COMPLIANCE ASSESSMENT IN DRUG TRIALS: HAS THERE BEEN IMPROVEMENT IN TWO DECADES?

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ABSTRACT

Background
Compliance is a key element in the success of therapy, both in practice and research. A study from 1974 demonstrated that compliance in clinical trials was only determined in 19% of studies requiring it.

Objectives
The objective was to determine if there has been an improvement in compliance assessment in clinical trials.

Methods
All drug studies published in the *British Medical Journal*, *Journal of Pediatrics*, and *Lancet* from 1997 to 1999 were reviewed. Clinical trials were evaluated as to their measurement of compliance and the method of assessment.

Results
Of 303 studies in which the effects of drugs were reported, 165 required the incorporation of a measure of compliance, 86 did not, and in 52, compliance could not be measured. Of the studies requiring estimation of compliance, compliance was evaluated in 78 (47%). This rate did not vary between the journals examined or between trials in adults or children. The most common methods used to evaluate compliance were pill count (33%) and self report (25%). The use of drug assays (14%) and close supervision (9%) was less common. Electronic devices and other methods were uncommonly used (5%). In 16% of cases, a combination of methods was used.

Conclusion
Although the rate of evaluation of compliance in drug trials has improved over the past 25 years, it continues to be examined in less than half of the clinical studies of drug effects in which compliance assessment is required. This rate appears to be similar in paediatric and adult drug studies.

***Key Words*:** *Compliance, assessment, drug trial*

Compliance, a term that is often used interchangeably with adherence, is often defined as the extent to which a person's behaviour, in this instance the taking of prescribed drugs, coincides with medical and health advice.[1] Compliance is a key element in the success of therapy, both in practice and research. In clinical practice poor compliance affects the outcome of many diseases; furthermore, in research it introduces a risk of bias in the interpretation of the results of drug trials.[2]

Despite its' potential influence on the outcome of drug research, Soutter et al. previously showed that only 19% of clinical trials reported in the British Medical Journal and Lancet from 1972 to 1974 undertook an objective assessment of compliance.[3] The purpose of the current study was to ascertain if there has been an improvement in

the evaluation of compliance in the 25 years since this initial paper was published. As the earlier data only addressed research in adults, adult and paediatric trials were also compared.

METHODS

All articles evaluating drug effects published between 1997 and 1999 in the British Medical Journal, the Lancet, and the Journal of Pediatrics were reviewed using a format similar to that previously described by Soutter et al.[3] to determine if compliance was assessed. The former two journals were selected, as they were the journals previously studied and the latter was chosen, as it is one of the leading paediatric journals widely read by a varied audience. Review articles, letters to the editor, editorial comments and preliminary reports were excluded as were studies evaluating the efficacy of diet therapies, lifestyle changes, or immunizations.

Trials were subsequently divided by one of the investigators (SJ) into the following three categories[3]

1. Compliance assessment unnecessary – Studies were allocated to this group as a result of the mode of administration resulting in the patient having no control over adherence;
2. Compliance assessment possible and necessary – Upon being allocated to this group, the studies were further divided into two groups: studies where an acceptable and appropriate method was employed and those in which no acceptable measure was used, or was not documented; and
3. Trials in which assessment was impossible – Studies in this group were retrospective analyses.

The methods by which compliance was assessed were also documented. These methods were categorised as follows: pill counts, self/parental reports, drug assays, close supervision, electronic devices and other methods.

RESULTS

A total of 303 studies were published in the aforementioned journals between January 1997 and December 1999. There was no significant difference between the individual publications as to the distribution of studies within the categories. Of the 303 studies reviewed, 165 (55%) required the incorporation of an objective measure of compliance. Within this group of papers, compliance was evaluated in 78 studies (47%). This rate did not vary significantly between the journals (Table 1).

The most popular methods of evaluation were pill counts (33%) and self report (25%). More uncommon forms of assessment were drug assays (14%), close supervision (9%), electronic devices and other methods (5%). In 16% of the studies a combination of assessment methods were used. The most common combination was self/parental reports and pill counts. In 17% of trials, it was considered impossible to adequately assess compliance. In 86 (28%) of the studies, compliance assessment was deemed to be unnecessary. A majority of these papers involved the administration of medications in an in-patient setting.

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TABLE 1 Comparison of Compliance Assessment between Journals

Journal	Assessed	Not Assessed	Total
Br Med J [a,b]	20 (57%)	15 (43%)	35
J Pediatr [a,c]	19 (50%)	19 (50%)	38
Lancet [b,c]	39 (42%)	53 (58%)	92
Total	78 (47%)	87 (53%)	165

[a] $p = 0.54$ [b] $p = 0.14$ [c] $p = 0.43$

DISCUSSION

The above findings may reflect the lack of availability of an inexpensive and accurate method of practically estimating compliance. The absence of a gold standard for the measurement of compliance as well as the additional expense involved in terms of time and money likely contributes to the lack of compliance assessment in many clinical trials. In addition, although the importance of determining compliance in clinical practice is common knowledge, much less has been written about the consequences of ignoring compliance in research studies.

Disregarding poor compliance may introduce bias into the interpretation of the results of a clinical trial. Failure to identify those patients who do not take their medications may lead to an underestimation of the efficacy of the treatment. Overestimation of the dose requirement may occur as the dose-response curve under an intention to treat analysis may be effectively shifted to the right.[4] On the other hand, the new drug's safety profile might appear falsely optimistic as dose-related toxicities would appear to be less frequent and less severe.[5] Analysis of compliance helps to determine the degree of exposure to drug and robustness of data.[5]

Ideally, if compliance is measured during a clinical trial it could be viewed as a dosing experiment where the dose actually taken could be correlated with the effects seen, both beneficial and toxic. The effects of varying levels of compliance could then be included in the labeling of the drug. Although there has been an increased acknowledgement of the role of compliance in clinical practice, the problems pertaining to compliance assessment in the design of clinical trials appear to persist today. Although there has been improvement, the majority of research studies are still undertaken without any assessment of patient adherence. It also appears it is no more likely for clinical trials among adults to estimate compliance than trials involving children. Without this information, inappropriate conclusions may be reached regarding the efficacy and safety of medications.

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