxicity with ciprofloxacin	Monitor clinical status No effect of ciprofloxacin on temazepam metabolism
Ampicillin (Penicillins) Phenytoin	(displacement from binding)	Possible increased phenytoin toxicity with high-dose intravenous Penicillin	Monitor clinical status
Decadron (Corticosteroids) Valium (Benzodiazepines)	(probably increased metabolism; CYP3A4)	Possible decreased midazolam effect	Consider dose adjustment
Valium (Benzodiazepines) Valproic acid (Valproate)	(displacement from binding and decreased metabolism-glucuronidation)	Possible IV diazepam toxicity Possible midazolam toxicity	Use IV diazepam with caution Avoid concurrent use Monitor midazolam Monitor clinical status

Table-1. Summary of benzodiazepine related drug-drug interactions.



the condition of seriously ill patient, so they require alteration in therapy. This data shows that benzodiazepines and their derivatives are frequently prescribed to indoor patients. They are at higher risk of developing drug-drug interactions related to

benzodiazepines. Benzodiazepines pointed out the action of assault epilepsy and emergencies. These are amongst the mainly constructive AEDs accessible for treating patients with position epilepticus or sensitive cyclic seizures. Additional faults comprise unpleasant events, such as sedation, drug interactions and cognitive impairment.

There are chances that benzodiazepines even at therapeutic doses may produce toxic effects or may become ineffective due to drug-drug interactions. Currently in Pakistan, hospitals are not equipped with drug interaction detecting software and the frequency of prevalence of drug interactions is very high. If this study is conducted on large scale in hospitals in Pakistan, more reliable results can be obtained.

CONCLUSIONS

The main outcomes of this study are that the frequent use of benzodiazepines can increase the percentage of drug interactions in indoor patients that can result in toxicity or ineffectiveness of the drug at therapeutic dose. Poly pharmacy in indoor patients in hospitals can result in moderate to severe drug interactions which require close monitoring to ensure patient safety. Patients in medical wards especially are using many medications at a time leading to DDIs. In order to minimize benzodiazepine toxicity in hospitalized patients, implementation of computerized software programs can help health care professionals in determining the risks of potential DDIs especially related to benzodiazepines.

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A man may die, nations may rise and fall,
but an idea lives on.

John F. Kennedy