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The Importance of Non-biological Factors in Influencing the Outcome of Clinical Trials

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The outcome of clinical drug trials is influenced both by biological and by non-biological factors. Non-biological factors can be subdivided into methodological factors and non-drug factors. The former are related to the definition and measurement of treatment course, response, and outcome itself; the latter cover characteristics of the patient, the treatment milieu, the patient's milieu apart from treatment, and (planned) psychosocial interventions. Although their mechanism of interaction with treatment outcome is not yet fully understood, these non-drug factors should be routinely monitored in clinical trials for three practical reasons: (a) to control for the heterogeneity of outcome; (b) to develop individualised outcome predictors; and (c) to promote the development of individualised guidelines for treatment indication.

The outcome of clinical drug trials in psychiatric disorders is the result of a complex process, involving the interaction of biological and non-biological factors. The measurement of 'outcome' itself is a complex task, requiring a multidimensional concept, adequate instruments, and adequate timing of assessment. Therefore, methodological factors contribute heavily to the characteristics of outcome and related concepts (e.g. treatment response). In addition, the illness course and its change by drug treatment are themselves influenced by various factors. These latter factors, which are often referred to as potential outcome/response 'predictors', are sampled from a wide area of patient and environmental characteristics. Although mainly described in psychological and sociological terminology, they are not necessarily non-biological in nature. Since the kind and mechanism of their treatment influence is far from clear, the more preferable, neutral term for them is 'non-drug' factors.

Methodological factors influencing outcome assessment

Illness course

The continuum of illness course and some major areas of assessment are schematically represented in Fig. 1. The true continuum could be reconstructed by use of a sufficiently dense time frame ($\Delta t \rightarrow 0$) on certain assessment levels. The time frame required depends on the illness stage under study (acute/post-acute/chronic) and the corresponding gradient of change. However, since assessment instruments usually cover a certain time period in retrospect, very short time intervals are neither necessary nor feasible to model the true course under treatment conditions.

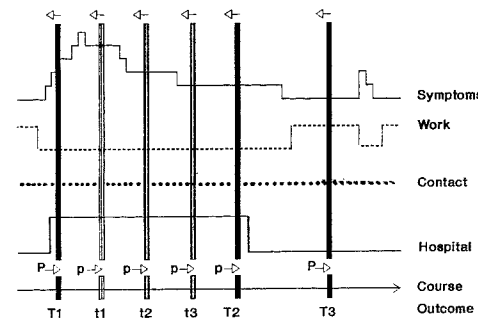

Fig. 1 Illness course and the continuum of outcome dimensions: time frame of assessment (T, t) and prediction (P, p).

Outcome

'Outcome' refers to a cross-sectional aspect of illness course. According to a multidimensional concept, various measures are required which are sensitive to the expected treatment effects in different target areas. These areas are of different importance depending on the stage of illness/treatment (e.g. acute v. long-term). The main areas covered are symptoms, work function, social contacts, and need for hospitalisation; another – inconsistently defined – construct which has recently been given more attention in evaluating the outcome of drug studies is quality of life (Awad, 1992). As has been shown in schizophrenia (Gaebel *et al*, 1986), cross-sectionally these different areas are moderately intercorrelated, but longitudinally they are best predicted individually (Tables 1 and 2). Therefore, they have been conceptualised as 'open linked systems'. According to Strauss & Carpenter (1974),

Table 1
Intercorrelation of four outcome measures during first/third year after index discharge in 86 ICD-9 schizophrenics (Gaebel *et al*, 1986)

	Non-hospitalisation	Social contacts	Employment	Absence of symptoms
Non-hospitalisation	1.00	NS/NS	NS/0.37***	0.25*/0.26*
Social contacts	–	1.00	0.29**/0.30**	NS/0.27*
Employment	–	–	1.00	0.37***/0.59***
Absence of symptoms	–	–	–	1.00

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

"each system is open in the sense of influencing and being influenced by outside variables; the systems are linked in the sense of having definite but incomplete interdependence; conceived in this framework each outcome process, work, social relationships, symptoms, and need for hospitalization might be considered as a system". Accordingly, there are many outcomes instead of a single outcome. For instance, the characterisation of a biological variable as a state or trait marker requires a clear definition of 'remission' by means of a target symptom measure. In schizophrenia, patients whose positive symptoms are in remission often still demonstrate substantial negative symptoms. Whether or not we say that the disorder is in remission depends on our definition. It is evident that there is no outcome apart from what is arbitrarily defined as such.

Response

Response is a treatment-related concept of illness course. It refers to a defined change of illness course, either before or after treatment, in a certain outcome system, due to the influence of treatment. However, a causal treatment influence may be inferred only if an appropriate study design allows for the control of spontaneous changes in the illness course (e.g. placebo control). Therefore, in evaluating drug treatment effects, response 'on drug' has to be distinguished from response 'to drug' (May & Goldberg, 1978). The type and latency of treatment effects must influence the choice of target symptoms, treatment duration, and time frame of measurement.

Target symptoms

In acute drug trials, signs and symptoms of a given disorder are the target areas for measuring response. Usually, they are combined in a syndrome score or the total score of a rating scale which is applied repeatedly, at least once at the beginning and once at the end of a trial. As with global response statements such as 'better' or 'worse', there are at least two potential disadvantages of composite-scale scores. First, the mixture of signs and symptoms blurs any differential effects of a drug, informing just about change in illness severity. Second, signs and symptoms are from different data sources: the former are directly observed by the rater; the latter are reported by the patient (Alpert, 1985). From the viewpoint not only of reliability but also of validity, signs (i.e. objectively monitored features of illness behaviour) may be sometimes more preferable than patients' self-reports. With respect to a 'functionally' orientated psychopathology (Van Praag *et al*, 1987), which aims at underlying psychobiological dysfunctions and their drug reactivity, the target areas of drug response should be refined by means of objective assessment methods and experimental conditions (Gaebel & Renfordt, 1989).

Table 2
Correlation of one-year outcome with three-year outcome in 86 ICD-9 schizophrenics (Gaebel *et al*, 1986)

	Three-year outcome			
	Non-hospitalisation	Social contacts	Employment	Absence of symptoms
One-year outcome				
Non-hospitalisation	0.35***	NS	NS	NS
Social contacts	NS	0.36***	NS	NS
Employment	0.22*	NS	0.63***	0.40***
Absence of symptoms	0.26*	0.20*	0.52***	0.38***

*$P<0.05$; ***$P<0.001$.

Treatment duration and time frame of measurement

Response to psychoactive drugs, such as typical neuroleptics or tricyclic antidepressants, develops with a certain time delay. However, if one looks at the exponential curves of change with time, responders (on or to drug) appear to improve more rapidly than non-responders (Fig. 2). Therefore, response is also a time-related measure of treatment outcome. Partial response/non-response/treatment refractoriness are always arbitrarily defined, meaning that a certain criterion of change with time has not been met. It is not known whether the longer time course of change in 'non'-responders reflects the slow but natural self-limitation of an illness episode (accelerated by drug only in the case of responders), or whether it reflects a kind of partial (e.g. placebo) responding.

No doubt the necessarily arbitrary definition of all three criteria has a definite influence on the measurement of outcome.

Non-drug factors influencing outcome

In addition to the methodological aspects discussed above, a number of non-drug factors contribute to the heterogeneity of outcome, 'predictors':

(a) age
(b) sex
(c) social adjustment
(d) personality
(e) family history
(f) precipitating events
(g) illness course
(h) symptoms
(i) diagnosis
(j) biological findings
  (i) before treatment
  (ii) after challenge.

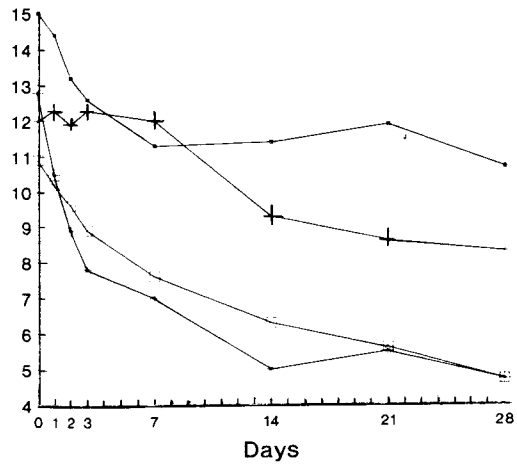

Fig. 2 Time curves of change in thought disorder (THOT; Brief Psychiatric Rating Scale) in 50 acute RDC schizophrenics on drug (perazine) for 28 days: —●— male non-responders; —+— female non-responders; —✱— male responders; —□— female responders. MANOVA results: response, $F_{1,46} = 23.90$, $P < 0.0001$; course, $F_{3,40} = 14.08$, $P < 0.0001$. (From Gaebel *et al*, 1988.)

However, the meaning of correlations between predictors and outcome is far from clear. Generally, most of these variables are 'indicators' for unknown processes, relating in unknown ways to the outcome. Many of these relationships depend on the particular definition of outcome. It has to be kept in mind that the status of these variables is almost never that of an outcome 'determinant' – even the biological determinants of drug response are still unknown. Hence, what is called 'influence' is at best a statistically associated 'risk factor' for treatment failure and/or side-effects, or a 'predictor' for treatment response. In the individual case, however, these predictors are usually of little help when we have to decide in advance whether or not a specific treatment method should be applied.

To contribute to scientific development in this field, researchers should generally include potential predictors in clinical trials (Carpenter *et al*, 1981). However, appropriate guidelines are not yet available. Moreover, to make study results better comparable, the calculation of sensitivity (true-positive rate) and specificity (true-negative rate) of a predictive measure with respect to different cut-off points has been proposed. 'Receiver operating characteristics' methods allow the significance of different outcome predictors to be assessed and compared graphically (Hsiao *et al*, 1989).

Patient characteristics

If we consider the patient as a biological/non-biological multilevel system (Engel, 1980), the intervening levels shown in Fig. 3 may be involved in contributing to the complexities of outcome in drug treatment. In the 'black box' (Fig. 3), at least two system levels of a non-biological nature are of superior importance: compliance and subjective response. Both relate to patients' attitudes and expectations, modified by personality, sex, education, and so on, but also by illness characteristics – diagnosis, lack of insight, paranoid tendencies, increased body awareness, and so on – which all may contribute to subjective dislike or even refusal of drugs. Since the ultimate clinical effect is evaluated not only from an

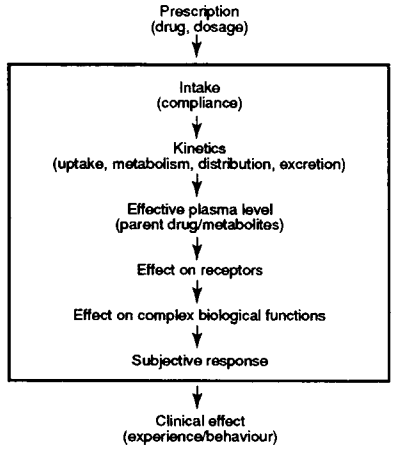

Fig. 3 Intervening system levels contributing to the complexities of outcome in drug treatment. (From Helmchen & Gaebel, 1987.)

objective/behavioural but also from a subjective/experiential perspective, attitudes and expectations do play a great role in patients' evaluation of and adherence to treatment. These attitudes are now accessible by self-administered questionnaires such as the Drug Attitude Inventory (Hogan & Awad, 1983). Instruments like this should be routinely included in clinical trials to identify the potential non-complier and/or subjective non-responder. From their research with the test-dose approach, Van Putten & May (1978) have clearly demonstrated that 'dysphoric' responders to a neuroleptic test dose have a poorer outcome and/or are potential non-compliers. Since the clinical non-compliance rates concerning the intake of neuroleptic drugs range from 11% to 48% (Johnson, 1984) depending on the treatment setting, it is important to take 'the consumer's' perspective into account (Van Putten & May, 1978). Choice of an intramuscular administration route may be one way to overcome problems with compliance. A better way may be to change attitudes in a therapeutic context. In clinical trials it is important to identify the potential non-complier or drop-out at an early stage of treatment.

Treatment-milieu characteristics

Treatment-milieu characteristics cover therapist variables, patient – physician interaction, and setting characteristics. The enthusiastic, skilled therapist serves as a 'facilitator' who influences outcome in indirect ways such as keeping patients in treatment, inspiring hope and confidence, and achieving patient co-operation and compliance with a treatment regimen (Tuma *et al*, 1978). Shapiro (1969) concludes from several studies that the therapist's commitment to pharmacotherapy, based on knowledge about the treatment and interest in the patient, is a prerequisite for treatment success.

Concerning setting variables, psychotic patients seem to benefit primarily from a milieu with a high level of support, practical orientation, order and organisation, and a low level of anger and aggression as measured by the Ward Atmosphere Scale (Moos & Schwartz, 1972; Moos *et al*, 1973; Friis, 1986). The negative results of therapy in a democratic and permissive milieu (Spadoni & Smith, 1969) and the positive results in a hierarchically orientated milieu, centred around a medical model (Carpenter *et al*, 1977), fit into this context.

In practice, treatment-milieu factors and drug effects interact in complex, often unforeseeable ways. It should be remembered that the combination of two active treatment principles, A and B, may lead to different interactions, such as addition and potentiation but also inhibition and inversion (Gaebel & Linden, 1984). The study of Hogarty *et al* (1974) is a good example of the interaction type of dependency, where major role therapy is effective in combination with neuroleptic drugs, but not alone.

Particularly in multicentre studies, possible differences in therapist orientation and treatment setting are usually not taken into account. However, differences in patient drop-out rate and/or treatment outcome may be related to (covert) differences in treatment-milieu characteristics.

Patient-milieu characteristics

The social context of schizophrenia (Wing, 1978) contributes in many respects to the outcome of the disorder. Concerning the macro-context, the illness course seems to be more benign in developing than in developed countries (World Health Organization, 1979). Similarly, differences concerning the rate of hospital readmission have been observed between a rural area in southern Germany (lower rate) and the city of Berlin (Pietzcker & Gaebel, 1983). It is not known which factors are responsible for these differences. Possibly, higher tolerance of the environment in developing countries and rural areas is of importance.

In a micro-context, the contribution of independent life events to the course of illness (relapse) seems to be less powerful than the effect of drug treatment (Hirsch *et al*, 1993). However, the quality of schizophrenics' heterosexual adjustment does seem to interact with neuroleptic treatment: patients

who are heterosexually better adjusted seem to profit more from continuous maintenance medication than those who are poorly adjusted (Gaebel & Pietzcker, 1987). Similar results have been reported by Goldberg *et al* (1977). Better pre-morbid adjustment of married patients (particularly male) and better assistance in compliance may be the critical components of this variable. More directly, the behaviour and attitudes of key relatives towards the patient seem to have an impact on the illness outcome. Accordingly, patients from homes with high 'expressed emotions' (EE) seem to suffer from a higher relapse rate than others in the nine months following discharge from index hospital stay (Vaughn & Leff, 1976; Vaughn *et al*, 1982). In contrast to the nine-month report, however, after two years patients from low-EE homes seemed to profit from maintenance medication whereas those from high-EE homes did not (Leff & Vaughn, 1981). Hogarty *et al* (1988) found no interaction between standard/low dose and high/low EE over two years. Because of methodological limitations, several problems with the EE concept still remain unsolved (Koenigsberg & Handley, 1986). Overlap with illness variables (e.g. illness duration) has been reported (MacMillan *et al*, 1986).

Although May & Goldberg's (1978) statement still holds, that "drug treatment tends to override (but not entirely) the effect on prognosis of the usual demographic and history variables", outcome research is increasingly concerned with the interaction of biological and non-biological processes. At present, the diathesis–stress or vulnerability models allow researchers to best integrate the effects of social factors and maintenance neuroleptics on the illness course of schizophrenics (Leff, 1985; Clements & Turpin, 1992).

Psychosocial interventions

It is known from the early integrative treatment studies that the powerful effects of drug treatment on illness course and outcome can be augmented by psychosocial intervention (Hogarty *et al*, 1974). Whether carried out on an in-patient or out-patient basis, current psychosocial treatment programmes usually include the families and focus on areas such as psychoeducation, teaching about prodromal symptoms, information about drug treatment and side-effects, exploration of potential stressors, problem-solving, and social-skills training (Clarkin *et al*, 1991; Barrowclough & Tarrier, 1992; Birchwood *et al*, 1992; Vaccaro & Roberts, 1992). Designs of clinical drug trials should be increasingly concerned with the inclusion of planned psychosocial interventions to evaluate their contribution to the outcome of drug treatment.

Conclusions

The outcome of clinical drug trials is in part dependent on conceptual and methodological factors such as definition and measurement of treatment course, response, and outcome itself. In addition, non-drug factors such as patient characteristics, treatment and non-treatment milieu, as well as (planned) psychosocial interventions can all contribute to outcome in a way which as yet is not fully understood. Although at first sight they are of a 'non-biological' (i.e. psychosocial) nature, these factors must also exert a biological influence on the individual's psychobiological make-up. According to the biopsychosocial model (Engel, 1980; Goodman, 1991), which is now generally accepted in medicine and psychiatry, illness vulnerability itself is conceptualised in non-biological as well as biological terms. Accordingly, the biological aspects of non-biological factors influencing the outcome of drug trials are still to be identified.

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