COMPLIANCE WITH MEDICATION REGIMENS BY PSYCHIATRIC OUT-PATIENTS :

A FOLLOW UP STUDY OF PATIENTS DISCHARGED FROM VALKENBERG HOSPITAL, CAPE TOWN.

(DISSERTATION SUBMITTED AS PART REQUIREMENT FOR THE DEGREE M.Med (PSYCH.) OF THE UNIVERSITY OF CAPE TOWN).

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INTRODUCTION :

A large part of medical practice no matter how general or specialised, is complicated by two problems, viz. :

1) The degree to which treatments are specific (the placebo problem) and,

2) The extent to which treatments are implemented (the compliance or adherence problem).

There has been an upsurge of interest in these two aspects of medical management in recent years, paralleling the increased prominence given to social and epidemiological issues in all branches of medicine, a fuller understanding of which is essential prior to the planning and implementation of Health Services at national and community level. The geometrically escalating cost of providing medical services, consequent upon recent inflationary economic trends, has highlighted the need for realistic cost-benefit analyses of all treatment modalities. It is obvious that any stratagems which improve the utilisation of the currently available Health Services, at minimal extra cost, such as the improvement of patient compliance, will lead to an optimisation of any such cost-benefit ratios. (Underlying this statement is, of course, the assumption that compliance by the patient with his treatment regimen is accepted by the medical fraternity as being unequivocally essential). With these general provisos in mind, it was decided to include the assessment of compliance with medication regimens as a subsection of the study into major psychiatric illness undertaken by the Medical Research Council Unit for Social Psychiatry, at Groote Schuur Hospital. This study entails the full medical, psychiatric and social assessment of a cohort of patients admitted to Valkenberg Hospital, and their follow up for a further five years after the initial admission.

The aims of the Compliance Study are multiple and sequential, namely ;

1) The quantitative assessment of the percentages of patients, within and across the various race groups, who comply with their medication regimens following discharge from the hospital.

2) The qualitative assessment of the reasons given by patients and family members for poor compliance, where it exists.

3) The correlation of good or poor compliance with other patients variables such as age, sex, race and diagnosis.

4) The assessment of the role of compliance in subsequent relapse and readmission.

5) Ultimately, it is hoped that these findings may be of practical benefit in improving the treatment of the population concerned.

As the study is still in progress, this dissertation is limited to the initial stages outlined, namely the quantitative assessment of compliance across the various race groups, the reasons ascertained for poor compliance, and discussion of significant differences where noted.

To begin with, a brief overview will be given of the scope and definition of the compliance problem as seen on a global scale. Thereafter the methodology,

results and conclusions of the local study are presented.

LITERATURE REVIEW

As with other areas of medical knowledge, information on compliance is roughly doubling in amount every five years. Haynes and Sackett (1976) developed an annotated bibliography of 246 articles written up to 1973.

PERIOD	NUMBER OF PUBLICATIONS
1956 - 1960	12
1961 - 1965	45
1966 - 1970	79
1971 - 1975	133

The definitive overview with special reference to Psychiatry is generally held to be that by Blackwell (1976).

Haynes and Sackett's book "Compliance with therapeutic Regimens" covers every aspect of Medical Practice, but lacks the depth and sophistication of the Blackwell article.

The most accessible and comprehensive general review article is probably that by Marston (1970) that appeared in a Nursing Journal acknowledging, perhaps, the role of this profession as the traditional bearers of the compliance problem.

Defining the term "compliance" is not easy. The list of medical subject headings in the Index Medicus has only included the category "Patient Compliance" since 1975.

Before then, the major descriptive term was "patient drop-out". (Interestingly, the word "compliance" has no counterpart in Afrikaans, Dutch or German where, perhaps, the Calvinist ethic takes patient co-operation for granted). In America the coercive connotation of the word "compliance" has lead to an increased use of the word "adherence", supposedly to acknowledge the right of the patient to follow or ignore his physicians advice. To all intents and purposes, the terms can be considered synonymous.

The 1st International Congress on Patient Counselling defined the problem as follows; "When a patient does not follow the treatment schedules suggested to him by the physician, for the management of some illness, the patient can be described as non-compliant".

This definition is both unduly restrictive and inadequately descriptive. Compliance encompasses a wide variety of behaviours on the part of the patient :-

1) Failure to enter a treatment programme

2) Premature termination of therapy

3) Incomplete implementation of instructions
   - including those pertaining to prescribed medications.

A further problem arises when trying to define the boundary between good and bad compliance, e.g. When is the patient to be considered non-compliant ? Is it when he takes the tablets incorrectly, i.e. either too infrequently or too often

by his own conscious designs, or is it only non-compliance if the mistakes are due to ignorance ? Or is it both ? How wrong must the patient be in taking his tablets to be considered non-compliant ? What should we make of the patient who takes his neuroleptic tablet twice a day instead of three times ? This type of question, which usually begets yet another, is not merely nit-picking, but highlights the strict criteria needed for a scientific study, the lack of which has flawed the methodology of many retrospective studies. In only half of the studies reviewed by Haynes and Sackett was the term "compliance", described in a manner adequate to permit independent replication.

The criteria for our local study are discussed later.

Of the 320 articles listed in the 2 major sources (Haynes and Sackett, 1976, Pothier, 1975), 55 (17%) deal directly with psychiatry. Almost every kind of patient has been studied, including alcoholics, (Rosenberg, 1973), narcotic addicts, (Adams, 1971), psychotherapy clients, (Heine, 1960) and (Seeman, 1974), depressed, anxious and schizophrenic adults, (Park, 1964, Harris, 1976, Hogarty, 1973), and disturbed or retarded children.

(Wikler, 1974). Compliance problems have been evaluated in a variety of settings :-

1) In-patient Units (Hare & Willcox, 1967)
2) Out-patient Clinics (Carr & Whittenbaugh, 1968)
3) Community Mental Health Centres (Kline & King, 1973)
4) Halfway Houses (Orford, 1974)
5) Home visits (Nicholson, 1967).

The studies quoted attend variously to the quantitative aspects of compliance i.e. the percentages of compliers vs. non-compliers, and the qualitative aspects such as the reasons for good or bad compliance, and the relationships to other independent variables.

Factors leading to better compliance have been known for a long time, the most important of which are :-

1) Improved doctor-patient relationship
2) Same doctor being seen at each visit
3) Improved explanation by doctor of the reasons for, and functions of, the tablets
4) Simpler treatment regimens, especially the reduction of the number of doses per day
5) Decreased number of types of medication
6) Shorter clinic waiting time
7) Social supervision (Compliance poor in patients living alone)
8) Compliance is better for acute illnesses where immediate benefit is more tangible than the distant consequences of those illnesses treated prophylactically. Notably hypertension, hyperlipidaemia and bipolar affective disorder

9) Some studies have shown that a good prognosis is associated with better compliance.

It must be again stressed that these factors have long been known, it is their implementation that remains the problem. Many studies have shown that there is no stereotype "drug defaulter". The interaction between patient and physician is more complex than that opinion often expressed by doctors, namely, that certain patients have "unco-operative personalities".

Mc Clellan and Cowan (1970) showed that even skilled psychiatrists cannot accurately predict which patient will or will not comply. The psychiatrists were wrong 20% of the time and interestingly, 71% of their mistakes were in the direction of believing that patients were not complying when in fact they were.

Blackwell (1976) maintains that the crux of the problem lies in the dynamics of being cared for. Motivation and patients' attitudes to illness are secondary. Cultural concepts of illness are central to how the patient views the physician, let alone how he views the treatment.

Raskin (1961) offers a pragmatic dynamic interpretation of non-compliance, which is interpreted as a way of denying anxiety, expressing hostility or challenging the roles in the game.

ERRORS in drug adherence may be categorised into 4 groups (Malahy, 1966) :

1) Errors of omission

2) Errors of purpose

3) Errors of dosage

4) Mistakes in timing or sequence.

The literature is restricted mainly to the study of errors of omission. Most studies have relied on spot checks as opposed to repeated observations, as the problem of accurate assessment is complicated by the "Hawthorne effect" : namely that, with increasing attention being shown by investigators, the compliance problem decreases and the placebo effect increases. (Blackwell, 1976).

Consequently, most of the conclusions reported in the literature are based on findings in which a single observation suggests that a significant portion, or all of the medication has been omitted.

METHODS OF MEASUREMENT

These can be subdivided into :-

1) Subjective e.g. asking the patient or family member about compliance.

2) Objective e.g. testing a body fluid for the presence of a drug metabolite.

There are 4 frequently used methods of assessing compliance with medication regimens.

1) Patient and/or family interrogation.

This method is often unreliable. Willcox (1965) found that 31% of out-patients claiming to be taking their drugs, had negative urine tests.

2) Tablet estimates (Pill counts).

Frequently misleading because there is no assurance that what has left the bottle was taken by the patient.

3) Drug markers.

Inert harmless chemical markers that show up in various body fluids e.g. RIBOFLAVIN was previously used as a urine marker.

4) Direct drug or metabolite detection.

The most reliable method, especially if applied without prior warning.

Common examples include the measurement of serum concentrations of lithium, anticonvulsants and digitalis.

The presence of phenothiazine metabolites can be detected in the urine using the Forrest reagent. This is a reliable colorimetric test developed by Drs. Fred and Irene Forrest a husband and wife team of psychiatrist and biochemist. (Discussed in detail in Appendix B).

Utilising these various methods either singly or in combination, non-compliance is reported in between 25 and 50 percent of out-patients and a variable smaller number of in-patients. As well as quoting numbers, the literature also debates the significance of non-compliance with regards to morbidity in schizophrenia, the pros and cons of self regulation of dosage (Uhlenhuth, 1965) the economic wastage, hazards to health and the possible distortion of therapeutic trials. (Porter, 1969).

No comparable studies have been performed in South Africa, hence the need to include compliance assessment in the MRC Unit Valkenberg Study.

VALKENBERG HOSPITAL COMPLIANCE STUDY - METHODOLOGY

A questionaire (Appendix A) was devised for administration by research assistants at unannounced follow up home visits, made approximately 6 months after the patient was discharged from hospital.

The study population consisted of the patients collected in the Valkenberg cohort, i.e. staggered sequential admissions to Valkenberg Hospital for a six month period in 1981.

The cohort was subdivided along ethnic lines and consisted of :-

160 Whites

150 Coloureds

150 Blacks (mainly Xhosa)

The population followed up was obviously fewer in number than the original cohort due to various factors :

1) Patients lost to follow up

2) Patients who died in hospital

3) Patients who remained in hospital

4) Patients completely discharged on no treatment.

The final population followed up consisted of :-

113 Whites

116 Coloureds

115 Blacks

The questionaire itself is straightforward, and for the most part requires simple yes or no answers.

However, certain aspects deserve comment. It was initially decided to rate responses on a 3 point scale, in keeping with the 3 point scale used in other data gathering implements such as the PSE. It was also initially deemed important to assess the 'grey area' between the two extremes possible in answering such questions as No. 6. "Does the patient/family know what the tablets are for ? "

Possible ratings :-		
	Aware	(1)
	Partially aware	(2)
	No awareness	(3)

However, retrospectively it was realised that the 3 point scale was a methodological error that introduced problems into the statistical analysis of the results.

This initial part of the follow up study is not severely affected, but for the second part (i.e. the correlation of good or poor compliance with other patient variables) it is proving necessary to include the middle rating category, especially where compliance was rated as "moderate" (Questions 7 + 9), into either the good or poor categories. On clinical grounds it was decided to include the "moderate" category with "poor", though this is not completely satisfactory as the significance of intermittent medication for a condition such as schizophrenia or an anxiety state is not as demonstrably unequivocally inadvisable as would be the case in conditions such as epilepsy or lithium controlled Bipolar Affective Disorder.

The questionaire provides information on the following aspects of post discharge treatment.

1) Type of medication
   - Modecate
   - Lithium
   - Phenothiazines other than Modecate.
2) Awareness of appointments
3) Supervision of medication
4) Awareness of medication regimen
5) Awareness of medication function
6) Compliance with medication regimen (see below)
7) Reasons given for poor compliance.

METHODS USED TO ASSESS COMPLIANCE

Unlike all the studies reviewed in the literature, this study used three separate measures of compliance (Question 7) and provided an opportunity for the research worker to make his or her own subjective rating based on the previous measures plus their own impressions and feelings in general about the patient and family (Question 9). Multiple assessment methods were included so that inter-rating reliability could be assessed, specifically the correlation between the subjective measure (family opinion) and the objective measure (Urine test). It was also hoped that perhaps one method would emerge as the most reliable and easiest to undertake, and that this superior assessment method could then be utilised in any future studies or incorporated into the current out-patient services. It is noteworthy that none of the studies reviewed promote any one method over the others. Whereas the family's opinion was sought, it was later realised that our failure to include a question asking the patients themselves about their compliance, was an unfortunate omission.

URINE TESTING

The research workers were supplied with 10 ml test tubes each containing 1 ml of the General Forrest Reagent (Reviewed in detail in Appendix B). On the addition of an equal amount of urine containing phenothiazine (and Imipramine) metabolites, the solution turns a variable shade of blue, proving that a clinically significant dosage of phenothiazine has been ingested in the past three days. The test does not allow for the potency of the drug administered, or indicate its anti-psychotic activity in any way. Fluphenazine depot (Modecate) 25 mgs monthly will not induce a colour change, but doses of 25 mgs weekly may cause the lightest shade of blue to appear. Overall there were no problems encountered in using the reagent which was initially tested in a Pilot study in the acute admission wards at Valkenberg Hospital. Urine samples were obtained from 10 psychotic patients receiving a variety of phenothiazines including Chlorpromazine, Perphenazine and Trifluoperazine in normal doses. A further five samples were collected from nursing and medical staff. In every case the Forrest reagent reacted appropriately. Of special importance was the absence of any false negatives in the patient sample as the problem of possible drug rejection or non-absorption was not taken into account in planning the study, and is worthy of further assessment at a later stage (Wilson, J.D., 1967).

RESULTS

There were no problems of note experienced by the field workers, with only 5 patients unexplainably lost to follow up. The data from the first 6 - monthly follow-up was available by June, 1983 and the first computer print-out of results was received in August, 1983.

This original print-out revealed many coding and tabulating errors and necessitated extensive revision. The final corrected working print-out was available by January, 1984. Significance levels for differences present within a particular system i.e. across the 3 race groups, were supplied with the print-out. Significance levels between any 2 race groups were calculated individually where necessary using a suitably programmed desk-top calculator. Differences were taken to be significant at the level $P < 0,05$.

The results are presented under the following headings :-

TABLE I MEDICATION TYPE

TABLE II RECEIPT AND SUPERVISION OF MEDICATION

TABLE III AWARENESS OF TREATMENT AND REGIMEN

TABLE IV COMPLIANCE : 1. FAMILY OPINION

TABLE V COMPLIANCE : 2. PILL COUNT

TABLE VI COMPLIANCE : 3. URINE TEST

TABLE VII COMPLIANCE : 4. INTERVIEWER ASSESSMENT

TABLE VIII REASONS FOR NOT COMPLYING

Discussion and comment immediately follows each table.

RESULTS

1) Medication Prescribed

TABLE I

MEDICATION TYPE

(Percentage frequencies)

	Whole cohort	W	C	B	Differences
Modecate	32	24	32	40	B : W (p 0,05)
Lithium	8	15	6	3	W : B (p 0,01)
Phenothiazine*	53	38	60	59	C & B : W (p 0,005)
All pills	92	90	94	91	NS

*Includes Modecate and other phenothiazines; excludes Modecate only.

TABLE I

For the cohort as a whole, almost all are on some type of oral medication.

Just over half are on a phenothiazine and a third on Modecate.

Relatively few patients were prescribed lithium.

DIFFERENCES :

° Modecate :

Significantly more Blacks (40%) are on Modecate than Whites (24%). The percentage of Coloureds on Modecate is in between (32%) but is not significantly different from either B or W.

° Lithium :

The prescription of Lithium shows the reverse trend i.e. significantly more Whites (15%) compared with Blacks (3%). Once again the figure for Coloureds is in between and not significantly different to either B or W.

- Phenothiazines :

  Significantly more Coloureds and Blacks were prescribed phenothiazines (60% & 59%) than Whites (38%).

- Pills :

  No significant differences.

DISCUSSION

92% of people who leave hospital are on pills. This has important implications as regards the provision of out-patient services.

1) Pharmacies are needed.
2) Pharmacy staff, professional and clerical, are needed.
3) Logistical problems arise regarding the implementation of a distribution system to supply medication to country areas.

   (It should be mentioned here that not one patient referred to a District Nurse, had ever been visited at home, or contacted to attend the local clinic. This problem needs special attention).

The differences between the races in the type of medication prescribed might reflect any of 3 things :

1) Diagnostic differences between the races, (possibly more Blacks suffer from that type of illness for which Modecate is routinely prescribed).
2) Diagnostic ability or policy of doctors may vary according to the race group of the patient.
3) Prescription policy of doctors. Even if diagnoses are the same, more Blacks may be receiving Modecate because of previously unverified but nonetheless generally accepted beliefs that "they don't comply". There is also a common myth that Blacks "prefer injections" - this has also never been tested. Furthermore it is accepted by staff in the acute admission wards, that toxins - particularly dagga and Mandrax, play a greater role in the illnesses of Coloureds and Blacks than they do in Whites. Hence Modecate is almost routinely given so that the patient "has something in him next time he smokes".

   It is hoped that many of these speculations that arise from the different types of medication within the various race groups will be answered during the second phase of the follow-up study i.e. when compliance is correlated with other variables such as age, sex, diagnosis and substance abuse (if possible).

2) Receipt of Medication

TABLE II

RECEIPT AND SUPERVISION OF MEDICATION

	Cohort	W	C	B	Differences
Modecate : regularly received	63%	81%	70%	47%	W & C : B
Lithium : regularly received	79%	15/17	5/8	2/3	Too few for stats.
Lithium assessed	68%	15/17	2/8	1/3	Too few for stats.
Medication supervised	33%	29%	42%	27%	C : W & B

TABLE II

For the cohort as a whole two-thirds of those on modecate receive it regularly, but less than half of the Blacks (who were actually prescribed modecate more often) received it regularly. Medication is supervised in only one-third of patients. This is an important factor leading to poor compliance.

DIFFERENCES :

°Modecate :

Significantly less Blacks receive their modecate than Whites and Coloureds. i.e. those who are prescribed the most, get it the least. Further breakdown of the data shows that, of those Blacks who have received their Modecate irregularly, over a quarter never received it at all.

	REGULAR	IRREGULAR	NOT AT ALL
BLACKS	47%	25%	28%

°Lithium :

Too few patients were prescribed lithium for significant statistical analysis but most Whites on Lithium received and had it assessed regularly (15/17).

°Supervision :

Interestingly significantly more Coloureds had their medication supervised, probably because of the social conditions whereby they are more likely to be living with the extended family, whereas Whites live alone, as do the Blacks - many of whom are in Cape Town without families.

3) Awareness of Treatment and Regime

TABLE III

AWARENESS OF TREATMENT AND REGIME

(Percentage frequencies)

	Whole cohort	W	C	B	Differences
Awareness of next appointment	62	83	63	42	W : C : B
Awareness of treatment regime *	60	80	65	34	W & C : B
Awareness of what pills are for *	76	90	82	57	W & C : B

*Figures refer to "good" awareness only.

+Figures include "mod" and "good" awareness i.e. "nerves" as well as full explanation.

(Full awareness : 72% w to 13% c 13% b; p 0,001)

TABLE III

For the cohort as a whole, approximately two-thirds were aware of their next appointment and their treatment regimes. Three-quarters knew what the pills were for. (Patients were classified as having moderate awareness if they said the pills were for "nerves").

DIFFERENCES :

°Appointment :

The awareness of next appointment was significantly different between all the race groups.

°Regimen :

Only one-third of the Blacks knew how to take their pills. This has serious implications as far as treatment efficiency is concerned. It appears that Blacks as a group are not assimilating these instructions, and there are many possible reasons for this, including :

1) Not being told correctly
2) Not understanding instructions
3) Viewing the illness differently from the other groups.

This aspect of poor compliance needs further assessment.

°Compliance :

There are 4 measures of compliance and each will be presented in turn.

a) Family opinion :

TABLE IV

COMPLIANCE : 1. FAMILY OPINION

(Percentage frequencies)

	Good	Mod + Poor
Cohort	57	43
W	76	23
C	60	40
B	36	64

Differences : W : C : B

TABLE IV

By this measure, just over half of the cohort are complying, but there are significant differences between all the groups.

TABLE V

COMPLIANCE : 2. PILL COUNT

(Percentage frequencies)

This applies only to those on pills (actually almost everyone). Interviewers checked pills at home.

	Good	Mod + Poor
Cohort	52	48
W	75	25
C	50	50
B	33	67

Differences : W : C : B

TABLE V

These figures are almost the same as for family opinion, with identical significant differences.

TABLE VI

COMPLIANCE : 3. URINE

(Percentage frequencies)

Only applies to those on Oral Phenothiazines.

	Good	Mod + Poor
Cohort	51	49
W	74	26
C	56	44
B	32	68

Differences B : C & W

TABLE VI

Exactly the same pattern as before (except level of significance changes slightly for the Coloureds).

TABLE VII

COMPLIANCE : 4. INTERVIEWER ASSESSMENT

(Percentage frequencies)

This is a GLOBAL assessment taking all the above factors into account, i.e. family opinion, pill count, urine test as well as overall impression.

	Good	Mod + Poor
Cohort	50	50
W	73	27
C	47	53
B	31	69

Differences : W : C : B

TABLE VII

The interviewer's subjective impression corresponds with the other measures, and although it cannot be said which measure is the most reliable, this method takes all the factors into account.

The inter-racial differences are all statistically significant and have important implications as regards waste of money and unused medication lying around.

TABLE VIII

REASONS FOR NOT COMPLYING

(Percentage frequencies)

Applies to those the interviewer felt were not complying or were complying poorly. Items are NOT mutually exclusive and to some extent overlap.

Reasons	W	C	B	Difference
	(N = 29)	(N = 48)	(N = 75)	
Regimen ignorance	7	62	50	W : C & B
Side effects	57	37	42	-
Resistance	83	90	84	-
Interference	3	4	4	-
Stigma	7	13	0	-
Tabs not received	0	0	0	-
Didn't attend	62	94	81	W : C
No bus fare	0	0	3	NS

° Most important reasons given by all 3 groups : resistance and did not attend.

° The interesting thing is that C & B claimed ignorance, yet very few W did (ties in with compliance results).

° Important : no one said they did not receive their tablets.

° Difference between W & C as 94% C did not attend (that is more than B) but overlaps with other measures too - it is suspected that the higher prevalence of substance abuse is linked to this high percentage.

SUMMARY OF RESULTS

Significant racial differences were shown in respect of all aspects of compliance, with the element of active resistance to treatment being more prevalent in the Coloureds and Blacks, as shown by the higher rate of "failure to attend".

CONCLUSIONS

The four measures of compliance confirm that drug defaulting is a problem in the Cape situation comparable to the worst assessed elsewhere (predominantly Britain and the USA).

Approximately only 50% of the whole Valkenberg Cohort were good compliers. Blackwell (1973) found that the studies to date for the U.S.A. produced figures ranging from 25 - 50% poor compliance.

Our study confirmed the supposition that compliance is poorer amongst Blacks compared with Whites, though this findings applies to the heterogeneous groups as a whole and is only the first step in assessing the role of non-compliance

in relapse and re-admission. The reasons given for poor compliance were only superficially assessed but the very significant difference between the Whites and the other groups as regards ignorance of the medication regimens, is something that can be worked on immediately, with a little further study to assess exactly the level of information communication breakdown. The element of active resistance to treatment is the same across all race groups and it seems likely that the factor of "uncooperative personality" is the same for all groups and is probably similar the world over, as the figures for compliance in the Whites are closest to the average reported in the literature (which is basically concerned with a similar socio-cultural group).

The finding that no patients claimed not to have received their medication is gratifying and indicative that the current distribution system is adequate and efficient.

These initial findings are enough to indicate that there is a compliance problem and that it is a significant one, however it is hoped that the intentional and unintentional aspects of poor compliance in the Cape setting, will be further elucidated following the correlation of patient variables such as age, sex and diagnosis.

It is hypothesised that, following this manoevre, the widely differing rates for good compliance shown by each race group will be seen to be due mainly to ignorance by Blacks, of all the facets of psychiatric illness culturally assimilated by the socioeconomically more priviledged Whites.

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Appendix A

COMPLIANCE WITH MEDICATION

1. Is patient on Modecate ?

Yes (2)
No (1) ( )

If Yes :

+ Patient receives Modecate regularly (1)
Patient receives Modecate irregularly (2)
Patient has not received Modecate (3) ( )

2. Is patient on Lithium ?

Yes (2)
No (1) ( )

If Yes :

Has Lithium level been assessed regularly ?

Yes (2)
No (1) ( )

+ Patient receives Lithium regularly (1)
Patient receives Lithium irregularly (2)
Patient has not received Lithium (3) ( )

3. Is patient / family aware of the next appointment ?

Yes (2)
No (1) ( )

4. Is the patient's medication supervised ?

Yes (2)
No (1) ( )

If Yes :

+ Medication is always supervised (1)
Medication is sometimes supervised (2)
Medication is not supervised (3) ( )

5. Does patient / person administering the tablets know how many different sorts of tablets he has to take, their colour, and how many he has to take a day ?

+ Aware (1)
Partially aware (2)
No awareness (3) ( )

6. Does the patient / family know what the tablets are for ?

+ Aware (1)
Partially aware (2)
No awareness (3) ( )

7. Compliance

In the opinion of the family, does the patient comply with his medication ?

+ Good compliance (1)
Moderate compliance (2)
Poor compliance (3) ( )

Pill Count

After counting left-over pills, the interviewer should rate whether there was -

+ Good compliance	(1)	
Moderate compliance	(2)	
Poor compliance	(3)	( )

Urine Sample

From patients on Phenothiazine :

+ Good compliance	(1)	
Moderate compliance	(2)	
Poor compliance	(3)	( )

8. If poor / no compliance (Specify patient's reasons)

	Yes	No	
Ignorance of regime	(2)	(1)	( )
Side effects of medication	(2)	(1)	( )
Active resistance by patient	(2)	(1)	( )
Outside pressure / advice	(2)	(1)	( )
Stigma of mental illness	(2)	(1)	( )
Tablets not received	(2)	(1)	( )
Did not attend clinic	(2)	(1)	( )
Other	(2)	(1)	( )

Specify .....

.....

9. Interviewer assessment of overall compliance :

+ Good compliance	(1)	
Moderate compliance	(2)	
Poor compliance	(3)	( )

APPENDIX B

THE FORREST TEST

In the late 1950's Drs. Fred and Irene Forrest of the Veterans Administration Hospital, Palo Alto, California, developed a series of tests designed to show the presence of Phenothiazine derivatives in the urine. The search for a suitable test stemmed directly from the need to assess whether or not the patients were taking their medication. (The 20 original papers on this research are succinctly reviewed in Forrest et al - (1961)).

During their early work into the metabolic fate of phenothiazine compounds, some incidental observations indicated that chlorpromazine had a very reactive nucleus tending to produce a variety of oxidative derivatives. These observations included the obvious autoxidation of aqueous chlorpromazine solutions, rapidly turning brown when exposed to daylight, and the photosensitivity of patients on chlorpromazine therapy. Assuming that some of the more reactive intermediates might be demonstrable in the urine, a search for a simple suitable reagent was started and resulted in the first rapid urine color test for chlorpromazine being developed in 1957, whereby an acid solution of Ferric Chloride, mixed with urine, yielded a scale of purple colours proportionate to drug intake. A subsequent search of the literature showed that whereas there were few pertinent data for chlorpromazine, there was a vast body of literature for the parent compound Phenothiazine. The entire Phenothiazine field from its synthesis by Bernthsen in 1883 to that time, the 1950's including all industrial and pharmacologic applications had been comprehensively and competently reviewed by Massie (1954). Animal studies on the metabolism and excretion of phenothiazine showed that the type and amount of drug metabolites varied from species to species, but that the urines contained one or more partially oxidised or hydroxylated intermediary metabolites in all instances. (De Eds 1938, Collier 1940, De Eds 1940, Clare 1947). The first basic metabolic data for chlorpromazine were reported by Salzman et al. (1955). They identified, in human urine, the chemically unchanged, unoxidised chlorpromazine and its sulfoxide. These 2 compounds essentially the beginning and the end of the human metabolic process account for only 5 - 12% of the daily drug dose, hence a large balance is left unaccounted for. Furthermore neither of these 2 compounds is responsible for the intense purple color reactions, as unoxidised chlorpromazine yields a pink colour, white sulfoxide produces no colour at all with the original test reagent.

Forrest and co-workers speculated that the partially oxidised, highly reactive intermediary drug metabolites might act as oxido-reduction systems and tried to duplicate the physiological metabolism of chlorpromazine in vitro by ultraviolet irradiation of aqueous drug solutions (Forrest et al. 1958). While this did not produce any sulfoxide, it did lead to the formation of an oxidative intermediate closely resembling the urinary metabolites responsible for the colour test. While continuing to investigate the chemical nature of the elusive intermediates, the initial rapid urine colour test for chlorpromazine was modified for the purpose of demonstrating other urinary phenothiazine drugs and to provide objective criteria for their intake. Initially 7 separate tests were developed, later streamlined to 4, including the "FPN" Universal Test Reagent that was used in the Valkenberg Compliance Study.

This table shows which test solution demonstrates the metabolites of which drug.

FORREST REAGENT NUMBER	DRUGS TESTED	TEST SOLUTION	PERFORMANCE OF TEST
I	Chlorpromazine	20 parts 5% Ferric Chloride. 80 parts 10% Sulphuric Acid.	Mix 1 ml urine with 1 ml solution. Read promptly.
II	Promazine Mepazine	Same as above.	Same as above, (but colour range is darker).
III	Thioridazine	2 parts 5% Ferric Chloride. 98 parts 30% Sulphuric Acid.	Mix 1 ml urine with 1 ml solution. Read within 20 seconds.
IV	Imipramine	25 parts 0,2% Potassium Dichromate. 25 parts 30% Sulphuric Acid. 25 parts 20% Perchloric Acid. 25 parts 50% Nitric Acid.	Mix 0,5 mls urine with 1 ml solution. Read promptly.
V	Most phenothiazines e.g. Chlorpromazine Thioridazine Promazine Trifluoperazine Perphenazine Diphenhydramine etc.	"FPN" Universal Reagent. 5 parts 5% Ferric Chloride. 45 parts 20% Perchloric Acid. 50 parts 50% Nitric Acid.	Mix 1 ml urine with 1 ml solution. Read immediately. Disregard all colours appearing after a delay of 10 seconds or more.

A positive result in each case indicated by the appearance of variable shades of blue, the intensity of which, roughly correlates with the daily dosage intake of phenothiazine.

The Forrest Reagents are cheap to produce and stable for long periods in light proof bottles. The test has been validated in independent studies by Pollack (1958).

It is interesting that there is no literature concerning the Forrest test appearing after 1961. The test was developed for the express purpose of checking on patient compliance, was in vogue for a few years and then shelved for reasons that are purely speculative.

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