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***Review Article***

# Treatment Adherence

By BARRY BLACKWELL

A large part of medical practice is complicated by two problems; the degree to which treatments are specific (the placebo problem) and the extent to which they are implemented (the adherence problem). Depending on setting and circumstance, up to half of the benefits of treatment are either non-specific or never obtained. This review considers the problem of adherence in the context of use of medication in psychiatry.

## Scope of the Problem

Two major sources of information document an upsurge of interest in the extent to which patients adhere to therapeutic regimens. In preparation for the First International Workshop on Therapeutic Compliance, Haynes and Sackett (1976) developed an annotated bibliography which included 246 articles written up to 1973. The National Library of Medicine has since added a further 74 references in English up to September 1975 (Pothier, 1975). As with other areas of medical knowledge, information on adherence is roughly doubling in amount every five years. Between 1956 and 1960 there were 12 publications, from 1961 to 1965 there were 45, from 1966 to 1970 there were 79, and in the most recent five-year interval (up to September 1975) there were 133 articles. In April 1976 the First International Congress on Patient Counseling devoted a major session to Patient Compliance with Therapeutic Regimens. This increase in interest must be determined by both social and scientific influences. Among the former are an enhanced awareness of patient rights and a decline in professional paternalism. Some slackening in the pace of drug discovery may have encouraged closer attention to the better use of existing remedies. There has also been an increased interest in establishing the benefits of preventive health programs in diseases such as hypertension, hyperlipidaemia and recurrent mania, where adherence is a particular problem because the short-term side effects or sacrifices of treatment often appear to exceed the remote consequences of the disease. Finally, there have been technological advances which facilitate drug detection in body fluids, and these have enabled more accurate study of the adherence issue.

## Definition of the Problem

The list of medical subject headings (MESH) compiled by the National Library of Medicine has included the term 'patient compliance' only since 1975; before then the major descriptive term was 'patient drop-out'. It is interesting that the word 'compliance' has no counterpart in the German or Dutch languages (where perhaps adherence is taken for granted). In America the coercive connotation of the word 'compliance' has led to increased use of 'adherence' as an alternative. The First International Congress on Patient Counseling defined the problem as: 'when a patient does not follow the treatment schedules suggested to him by the physician for the management of some illness, then the patient can be described as non-compliant.'

This definition is both unduly restrictive and inadequately descriptive. Adherence is a problem encountered by all health professionals. It encompasses a wide variety of behaviours on the part of the patient: failure to enter a treatment program, premature termination of therapy, and incomplete implementation of instructions, including prescriptions. In this review the term 'adherence' will be preferred, but is to be considered synonymous with 'compliance'.



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### Problems of Study

Despite the wealth of literature, adherence is an inadequately studied subject. Haynes and Sackett's (1976) annotated bibliography included a careful appraisal of the scientific merit and study design of each publication. Of the 185 studies that were evaluated less than a quarter obtained scores of 12 or over on a 24 point scale, and only 15 per cent had a randomized design. Another major problem of interpretation has been the lack of definition of the term 'compliance'. In only half the studies was this described in a manner adequate to permit independent replication.

This lack of sound information is partly inherent in the problem. Unlike the placebo response, which increases with attention paid to people, poor adherence tends to disappear under scrutiny. This may continue to be a problem, since it can only be avoided by subterfuge or strategies unacceptable in today's climate of informed consent.

Taken together these inadequacies in data collection have contributed to a marked lack of consensus in the conclusions derived from studies on adherence.

### Adherence and the Psychiatrist

There are two reasons why psychiatrists need concern themselves with the problems of adherence. The first is the implication it has for personal practice; another is to provide expert consultation to other health professionals on the management of adherence in general medical practice. Two of the most significant contributions of psychiatry to the rest of medicine may well be an understanding of the extent to which treatment is specific and of the degree to which treatment can be implemented.

Out of the 320 articles listed in the two major sources (Haynes and Sackett, 1976; Pothier, 1975) and in a previous review (Blackwell, 1973b) 55 (17 per cent) deal directly with problems in psychiatry. Table I lists these studies by author, treatment population and type of adherence problem. Almost every kind of patient has been studied, including narcotic addicts, alcoholics, psychotherapy clients, depressed, anxious and schizophrenic adults, and disturbed or retarded children. Adherence problems have been evaluated in a variety of settings, including in-patient units, out-patient clinics, community mental health centres, halfway houses and child guidance clinics. Problems relating to drug treatment account for just under half of the studies, and the remainder pay attention to issues such as failure of first attendance after referral ('no shows'), premature discharge from hospital (against medical advice or 'AMA'), early or late drop-outs from treatment, refusal to attend follow-up, and attendance patterns in general.

It is difficult and sometimes inappropriate to derive general conclusions from such heterogeneous data. The behaviour of patients may be differently determined between those who decline referral, drop out early, terminate against advice or stay in treatment but frustrate effective care. This review is mainly concerned with the specific problems relating to drug adherence in psychiatric patients, but reference will be made to more general aspects when relevant in order to create a model for understanding that can be applied both in psychiatric practice and in consultation to medical colleagues.

### Drug Adherence in Psychiatric Populations

#### 1 *Types of Non-Adherence to Drug Therapy*

Errors in drug adherence may be categorized into four groups (Malahy, 1966): errors of omission, errors of purpose (taking medicine for the wrong reasons), errors of dosage, and mistakes in timing or sequence. Schwartz *et al* (1962) added another group of patients who took additional medications not prescribed by the physician, of which nearly half were potentially dangerous. The literature on non-adherence in drug therapy has confined itself almost entirely to the study of errors of omission. Unfortunately, the method of calculation differs between studies and has been variously defined—from taking less than the correct amounts to taking none at all of the prescribed medication. Another problem has been the tendency to rely on isolated spot checks rather than on repeated observations. Two studies have addressed this issue. Pollack (1958) noted that nine psychiatric patients tested repeatedly negative for drugs on 27 occasions, and Willcox *et al* (1965) examined the urine of twelve psy-

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TABLE I

*Adherence studies in psychiatric populations*

| Author(s) | Year | Treatment populations | Type of adherence |
|---|---|---|---|
| Adams, Capel & Bloom, *et al* | 1971 | Narcotic addicts | Treatment dropouts |
| Adler, Goin, Yamamoto | 1963 | General out-patients | Failed first attendance |
| Atkinson | 1971 | Neuropsychiatric in-patients | Discharge 'against medical advice' |
| Brown & Brewster | 1973 | Narcotic addicts | Treatment dropouts |
| Bumpass, Via & Forgotson, *et al* | 1974 | Analytic psychotherapy | Therapeutic alliance |
| Carr & Whittenbaugh | 1968 | General out-patients | Cooperation in follow-up |
| Cusky, Chambers & Weiland | 1971 | Narcotic addicts | Treatment dropouts |
| Deykin, Weissman & Tanner, *et al* | 1975 | Depressed out-patients | Treatment dropouts<br>Attendance patterns |
| Ewalt, Cohen & Harmatz | 1972 | Child guidance clinic | Attendance patterns |
| Fiester, Mahrer & Giambra, *et al* | 1974 | Community Mental health centre | Treatment dropouts |
| Forest, Geiter & Snow, *et al* | 1964 | Schizophrenic in-patients | Drug compliance—phenothiazines |
| Glick | 1965 | Depressed out-patients | Dropouts in drug study |
| Gould, Paulson & Daniels-Epps | 1970 | General out-patients | Failed first attendance |
| Hare & Willcox | 1967 | General in-patients | Drug compliance—chlorpromazine, amitriptyline |
| Harris | 1974 | Anxious out-patients | Drug compliance—minor tranquillizer |
| Heine & Trosman | 1960 | General out-patients | Treatment dropouts |
| Hoenig & Ragg | 1966 | General out-patients | Failed first attendance |
| Hogarty & Goldberg | 1973 | Schizophrenic out-patients | Relapse rates—drug & social therapy |
| Howard, Rickels & Mock *et al* | 1970 | Neurotic out-patients | Dropouts in drug study |
| Irwin, Weitzell & Morgan | 1971 | General in-patients & out-patients | Drug compliance—phenothiazines |
| Johnson & Freeman | 1972 | Schizophrenic out-patients | Attendance & relapse—long acting phenothiazines |
| Kidd & Euphrat | 1971 | Community mental health centre | Failed first attendance |
| Kline & King | 1973 | Community mental health centre | Treatment dropouts |
| Krakowski & Smart | 1974 | Narcotic addicts | Treatment dropouts |
| Krebs | 1971 | Community mental health centre | Attendance patterns |
| Lipman, Rickels & Uhlenhuth, *et al* | 1965 | Neurotic out-patients | Drug compliance—minor tranquillizers |
| Mason, Forrest & Forrest, *et al* | 1963 | Schizophrenic out-patients | Relapse—phenothiazines |
| McCabe, Kurland & Sullivan | 1974 | Narcotic addicts | Treatment dropouts |
| McClellan & Cowan | 1970 | General out-patients | Drug compliance—antidepressants & major tranquillizers |
| Mester | 1972 | General out-patients | Drug compliance—all drugs |
| Michaux | 1961 | General outpatients | Drug compliance—major tranquillizers |

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TABLE 1—*Continued*

| Author(s) | Year | Treatment populations | Type of adherence |
|---|---|---|---|
| Orford | 1974 | Alcoholics Halfway house | Treatment dropouts |
| Pam, Rachlin & Bryskin, *et al* | 1973 | Psychiatric in-patients | Discharge 'against medical advice' |
| Park & Lipman | 1964 | Depressed out-patients | Drug compliance—drug study |
| Parkes, Brown & Monck | 1962 | Schizophrenic out-patients | Drug compliance—major tranquillizers |
| Pollack | 1958 | Schizophrenic in-patients | Drug compliance—phenothiazines |
| Porter | 1969 | Depressed patients in general practice | Drug compliance—antidepressants |
| Raynes & Warren | 1971 | Community mental health centre | Dropouts after first visit |
| Raynes & Patch | 1973 | Narcotic addicts | Early dropouts |
| Renton, *et al* | 1963 | Schizophrenic out-patients | Drug compliance—phenothiazines |
| Reynolds, Joyce & Swift, *et al* | 1965 | Miscellaneous out-patients | Drug compliance—barbiturates |
| Richards | 1964 | Schizophrenic in-patients | Drug compliance—major tranquillizers |
| Rickels & Briscoe | 1970 | Neurotic out-patients | Drug compliance in drug study |
| Rickels, Boren & Stuart | 1964 | Neurotic out-patients | Dropouts in drug study |
| Rickels, Raab & Gordon, *et al* | 1968 | Neurotic out-patients | Drug compliance in drug study |
| Rosenberg & Raynes | 1973 | Alcoholic out-patients | Treatment dropouts |
| Rosenberg, Davidson & Patch | 1972 | Narcotic addicts | Treatment dropouts |
| Seeman | 1974 | Psychotherapy out-patients | Treatment dropouts |
| Shapiro | 1974 | Child & Family out-patients | Treatment dropouts |
| Tapp, Slaikeu & Tulkin | 1974 | General out-patients | Failed first attendance |
| Uhlenhuth, Park & Lipman *et al* | 1965 | Neurotic out-patients | Drug compliance in drug study |
| Van Putten | 1975 | Manic-depressive out-patients | Drug compliance—lithium |
| Wikler & Stoycheff | 1974 | Subnormal child out-patients | Treatment compliance |
| Willcox, Gillan & Hare | 1965 | General out-patients | Drug compliance—imipramine & chlorpromazine |
| Wilson & Enoch | 1967 | Schizophrenic in-patients | Drug compliance |

chiatric out-patients from three to five times and found that all except one were consistently non-adherent. Most of the conclusions derived from the literature are therefore based on findings in which a single observation suggests that a significant portion or all of the medication has been omitted.

### 2 *Methods of Detection*

None of the methods of detecting or studying non-adherence are without shortcomings or difficulties. The methods used in studying this problem include the following:

(a) *Interrogation* Asking the patient about tablet taking is not always reliable. Thirty-one per cent of psychiatric out-patients who claimed to be taking their drugs had a negative urine test (Willcox *et al*, 1965). Park and Lipman (1964) showed that while verbal reports suggested that only 15 per cent of out-patients were non-adherent, a pill count revealed an actual figure of 51 per cent. These authors made the interesting observation that patients are

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more likely to be accurate if a major problem exists. This was later confirmed in a large survey involving over 300 psychiatric clinic and general practice patients (Rickels and Briscoe, 1970). Over two-thirds with major problems in adherence recognized their own difficulties, compared to a quarter of those whose records indicated minor oversights. Success of interrogation may clearly depend on the type of patient concerned. Schizophrenic in-patients are especially noted for the lengths to which they may go to 'cheek' medication (Neve, 1958).

(b) *Tablet Estimates* Counting tablets may be as misleading as interrogation, since there is no assurance that what has left the bottle has been through the patient. Porter (1969) found that 3 out of 19 patients taking Imipramine had negative urine tests but complete pill counts.

(c) *Drug Markers* Attempts have been made to find substances neither harmful nor alarming to the patient that can be reliably identified in body fluids as indexes of adherence. A frequently used urine marker has been riboflavin, which has been successfully employed in psychiatric populations (Scarpatti *et al*, 1964). A single attempt has been made to utilize the stools of psychiatric patients by giving an opaque barium sulphate tracer which was detected by x-rays in the faeces (Esser *et al*, 1969). False negatives occurred in those who chewed their capsules or remained constipated for longer than the life of the marker.

(d) *Drug Detection* Testing the patient's urine is the simplest and most convenient means of drug identification, especially since it is the major route of excretion for most drugs. The first urine test for phenothiazines was developed in 1957 by Drs Fred and Irene Forrest, a husband and wife team of psychiatrist and biochemist, who devised a series of ferric chloride colour reactions for both phenothiazines and tricyclic antidepressants (Forrest *et al*, 1961). These tests have become known by their name, and their validity has been independently corroborated (Pollack, 1958). Additional tests for phenothiazines have been developed for use in mentally retarded children and other psychiatric populations, but have not proved sufficiently sensitive or reliable (Sprogis *et al*, 1957; Neve, 1958). A more sensitive test was developed by Willcox *et al* (1965), but it is more complex and has not become a standard procedure.

## Extent and Significance of Non-Adherence to Drugs

A previous review (Blackwell, 1973a) revealed that significant omission of medication occurs in between 25 and 50 per cent of out-patients but is less common among in-patients. The significance of such findings had been most intensively debated in the treatment of schizophrenia, where the paradox of declining hospital populations and rising readmission rates has given rise to the 'revolving door' concept. A previous review of the literature (Hughes and Little, 1967) was sceptical of the need for continuous medication among schizophrenic in-patients. The authors claimed to prove their point by controlled withdrawal of phenothiazines from 21 patients, 17 of whom remained well eighteen months later, even though the ward became 'a rather noisier place'. Patients in this study received intensive milieu therapy and support. The results conflict with those of a large collaborative Veterans Administration study (Caffey *et al*, 1964). Twenty-five per cent of 348 in-patients relapsed within sixteen weeks of having a placebo substituted for maintenance phenothiazines. In another study, controlled prospective evaluation of schizophrenic patients discharged from hospital found that after six to eighteen months 82 per cent of drug-treated patients were still at home, but only 37 per cent of those on placebo remained outside hospital (Scarpatti *et al*, 1964). Forrest *et al* (1964) documented the injudicious effects of non-adherence on readmission rates in 3000 chronic psychiatric patients studied over a ten-year period. Some studies do not confirm such a clear-cut association between non-adherence and morbidity in schizophrenia (Renton *et al*, 1963), but one dramatic finding was that izoniazid reduced the incidence of tuberculosis by 80 per cent in general patient populations, but by only eighteen per cent in schizophrenics who adhered less readily to treatment (Ferebee, 1964).

A more charitable view of the consequences of non-adherence was proposed by Uhlenhuth *et al*

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(1965), who made the interesting speculation that non-adherence might reflect the patient's own efforts to self-regulate dosage, due to the very wide individual differences known to occur in drug metabolism.

More remote consequences of the adherence problem are the economic wastage involved and the potential hazard to health created by cupboards stocked with unused or unidentifiable tablets accumulated over the years. A survey of an English town revealed that 500 out of 30,000 households had unused drugs available. Sedatives, tranquillizers and hypnotics formed the largest single category (Nicholson, 1967). The potential significance of this finding was illustrated by Robin and Freeman-Browne (1968), who examined unused medications in the homes of psychiatric patients and found that those with suicidal risk often had supplies of potentially lethal medications available.

A final important consequence is the part non-adherence may play in distorting the outcome of therapeutic trials. This has been as repeatedly emphasized as it has been ignored (Maddock, 1967; Porter, 1969; Uhlenhuth *et al*, 1965), but the majority of drug studies continue to fail to make any attempt at measuring non-adherence and its contribution to treatment outcome.

## Risk Factors Contributing to Non-Adherence

Attempts to identify features associated with non-adherence have yielded conflicting results with low consensus. A contributory factor has been the poor quality of the research, with a tendency to study relatively superficial, easily observable or readily measurable end points. For instance, Haynes and Sackett (1976) identified more than two hundred variables that had been measured, but results from separate studies were often contradictory. Table II comprises the few features for which there are at least four studies yielding the same conclusion concerning the effect of that feature on increasing or decreasing adherence.

These findings in the general literature reflect a similar uncertainty in studies on psychiatric populations. By conceptualizing the problem as a complex interaction between variables, potential risk factors contributing to non-adherence can be identified in the patient, the illness, the physician, the treatment setting and the medication itself.

Table II
*Risk factors effecting adherence to medication**

| Increase | Decrease |
|---|---|
| Patient considers disease serious | Complexity |
| Family stability | Degree of behaviour change required |
| Compliance with other aspects | Clinic waiting time |
| Patient satisfaction | |
| Close supervision by physician | |

*Derived from Haynes & Sackett, 1976

### 1 *The patient*

Attempts to distil complex human behaviour into stereotypes are seldom rewarded. This proved true in the search for a 'placebo reactor', and has also been the fate of attempts to define a 'drug defaulter' (Blackwell, 1972). Almost fifty years ago Hartshorne and May (1928) showed that individuals who are unreliable in one situation may not be in another. Following extensive research in general practice on both medical and psychiatric problems, Porter (1969) concluded 'it has not proved possible to identify an uncooperative type. Every patient is a potential defaulter; compliance can never be assumed.'

#### (a) *Attitudes and Illness Behaviour*

People's willingness to seek help, to be cared for and to accept or reject advice are basic characteristics which are reflected in how they take medication. Variations of the attitudes that underlie this behaviour have ranged from descriptive to speculative. The latter includes an observation (Scott, 1960) that pills and capsules resemble nothing so much the breast and the penis (elixirs presumably fall into the category of mother's milk). Better substantiated observations on the influence of attitudes on

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adherence behaviour are provided by a number of studies in the general medical literature. A study of farm workers with cardiac disease (Davis, 1967) showed that those with a low adherence more often endorsed statements on a health attitude questionnaire such as 'if you wait long enough you can get over any illness'; 'illness and trouble is one way God shows his displeasure'; 'some of the old fashioned remedies are still better than the things you get at the drugstore'. Another study (Stimson, 1974) illustrated the beliefs about medication which reduce adherence, including 'you only take medicines when you are ill, not when you are better' or 'you need to give your body some "rest" from the medicine once in a while, otherwise your body becomes dependent on it or immune to it'. Every individual's behavior in relation to health and illness is determined by such personal and culturally endorsed belief systems; in a longitudinal study over fifty years in Vienna, Linz (1964) found that people of that region who once attributed their aches and pains to the wrath of God were now preoccupied with their health. Behaviour in response to such attributions has presumably changed over half a century from visiting the priest (who invoked prayer) to calling on a physician (who writes a prescription).

Sociologists who have studied how people behave in relation to health and disease have devised models to describe patterns of response; Becker (1974) refers to the 'health belief' model and Mechanic to an 'illness behaviour' model. He says: 'whether by reason of earlier experiences with illness, differential training in respect to symptoms or whatever, some persons will make light of symptoms, shrug them off and avoid seeking medical care; others will respond to the slightest twinges of pain or discomfort by quickly seeking such medical care as is available' (Mechanic and Volkart, 1961).

An individual's belief systems and tendency toward illness behaviour may influence both his utilization of mental health resources in general and his acceptance of medication in particular. Fiester *et al* (1974) studied the patients at a community mental health centre and distinguished those who dropped out of treatment almost immediately from those who continued in the program. The drop-outs shared a set of unique characteristics which identified them as people who 'shun the treatment philosophies and methods of mental health practitioners, clinics and hospitals'. The beliefs and behaviours of those people who choose to attend but not to comply with treatment are still more complex. A collaborative Veterans Administration study of out-patients yielded some information in this respect (Michaux, 1961; Raskin, 1961). Patients were prescribed medication by one doctor, but attended for psychotherapy with another. Resistance to medication expressed verbally to the therapist was found later to correlate significantly with low adherence. A group of 37 individuals who were persistently non-adherent were found on testing to show a greater degree of overt hostility and aggression to the prescribing physician (but they also expressed angry feelings toward psychotherapy). The paradox of these patients can be partly resolved by noting that anger towards the therapist and poor adherence with therapeutic regimens are ways of sustaining attention and concern in those who value care taking highly (Wooley and Blackwell, 1975). Further support for this suggestion can be derived from the study by Richards (1964), who used Osgood's Semantic Differential Scale to determine the attitudes of 30 schizophrenic in-patients with high or low adherence to medication. The author's description of the chronic schizophrenic medication was of 'a closed ward patient who resents coercion, yet doesn't value freedom highly and doesn't dislike the hospital but dislikes his parents. He has been in the hospital for five or six years, yet hasn't been convinced that taking medication will make him better. Forcing this patient to swallow medicine is very different from insisting that an acutely ill, agitated, recently admitted patient accept medication.'

The acceptability of treatment recommendations may not only differ between individuals but may vary over time. This issue has been best studied in patients who abandon psychotherapy. Interactions between the therapist and client, which may result in the rejection of treatment have been categorized by Seeman (1974). She carefully documents the differing

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therapeutic interactions that may provoke rejection of treatment based on the early experiences of dependent, schizophrenic, and obsessional patients.

In addition there is a subtle interaction between the individual and environmental situation in which the failure to take medication occurs. Bakker and Dightman (1964) studied the personalities of women who failed to take oral contraceptives regularly. They were more immature, irresponsible and impulsive, but in addition their personality profiles deviated more from their husbands than did those of women who took the pill regularly. Though there is no direct confirmation within the psychiatric literature, it is possible to speculate that poor adherence with medication leads to results which elicit caretaking responses from the environment, and these enable the subject to avoid the anxieties of independent existence and lead to adoption of the 'sick role'. In this way it is possible to exchange a back ward in the hospital for a back room in the community.

(b) *Socio-economic factors*

American heroin addicts allege that difficulty in finding the money to pay for their methadone is the major factor in their drop-out from treatment (Adams *et al*, 1971). Another study reporting a relationship with socio-economic variables was among neurotic out-patients treated with meprobamate, where good adherence was associated with being middle-class, well educated and white (Lipman *et al*, 1965). This constellation of attributes led the authors to consider such patients as those likely to 'abide by the rules of the game'. Intelligent middle-class patients are known to be aggressive in seeking help of all kinds and may be equally resolute in obtaining value for money by taking what they pay for. However, this supposition is not supported by a study using attendance as a means of evaluating a community mental health program (Krebs, 1971). This study found that patients on welfare and covered by private insurance kept as many appointments as a group of patients paying for their own care.

(c) *Social supervision*

A consistent finding has been the supervisory role of a partner or spouse in ensuring that medication is taken as ordered. Porter (1969) found that among general practice patients on chronic medication social isolation (living alone) was the major contribution to non-adherence. This feature is most likely to occur among the elderly or unwanted in society, so that it may be expected to contribute to poor adherence in geriatric and schizophrenic populations. In psychiatric out-patients, Willcox *et al* (1965) noted that 52 per cent of men living alone failed to take drugs, compared to 35 per cent of those living with their wives. When Parkes *et al* (1962) investigated the fate of schizophrenic patients discharged into the community, they found that it made no difference whether the patient obtained his drugs from a psychiatrist or a general practitioner, but 82 per cent of those whose drug-taking was supervised by a relative or friend took their drugs as ordered, compared to 46 per cent of those who were not supervised; an important corollary to this observation was the fact that there were three times as many patients in the unsupervised group. Renton *et al* (1963) also found that schizophrenics living with their families were more likely to adhere.

2 *The illness*

The general medical literature suggests that adherence is affected not only by the nature of the illness but by its duration and the consequences of stopping medication. Non-adherence in chronic diseases such as tuberculosis and schizophrenia tends to increase with the duration of remission (Blackwell, 1973a). Adherence is usually encouraged when the consequences of decreasing medication are immediate and disruptive (as with diabetes). In schizophrenia and severe manic-depressive disorders the disruptive consequences of non-adherence are mitigated by the way symptoms develop insidiously after treatment ceases, thus blurring the cause and effect relationship for patients, relatives and professionals.

In psychiatric patients, capacity to cooperate may be impaired by the illness as well as by attitudes toward health and treatment. Renton

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*et al* (1963), found that non-adherence was highest in schizophrenics who were the most ill at the time of discharge, but found it difficult to disentangle the question whether this was the cause or result of further deterioriation. Those who were less ill attended out-patient clinics and adhered to medication more faithfully. Among the more common symptoms which alter adherence in psychiatric practice are the paranoid delusions which cause the schizophrenic to equate drugs with poison. Wilson and Enoch (1967) found that out of 8 schizophrenics with persistently negative urines, 7 had paranoid delusions (compared with only two in a control group). In a recent report on maintenance therapy with lithium in manic-depressive illness, Van Putten (1975) reports that refusal to take lithium was a significant problem in 9 out of 16 patients. This was contributed to by the use of denial and lack of awareness of personal feelings and their relationship to treatment.

Poor adherence not only occurs in psychotic states where insight may be lost, but has been shown to occur in neurotic illnesses. Lipman *et al* (1965) found that low adherence was most common among the most anxious out-patients who had been given a poorer prognosis and had been treated eleswhere before. They speculate that the treatment was rejected by this group of patients as being insufficiently potent.

3 *The physician*

The behaviour and attitudes of the physician can be expected to influence patient adherence with medication. The physician's own reluctance to recognize this fact constitutes a major obstacle to effective management. In one study two-thirds of physicians attributed the problem of faulty adherence to their patient's 'uncooperative personality', and only a quarter thought that the physician himself might be contributory (Gillum and Barsky, 1974). Therapists' attitudes both to the patient and to the role of medication may play an important part in treatment adherence. One study in a child guidance clinic (Shapiro, 1974) found that the psychopathology of those clients who remained in treatment was similar to that of those who dropped out. However, those who continued were differentiated by the fact that therapists' affective responses were consistently more positive and the prognosis made initially was more optimistic. That this fact is more closely related to drug therapy was demonstrated by Reynolds *et al* (1965) in a double blind study comparing barbiturates to placebo. The patients of one therapist ('promoting') were more adherent and complained less of side effects than those of the other ('protecting') who were less adherent and complained more. The successful therapist inquired more after improvement, reassured about side effects and gave more hope for benefit. Rickels and his collaborators (1968) have frequently demonstrated the significance of such factors in the outcome of treatment with drugs given to psychiatric patients in out-patient settings. In schizophrenia, Irwin *et al* (1971) found that 39 per cent of out-patients were non-adherent if they were treated by a physician who did not believe in drugs, compared to 25 per cent of those cared for by a doctor who viewed medications as essential. However, the numbers were small and the differences not significant.

4 *The treatment setting*

The treatment setting may have important effects on adherence as a result of the degree of supervision and support provided. Hare and Willcox (1967) found that the incidence of non-adherence increased progressively from 19 per cent among in-patients; 37 per cent in day patients and 40 per cent in out-patients at the same hospitals. Irwin *et al* (1971) also found that non-adherence occurred in 7 per cent of schizophrenics in a closed ward compared to 32 per cent of open ward patients; when the closed ward patients went on Christmas vacation the rate rose to 63 per cent by the time the patients returned to the ward after two to four weeks at home.

Many other aspects of the treatment setting may also contribute toward patient adherence with the treatment program in general and medication in particular. For instance, in the general medical area Finnerty *et al* (1973) found that they reduced the number of drop-outs in their hypertension clinic from 42 per cent to 8 per cent in one year by decreasing clinic



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waiting time and offering a more personalized service. In the out-patient psychiatric clinic, Raynes and Warren (1971) have drawn attention to the deleterious effect on adherence of 'excessively compulsive and long-winded intake procedures', which they describe as 'endogenous defence mechanisms'. The same point has been made in the community mental health centre setting. Kline and King (1973) suggest that uncooperative patients who fail to take medication are often 'pushed out' or 'eased out' of treatment by subtle staff pressures.

An important aspect of supervision is continuity of care. Wikler and Stoycheff (1974) found that parental adherence to post-discharge recommendations for retarded children were highest when post-discharge contact was maintained with the institution.

5 *Medication*

A number of features associated with medication may affect adherence.

(a) *Therapeutic regimen* A study of parental compliance with recommendations for retarded children showed that two-thirds of those receiving one or two recommendations followed them all, whereas only a fourth of the group receiving three or more did so (Wikler and Stoycheff, 1974). The same considerations apply to complexity of medication regimens. There is clear evidence that adherence is adversely affected when multiple medications are prescribed or drugs are given in frequent divided doses (Porter, 1969; Malahy, 1966; Gatley, 1968). These observations and increasing knowledge about the metabolism of psychotropic drugs has led to the widespread popularity of once daily therapeutic regimens as a means of improving adherence (Blackwell, 1973c).

(b) *Labelling and drug delivery systems*

In recent literature there has been considerable interest in the influence of medication labelling on treatment adherence. Though this work is exclusively in the general medical area, its implications can safely be translated to psychiatric populations. Results may even represent an underestimate of the problem when difficulties in comprehension and assuming self-responsibility are taken into consideration.

The difficulty patients experience in directly following labelling instructions has been repeatedly demonstrated. One study (Mazzulo *et al*, 1974) found that when patients were each asked to interpret directions on ten different prescriptions, not once were they correct. In another study (Boyd *et al*, 1974), 60 per cent of patients made errors of interpretation, and lack of comprehension was correlated with poor adherence. Hermann (1973) found that almost half of 450 patients were either unable to take medications on schedule or deviated significantly from the intended dose.

These findings have encouraged attempts to increase adherence by improving drug packaging. Studies in hypertension have provided a model for this type of intervention, because patients are required to take multiple medications for prolonged periods. This is often true for psychiatric patients also, to whom the results can probably be generalized. Two studies (Moulding, 1961; Linkewich *et al*, 1974) have shown three-fold improvements in adherence following the use of a calendar packet, and another (Blackwell, 1976) has shown improved compliance and reduced blood pressure with the use of a plastic container constructed to hold a week's medication by time of day and day of week.

A number of attempts have been made to improve adherence in psychiatric patients who have failed to take their medication as tablets by offering phenothiazines in a different formulation. Wilson and Enoch (1967) found that urines tested by the Forrest reagent changed from negative to positive in schizophrenic patients who were switched from chlorpromazine tablets to identical doses of a liquid formulation.

One consequence of the recognition of the adherence problem in schizophrenic patients has been the development of the long-acting intramuscular neuroleptics. Based on over three years of experience with more than 200 patients, Freeman (1973) suggested that adherence can be significantly improved in schizophrenic out-patients. In a follow-up period of thirteen months, he reported that only 16 per cent of patients discontinued long-acting injections, compared to a figure of up to

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50 per cent recorded in the literature for similar patients taking oral medication. It is possible that the high adherence rates in this clinic were contributed to by attention to the adherence issue and careful follow up of non-attenders and not only to the route of administration of medication.

(c) *Side effects*

The patient with side effects might logically be expected to reject medication. Michaux (1961) found a significant correlation between occurrence of side effects and dosage deviation in male psychiatric out-patients, and Parkes *et al* (1962) discovered that side effects were claimed by 7 of 65 schizophrenic patients who ceased medication soon after discharge from hospital. Renton *et al* (1963) also found that side effects (particularly sedation) were invoked by patients who ceased to take their drugs. Since drugs generally produce more side effects than placebos, this factor may also account for important differences in the adherence of subjects in drug trials. This was confirmed by Porter (1969) in the trial of imipramine in general practice; out of 19 non-adherent subjects 14 were taking drug, and only five placebo.

(d) *Type of medication* Several studies have suggested differences between drugs which may be a direct reflection of patient preference based on side effect potential. For instance, Irwin *et al* (1971), found that 55 per cent of schizophrenic out-patients on thioridazine were non-adherent compared to only 15 per cent on chlorpromazine. A similar difference with the same two drugs was reported by McClellan and Cowan (1970). In the first of these studies, the authors speculated whether this might be due to the paradoxical fact that thioridazine produced fewer side effects, so that the patients surmised the drug was 'doing nothing' and ceased taking it. Another study which suggests that patients may sense when treatment is inadequate or inappropriate is the interesting finding of Willcox *et al* (1965) that the highest default rate in psychiatric out-patients was among depressed patients treated with chlorpromazine. Seventy per cent of this group had negative urines, compared to 32 per cent of schizophrenic patients given chlorpromazine and 44 per cent of depressed patients prescribed impramine.

## Management of Adherence Problems

The almost bewildering diversity, rapid development and lack of consensus in the literature limit the conviction with which suggestions to improve management are made. In the future, modifications intended to alter adherence may be evaluated by appropriate trial methodology of the kind used recently in hypertension programs (Sackett *et al*, 1975). But improved management need not wait on proof; changes are appropriate based on evidence at probability levels below five per cent when the diseases are troublesome and the remedies bland.

Better management requires recognition of the problem and attention to both patient education and treatment regimens.

### 1 *Recognition of non-adherence*

Though some physicians may cherish the illusion that they can intuitively detect drug defaulters, the evidence indicates otherwise. Skilled psychiatrists have been shown to err in up to 20 per cent of their predictions concerning which out-patients are taking their drugs, though it is interesting that 71 per cent of mistakes were in the direction of believing that patients were not taking their drugs when in fact they were (McClellan and Cowan, 1970). The review of the literature makes it clear that there is no stereotypical 'drug defaulter' and consequently no simple or single solution to the question of how the problem should be handled. Whether or not a patient takes his medcation correctly results from a complex interaction between the patient, his illness, the physician and the medication he prescribes.

In a problem without clear-cut causes it remains possible to recognize 'risk factors' which can contribute to low adherence without being singly sufficient or necessary to cause it. Some of the factors suggested in the literature are immutable demographic variables (such as age, sex, race and socio-economic status). Others are amenable to improvement (such as drug regimen and clinic management), while some are more resistant to change (patient attitudes and physician behaviour). Knowledge of these risk factors may help one to understand whether an individual patient and family believe

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in and experience benefits of treatment that outweigh the frustrations, inconveniences and sacrifices of obtaining or persisting with it.

2 *Adherence monitoring*

An important question is the extent to which it is possible or practical to monitor adherence in the clinic. Though none of the methods discussed earlier is ideal, a number of attempts have been made. The simplest method is that described by Mayer (1969), who resorted to prescribing in multiples of sevens instead of tens and questioning the patients after a corresponding number of weeks. Others have given the patient tablets in excess of requirements in order to compute the discrepancy between actual and expected treatment taken (Porter, 1969).

Except in special circumstances, blood tests are clearly too inconvenient or expensive. The Forrest urine test is cheap and easy to administer but the tests are only semi-quantitative, and rare false negatives may occur with low doses of the most potent phenothiazines, particularly when the urine specimen is dilute. Quantities of less than 20 mgs. per day are not detected unless the urine is obtained one and one-half to three hours after drug intake. In schizophrenia, relapse is not closely correlated with a disappearance of colour from the urine; this occurs at an individually variable rate. In addition, false positives may occur during oestrogen therapy, with liver failure or during pregnancy. The originators of the Forrest tests have received over thirty thousand requests for reprints, but hardly any clinics or hospitals use it as a routine procedure. This reluctance is probably based less on methodological shortcomings than on uncertainty about how to confront individuals with the information obtained. This same criticism might apply to all attempts at routine monitoring of adherence. That this need not be so is suggested by the finding of Francis and co-workers (1969), who obtained reliable reports. They had previously spent a year in pre-testing a set of open-ended, non-threatening, non-judgemental questions, e.g. 'You don't seem to be doing quite as well as we hoped; are you having any difficulties with the medication or is there something I didn't explain?'

3 *Patient education and motivation*

Interest in patient education has been an inevitable outcome of the adherence problem; the need seems clear, but the motivation is sometimes lacking. A recent survey (Joubert and Lasagna, 1975) revealed that 92 per cent of patients wanted complete information on the drugs they were taking, but a clear majority (65 per cent) did not wish to take the responsibility for deciding when to administer them. Another finding was that patients who attended physicians regularly knew less about drugs than those who managed their own minor illnesses. This ambivalence tends to support the notion that some patients may value being cared for more highly than the chemicals they are prescribed.

Some resistance to patient education also comes from physicians. A survey conducted by pharmacists (Ascione and Ravin, 1975) found that a fifth of physicans in one hospital did not wish patients to be told anything about the drugs they were taking, and another quarter wanted the patients to be given only restricted information.

Coupled with this ambivalence about the need for education in drug adherence there is some doubt concerning its effectiveness in general populations. Studies in hypertension have shown that both public health nurses (Wilber and Barrow, 1969) and hospital pharmacists (McKenny *et al*, 1973) can have a dramatic impact on improving drug adherence, but the benefits are poorly sustained and adherence returns to baseline once supervision is withdrawn. These studies made attempts to educate the patient about hypertension, and each assumed that this played a major role in improvement. The study using hospital pharmacists demonstrated by questionnaire that significant learning had occurred with an increase in patient knowledge about hypertension, compared to a control group.

Another very recent study in hypertension has confirmed lack of specific impact of educational strategies in modifying the aherence problem (Sackett *et al*, 1975). These generally

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discouraging results concerning the educational process resulted in an editorial in the *American Medical Association Journal* entitled, 'You Can Lead a Horse to Water . . .'. This stated: 'No one suggests to the clergy to stop quoting scripture because sin and crime continue unabated. Health education is an ethical imperative' (Vaisrub, 1975).

One major error in educational strategy has been the reliance placed on fear as a motivational tool. This is an area of extensive research, including studies in such 'at risk' subjects as cigarette smokers, obese individuals, alcoholics and those exposed to industrial hazards. Results of these studies are conflicting; in some people fear appears to be an effective change stimulus but not in others. Leventhal (1971) has attempted to resolve these incompatible findings by constructing a two-factor model. The response of an individual to a fearful message ('You may have to go to hospital if you don't take your medicine') is determined by their belief in the efficacy of treatment and perception of their own vulnerability.

The interplay of these two belief systems determines the likelihood of adherence. When the belief in treatment is high and the concept of vulnerability is moderate to low, patients are most likely to be adherent. This principle is illustrated by the recent finding that end-stage hypertensive patients on renal dialysis do not take propranalol (Briggs *et al*, 1975). In the highly vulnerable individual, treatment may become an unbearable intimation of morbidity or mortality. If taking medication is a reminder of sickness, then forgetting to take medication avoids anxiety and is reinforced as a behaviour. An even more paradoxical example is of the alcoholic exhorted to abstain by threats of cirrhosis who copes with the immediate fear this produces by drinking.

Even without fear and exhortation, the failure of cognitive learning to change behaviour is hardly surprising in the face of attitudes and reward systems around such fundamental needs as being cared for. A much broader definition of the problem is needed so that education addresses itself not only to knowledge but to motivation and self-management skills. The need for adherence is best appreciated by a patient only when the attitudes and beliefs which affect motivation are understood, and motivation to change is best increased by teaching the skills that make change possible. This requires the use of both adult educational methodology and strategies for changing behaviour. This educational process involves clear definition of goals, active involvement of the participants, multiple learning media and feedback of results (Rosenberg, 1976). In addition, acquisition of new information by patients is facilitated by clarity, brevity and dialogue in the communication process, and is impaired by anxiety, social distance and technical terminology. These educational precepts fit well with Parsons' (1951) definition of the sick role as one in which client and helper should have complementary expectations, mutually defined goals and clear roles.

Despite their face validity, these techniques in patient education and motivation are only just beginning to be implemented and studied in patient adherence. In a Chicago clinic, the parents of children with congenital heart disease were studied to show the effect of communication methods on the retention of information immediately after an interview and one month later (Kupst *et al*, 1975). Immediate retention was impaired by parental anxiety and improved by repetition of this information by the physician or re-statement by the parents. At one month's follow up, the best retention of facts occurred in the group where the parents had been requested to report back to the physician the facts imparted. Thus involvement in the information exchange was the most important factor in information retention.

An attempt at self-involvement as a means of enhancing factual learning about drugs has been the very recent suggestion that package inserts should be provided to the patient as well as the physician (Joubert and Lasagna, 1975). Results of this survey also indicated that though patients were eager for additional information, only 10 per cent of the patients preferred the package inserts as the only source of drug information compared to personal counselling by a physician or pharmacist. This preference for personal interaction is supported by the findings in a study on the effect of package

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inserts on patient adherence (Clinite and Kabat, 1969). This showed that medication errors were most frequent in patients given printed instructions only, and lowest in those given both verbal and written directions.

These same principles can readily be applied in practice to psychiatric populations, but they remain to be pioneered and proved.

4 *Strategies and skills*

Once the need for treatment is imparted, strategies and skills must be developed to improve adherence and establish motivation. Application of effective strategies to bring about increased adherence is only just beginning now that the search for a stereotype has failed and the inadequacy of indoctrination and impermanency of supervision have been recognized. The methods are therefore either speculative or under study and still unproven. They are mostly borrowed from the psychological literature based on learning theory as a tool for changing behaviour. The methods are being most vigorously applied in areas of preventive medicine, including the long-term management of hypertension and blood lipid disorders (Pomerleau *et al*, 1975). Basic goals of these methods are to fit the medication within the life style of the individual patient and to further enhance motivation through self-management. These goals are accomplished by variety of behavioural strategies. The patient is encouraged to monitor his drug-taking in relation to life events or experiences, if necessary by keeping a daily diary. This focuses attention on the antecedents and consequences of drug-taking, and helps to identify the most convenient or rewarding times for taking the drug. Self and social reward systems within the family or patient group are developed by contingency contracting, so that drug-taking is reinforced. The anxieties associated with drug-taking are identified and dealt with by simple explanation or stress management techniques. Simple regimens are developed first and success encouraged or rewarded before attempting complicated regimens.

These psychological strategies have been applied first to medical problems, but they may be equally appropriate to selected psychiatric populations or individual patients. To develop self-control and social reward systems could be expected to improve self-esteem in some patients, but may also reveal in others dependency issues or inadequate coping devices that will require attention.

5 *Medication regimen*

The medication itself plays an obvious part in management. The complexity of the regimen should be kept to a minimum by prescribing the least possible number of medications and daily dosages.

This can make for adherence not only because of simplicity and economy but also because the impact of some side effects may be reduced. Anticholinergic effects such as dry mouth and blurred vision are not troublesome during sleep. Sedative effects are capitalized on if medications are given only at night, with the added advantage that a hypnotic can be avoided, further reducing the complexity of the regimen.

In accordance with the educational principles suggested, explanations should be given of the nature and name of the drug and of its immediate or delayed beneficial actions, side effects and predicted duration of administration. Both verbal and written explanations may help, supported by invitations to dialogue using a 'tell me what you heard me say' technique. Repeated information and discussion is valuable, since initial interviews are often impaired by anxiety. These may come from multiple sources, including physician, pharmacist, clinic professionals, family members and patient groups. The presence of a medication 'ombudsman' in the clinic may encourage more open communication. Use can be made of visual charts and patient handbooks that describe drug action in easily understandable ways.

Special packaging of the type described earlier may be of assistance to some patients, but such devices also suffer from the disadvantage that they are expensive and time-consuming to fill and not child-proof (McKenny, 1976).

Finally, management of the adherence problem depends partly on a careful assessment of the capacity and willingness of the patient for self-responsibility balanced against the need for continuing supervision. This should be

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tested and not assumed by giving individuals increasing responsibility for self-care. Patients are often expected to graduate over night from total dependency in hospitals to complete independency at home. They can often be given control over their own medication before discharge, educated and encouraged to seek advice when necessary. For those who require or seek closer supervision, involvement of family and careful continuous follow-up may be important ways to facilitate adherence.

## Summary and Conclusions

1 Failure of the patient to adhere or comply with treatment is a major problem in medical and psychiatric practice.

2 As a result of social and scientific influences interest in adherence is increasing rapidly; the literature is doubling in size every five years.

3 Treatment adherence includes entry into treatment, termination of therapy or the implementation of instructions, including prescriptions for medication.

4 Adherence has been extensively but inadequately studied. A minority of studies have adequate design or definition of terms, in part because adherence is difficult to study.

5 Knowledge of the adherence problem is important for psychiatrists both in personal practice and in consultation to other physicians.

6 Fifty-five studies deal with adherence in psychiatric populations. Almost every kind of population and problem has been studied and about half concern drug treatment.

7 Problems in drug adherence include errors of omission, purpose, dosage and timing and the taking of inadvertent combinations. The literature concentrates on failure to take significant portions of medication, often observed on only a single occasion.

8 Methods of detection include interrogation, tablet estimates, drug markers and drug identification in body fluids.

9 Non-adherence is reported in between 25 and 50 per cent of out-patients and fewer in-patients; the significance is debated in the literature with regard to morbidity in schizophrenia, self-regulation of dosage, economic wastage, hazards to health and distortion of therapeutic trials.

10 There is scant consensus on features that consistently influence adherence, despite the study of more than two hundred variables. A complex interaction of risk factors is involved between the patient, illness, physician, treatment setting and medication.

11 There is no stereotypical drug defaulter, but contributory factors include patient attitudes and behaviour in respect to health, illness, physicians and treatment. Socio-economic factors and degree of social supervision may also influence a patient's adherence.

12 The duration of disease, the degree and rapidity of relapse and certain symptoms of illness may influence adherence.

13 The physician's behaviour and attitudes to the patient or treatment can affect adherence.

14 Adherence is influenced by the treatment setting and is related to degree of supervision, support and follow up.

15 Adherence is reduced by complex treatment regimens and by side effects. It may also be altered by labelling, packaging or formulation of the medication and by the type of drug.

16 Management of adherence depends on knowledge of risk factors, skill in patient education and motivation, use of strategies to modify drug-taking behaviour and manipulations of the treatment regimen.

17 Although non-adherence is difficult to detect, risk factors can be identified; some are immutable, others amenable to improvement and a few are resistant to change.

18 Attempts to monitor adherence are seldom made, although techniques are available; non-threatening, open-ended questions can be effective.

19 Patients and physicians are often ambivalent about patient education, which sometimes fails to have any lasting impact. Improvements in educational strategy include avoidance of fear and use of adult educational methods to improve motivation as well as impart knowledge.

20 Techniques exist designed to help fit medication within the individual's lifestyle and to enhance motivation through self management.

21 These educational and behavioural strategies have been developed in preventive health programs but remain to be pioneered and proved in psychiatric populations.

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22 The medication regimen can be modified to enhance adherence by reduction of complexity or side effects. Information exchange with patients about drugs and evaluation of the capacity for self care are important factors.

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