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Prediction: Nonsense or Hope?

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Psychiatry and psychopharmacology are no longer aiming to make a decisive breakthrough at the end of the century. Rather than seeking explanations, research workers are looking for 'predictions'. Three main types of prediction are emerging: a tautological, a heuristic, and an irrelevant one. Few predictions found in the recent literature can be marked as 'logical' ones. Nevertheless, predictions play two important roles: they generate new hypotheses that can be falsified in properly designed scientific experiments; they also may serve to falsify given hypotheses. The main recent findings on predictions in psychiatry are briefly summarised.

The term 'prediction' (predict = to tell in advance) is related to 'correlation', 'causality', and 'forecasting', having thus important philosophical connotations. There is a tendency to mistake prediction for causality in contemporary science, as predictors are often suspected of being the cause of the events they relate to. Causality means that all phenomena occur as consequences of other phenomena. However, the relationship between two or a few phenomena ('correlation') represents always rough abstraction. There are at least two types of what are called 'causes': crucial stimuli and conditions. Nevertheless, this concept is based on the mechanistic science of the 19th century. Taking subjectivity (of animals) into account, it is preferable to talk about a reaction rather than about consequence. In addition, the period of time between 'cause' and 'consequence' gets longer or irregular, so that often the correlation becomes fuzzy and difficult to find. Moreover, there occurs purposefulness as an important feature complicating the one-way temporal direction of causality.

Aristotle, in *The Physics* (1; 2, VII, 198a) (Heinemann (1980) edition, London), saw four main kinds of cause:

- (a) substantial (Latin *Causa materialis*, Greek ΑΙΤΙΑΙ ΗΥΛΕ)
- (b) formal (Latin *Causa formalis*, Greek ΑΙΤΙΑΙ ΕΙΔΟΣ)
- (c) moving (Latin *Causa movens*, Greek ΑΙΤΙΑΙ ΤΟ ΚΙΝΗΣΑΝ)
- (d) purposeful (Latin *Causa finalis*, Greek ΑΙΤΙΑΙ ΗΥ ΗΕΝΕΚΑ).

This understanding of order was replaced in the 18th century by mechanistic materialists Holbach (1770) and La Mettrie (1747), following the discoveries of Galileo and Newton: causality was understood in the mathematical sense as a transfer

of energy from one body to another. This was then criticised by empiricists (e.g. Hume, in his *Works*) who stressed that cause is nothing but habit. The only reason to infer causality comes from a temporal association; were it so, causality could not be distinguished from correlation. Immanuel Kant (1781) then postulated that things in themselves are on principle unknowable, and everything we study is nothing but the world of phenomena; reality cannot be built on custom only; causality is one of the categories of our mind; we tend to chain up events and to formulate laws; causality is valid only in the world of phenomena, but not in the world in itself. Positivists (e.g. August Comte and John Stuart Mill) formulated four methods for discovering causality: (a) the method of identity (e.g. of two phenomena); (b) the method of difference (missing phenomenon 1 causes absence of phenomenon 2); (c) the method of grouped changes (if it is not possible to remove a phenomenon, the changes are correlated); (d) the method of residuals (stepwise exclusion of several phenomena; suspect cause can be hidden in the remaining ones). The crisis of modern science warns us not to overestimate this understanding of causality. It makes us aware of the limits of reductionism: we can search for causal relationships at a certain level of knowledge but we are not able to find causal relationships between two different levels, e.g. the psychological one (mind) and the biological one (body). This represents also the limitation of the explanatory attempts of artificial intelligence. That is also why we are openly searching not for causes but for 'markers'. Markers have predictive rather than explanatory power. Psychopharmacology has resigned from attempting to make a decisive breakthrough at the end of the century. Nevertheless, it defends the rest of the field, searching for 'predictions'.

Table 1
Summary of recent predictions in psychiatry

What is predicted	Predictor	Tool	Result	Reference	Type/note
Drug dose	Test dose	Pharmacokinetic model; blood level	Test doses can predict drug dose	Swartz, 1991	Logical
Therapeutic outcome of bulimic patients	Personality variables	Borderline Syndrome (BS) Index, Giessen Test (GT), etc.	High score in BS test and self-experience of dominance (GT) predict poor prognosis	Herzog <i>et al.</i> , 1991	Heuristic
Social skill acquisition in schizophrenics and major depressives	Memory and symptomatology	Clinical examination, Wechsler Scales, etc.	Poor memory is related to pre-treatment social-skill impairment and slower improvement during the intervention in schizophrenia, but not in major depression. Symptomatology is not related to social skill	Mueser <i>et al.</i> , 1991	Tautological
Recovery of depressed patients	Large set of variables	Stepwise multiple logistic regression	ECT, personality disorder, chronicity, anxiety disorder, organic mental disorder and dysthymia predict recovery	Black <i>et al.</i> , 1991	Heuristic
Benefit from cognitive-behavioural therapies of patients with major depression, dysthymia, or generalised anxiety disorder	Intelligence	Personality inventory	Intelligence measures do not predict outcome	Haaga <i>et al.</i> , 1991	Irrelevant (major depression is not a question of intelligence; cognitive therapy is not a main relevant treatment of these disorders)
Therapeutic alliance and psychotherapy outcome	Object relations; interpersonal functioning	Interview questionnaire	Quality of object relations predicted therapy outcome	Piper <i>et al.</i> , 1991	Tautological
Therapeutic response to various types of antidepressant	State of monoaminergic transmission	MHPG, 5-HIAA, HVA levels	Monoamine pre-treatment levels do not significantly predict therapeutic response	Balon, 1991	Combined logical and heuristic
Steady-state plasma level	Single test dose	Blood level, linear regression model	Strong correlation of log steady-state plasma level, 24 h plasma level, and doses of haloperidol	Javald <i>et al.</i> , 1991	Tautological ('the more you use the more you have')
Anxiety, depression, anger, etc.	Headache	Standardised psychometric tests	Headache subjects showed higher anxiety, depression, and hostility	Hatch <i>et al.</i> , 1991	Irrelevant (headache may be a symptom of depression, or the consequence of anxiety; there is also reversed relationship, etc.)
Long-term outcome in schizophrenia	Symptoms; psychological and personality data	Clinical examination, medical records, discriminant analysis	'Atypical' symptoms are associated with favourable outcome; 'high-risk personality', and duration and severity of illness are related to bad prognosis	Jonsson & Nyman, 1991	Heuristic (107 predictor variables) and tautological (long duration of illness means bad prognosis)

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Table 1
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What is predicted	Predictor	Tool	Result	Reference	Type/note
Response to psychotherapy and pharmacotherapy	Patient characteristics	Clinical examination, medical records, scales (HRSD ¹ , BDI), personality inventory	Better social functioning predicted superior response to interpersonal psychotherapy; better cognitive functioning predicted better response to cognitive-behaviour therapy and to imipramine; high work dysfunction and severity of depression predicted superior response to imipramine	Sotsky <i>et al.</i> , 1991	Logical (hypothesis); irrelevant guidance of proof (the ability to undergo treatment may be confused with treatment response, etc.)
Cancer; coronary heart disease	Coffee consumption; personality	Personality inventory; questionnaire	In cancer-prone probands, coffee consumption was related to low incidence of cancer and high incidence of coronary heart disease. The same in coronary heart disease prone probands with the opposite influence of diazepam	Grossarth-Maticek & Eysenck, 1990	Heuristic
Response to clozapine in schizophrenic patients	Prefrontal sulcal prominence	Brain CT, Brief Psychiatric Rating Scale, regression analysis	Prefrontal sulcal prominence is inversely related to response to clozapine	Freidman <i>et al.</i> , 1991	Heuristic
Response to lithium	Various manic symptoms	Examination, rating scales	Elation, grandiosity, paranoia, irritability, delusions, and hallucinations did not predict treatment response	Miller <i>et al.</i> , 1991	Heuristic
Treatment response	Chronology between panic disorder and avoidance behaviour; onset of panic disorder	Descriptive data	Neither the chronology between panic disorder and avoidance behaviour nor the age of onset of panic disorder predicted outcome in short-term treatment with alprazolam or imipramine	Buller <i>et al.</i> , 1991	Irrelevant (artificial distinction between the onset of avoidance behaviour and panic disorder)
Therapeutic outcome in depression	'Neuroticism'	Self-report personality inventories	'Neuroticism' predicted poor outcome	Hirschfeld <i>et al.</i> , 1986; Weissman <i>et al.</i> , 1978	Tautological (definition of depression as 'non-neurotic')
Utilisation of ambulatory services	Somatisation; psychiatric diagnoses; life stress	Diagnostic Interview Schedule; Life Experiences Inventory	Somatisers under stress made more visits to the clinic than did non-somatisers or somatisers who were not under stress	Miranda <i>et al.</i> , 1991	Tautological result
Prestige of medical specialities	Income; assigned social value	Questioning of 400 respondents	Income is the single best predictor of prestige, surgery and cardiology being at the top and dermatology and psychiatry at the bottom	Rosoff & Leone, 1991	Tautological
Suicide	Number of prior suicide attempts, suicide ideation on admission, bipolar disorder, gender, outcome at discharge etc.	Stepwise multiple logistic regression	It is not possible to predict suicide	Goldstein <i>et al.</i> , 1991	Heuristic

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Table 1
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What is predicted	Predictor	Tool	Result	Reference	Type/note
Post-operative changes in cognitive function in left temporal lobectomy (LTL) and in right temporal lobectomy (RTL) patients	Pre-operative ability levels	A battery of memory, language and visuospatial tasks	Higher pre-operative performance on the memory and language measures were associated with larger decrements among LTL but not RTL patients	Chelune <i>et al.</i> , 1991	Irrelevant (the law of initial value?)
Clinical response to psychoactive drugs	Event-related potentials	EEG	Promising to discriminate responders and non-responders	Hegerl & Herrmann, 1990	Heuristic
Suicide	Hopelessness	Beck Hopelessness Scale (BHS)	A cut-off score of 9 on BHS appears to be predictive of eventual suicide	Beck & Weishaar, 1990	Tautological
Diet-breaking behaviour	An internal attributional style for negative events	Psychological assessment	Attribution of 'global' causes for a lapse predicts a more serious relapse during the period of dietary restriction	Ogden & Wardle, 1990	Tautological
Occurrence of neuroleptic-induced extrapyramidal syndromes	Past history of neuroleptic-induced extrapyramidal syndromes	Charts of patients	Previous extrapyramidal syndromes correctly predicted extrapyramidal syndromes in subsequent treatment for 84% of patients	Keppers & Casey, 1991	Tautological
Ventricle/brain ratio (VBR)	A history of abnormal delivery and the presence of left-handedness	Case records; computed tomography; multiple regression analysis	A history of abnormal delivery and the presence of left-handedness were significant predictors of an enlarged VBR	Pearlson <i>et al.</i> , 1989	Heuristic
Cardiovascular responses to a mental arithmetic task	Baseline measures of receptors (R) and non-receptors (NR)	Lymphocyte beta-receptor density and sensitivity (R), plasma catecholamines, heart rate, blood pressure (NR), multiple statistics	R explained 48.4% of the variance in heart-rate response; both R and NR predicted 76.6% of the variance	Milis <i>et al.</i> , 1990	Heuristic
Antidepressant treatment outcome	Amphetamine challenge test (ACT) response	ACT; How I Feel Scale (HIF); HRSD ¹ ; regression analysis; desipramine and alprazolam treatment	Improvement in the HIF total score after ACT predicted HRSD improvement after treatment	Kravitz <i>et al.</i> , 1990b	Logical
Remission pattern	86 traits chosen from rehabilitation automated information system	Non-uniform statistics and Bayes' method	76% of prognoses correct	Burkovski <i>et al.</i> , 1990	Heuristic
Benefit from group psychotherapy	Personality features; attitudes to treatment	Claybury Selection Battery; SCL-90	Attitudes to treatment correlated significantly with outcome	Pearson & Girling, 1990	Heuristic
Response to cognitive therapy in depression	REM latency	REM latency \leq 65 min as a criterion; diagnostic criteria; HRSD ¹	There was no systematic relationship between pre-treatment REM latency and response to cognitive therapy	Jarrett <i>et al.</i> , 1990	Logical (testing the 'endogeneity' hypothesis)

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Table 1
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What is predicted	Predictor	Tool	Result	Reference	Type/note
Haloperidol-related dyskinesias	Baseline stereotypic movements; demographic variables	Clinical assessment; demographic data	No significant predictors of development of dyskinesias were found. IQ was negatively related to stereotypies	Campbell <i>et al.</i> , 1990	Heuristic
Prognosis of schizophreniform disorder	Four prognostic features according to DSM-III-R	DSM-III-R; two or more features predict good prognosis; 16 schizophrenic patients followed up	No correlation was observed between the presence of two or more features and favourable outcome	Guldberg <i>et al.</i> , 1990	Logical (falsifying given hypothesis)
Response to ECT	Psychomotor disturbance assessed by the CORE rating system	CORE rating system; multivariate analyses	Psychomotor disturbance significantly predicts response to ECT	Hickie <i>et al.</i> , 1990	Heuristic
Response to a stressful life event in elderly persons	Coping strategy	Ways of Coping Questionnaire (WOCQ); canonical analysis; 81 persons	Avoidant coping predicted psychological disturbance	Smith <i>et al.</i> , 1990	Tautological
Response to lithium in bipolar patients	Previous pattern of course of illness	Patients divided in four groups: MDI (sequence mania-depression-interval), DMI, CC-LC (continuous long cycles), and CC-RC (rapid cycles); further course followed	High response rate to Li ⁺ in MDI group; low response in DMI and CC-RC groups	May, 1990	Heuristic
Steady-state plasma haloperidol concentrations	Two blood samples after 20 mg test dose	Pharmacokinetic model	Two blood samples predicted steady-state blood level accurately in contrast to mg/kg/day dosage; both methods were less predictive when the daily dose exceeded 0.47 mg/kg	Miller <i>et al.</i> , 1990	Logical
Outcome of treatment with antidepressants	Early improvement	HRSD ¹ ; HRSA ¹ ; desipramine, alprazolam, combination	Early improvement predicted total HRSD improvement, mostly in alprazolam group	Kravitz <i>et al.</i> , 1990a	Tautological
Response to total sleep deprivation (TSD)	Diurnal variation of mood	Self-ratings; HRSD ¹	Feeling better in the evening predicts better response to TSD	Reinink <i>et al.</i> , 1990	Logical
REM abnormalities seen in endogenous depression (ED)	Treatment of neonatal rat with clomipramine	EEG	Neonatal treatment with clomipramine led to adult REM abnormalities typical for ED	Vogel <i>et al.</i> , 1990	Logical

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Table 1
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What is predicted	Predictor	Tool	Result	Reference	Type/note
Decreased sexual activity	Treatment of neonatal rat with clomipramine	Observation	Neonatal treatment with clomipramine led to adult decrease in sexual activity in Long-Evans rats	Neill <i>et al.</i> , 1990	Logical
Outcome of schizophrenia	Clinical, genealogical, and historical data	Multiple regression; 58 in-patients	Baseline positive syndrome (not negative!) predicted poor outcome; thought disturbance portended the worst prognosis, depressive syndrome the best one	Kay & Murrill, 1990	Heuristic
Alcoholism according to DSM-III	Antisocial personality (ASP), gender, family history of alcoholism (FHA)	DSM-III; Family History Research Diagnostic Criteria; NIMH Diagnostic Interview Schedule	ASP, then gender and finally FHA, but not age, were significant predictors of DSM-III alcoholism	Stabenau, 1990	Heuristic
Response to neuroleptic treatment (length of stay in hospital)	Early response to medication	40 psychotic in-patients; clinical assessment	Neuroleptic trial response on the fixed dose could be accurately predicted for 65% of the patients by day 3 of the trial (for 80% by day 7)	Zemlan <i>et al.</i> , 1990	Tautological
Type of depression	Personality	42 case records	The ratio of assignments to 'manic type' and 'melancholic type' decreases from mania, to bipolar I and II disorders, and to unipolar depression	Zerssen & Possel, 1990	Irrelevant methodology
Suicidal attempts (SA)	Huge number of variables	Case records (69 with SA, 163 without); logistic regression analysis	Suicidal ideation, marital isolation, neurovegetative signs, feelings of failure, and alcoholism or bipolar II are associated with suicidal attempts	Bulik <i>et al.</i> , 1990	Heuristic

1. HRSA, Hamilton Rating Scale for Anxiety (Hamilton, 1959); HRSD, Hamilton Rating Scale for Depression (Hamilton, 1967).

From the literature on prediction in psychiatry and psychopharmacology (Table 1), three main types of prediction can be seen to emerge: a tautological, a heuristic, and an irrelevant one. Tautological prediction may be characterised by the statement, "The more depressed you are, the more depressed you will be next time", or, "The better you respond to the antidepressant, the better responder to it you are going to be." This type of prediction seems to be the most accurate and successful. For example, 'duration and severity of illness' predicted 'bad prognosis' in a study of 92 schizophrenic patients (Jonsson & Nyman, 1991).

Heuristic prediction should also be called 'fishing'. It often emerges as a 'correlation' on endless sheets of print-out, with multiple regression analyses not primarily testing a specific hypothesis. It is characterised by the statement "we have also found . . ." which can be also understood as "we have caught . . .". Black *et al* (1991), for example, tried to predict recovery in a group of 1471 depressives by six variables: electroconvulsive therapy (ECT), personality disorder, chronicity, anxiety disorder, organic mental disorder, and dysthymia. This approach often works in spite of an incompatible mixture of plums, apples, and nuts at first sight.

The irrelevant prediction differs from the preceding type by the absence of heuristic power; for example when measuring the mood of normal volunteers using tools pertinent for pathology (e.g. the Hamilton Rating Scale for Depression) or omitting the placebo effect (see Young & Fogg, 1990). Few predictions found in the recent literature can be marked as 'logical' ones; e.g. the prediction of steady-state plasma drug concentrations accomplished by obtaining two blood samples after a single test dose (Miller *et al*, 1990).

Nevertheless, in spite of the cautious skepticism, I do believe that our contemporary approach can produce new knowledge. The correlations and predictions we find play two important roles. First, they generate new hypotheses that can be falsified in properly designed scientific experiments; in this way they drive scientific progress. For example, Eysenck's finding (1990) that some personality traits can predict cancer in healthy probands with 81% accuracy is challenging. It generates additional falsifiable hypotheses about the connections between particular personality features, the immune system, and carcinogenesis.

Second, correlations and predictions may serve to falsify given hypotheses. For example, according to the pure monoaminergic hypothesis of depression, the pre-treatment blood or cerebrospinal fluid levels of MHPG and 5-HIAA should predict the

differential therapeutic response to antidepressants which block noradrenaline or 5-HT uptake. However, the hypothesis seems to be falsified by Balon's report of contradictory or inconclusive results (1991).

In psychopharmacology, many of the recent studies and summaries concern predictors of response to tricyclic antidepressants (TCAs) (Friedel, 1983; Brotman *et al*, 1987; Joyce & Paykel, 1989). In general, 'typical' neurovegetative symptoms (anorexia, weight loss, late insomnia, psychomotor retardation) and lack of mood reactivity have been associated with favourable response to TCAs. On the other hand, neurotic, hypochondriacal, and hysterical traits as well as multiple prior episodes, delusions, and psychomotor agitation belong to predictors of poor response (for review see Kocsis (1990)). The fact that an extensive search for biological predictors of response has failed to produce clinically useful measures is explained by Kocsis (1990) by several factors. First, there is no fully reliable definition of response (ideally, non-responders, partial responders, complete responders, and true pharmacological responders should be examined separately). Second, the importance of compliance should not be underestimated. Third, the severity of depression and the occurrence of psychotic features should not be confused. Fourth, the definitions of chronic depression and atypical depression should be better conceptualised. Nevertheless, one may hope that besides theoretically important biological markers, also clinically useful ones will be identified, hand in hand with understanding of the biological underpinnings of affective disorders.

In conclusion, we should keep in mind the distinction between tautological predictions (definitions), heuristic predictions (fishing), logical predictions (models), and irrelevant predictions (mistakes). Some predictors are markers, some are conditions, some are triggers. Predictors are sometimes understood as 'risk factors' (Blumenthal, 1990). However, they are only exceptionally supposed to be causes.

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