THE PHARMACIST'S ROLE IN PREVENTING MEDICATION ERRORS MADE BY
CARDIAC AND HYPERLIPOPROTEINEMIC OUTPATIENTS

by

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ABSTRACT

A study involving cardiac and hyperlipoproteinemic outpatients was carried out to determine whether medication compliance was affected by additional medication instruction provided by a pharmacist. Other investigations of possible compliance differences between cardiac and hyperlipoproteinemic instructed and uninstructed groups were also made, as were tests of independence among medication errors and medication knowledge, amount of formal education, and marital status of the cardiac and hyperlipoproteinemic samples.

Two samples of 14 cardiac and 20 hyperlipoproteinemic outpatients were each randomly divided into experimental and control groups. The experimental groups received instruction concerning the prescribed use of their medication by the investigator/pharmacist. The control groups did not receive instruction. A home interview, including pill count, was utilized in determining compliance.

Those groups which received instruction made fewer medication errors than the control groups which did not receive instruction. This difference in medication errors was significant for both cardiac and hyperlipoproteinemic outpatients.

The cardiac instructed group made more medication errors than the hyperlipoproteinemic instructed group. The cardiac uninstructed group also made more medication errors than the uninstructed

hyperlipoproteinemic group. This difference in medication errors between cardiac and hyperlipoproteinemic groups was significant.

Medication errors were independent of medication knowledge, amount of formal education, and marital status among the cardiac confined groups. Medication errors were also independent of medication knowledge and formal education among the hyperlipoproteinemic groups; however, dependence did exist between medication error and marital status among the hyperlipoproteinemic outpatients.

CHAPTER 1

INTRODUCTION

Chemotherapy is an important part of many patients' medical management. Specific biological and chemical agents are frequently prescribed by the physician based upon the needs of the patient. The therapeutic effectiveness of these agents initially depends upon their proper administration to the patient at specific intervals and in definite quantities.

This does not usually present a problem as far as the hospitalized patient is concerned. The physician prescribes, the pharmacist dispenses, and the nurse administers the medication. The patient is completely relieved of any responsibility for controlling his drug therapy. A serious problem may arise, however, in drug therapy for the outpatient. Again the physician prescribes and the pharmacist dispenses the medication, but here the similarity ends. The outpatient, in most cases, has the sole responsibility for administering his own medication. He is often provided instructions for taking the prescribed medication by the physician, and it is assumed he will follow the specified regimen.

Studies have shown, however, that the outpatient often omits taking the prescribed medication or takes it incorrectly. Wilcox, Gillian and Hare (1965), in analyzing the urine of psychiatric outpatients for the presence of promazine and/or imipramine metabolites,

found 48 percent of 125 outpatients not taking the medication as prescribed. Similarly, Bergman and Werner (1965) found a high percentage of non-compliance in 59 children receiving a ten-day regimen of oral penicillin. Pill count and urinalysis were employed to measure compliance. Their results showed that by the ninth day of therapy, 82 percent of the children had stopped taking the penicillin. Dixon, Stradling and Wooten (1957), in determining the frequency which tuberculous patients took PAS, also found a high rate of non-compliance. Of 151 outpatients taking PAS, only 50 percent gave a positive urine test for the presence of the drug. In a different approach for determining compliance, Watkins et al. (1967) observed diabetic patients administering insulin in their homes. This study found that 58 percent of 115 patients made dosage errors. An investigation by Nugent and associates (1965) into the toxicities of steroids when lengthening the interval between doses found non-compliance a serious problem. In their population of 28 arthritic patients, 25 percent were erring by more than 25 percent of the advised dose for more than half of the six-month observation period. Elderly, chronically ill outpatients were also guilty of misusing prescribed medication. Schwartz et al. (1962) interviewed 220 randomly selected elderly outpatients concerning their use of medication. The study found that 47 percent frequently omitted taking their medication.

These studies revealed that outpatients being treated for many different disorders with various medications frequently are unreliable in following a prescribed dosage regimen. Stewart and Cluff (1972) in

an article dealing with outpatient medication stated that there are indications that suggest non-compliance is becoming a major public health problem.

Several serious consequences may result from misusing prescription medication. First, by omitting or taking medication incorrectly, the patient's condition may deteriorate clinically (Roberts and Deuschle 1959). Evidence of this occurs when a resistant mycobacterium emerges in the tuberculous patient erring in self-administration of prophylactic INH. Similarly, the ambulant patient with a history of congestive heart failure by misusing prescribed digitalis preparations may require hospitalization for exacerbations of congestive heart failure or digitalis intoxication.

Self-treatment with accumulated prescription medication from previous illnesses is a second undesirable consequence. Patients often keep the remainder of unused medication for later use if the need arises (Wilcox et al. 1965). Not knowing the basic pharmacology of the medication nor the etiology of the present illness, the patient could actually be doing himself harm. There is also the possibility of the patient taking unused medicine concurrently with a new prescription which might be chemically or therapeutically incompatible.

A third consequence that may result from the patient misusing prescribed medication is the physician's loss of confidence in an otherwise effective drug regimen (Roberts and Deuschle 1959).

There have been a number of proposals as to why outpatients often omit taking prescribed medication, including forgetfulness, demographic

factors, undesirable side effects, psychological reasons, poor instructions and lack of medication knowledge. A number of studies have attempted to show that one or possibly a combination of these factors interfere with compliance. Forgetfulness was the most frequently cited reason in a study by Moulding (1961). To improve compliance, medication was attached to a calendar which was then suspended in a conspicuous place within the house. Yet, patients who were non-compliant admitted they had difficulty in remembering the medication. Berry, Ross and Deuschle (1963), in a study involving tuberculous patients, suggested reliability may be associated with marital status, age, education, and race. Undesirable side effects such as nausea, anorexia, diarrhea, or distaste appeared to have kept another group of tuberculous patients from taking their PAS regularly (Dixon et al. 1957). Psychological reasons have also been attributed to omittance. Davis (1967) stated in his study that the physician's instructions, no matter how simple, may cause some dissonance with the patient's life style which may result in his refusal to follow a specified regimen. Inadequate and/or confusing instructions by the physician have also been implicated (Korsch and Negrette 1972). Latiolais and Berry (1969), in their study of medication errors made by outpatients, found that the most prevalent reason for medication misuse, 33 percent of total errors, was due to the patient misunderstanding instructions. In another study by Curtis (1961) it was found that of the 16 patients making errors, only 37 percent had accurate knowledge of the purpose of the drug, while of the 10 patients with no errors, 60 percent knew the purpose of the medication.

Mohler, Wallin and Dreyfus' (1965) study in patient compliance and Griener's (1972) research in patient discharge planning support the assumption that if the patient is given the opportunity to understand the rationale behind the medication, and if explicit directions concerning methods of administration and dosage regimen are provided, compliance may increase.

The physician usually provides the patient with information concerning his medication when the prescription is written, yet it is not uncommon for the patient to misinterpret or quickly forget. Therefore, instructions should be given again when the prescription is filled and dispensed. This procedure could clarify any misunderstanding the patient may have concerning chemotherapy and would reinforce the need for explicit compliance to his prescribed medication regimen. The patient should receive this additional information from someone knowledgeable concerning the uses, side effects, dosages, and contraindication of drugs. Since the pharmacist possesses this knowledge and is capable of expanding his role into patient oriented activities, he seems the logical one to assume this function.

Purpose

This research attempted to determine if comprehensive instruction provided by a pharmacist concerning the proper use of prescribed medication to outpatients would decrease medication errors. The samples employed by this study consisted of cardiac and hyperlipoproteinemic outpatients from the Tucson Veterans' Administration Hospital. The following major hypothesis was investigated:

1. No difference in medication errors exists between groups of cardiac and hyperlipoproteinemic outpatients who received comprehensive instruction by a pharmacist and their respective control groups who do not receive such instruction.

Outpatients with different medical conditions receiving different medication may comply differently to prescribed drug regimens. The following two hypotheses were studied to determine if this was true and if instruction by a pharmacist affected compliance between groups:

2. No difference in medication errors exists between cardiac and hyperlipoproteinemic outpatients who do not receive instruction.

3. No difference in medication errors exists between cardiac and hyperlipoproteinemic outpatients who receive instruction.

It may be possible to identify characteristics of outpatients who tend to be unreliable. Consequently, the following hypotheses were instigated:

4. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups knowledge of the name or purpose of the medication.

5. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups formal education.

6. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups marital status.

Assumption

It was assumed that this study's outpatient samples erred in taking their prescribed medication. This assumption was based upon the findings of various studies reported in the literature during the past three decades which dealt with medication compliance and non-compliance.

Limitations

The pill count method for determining errors is open to objections since there is no means of determining if the patient disposed of the missing medication other than by the oral route.

The study samples do not represent a diversified socioeconomic population. Also as a result of restricting the study to the Veterans' Administration Hospital outpatient clinic, the samples are comprised mostly of men. Only one woman met this study's criteria enabling her to be included in the hyperlipoproteinemic sample.

The size of the samples are small because of the extreme difficulty of obtaining patients prescribed the same medication and dosage schedule.

Definitions

An error is defined as (1) an excess or deficit in the amount of medication remaining at the time of the home visit, and/or (2) concurrent administration of one or more discontinued prescription medications.

Comprehensive instruction is defined as a thorough explanation by the pharmacist/investigator concerning the name, intended use, proper dosage, and important precautions of each medication.

CHAPTER 2

DESIGN OF STUDY

This study employed a randomized, single factor design in testing the major hypothesis. Accordingly, definitive factors affecting the behavior of a defined and randomly selected experimental group were held constant. The experimental group was then subjected to instruction and the subsequent behavior of the experimental group was compared with that of a control group. Any difference in behavior was then attributed to the treatment.

This design required that the sample be approximately homogeneous (Hicks 1964). Therefore, the selection of a sample involved several considerations. The first decision was to eliminate variables in the number of medications, the kinds of medication, and various dosage schedules. Studies have shown that these factors are difficult to statistically compare. Vere (1965) found that the number of errors in taking medication increased as the total number of medications increased. Therefore, a patient taking one medication could not be compared with a patient taking more than one. Dixon et al. (1957) found that the type of medication is also an important variable, for one drug may cause a greater frequency of undesirable side effects than another. Consequently, a patient receiving a drug with many potential side effects may not comply as readily as one who receives a drug with few potential side

effects. Similarly, Clinite and Kabat (1969) found that a relationship existed between the number of doses and the chance for omission.

Therefore, a patient taking one dose daily could not be compared fairly with a patient taking four doses a day.

To avoid these variables it was decided to select patients based upon the medication they were prescribed. This led to a second consideration because few patients receive the same medication with the same instructions.

To secure a homogeneous sample, a hospital with a large, active outpatient clinic had to be selected as the site for this study. The Tucson Veterans' Administration Hospital was the only hospital in the city that could meet this criteria.

The cardiac clinic at the Veterans' Administration Hospital was the most active of the outpatient clinics. Consequently, cardiac patients were screened as a potential sample. Over 300 patient charts were reviewed to determine how many patients were receiving the same medication. Twenty-five patients were found to be taking digoxin, furosemide or hydrochlorothiazide, and potassium chloride or triamterene. These 25 cardiac patients were selected for this study. It was decided, however, to base the results on only the digoxin and the diuretic errors. The potassium supplement errors were not included because some patients received elixir KCl and others received triamterene. Since these two drugs were dispensed in different dosage forms, an accurate determination of compliance would have been difficult.

The 25 cardiac patients were randomly divided, by means of a random table, into a control group and an experimental group. Suspecting that a few patients might be dropped from the study, the investigator planned to base the results on a sample of 20 cardiac patients.

Patients with different medical conditions may react differently to instructions by a pharmacist. Therefore, a comparison of patients with two different conditions receiving different medication was attempted to provide a greater insight into the effects of medication instruction by a pharmacist. This necessitated the securing of a second sample of patients all taking similar medication. Again, the problem of locating a sample meeting certain criteria existed. Fortunately, a cardiologist and an endocrinologist at the Veterans' Administration Hospital, in conjunction with Merck, Sharp and Dohme Laboratories, were conducting a controlled, double blind, clinical study with an experimental agent, halefenate, and clofibrate. Their study involved about 45 patients with elevated serum cholesterol and/or triglyceride levels receiving either halefenate and a placebo, or clofibrate and a placebo. The placebos appeared to be active drugs, so it was impossible for either the physician or the patient to know which was the active drug and which was the placebo. If an emergency arose, the physician could have broken the seal on the medication label to determine which medication the patient was actually taking.

Since all these patients received the same medication in appearance and dosage, it was decided to include this second sample in this study. To enable a comparison with the cardiac patients, 25

randomly selected hyperlipoproteinemic patients taking the two drugs were randomly divided into control and experimental groups. Again, suspecting that a few patients might be dropped from the study, the results were based on a sample population of 20 hyperlipoproteinemic patients.

Methodology

The cardiac clinic was held every Tuesday afternoon from 1:00 p.m. until all the patients were seen. The length of the clinic varied, depending upon the number of cardiologists, residents, interns and students present. It seldom lasted beyond 4:30 p.m. The number of patients attending the clinic usually varied between 25 and 35. The investigator, having selected the sample earlier, knew when each patient in the study sample would visit the clinic. Usually no more than four patients in the study were scheduled to attend the same clinic.

The lipid clinic was held every Wednesday morning from 7:30 a.m. to 8:30 a.m. This clinic was much smaller, seldom more than eight patients attended each week, yet because it was a double blind, clinical study with all patients receiving the same medication, the investigator usually secured four patients at each clinic.

All cardiac and hyperlipoproteinemic patients included in this research were initially seen by the investigator just before the clinic began. The patient's name was called by either the investigator or the outpatient nurse. The patient was directed into an examining room. Inside the room the investigator introduced himself as a pharmacist and a graduate student. The investigator then explained that he was involved in research and would like to visit the patient at his home in 20 days.

Details were avoided in asking the patients' permission for a home visit so as to prevent them from suspecting a followup of some type. This precaution was probably not necessary because few patients questioned the home visit. Twenty days following the clinic visit was arbitrarily chosen as the time for the followup interview. This amount of time enabled the patients to misuse their medication if they were so inclined.

During the initial clinic interview, those patients assigned to the groups not receiving instruction were asked if they were taking the medication they received at their last clinic visit. Those patients in the cardiac group not receiving instruction were told to have their prescriptions filled and to take only the newly filled medication. The Veterans' Administration Hospital Pharmacy dispenses only a 30-day supply of medication which is prepacked. This provided the investigator an easy assessment of how much medication each patient received. Patients in the lipid group not receiving instruction were given a new month's supply of medication at this initial interview. This medication had been precounted by Merck, Sharp and Dohme Laboratories which again provided easy assessment.

During the initial clinic interview, those patients assigned to the groups receiving instruction were asked to return to the investigator after seeing the physician and before leaving the hospital. After each patient in the cardiac instructed group saw a physician, the investigator took the patient's prescriptions to the pharmacy to be filled. Each patient was instructed to wait in the outpatient area until the investigator returned with the medication. The investigator usually spent between five and ten minutes filling the prescriptions. Patients in the lipid

instructed group did not have to wait for their prescriptions to be filled after seeing the physician. The medication for the hyperlipoproteinemic patients had been labeled the previous night and was taken to the outpatient clinic before the clinic began.

With the medication in hand, the investigator again summoned each patient to be instructed to the examining room. The investigator took each medication separately, displayed the medication so that the patient could see the size, shape and color, then proceeded to instruct the patient in the proper use. Each medication was dealt with similarly. Appendix A outlines the procedure provided each patient for each medication. This procedure however was only a guideline because the investigator found early in the study that instructions had to be individualized for each patient, depending upon the patient's depth of understanding. Generally, a positive approach to counseling each patient was employed. For instance, cardiac patients were told that if they took their medications as prescribed they may stay well and remain out of the hospital.

Twenty days following the clinic visit, each patient was seen at his home. Upon entering the home, the investigator asked to be shown all the medication the patient was taking and where it was kept. This procedure was followed to determine if the patient was taking medication other than that which was prescribed. A structured interview (see Appendix B) was then closely followed in collecting data. Toward the end of the interview, the investigator counted the remaining prescription medication with an Abbott pill tray.

Twenty-five patients in each of the two samples were interviewed at home. Eleven of the 25 patients in the cardiac population were eliminated from the study for the following reasons. Two patients were found to be taking other prescription medication from a physician not associated with the Veterans' Administration Hospital. Three patients had been taking the same medication from two different containers. This prevented an accurate determination of the amount of medication taken in the 20-day period. The remaining six patients were eliminated because their dosage regimens were changed during the clinic visit. Five patients in the hyperlipoproteinemic group were eliminated because they were taking other medication prescribed by private physicians. The remaining cardiac and hyperlipoproteinemic samples as a result consisted of 34 patients; seven cardiac and ten hyperlipoproteinemic patients in each uninstructed and instructed group.

CHAPTER 3

RESULTS AND DISCUSSION OF DATA

The data compiled for each patient was analyzed to determine if further instruction provided by a pharmacist had increased compliance. Analysis was also done to determine if patients with different medical conditions complied differently. Other variables analyzed in relation to compliance were knowledge of the medication, amount of formal education, and marital status.

Compliance in this study was determined by comparing the amount of medication remaining at the end of 20 days to the amount that should be remaining if the medication was taken as prescribed. Each dose in excess or missed was tabulated as an error. For instance, a patient in the hyperlipoproteinemic group receiving one dose of halefenate daily and two doses of clofibrate daily could have made a maximum of 60 errors in a 20-day period if neither of the drugs were taken. If there was an excess of medication remaining it was assumed the patient took less than the prescribed dose or omitted doses completely. Similarly, if there was a shortage of medication remaining it was assumed the patient took more medication than what was prescribed.

No attempt was made to measure the time interval between doses of medication or to consider the timing sequence of doses an error.

The only possible assessment of this parameter would have to come from the patient. Joyce (1962) stated that the patient's assessment alone is notoriously unreliable. Similarly, Gordis, Markowitz, and Lilienfield (1969) in a study evaluating compliance based on histories given by the patient compared with a urinalysis for the presence of the drug, found a very large discrepancy. In the group of patients studied, 69 to 73 percent would be considered compliers based on histories, but only 33 to 42 percent were compliers based on the urinalysis. In view of this research, obtaining reliable data would have been very difficult among this study's ambulant patients. Therefore, the use of this parameter was precluded.

The definition of an error in this study also included prescription medication that had been discontinued by the physician but was still being taken by the patient. During the collection of data none of the patients interviewed admitted to taking other prescription medication nor did the investigator see other prescribed medication when shown where the medication was kept in the house. It was assumed from these findings that the use of discontinued prescription medication did not occur in this study.

This type of drug misuse does exist, however. Malahy (1966) found 13 discontinued medication errors among her sample of 40 patients having diversified medical problems. One patient had continued to take an oral hypoglycemic agent unknown by the attending resident. Another patient suffering from gastrointestinal disturbances was taking prescribed aspirin for his arthritis without the knowledge of the

attending physician. Latiolais and Berry (1969) in their study of medication misuse also found this to be a problem. Discontinued medication accounted for eight of 105 total errors among a cross section of 180 indigent patients.

Analysis of Errors

In tabulating errors the cardiac uninstructed group was labeled I and the cardiac instructed group was labeled II for easy identification. The hyperlipoproteinemic sample was similarly comprised of two groups and were labeled III, uninstructed group and IV, instructed group. Data obtained during the home interview appears in Tables 1 through 4.

The seven patients in group I misused digoxin 35.7 percent or 50 of 140 total doses. Errors involving the diuretic were also high in this group. The seven patients erred on 36.4 percent of the doses, or misused 51 of 140 total doses. Combined misuse of the digoxin and the diuretic was 36 percent, or 101 of 280 doses. Only one patient in group I was found to have complied perfectly.

In contrast, the seven instructed patients in group II erred 7.9 percent, or misused 11 of 140 total doses of the digoxin. Errors involving the diuretic were nearly as low. These seven patients erred 8.6 percent, or 12 of 140 total doses. Combined, group II had an error rate of 8.2 percent or misused 23 of 280 doses. Four of the seven patients in this group had perfect compliance.

The hyperlipoproteinemic sample results were not as definitive as those of the cardiac sample, yet differences seemed to exist between

Table 1. Medication Errors, Knowledge, Education and Marital Status of Uninstructed Cardiac Outpatients (Group I).

Patient	Digoxin		Diuretic		Total		Knowledge	Education (years)	Marital Status
	Errors	Percent	Errors	Percent	Errors	Percent			
1	20	100	20	100	40	100	yes	11	yes
2	0	0	0	0	0	0	yes	12	yes
3	2	10	3	15	5	12.5	yes	14	yes
4	3	15	3	15	6	15	yes	0	no
5	20	100	0	0	20	50	no	4	yes
6	5	25	5	25	10	25	yes	6	yes
7	0	0	20	100	20	50	yes	12	no
	50	35.7	51	36.4	101	36			

Table 2. Medication Errors, Knowledge, Education and Marital Status of Instructed Cardiac Outpatients (Group II).

Patient	Digoxin		Diuretic		Total		Knowledge	Education (years)	Marital Status
	Errors	Percent	Errors	Percent	Errors	Percent			
8	0	0	0	0	0	0	no	0	yes
9	2	10	2	10	4	12	yes	12	yes
10	0	0	0	0	0	0	yes	8	yes
11	3	15	3	15	6	15	yes	12	yes
12	6	30	7	35	13	32.5	yes	0	yes
13	0	0	0	0	0	0	yes	14	yes
14	0	0	0	0	0	0	yes	11	yes
	11	7.9	12	8.6	23	8.2			

Table 3. Medication Errors, Knowledge, Education and Marital Status of Uninstructed Hyperlipoproteinemic Outpatients (Group III).

Patient	Halepenate		Clofibrate		Total		Knowledge	Education (years)	Marital Status
	Errors	Percent	Errors	Percent	Errors	Percent			
15	1	5	3	7.5	4	6.7	no	7	no
16	1	5	3	7.5	4	6.7	yes	13	yes
17	4	20	9	22.5	13	21.7	yes	12	no
18	1	5	2	5	3	5	yes	8	no
19	0	0	2	5	2	3.3	yes	12	no
20	1	5	3	7.5	4	6.7	yes	13	yes
21	1	5	0	0	1	1.7	yes	10	yes
22	3	15	5	12.5	8	13.3	yes	7	yes
23	0	0	5	12.5	5	8.3	yes	2	no
24	1	5	20	50	21	35	yes	20	yes
	13	6.5	52	13	65	10.8			

Table 4. Medication Errors, Knowledge, Education and Marital Status of Instructed Hyperlipoproteinemic Outpatients (Group IV).

Patient	Halepenate		Clofibrate		Total		Knowledge	Education (years)	Marital Status
	Errors	Percent	Errors	Percent	Errors	Percent			
25	1	5	2	5	3	5	yes	12	no
26	1	5	2	5	3	5	yes	15	yes
27	1	5	3	7.5	4	6.7	yes	12	no
28	2	10	3	7.5	5	8.3	yes	14	yes
29	0	0	0	0	0	0	yes	11	yes
30	3	15	5	12.5	8	13.3	yes	10	no
31	0	0	0	0	0	0	yes	15	yes
32	2	10	1	2.5	3	5	yes	8	no
33	0	0	0	0	0	0	yes	16	yes
34	0	0	0	0	0	0	yes	4	yes
	10	5	16	4	26	4.3			

groups. Group III erred in the dosage of halefenate 6.5 percent, or 13 of 200 total doses were misused. The misuse rate of clofibrate was somewhat higher with a 13 percent error rate, or 52 of 400 total doses. These two drugs combined accounted for 10.8 percent of errors or 65 of 600 doses. Every patient in this group erred one or more times. Group IV appeared to have done better. Halefenate errors amounted to five percent, or 10 of 200 doses. Clofibrate errors were even less. The ten patients erred four percent, or 16 of 400 total doses. The total errors of group IV combined revealed a misuse rate of 4.3 percent, or 26 of 600 doses. Four patients in this group had perfect compliance.

Statistical analysis was applied to these results in testing the first hypothesis: no difference exists between cardiac and hyperlipoproteinemic groups who receive instruction by a pharmacist and their respective control groups who do not receive such instruction. The Mann-Whitney U test was used to test the hypothesis at the five percent level.

The results, as shown in Tables 5 and 6, permit rejection of the first hypothesis. In the cardiac sample, a U of 11 or less would be significant at the five percent level. A U of 9.5 was obtained between these groups. A U of 27 or less was required for significance at the five percent level between the hyperlipoproteinemic groups. A U of 26 was obtained.

These results show that both cardiac and hyperlipoproteinemic groups who received instruction by the pharmacist/investigator made significantly fewer errors at the five percent level than their respective control groups who did not receive such instruction.

Table 5. Mann-Whitney U Test for Two Groups of Cardiac Patients.

GROUP I			GROUP II		
Patient N_1	Total Errors	Rank 1	Patient N_2	Total Errors	Rank II
1	40	14	12	13	11
5	20	12.5	11	6	8.5
7	20	12.5	9	4	6
6	10	10	8	0	3
4	6	8.5	10	0	3
3	5	7	13	0	3
2	0	3	14	0	3
7	101	67.5	7	23	37.5

$$U = N_1 N_2 + \frac{N_1 + 1}{2} - \sum R_1$$

$$U = 9.5$$

Table 6. Mann-Whitney U Test for Hyperlipoproteinemic Patients.

GROUP III			GROUP IV		
Patient N_1	Total Errors	Rank 1	Patient N_2	Total Errors	Rank II
24	21	20	30	8	17.5
4	13	19	28	5	15.5
22	8	17.5	27	4	12.5
23	5	15.5	25	3	8.5
15	4	12.5	26	3	8.5
16	4	12.5	32	3	8.5
20	4	12.5	29	0	2.5
18	3	8.5	31	0	2.5
19	2	6	33	0	2.5
21	1	5	34	0	2.5
10	65	129	10	26	81

$$U = N_1 N_2 + \frac{N_1 + 1}{2} - \sum R_1$$

$$U = 26$$

The difference in the number of errors committed among groups I and II might be partially attributed to three patients in group I. Patient 1 failed to have any prescriptions filled during his clinic visit. He had not been taking the daily doses of digoxin or the diuretic and therefore was assigned a total of forty errors. This patient stated he was feeling well and "did not need the medication now." He retained the written prescriptions, however, to be filled at a later date if he felt a need for them.

Patient 7 took the digoxin as prescribed, but failed to have the diuretic filled, thereby receiving 20 errors. This patient lived 50 miles from Tucson and often had his prescriptions filled at a local pharmacy near his home. This was his usual procedure because the restricted bus schedule to and from the clinic did not permit enough time for him to have the prescriptions filled at the hospital pharmacy. The convenience of the local pharmacy cost this patient the price of the prescriptions. He knew the digoxin was "important for my heart" and therefore paid for it, but refused to have the other prescriptions filled because of financial reasons. This patient had not been informed that the hospital pharmacy mails medication to veterans who have difficulty in coming to the hospital.

Patient 5 had the prescriptions filled at the hospital pharmacy but failed to take the digoxin and therefore received 20 errors. When asked about the digoxin during the home interview, this patient could not remember taking such a drug. A five-minute search through a kitchen shelf containing between 40 and 50 old prescription containers partially

filled with discontinued medication revealed the full bottle of digoxin. Apparently this patient's wife had stored the digoxin with her medication on the kitchen shelf. Perhaps because this patient did not know why he was given the digoxin, he quickly forgot he was told to take it.

Group II seemed to be free of any major errors. The investigator saw each patient following their appointment with the physician and personally filled their prescriptions. This procedure prevented any of the instructed patients from leaving the clinic without their prescribed medication. Each patient in group II was also given instruction beyond that which is usually given by the physician. Consequently, emphasis placed upon the importance of observing the prescribed regimen at the time the medication was dispensed appears to have resulted in greater compliance.

Non-compliance among the hyperlipoproteinemic sample was extremely low if compared with this study's cardiac population or with other compliance studies cited in the literature (Wilcox et al. 1965, Bergman and Werner 1965, Watkins et al. 1967). This high compliance rate possibly could have been attributed to the design of the double blind study being conducted by Merck, Sharp and Dohme. Each patient admitted to the Merck, Sharp and Dohme study received a thorough physical examination and an extensive interview by one of the two physicians collecting the clinical data for the research. These patients also received explicit explanations concerning their medical condition and the purpose of the medication they were prescribed. Emphasis was placed upon the

importance of taking the medication, and each patient was told to return the medication containers to each monthly clinic visit for replacement. Increased compliance may have been a result of these factors in this specialized research. Interestingly, however, those patients who received additional reinforcement concerning their prescribed medication regimen from the pharmacist/investigator appeared to have an even higher rate of compliance than those patients who did not receive the additional instruction.

Patients with different medical conditions receiving different medication may comply differently to their prescribed regimens. The second hypothesis was formulated to determine if there was a difference between this study's groups of cardiac and hyperlipoproteinemic patients. In making an appropriate statistical test the dosage regimen of each of the two samples had to be considered. Since each hyperlipoproteinemic patient had the potential of making 20 more errors than each cardiac patient, a proportional analysis was chosen. The z-test for significance of the difference between proportions was employed to test the second hypothesis, which stated that no difference in medication errors exists between cardiac and hyperlipoproteinemic outpatients who do not receive instruction. This hypothesis was rejected at the five percent level. A z of 1.64 or greater was required for rejection of this hypothesis. Since the z equaled 9, the two uninstructed groups differed significantly in errors. The cardiac group erred more frequently.

A test of significance was also formulated to determine if the two instructed groups complied differently. The third hypothesis stated that no difference in medication errors exists between cardiac and

hyperlipoproteinemic outpatients who receive instruction. The many factors affecting compliance of the uninstructed groups should obviously have had similar effects upon the instructed groups. Instruction provided by the investigator/pharmacist however was individualized for each patient. Consequently, the social, psychological, and physiological factors stated by Davis (1967) might have been equalized to some extent by the instruction. The following two examples will clarify this point. Patient 8, in addition to being partially blind, had received no formal education. When asked by the investigator to read the labels on the prescription containers during the clinic interview, this patient stated that the print was too small. Very little time was spent with this patient instructing him in the rationale for taking the medication. Instead, the investigator stressed the need for taking the medication as prescribed to stay well. This patient was also given a 4 x 8 inch note card upon which was written the following simplistic instructions in large printed letters: TAKE ONE PILL ORALLY FROM EACH CONTAINER EVERY MORNING. The home visit pill count revealed perfect compliance. At the other extreme, Patient 33 had a college education and enjoyed relatively good health. He experienced no difficulty in reading or understanding the directions written on the prescription label. Consequently, a greater amount of time was spent by the investigator explaining the rationale for taking the medication. The followup visit to this patient's home also revealed perfect compliance.

To determine if the instruction provided by the investigator/pharmacist affected errors in the two instructed groups, the z test between proportions was again employed. An obtained z of 2.44 allowed

the third hypothesis to be rejected at the five percent level, since the z required for significance was 1.64 or greater. The two instructed groups erred differently. Instructed cardiac outpatients made more medication errors than the instructed hyperlipoproteinemic outpatients. A cardiac uninstructed and instructed group made more errors than the hyperlipoproteinemic uninstructed and instructed groups. These results might be attributed to the Merck, Sharp and Dohme hyperlipoproteinemic study or possibly to human nature. Davis (1967) in research involving noncompliant behavior, stated compliance depends upon various sociological, psychological, and physiological factors. These factors include physician-patient relationship, outside influence by friends, attitudes toward work and health, and the severity and longevity of the medical condition. It is apparent that with these factors affecting compliance, two patients seeing the same physician, with basically the same disease, and receiving the same medication, may comply differently. Therefore, it is not at all surprising that compliance varied between this study's instructed and uninstructed cardiac and hyperlipoproteinemic groups of patients seeing different physicians and receiving different medication.

Fox (1958) in a study dealing with self-administration of drugs stated that "very little is known of the motives which impel a patient to take medicine and the best way to get him to do so." Since 1958, many compliance studies have tried to identify and characterize the unreliable patient by discovering relationships between the noncomplier and socioeconomic factors. These factors have included race, sex, education, age, income, urban or rural residence, knowledge of the

prescribed medication, and marital status. Unfortunately, the results of much of the research has been conflicting. In a study involving 122 tuberculous patients, Moulding, Onstad and Sbarbaro (1970) found a relationship between fewer errors and higher education and income. In a similar study involving 26 tuberculous patients, Berry et al. (1963) reported that there were no significant correlations between medication errors and income, race, marital status, or urban or rural residence. Other studies dealing with different medical conditions were also unable to find relationships. Wilcox et al. (1965) found no association between errors made by 125 psychiatric outpatients and age, sex, intelligence, or side effects. Similarly, Roth and Berger's (1960) study of patient cooperation in ulcer treatment found no correlation between the amount of antacid taken and age, symptoms, or length of disease.

In light of the previous research, this study nevertheless attempted to find an association between medication errors and medication knowledge, formal education, and marital status among the cardiac and hyperlipoproteinemic patients. Other factors such as race, age, sex, and income were not included because this study's limited samples and relative homogeneity would have prevented firm conclusions from being drawn. These factors are, however, important in the possible identification of noncompliant patients.

In this study, patients who knew the very basic reason for taking the medication they were prescribed were considered to possess medication knowledge. Each patient was required to know the name of the medication or the general purpose of the drug. For example, a

cardiac patient who was taking a "heart pill to strengthen my heart" and a "water pill to get rid of extra water" was considered knowledgeable. Similarly, a hyperlipoproteinemic patient who stated the medication he was taking "eliminated the fats from my blood" or for the "fats that thicken my blood" was also considered knowledgeable. Those patients who did not possess the very basic understanding, or were completely wrong in stating the medication purpose or name were not considered knowledgeable.

In determining if medication errors were independent of medication knowledge, patients in the cardiac and hyperlipoproteinemic samples were each divided into two groups; those who made a high number of errors and those who made a low number of errors. Patients who made two or more errors were placed in the high error category. Patients making less than two errors were placed in the low error category. These error frequencies were then placed in a 2 x 2 contingency table according to medication errors and knowledge, as shown in Table 7.

The fourth hypothesis stated that medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups knowledge of the name or purpose of the medication. Values calculated by the Fisher Exact Probability Test as shown in Appendix C reveals that with the marginal totals for the combined cardiac groups in Table 7 of 9 and 5, and with $A = 8$, the observed $C = 4$ is too large for rejection of the hypothesis. Appendix C also reveals that with the marginal totals for the hyperlipoproteinemic combined groups in Table 7 of 15 and 5, and with $A = 14$, the observed $C = 5$ is too large for rejection of the hypothesis. Consequently, the hypothesis for

Table 7. Medication Errors and Medication Knowledge of Cardiac and Hyperlipoproteinemic Outpatients.

<u>Errors</u>	CARDIAC OUTPATIENTS			<u>Errors</u>	HYPERLIPOPROTEINEMIC OUTPATIENTS		
	Informed	Uninformed			Informed	Uninformed	
High	8	1	9	High	14	1	15
Low	4	1	5	Low	5	0	5
	12	2	14		19	1	20

both cardiac and hyperlipoproteinemic outpatients was accepted at the 5 percent level. Medication errors were independent of medication knowledge in both cardiac and hyperlipoproteinemic combined groups.

These results may reflect the liberal criteria used by this study in determining knowledge. Only two of the 14 cardiac outpatients lacked basic understanding of the prescribed medication they received. Similarly, only one of the 20 hyperlipoproteinemic patients lacked understanding. Possibly more stringent criteria would have resulted in an association between errors and knowledge. Marsh and Pearlman (1972) found a very strong relationship between understanding the disease and compliance of 60 patients with congestive heart failure. Their criteria for understanding were rather sophisticated in relation to this study's definition. Patients who understood their disease in the Marsh and Pearlman study tended to take their medication significantly more frequent than those patients who lacked understanding.

Formal education was another variable this study attempted to associate with medication errors. The previous division of patient medication errors into high and low was again employed. Formal education

was divided into two categories; 0 to 8 years, and 9 to 20 years. A contingency table was again utilized as shown in Table 8.

Table 8. Medication Errors and Formal Education of Cardiac and Hyperlipoproteinemic Outpatients.

<u>Errors</u>	CARDIAC OUTPATIENTS Education in Years			<u>Errors</u>	HYPERLIPOPROTEINEMIC OUTPATIENTS Education in Years		
	0-8	9-20			0-8	9-20	
High	3	6	9	High	5	10	15
Low	1	4	5	Low	1	4	5
	4	10	14		6	14	20

The fifth hypothesis stated that medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups formal education. Values calculated by the Fisher Exact Probability Test as shown in Appendix C reveals that with the marginal totals for the cardiac combined groups in Table 8 of 9 and 5, and with $B = 6$, the observed $D = 4$ is too large for rejection of the hypothesis. Appendix C also reveals that with the marginal totals for the hyperlipoproteinemic in Table 8 of 15 and 5, and with $B = 10$, the observed $D = 4$ is too large for rejection of the hypothesis. Consequently, the hypothesis was accepted at the 5 percent level. Medication errors were independent of formal education in both cardiac and hyperlipoproteinemic combined groups.

A 2×2 contingency table and the Fisher Exact Test were used in determining if an association existed between errors and marital

status. The previous division of errors into high and low categories was also applied as shown in Table 9.

Table 9. Medication Errors and Marital Status of Cardiac and Hyperlipoproteinemic Outpatients.

<u>Errors</u>	CARDIAC OUTPATIENTS			<u>Errors</u>	HYPERLIPOPROTEINEMIC OUTPATIENTS		
	Married	Single			Married	Single	
High	7	2	9	High	6	9	15
Low	5	0	5	Low	5	0	5
	12	2	14		11	9	20

The sixth hypothesis stated that medication errors are independent of (a) the combined hyperlipoproteinemic groups, and (b) the combined hyperlipoproteinemic groups marital status. Values calculated by the Fisher Exact Probability Test as shown in Appendix C reveals that with the marginal totals for the cardiac combined groups in Table 9 of 9 and 5, and with $A = 7$, the observed $C = 5$ is too large for rejection of the hypothesis. Consequently, the hypothesis was accepted for the cardiac combined groups at the five percent level. Medication errors were independent of marital status for the cardiac groups. This results, however, suggests an interesting point. The two single cardiac patients made only high errors, whereas five of the twelve married patients made low errors.

These findings tend to correspond with the Berry et al. (1963) results. In their study dealing with tuberculous patients a nonsignificant relationship was found between errors and marital status. Of the four

single patients in their study, all had negative urine specimens when tested for the presence of INH.

The sixth hypothesis for the hyperlipoproteinemic combined groups was rejected at the five percent level. Values calculated by the Fisher Exact Probability Test as shown in Appendix C permits rejection since the marginal totals for the hyperlipoproteinemic combined groups in Table 9 of 15 and 5, and $B = 9$, and the observed $D = 0$ is equal to the calculated level of significance. Medication errors were dependent of marital status for the hyperlipoproteinemic groups.

CHAPTER 4

SUMMARY AND CONCLUSIONS

Summary

Results of clinical research in the area of outpatient medication compliance is in agreement that prescribed medication often was not taken or taken incorrectly. This degree of non-compliance, however, varied from study to study, depending upon the criteria employed in defining compliance and the types of medical patients studied. Nevertheless, non-compliance in these studies was high. The percentage of medication errors among patients in the various sample populations ranged from 25 to 80 percent.

One of the most common reasons for non-compliance was related to the lack of understanding by the patient concerning his medication and disease. A number of studies found that compliance increased when greater emphasis was placed upon the importance of the patient's medication regimen. The physician often provides instruction concerning the patient's medication regimen, yet it is not uncommon for the patient to forget or misinterpret the instructions. Therefore, compliance might increase if reinforcement of the prescribed regimen is provided when the medication is dispensed. Since the pharmacist usually dispenses the prescribed medication, he should utilize his drug knowledge in providing this service.

In view of the previous research, this study was undertaken to evaluate the effects which further instruction in the proper use of medication provided by a pharmacist might have upon compliance. Two relatively homogeneous samples were obtained from the Veterans' Administration Hospital in Tucson. One sample was comprised of 14 cardiac patients receiving digoxin, a diuretic, and a potassium supplement. The second sample was comprised of 20 hyperlipoproteinemic outpatients receiving either clofibrate and a haldenate placebo, or haldenate and a clofibrate placebo. These two samples were each randomly divided into control and experimental groups. The two control groups were seen in the outpatient clinic without any change in the regular routine. The experimental groups were subjected to one change in their routine clinic visit; instruction was given in the proper use of their medication by the investigator/pharmacist. Twenty days following the clinic appointment, the investigator visited each patient at home. A structured interview was followed and a pill count assessment made in collecting data.

The following hypothesis was tested to determine if compliance was affected by instruction in this study's samples.

1. No difference in medication errors exists between groups of cardiac and hyperlipoproteinemic outpatients who receive comprehensive instruction by a pharmacist and their respective control groups who do not receive such instruction.

This hypothesis was rejected at the five percent level. There was a significant difference in errors among cardiac and

hyperlipoproteinemic uninstructed and instructed groups. The instructed patients made significantly fewer errors than their respective uninstructed groups.

Patients with different medical conditions receiving different medication may comply differently to prescribed drug regimens. The following two hypotheses were tested to determine if this was true and if instruction by a pharmacist affected compliance between groups.

2. No difference in medication errors exists between cardiac and hyperlipoproteinemic outpatients who do not receive instruction.

3. No difference in medication errors exists between cardiac and hyperlipoproteinemic outpatients who receive instruction.

These two hypothesis were rejected at the five percent level. Errors between uninstructed groups were significantly different. The cardiac uninstructed group made more errors than the hyperlipoproteinemic uninstructed group. There was also the same significant difference in errors between instructed cardiac groups.

Non-compliance may be due to a number of variables. By determining what these factors are, patients who exhibit these traits could be identified as potential non-compliers. A greater effort could then be directed toward these patients to increase their compliance. The following three hypotheses were tested to determine if various factors were independent of medication errors.

4. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups knowledge of the name or purpose of the medication.

5. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups formal education.

6. Medication errors are independent of (a) the combined cardiac groups, and (b) the combined hyperlipoproteinemic groups knowledge of the name or purpose of the medication.

Hypotheses 4 and 5 were accepted at the five percent level.

Medication errors were independent of the medication knowledge and formal education. Hypothesis 6 for the cardiac combined groups was also accepted at the five percent level. Medication errors made by the cardiac outpatients were independent of their marital status. Hypothesis 6 for the hyperlipoproteinemic sample was rejected at the five percent level. Dependence existed between medication errors and marital status among these patients.

Conclusions

Despite the small number of outpatients in this study, the major hypothesis which stated that no difference in medication errors exists between groups of cardiac and hyperlipoproteinemic outpatients who receive comprehensive instruction by a pharmacist and their respective control groups who do not receive such instruction, was rejected at the five percent level. Those patients who received instruction by the investigator/pharmacist made fewer errors than those patients who did not receive instruction. The results of this study reinforce the concept which expresses the need for clinically oriented pharmacists to provide drug information services directly to the patient.

As shown by this investigation, the pharmacist can contribute to reducing medication errors by working with the physician in providing drug instruction and solving drug related problems which are ubiquitous in the outpatient clinic.

In testing the second and third hypotheses, this study found that the cardiac and hyperlipoproteinemic uninstructed groups, as well as the instructed groups, erred differently. The cardiac uninstructed and instructed groups made more errors than the hyperlipoproteinemic uninstructed and instructed groups. These results could be a result of a number of factors, including the Merck, Sharp and Dohme study, different disease states, different medication, and physician-patient relationship.

Knowledge of the name or use of the medication, and formal education were independent of medication errors in this study for both cardiac and hyperlipoproteinemic samples. Marital status was also independent of medication errors in the cardiac sample. These results may reflect the small samples employed by this study. Dependence did exist between marital status and medication errors in the hyperlipoproteinemic sample. Married patients tended to make fewer errors than single patients. Marital status might be one parameter which may aid in characterizing the non-compliant patient in specific disease states.

Recommendations for Further Study

A number of areas for further investigation were uncovered during this study. One of these areas is the effect of the pharmacist's instruction upon other disease states. Perhaps the pharmacist's instruction would be more effective in one medical condition than another. A comparison of different types of instruction to determine

which may be more effective is a second area for research. The extent of non-compliance among patients obtaining their prescriptions from community pharmacies, and the community pharmacists' role in preventing non-compliance are other areas of interest. Since the majority of patients have their prescriptions filled in community pharmacies, and the majority of the nation's pharmacists practice in the community, this would indeed be an area requiring research. Further investigation in an attempt to identify and characterize non-compliant patients should be carried out among diversified groups of patients.

APPENDIX A

INSTRUCTION SHEET

Name

Medication

1. Name of medication:
2. Basic concepts in the use of the medication:
3. How the medication should be taken:
4. The time the medication should be taken:
5. Special precautions:
6. When medication should be discontinued:

APPENDIX B

PATIENT IDENTIFICATION AND INTERVIEW

Name	Group Number			
Address	Clinic visit	Home visit		
Age	Sex	Marital status	Education	Dosage
Medication	Start of therapy			

1. What is the name of this medication? R W
2. What is the purpose of this medication? R W
3. How do you take this medication?
 - a. orally?
 - b. time of day?
 - c. with food or fluids?
4. Do you take any other prescription medication? (discontinued)
5. Amount of medication dispensed minus the amount remaining.
 - a. omission
 - b. overdose
6. Do you take any other medication which does not require a prescription?

APPENDIX C

TABLE OF CRITICAL VALUES OF D (OR C) IN
THE FISHER TEST*

Totals in right margin		B (or A)	Level of significance			
			.05	.025	.01	.005
A + B = 9	C + D = 5	9	2	1	1	1
		8	1	1	0	0
		7	0	0	-	-
		6	0	-	-	-
A + B = 15	C + D = 5	15	2	2	2	1
		14	2	1	1	1
		13	1	1	0	0
		12	1	0	0	0
		11	0	0	0	-
		10	0	0	-	-
		9	0	-	-	-

*Finney 1948.

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