Predictors of outcome in schizophrenia: the concept of time

J. A. Lieberman

Department of Psychiatry, Hillside Hospital, Long Island Jewish Medical Center, Glen Oaks, NY, U.S.A.

Concept and definition

The ability to predict the treatment response of patients with schizophrenia has been the goal of an extensive number of studies (reviewed in Lieberman and Kane 1986, Lieberman and Sobel 1993, Lieberman and Koreen 1993, Lieberman et al. 1994). Measures that have been examined as potential predictors of treatment outcome can be classified into several categories. These include historical, constitutional, environmental, phenomenologic and biologic variables. The ability of these measures to be predictive of treatment outcome is dependent on in what phase of the illness they are being assessed and when in the course of illness outcome is being assessed. In addition, there are a number of factors that can influence the expression and ability to identify measures that might be predictive of treatment outcome (Table 1).

Table 1. Factors that affect expression and identification of outcome predictors

- State vs trait dependency
- Maturational development and stage of the life cycle
- Medication status and duration of exposure

Let me illustrate these concepts with a few examples. Some measures, specifically biologic markers, can be state or trait dependent. A state dependent measure will be present only during specific phases of the illness. An example of a state dependent measure would be a putative biologic measure that may be predictive of outcome during the acute stage of illness such as growth hormone (GH) secretory levels in response to apomorphine or plasma homovanillic acid (pHVA), but is not present during periods of remission or after sustained drug treatment. A trait
dependent measure on the other hand, is present at all times presumably even prior to the onset of the illness. An example of a trait dependent measure would be smooth pursuit eye movement dysfunction or human leukocyte antigens (HLAs).

At the same time other variables will differ in when in the course of the illness they may be manifest. Female gender which has long been associated with better treatment outcome is obviously present and detectable from the time of birth if not before. Impairment in a patient’s level of premorbid functioning may not be detectable until later childhood or adolescence. While a patient’s development of negative symptoms of the deficit state may occur at anytime in the patient’s pre- or post-morbid course, i.e. prior to the onset, early or late in the course of their schizophrenia. Any assessment of the presence of abnormal brain morphology will be dependent on when in the patient’s life cycle the assessment is being performed. This is because there are age dependent changes that occur in the structures of interest for schizophrenia, specifically the ventricular system, cortical gyri and sulci and the subarachnoid space.

Finally, medication status and duration of exposure to medication can influence the expression and ability to identify potential predictors of treatment outcome. Plasma homovanillic acid (pHVA) levels which have been shown to be correlated with treatment outcome are altered by antipsychotic medication. Moreover, the duration of medication treatment will influence the level of pHVA at any given time. Similarly, plasma prolactin (PRL) levels are greatly influenced by the medication status of the patient and for how long the patient has been on or off antipsychotic medication at the time when PRL is being assessed.

**Time frame for prediction of treatment outcomes**

Treatment outcomes can be defined in various contexts. For acutely symptomatic patients it would be extremely valuable to be able to predict reliably their response to antipsychotic treatment, i.e. predict acute antipsychotic treatment response. For patients who are stable outpatients, it would also be valuable if we could predict which patients will relapse and when, and what dose of medication would be necessary to prevent relapse. At the same time we know that some patients will not have the same level of treatment response and outcome in the early phases of their illness as they will in the later phases. A significant proportion of patients will experience some progression of their illness and deterioration in their ability to respond to treatment over the course of their illness. Therefore, the short-term and long-term outcomes of patients will not necessarily be the same.

In determining the ability of specific measures to predict outcome we must understand that the strength of the predictive power of any variable will vary depending on the time-frame of the outcome to which it is being applied. Clearly, the most powerful and useful predictor is