

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'.

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-

TABLE I
Adherence studies in psychiatric populations

Author(s)	Year	Treatment populations	Type of adherence
Adams, Capel & Bloom, <i>et al</i>	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, <i>et al</i>	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, <i>et al</i>	1975	Depressed out-patients	Treatment dropouts
Ewalt, Cohen & Harmatz	1972	Child guidance clinic	Attendance patterns
Fiestler, Mahrer & Giambra, <i>et al</i>	1974	Community Mental health centre	Treatment dropouts
Forest, Geiter & Snow, <i>et al</i>	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
Hoening & Ragg	1966	General out-patients	Failed first attendance
Hogarty & Goldberg	1973	Schizophrenic out-patients	Relapse rates—drug & social therapy
Howard, Rickels & Mock <i>et al</i>	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, <i>et al</i>	1965	Neurotic out-patients	Drug compliance—minor tranquilizers
Mason, Forrest & Forrest, <i>et al</i>	1963	Schizophrenic out-patients	Relapse—phenothiazines
McCabe, Kurland & Sullivan	1974	Narcotic addicts	Treatment dropouts
McClellan & Cowan	1970	General out-patients	Drug compliance—antidepressants & major tranquilizers
Mester	1972	General out-patients	Drug compliance—all drugs
Michaux	1961	General outpatients	Drug compliance—major tranquilizers

TREATMENT ADHERENCE

TABLE 1—Continued

Author(s)	Year	Treatment populations	Type of adherence
Orford	1974	Alcoholics Halfway house	Treatment dropouts
Pam, Rachlin & Bryskin, <i>et al</i>	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 tranquilizers
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, <i>et al</i>	1963	Schizophrenic out-patients	Drug compliance—phenothiazines
Reynolds, Joyce & Swift, <i>et al</i>	1965	Miscellaneous out-patients	Drug compliance—barbiturates
Richards	1964	Schizophrenic in-patients	Drug compliance—major tranquilizers
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, <i>et al</i>	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 <i>et al</i>	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

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 isoniazid 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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