

## Quantitative Analysis of Drug- Drug Interactions of OTC Drugs with other Prescribed Drugs Collected from Different Hospitals and Clinics of Karachi, Pakistan.

Shajahan Shah<sup>1</sup>, Baquar Shyum Naqvi<sup>1</sup>, Ale-Zehra<sup>✉</sup>, Danish Ali<sup>1</sup>, Rehana Saeed<sup>1</sup>, Ghazala Raza Naqvi.<sup>2</sup>

<sup>1</sup>Department of Pharmaceutics, Faculty of Pharmacy, University of Karachi.

<sup>2</sup>Pharmaceutical Microbiology, Faculty of Pharmacy, Federal Urdu University.

### ABSTRACT

In the modern era of health profession, drug prescribing practices have become more complicated as the number of drug inventions is increasing with numerous diseases which lead to a situation to prescribe a concurrent therapy of more than one therapeutic regime at a time. Under these clinical circumstances, in spite of making a patient profile and close monitoring of medication dosage, there is an increased incidence tendency of drug interaction which may counteract the mechanism of each other. The core aim of the current study is to analyze the drug-drug interactions of OTC drugs with other prescribed drugs. For this purpose, a total number of 448 prescriptions were collected from different retail pharmacies and physician clinics running under the hospitals of Karachi, Pakistan over a period of 9 months (Jan, 2009 to Sep, 2009). Software Micromedex (R) Healthcare Series, Vol.142, 1974 – 2009, Thomson Reuter, was used as a reference to determine the interactions. The total numbers of 2124 of drug-drug combinations were reviewed under the study, out of which 357 drug-drug interactions were identified in the entire study. On the basis of Micromedex software drug-drug interaction categorization, these 357 drug-drug interactions were categorized into the Severity, Onset and Documentation. Based on Severity, 13 (3.46%) interactions were found to be Major, 275 (77.03%) were Moderate and 69 (19.33%) were Minor. Based on Onset, 115 (32%) interactions were reported as Rapid and 236 (66%) were Delayed, and 6 (2%) were not specified. Based on Documentation, 11 (3%) interactions were documented as an Excellent, 224 (63%) interactions were Good and 122 (34%) interactions were Fair. Overall, the end results of the entire study found interactions of Aspirin with ACE inhibitors and Clopidogrel, Iron, Zinc and Calcium with Ciprofloxacin, while Ibuprofen with Lisinopril as a top large number of interactions. However, the current study raises the awareness of the pharmacist to make an intervention strategy on emphasizing the proper prescribing practice and to take a holistic approach toward the further enrichment of opportunities subsist for greater involvement in safe and effective utilization of therapeutic regime.

**Keywords:** Drug-Drug Interactions, Interaction with OTC Drugs, Interactions With Prescribed Drugs.

### INTRODUCTION

With the passage of time, the development of new medicines is continuously increasing, the interactive potential of an increasing large number of possible drug combination has become more complex. However as drug therapy becomes more complex and because many patients are being treated with two or more drugs, the

ability to predict the magnitude of a specific action of any drug may diminish. <sup>1</sup>. The analysis of drug interactions has a long history, and many different approaches have been tried. It is important, therefore, that the nature of potential drug interactions will be properly analyzed and quantified <sup>2</sup>. Pharmacists can play a critical role in managing the medication therapy of patients at risk for

clinically important DDIs<sup>3</sup>. It is appropriate to focus on interactions between commonly used and/or commonly co prescribed drugs<sup>14</sup>.

A drug-drug interaction can be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or co administration of a second drug<sup>4</sup>. The most frequently involved drugs in potential DDIs include antithrombotic drugs, opioids, loop diuretics, ACE inhibitors, beta blockers, NSAIDs, corticosteroids, quinolone antibiotics, cardiac glycosides, thiazide diuretics, anesthetics, antidepressants, anticonvulsants and sedatives<sup>6</sup>. The risk of drug interactions increases exponentially with the number of drugs given to a patient<sup>5</sup>.

Drug interaction is frequently characterized either pharmacokinetic or pharmacodynamic<sup>7</sup>.

Pharmacokinetic interactions are those in which one drug alters the rate or extent of absorption, distribution, elimination, metabolism of another drug. This is most commonly measured by a change in one or more kinetic parameters, such as peak serum concentration-time curve, half-life, and total amount of drug excreted in urine, etc.<sup>8</sup>.

An important group of hepatic microsomal enzymes are the "mixed function oxidases", characterized by the cytochrome P450 isoenzymes. A drug that inhibits the CYP isozyme (eg, cimetidine, ciprofloxacin, propranolol, etc.), may decrease the metabolism and increase serum concentration of drugs that are substrates for that isozyme<sup>9</sup>. In most cases, the extent of drug interaction varies widely among individuals; this is likely dependent on interindividual differences in CYP3A4 tissue content, preexisting medical conditions and possibly, age. Interactions may occur under single dose conditions or only at steady state<sup>10</sup>. Although pharmacokinetic interactions often present challenging clinical problems and are publicized widely, pharmacodynamic interactions are the type that occurs most frequently<sup>9</sup>. The pharmacodynamic consequences may or may not closely follow pharmacokinetic changes<sup>10</sup>.

Interactions resulting from the use of two drugs with opposing effects should be among the easiest to detect. However, these are sometimes due to the secondary

effects of certain drugs and this and other factors may preclude early identification of such situations.

An excessive response attribute to the concurrent use of drugs having similar actions is the type of interaction that occurs most often and these potential problems warrant particular attention.

Drugs that differ considerably in their primary pharmacological actions may exhibit the same secondary effects. Some patients being treated with Antipsychotic agents such as Chlorpromazine are also given an Antiparkinson agent such as Trihexyphenidyl to control the Extrapyramidal effects of the form.

Several important drug interactions occur as a result of the ability of certain therapeutic agents to alter the concentration of electrolytes such as Potassium and Sodium. When these drugs are included in a therapeutic regimen, it is important that electrolyte concentrations are monitored periodically.

Hospitalized patients may be especially at risk, as they are more severely ill and multiple medications may be prescribed simultaneously<sup>15</sup>. The number of drugs taken per patient as well as the number of interactions per patient are higher during hospitalization than before admission (pre-admission), and fall back after the hospital stay (post-discharge), but not to the pre-admission level<sup>16</sup>.

The reduction of the risk of drug interactions is a challenge that embraces a number of considerations<sup>11</sup>. Although they could be applied to drug therapy in general, the following guidelines to reduce and manage drug interactions are offered to assist health professionals who have the responsibility of selecting and monitoring therapeutic regimens, identify the patient risk factors, take a thorough drug history, be knowledgeable about the actions of the drugs being used, consider therapeutic alternatives, avoid complex therapeutic regime when possible, educate the patient, monitor therapy, individualize therapy<sup>11</sup>.

Nowadays, the majority of patients receive more than one drug simultaneously. Since drug-drug interactions and side effects increase in a nonlinear fashion with the number of drugs administered, a drug, which might

interact with a commonly used co-medication, should be tested specifically and systematically in this regard before marketing. So far, no regulatory framework has precisely defined the requirements and the design of particular drug interaction studies<sup>12</sup>.

Many drugs which are used in current therapy have been able to influence many physiological systems.

There are many individuals who visit more than one physician and it is very common for a patient to be seen by one or more specialist in addition to a family physician and dentist. It is frequently difficult for one prescriber to be aware of all the medications that have been prescribed by others for a particular patient, and difficulties could arise from such situations.

Many of drug-drug interactions are involved in the concurrent use of a prescription drug with a non prescription drug or over the counter medicines (e.g., painkillers, aspirin, antacid, decongestants). Many patients do not take medicines in the manner as intended by the prescriber. Some have not received adequate instructions from the prescriber and the pharmacist regarding how and when to take their medication. The tendencies of some individuals to abuse or deliberately misuse drugs may also lead to an increased incidence of drug interaction. Many interactions that occur are undetected or unreported<sup>13</sup>.

#### **METHODOLOGY:**

The process involved the following steps:

- 1) Data collection.
- 2) Analysis of each prescription through micromedex software.

#### **1) DATA COLLECTION:**

A total of 448 prescriptions were collected from different patients who visit physician's clinics and retail pharmacies in the hospitals of Karachi, Pakistan, between Jan, 2009-Sep, 2009. A maximum of three prescriptions per physician were collected to avoid the duplication of prescriptions. Each prescription of the patients screened for the number of drug-drug interactions and was then copied and was assigned as a case number to maintain the confidentiality of physician as well as patient.

<b>Prescription Size (No. of drugs/Rx)</b>	<b>Number of prescriptions (n = 448)</b>
2	66
3	56
4	95
5	88
6	55
7	45
8	28
9	15

#### **INCLUSION CRITERIA:**

The patient's agreement to participate in the study aging between 18-70 years of both sexes and prescribed at least one OTC medications with other medicine of prescriptions having 02 or more than 02 medicines. The patient doesn't have permanent medical disability, which may hinder communication.

#### **2) Analysis of Each Prescription through Micromedex**

##### **HEALTHCARE SOFTWARE:**

To analyze the drug interaction, the following instructions would be followed as mentioned in **HELP** portion of micromedex software<sup>17</sup>.

Step 1: From the main page, click the **Drug Interactions** link, located below the **Use a tool** icon.

Step 2: On the Search page, click in the **Add Drug to Patient Profile:** field to activate it.

Step 3: In the **Add Drug to Patient Profile** field, type the brand or generic drug as the search term, such as *Tylenol*, or *Acetaminophen*.

Step 4: Click **SEARCH**.

Step 5: A dictionary list by route and form appears. Click the appropriate type and the system adds the drug to the patient profile.

**FOR SINGLE DRUG INTERACTIONS:**

For interaction information on a single drug: Click the **Single Drug Query** link located on the right side of the drug name.

**FOR MULTIPLE DRUG INTERACTIONS:**

To add additional drugs to the patient profile, repeat steps 2 through 5 until the patient drug profile is complete. To return to the Patient Drug Profile screen, press the **New Search** button. It may add or delete drugs and recalculate for interactions based on the new drug information. Click the Delete link beside the drug you wish to remove from the patient profile.

**DRUG INTERACTION FILTERS:**

The option of filtering interactions out of the calculation, based on the severity of the interaction and/or the type of documentation available for the interaction. The default setting are for all severities (Minor, Moderate and Major) and for all documentation types (Unlikely, Poor, Fair, Good, and Excellent). It may adjust results by selecting one of the drug interaction filters.

**CALCULATION OF DRUG INTERACTIONS:**

To calculate the drug interactions – click the **DISPLAY DRUG INTERACTIONS FOR PROFILE** button. The resulting page lists the interactions by category and ranks them from major to minor. Interactions are shown using generic drug names or drug classes. Click the link of the interaction for further details and information<sup>17</sup>.

**RESULT AND DISCUSSION:**

Considering the widespread usage of OTC drugs either self or prescribed, the overall incidence of serious drug-drug interactions increase in a non linear craze involving these medicines. Investigation of the clinically significance of OTC drug-drug interactions in out patients has not been reported significantly in Pakistan. The current research includes those drugs as OTC that was observed commonly in practice of dispensing without prescription in cultural society of Karachi, Pakistan. Similar kinds of studies have been conducted in out-

patient and in-patient settings internationally. The prospective review of the prescriptions was for drug-drug interaction which was developed by modifying various international studies. The present study was done by making a drug pair of OTC with prescribed drug in such a manner that the first one is considered as being an OTC as in Table (1).

The study revealed that the rate of drug-drug interactions of OTC with other prescribed drugs in outpatients is 16.8% overall. The present results of studies are lesser than the studies conducted internationally because in the current study only OTC and other medicines interactions are documented, instead of this if all interactions were documented then significantly higher interactions would be observed than the studies conducted internationally.

The study showed that in every second, prescription that is prescribed for any disease with OTC agents can have one drug-drug interaction, if the number of medications prescribed either 02 or greater than 02 (See in Table (3)). It has also been observed that every third prescription has a moderate drug-drug interaction that can lead to serious consequences also (see in table: (2)).

Classification of the drug-drug interaction on the basis of severity showed 3.64 % major interaction as shows in Table (2) that may be life-threatening and require medical intervention to minimize serious adverse effects, caused by 13 drug pairs in which Aspirin-Warfarin contributed 2.2%, and Aspirin-Citaloprim contributed 0.66%. Aspirin is the most widely used over-the-counter drug but its long term use leads to prolonged inhibition of blood coagulation by the effect on platelet activity (18, 19). The wide use of aspirin as over the counter drug depends on the local dispensing culture. It has been observed during the study that aspirin is also dispensed at general stores along with pharmacies, this leads to a habit of taking aspirin for common headaches and other pains by individuals. At high doses, aspirin has a direct hypoprothrombinemic effect<sup>20</sup>. Besides these, the current study has observed that aspirin and warfarin were prescribed concurrently, therefore the dosages should be individualized and parameters monitored (Prothrombin

Time (PT) or International Normalized Ratio (INR)) should be identified to assess efficacy and ensure safety<sup>21</sup>. The use of salicylates and warfarin is not completely in contraindication, but should be avoided whenever feasible, otherwise sodium salicylate, choline salicylate, salsalate, or magnesium salicylate would be a choice because of little effect on platelet function<sup>22</sup>. There is a burning need to teach people to avoid the use of aspirin for slight pains as much as possible.

The second major interaction analyzed between citalopram and aspirin (see Table. 1). Case-control and cohort studies have shown that the combined use of SSRIs and antiplatelet agents have been associated with an increased risk of bleeding. Bleeding events reported have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages. When an SSRI and an antiplatelet agent are given concurrently, monitor patient for signs of increased bleeding<sup>23</sup>. Aspirin with clopidogrel and ACE inhibitors were put in a rank of top large number of interactions as shown in Table (1). 77.03% of the interactions were classified as moderate interactions as shown in graph (1), caused by 275 drug pairs in which, Aspirin-ACE inhibitors/Clopidogrel, Ciprofloxacin-Zinc/Iron/Calcium and Ibuprofen-Lisinopril are noteworthy Table (1).

Aspirin inhibits the production of prostaglandins, including vasodilator and antithrombotic prostaglandins. The production of vasodilator prostaglandins may be an important counter-regulatory pathway in patients with heart failure. Angiotensin II can stimulate the production of vasodilator prostaglandins, and the use of Angiotensin Converting Enzyme (ACE) inhibitors could theoretically reduce renal prostaglandin synthesis. However, the overall effect of ACE inhibitors on prostaglandin synthesis and platelet aggregability remains controversial, and the data on the interaction between aspirin and ACE inhibitors is inconclusive<sup>24, 25</sup>. It's a present need to determine the optimal dose of aspirin with concomitant ACE inhibitors therapy and interaction occur either on hypertension or coronary artery disease, or heart failure patient<sup>26</sup>. Aspirin with Clopidogrel and ACE inhibitors were put in a ranking of top interactions

as described in Table (1).

It has been observed that usually patients were not aware of multivitamin or nutritional supplement interactions with other drugs. Self medication is an important issue in taking multivitamins. During counseling, patients complained about ineffective treatment of quinolones and upon investigation, it has been found they are taking that antibiotic with milk or juices considering it heavy medicines on the stomach while on the other hand quinolones are capable of forming chelate complexes with metal ions, including calcium, resulting in reduced bioavailability of the quinolone antibiotic<sup>27, 28, 29</sup> but bioavailability are less marked if a low dose of calcium carbonate or staggered administration is used. Therefore, ciprofloxacin should be taken two hours before or six hours after taking these products<sup>30</sup>. Interactions of ciprofloxacin with either calcium or iron are ranked the top largest number of interactions as shown in Table (1). Here there is a need for the physician to avert as much as possible to prescribe calcium supplement until fluoroquinolones are complete or provide patients with information about how to take these two drugs.

Most of the prescriptions have iron and ciprofloxacin administration at a time while it has been found that they significantly decrease the bioavailability of ciprofloxacin by 60%. Therefore, concurrent administration should be avoided (31) or think of decreasing iron temporarily or if possible, selecting another antibiotic or using an IV route for quinolone dosing but if combination is required, the quinolone should be given two hours before or four to six hours after iron dosing.

10.7% of interactions were minor as shown in graph: 1, caused by 15 drug pairs Table (2) in which 11% interaction was caused by Clopidogrel-Aspirin. In addition, of clopidogrel in patients treated with aspirin has decreased the incidence of in-stent thrombosis after percutaneous coronary interventions. There is a demand for reliable methods to measure the individual platelet inhibiting effect of this combination therapy<sup>32</sup>.

Classification of drug-drug interactions on the basis of onset of action reveals that 32% interactions were of rapid onset as shown in graph 2, which means that the

effect can be seen in 24 hours. As one third of the interactions were reported as rapid onset, so it's the responsibility of the physician and the pharmacist to closely monitor the prescription either after prescribing or dispensing the drug, respectively.

66 % of interactions were delayed onset as shown in graph 2 which means that the adverse drug event was expected after 24 hours of the administration of dose, some of these interactions can take a couple of weeks till the symptoms are obvious, and the remaining 2 % were not specified.

In this study, it has been observed that 3% of interactions were having excellent documentation as shown in graph 3 and there were controlled studies which have clearly established the existence of the interaction; 63% of interactions were of good documentation as shown in graph 3 and the literature strongly suggests the interaction exists, but well-controlled studies are lacking. Documentation of the remaining 34% interactions was fair as shown in graph 3 and the evidences were limited to the case reports having possibilities of some theoretical conflicts. One third of the interactions were found to be of fair documentation, there is a need for accurate documentations, however more than 50% of the documentation was found to be good, hence there is a need for more research for further evaluation.

Poly pharmacy is one of the considerable factors in the drug-drug interactions. The chance of interactions increases two folds with every increment of drug in the prescription. However, there was a decline in the drug-drug interactions observed in the prescriptions of patients who take more than ten drugs.

There was a direct relation between the number of drugs per prescription and the number of interactions. The probability of having at least one drug-drug interaction increases by 32% with every increment of a drug per prescription (see Table (3)). The relation between the number of drugs and interactions was not clearly established for the prescription which has more than ten drugs because of the limited sample size.

Limitations of the study include a small sample size which produced only 1505 drug pairs for the evaluation.

The results suggested that a large scale study should be conducted to analyze and verify the findings for the community at large. Other limitations include only selected diseases targeted and patient reservations to participate in the study.

130 drug pairs were identified to cause 514 drug-drug interactions out of which only top ten drug pairs were responsible to cause 50% of the identified drug-drug interactions like ibuprofen drug pairs as shown in Table (1). Ibuprofen is widely used in many countries for the relief of symptoms of pain, inflammation and fever. The evidence for the mode of action of ibuprofen is considered in relation to its actions in controlling inflammation, pain and fever, as well as the adverse effects of the drug. At low doses (800-1,200 mg day) which in many countries are approved for non-prescription sale, ibuprofen has a good safety profile comparable with paracetamol (33). Ibuprofen markedly blunts the effects of antihypertensive drugs. When Lisinopril is used in combination with ibuprofen, systolic BP elevated by 7.7-9.9 % (34). In the current research, the interaction of ibuprofen with lisinopril is also considered on top of interactions as shown in Table (1).

It was apparent that the reason of having such interactions was mostly lack of education about the drug-drug interaction. Healthcare professionals should be educated about these interactions and should be sensitized about the adverse drug effects produced by these interactions and how these can be prevented and managed.

Being a drug expert, the pharmacist is in a strategic position to detect and prevent drug interactions. By observing the preceding step and by strengthening communication with patients and other health professionals, the pharmacist has a valuable opportunity to make a significant contribution toward reducing the risk of drug-drug interactions and the further enhancement of the efficacy and safety of drug therapy.

#### **CONCLUSION:**

The current study was undertaken in order to raise the awareness of all health care professionals to avert the use

of multidrugs therapy as much as possible especially the unnecessary addition of multivitamins. Also, to educate the people to take a proper and most healthy natural diet. Aspirin has been found to be the most highly interactive

medicine. This study suggests steps to impede the use of common NSAIDS like aspirin and ibuprofen in minor pains and use them for other critical diseases.

**Table 1: Classification of 357 drug-drug interactions according to micromedex soft ware**

S.#	DRUG-DRUG INTERACTION	# of Rx	SEVERITY	ONSET	DOCUMENTATION
1	Aspirin -- citaloprim	3	Major	Not specified	Good
2	Aspirin -- Ramipril / Lisinopril / Captopril / Perindopril	33	Moderate	Rapid	Fair
3	Aspirin -Clopidogrel	27	Minor	Delayed	Fair
4	Aspirin -Furosemide	10	Moderate	Rapid	Good
5	Aspirin - Warfarin	10	Major	Delayed	Excellent
6	Aspirin -Glyburide	6	Moderate	Delayed	Good
7	Aspirin –Aluminum/Calcium / Magnesium	17	Moderate	Delayed	Fair
8	Aspirin -Verapamil	10	Moderate	Delayed	Good
9	Aspirin - Spironolactone	7	Moderate	Rapid	Fair
10	Aspirin -Insulin	6	Moderate	Delayed	Fair
11	Aspirin -- Nitroglycerin	4	Moderate	Rapid	Good
12	Aspirin -- Valproic Acid	4	Moderate	Delayed	Good
13	Iron -Omerprazole / Pantoprazol	20	Moderate	Rapid	Fair
14	Iron -Aluminum, Calcium Or Magnesium Containing Products	8	Minor	Delayed	Fair
15	Iron -Zinc	1	Moderate	Delayed	Excellent
16	Zinc/Iron/Calcium -Ciprofloxacin	19	Moderate	Rapid	Good
17	Aluminum/Calcium /Magnesium -Tetracycline	2	Moderate	Rapid	Good
18	Aluminum/Calcium /Magnesium -Ofloxacin/Levofloxacin	2	Moderate	Rapid	Fair
19	Acetaminopen – Phenytoin	6	Moderate	Delayed	Good
20	Calcium Carbonate -Thyroxine	1	Moderate	Delayed	Good
21	Calcium -Verapamil	1	Moderate	Rapid	Fair
22	Antacids -Propranolol	1	Moderate	Delayed	Good
23	Antacids -Digoxin	1	Moderate	Rapid	Good
24	Ibuprofen -Furosamide	19	Moderate	Delayed	Good

S.#	DRUG-DRUG INTERACTION	# of Rx	SEVERITY	ONSET	DOCUMENTATION
25	Ibuprofen – ofloxacin	15	Moderate	Delayed	Good
26	Ibuprofen– amlodipine	3	Moderate	Delayed	Good
27	Ibuprofen – Bisoprolol	17	Minor	Delayed	Good
28	Ibuprofen – captopril	15	Moderate	Rapid	Good
29	Ibuprofen – citalopram	5	Moderate	Delayed	Good
30	Ibuprofen – clopidogril	3	Moderate	Not specified	Good
31	Ibuprofen – glimepiride	15	Moderate	Delayed	Good
32	Ibuprofen – lisinopril	20	Moderate	Delayed	Good
33	Mefenamic acid -Magnesium hydroxide	1	Moderate	Rapid	Fair
34	Mefenamic acid -Furosamide	10	Moderate	Delayed	Good
35	Mefenamic acid – amlodipine	8	Moderate	Delayed	Good
36	Mefenamic acid -Atenolol	17	Minor	Delayed	Good
37	Diphenhydramine -Metoprolol	10	Moderate	Delayed	Good
	<b>Total</b>	<b>357</b>			

**Table 2: Quantitative analysis of 357 interactions of otc drugs with other prescribed drugs:**

Description	Sub description	No. of Cases	Total	Percentage
Severity*	Major	13	357	<b>3.6%</b>
	Moderate	275		<b>77.03%</b>
	Minor	69		<b>19.3%</b>
Onset*	Rapid	115	357	<b>32.2%</b>
	Delayed	236		<b>66.1%</b>
	Not specified	6		<b>1.6%</b>
Documentation*	Excellent	11	357	<b>3.0%</b>
	Good	224		<b>62.7%</b>
	Fair	122		<b>34.1%</b>

**\*Onset**

Rapid: adverse effects or any clinical conflicts probably occur within 24 hours of drug administration.

Delayed: adverse effects or any clinical conflicts probably do not occur within first 24 hours of drug administration.

**\*Severity**

Major: requires medical intercession to reduce or avert serious adverse effects otherwise it may be life threatening.

Moderate: the interaction requires a modification in therapy otherwise the interaction may result in an exacerbation of the patient's condition.

Minor: The interaction may have some degree of clinical effects. Symptoms may include an increase in the frequency or severity of side effects but generally would not necessitate a major change in therapy.

**\*Documentation:**

Excellent: the existence of the interaction has been clearly proven by controlled studies.

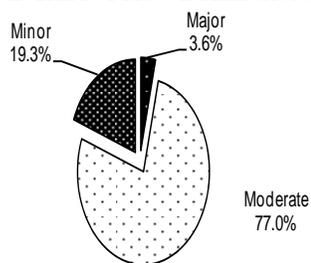
Good: Well-controlled studies are deficient to prove the existence of interaction but documentation strongly suggests the existence.

Fair: Pharmacological consideration leads clinicians to suspect the existing interaction otherwise the available documentation are deprived.<sup>17</sup>

**Table 3: # Of interactions with following breakup in 448 prescriptions:**

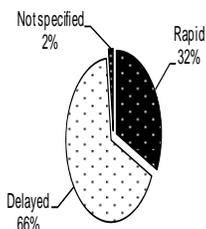
# OF PRESCRIPTION	# OF INTERACTIONS
130	01
157	02
70	03
91	00

**SEVERITY OF DRUG INTERACTIONS**



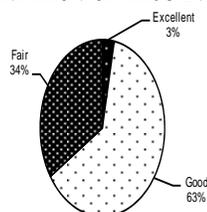
**GRAPH: 1**

ONSET OF DRUG INTERACTIONS



GRAPH: 2

DOCUMENTATION OF DRUG INTERACTIONS



GRAPH: 3

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