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Review article

Longitudinal studies: An essential component for complex psychiatric disorders

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ABSTRACT

Most psychiatric syndromes are chronic and lifetime in course. Kraepelin's seminal work pointed out a century ago that longitudinal/lifetime assessments were powerful aids in differentiating dementia praecox from manic-depressive disorder. Despite this, clinical research investigations in psychiatry have historically emphasized short-term and cross-sectional approaches.

This review of an array of longitudinal studies supports that they are arguably an essential component of psychiatric investigations, but that they must be coupled with other approaches. The use of standardized, validated, repeated assessments in a disease over the course of time must be incorporated with pathophysiology investigations to identify underlying mechanisms, biomarker studies, comparative effectiveness clinical trials to identify the best treatments for different causes, and translational strategies to provide the right treatments to the right patients at the right time. Strategies for incorporating longitudinal assessments into newer diagnostic proposals, such as the Research Domain Criteria (RDoC), are discussed.

Contents

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1. Introduction

The modern era of psychiatric research arguably was born with longitudinal studies and phenomenological characterizations of hospitalized psychiatric patients. Emil Kraepelin influenced the nosology of psychiatric disease with his detailed observational studies of the course and outcome of patients under his care at the University of Heidelberg (Kraepelin, 1921). Seminal to Kraepelin's distinction between dementia praecox (schizophrenia) and manic depressive insanity (bipolar disorder) was the longitudinal pattern that the disorders demonstrated. Kraepelin noted that it was the *pattern* of the illness that characterized the distinction between these disorders despite there being considerable overlap in symptoms and signs; no single symptom was pathognomonic for a specific disorder. Kraepelin also recognized that his proposed classifications based on longitudinal observations frequently were unable to accurately and unequivocally categorize many patients. Recent criticisms of what is termed the "Kraepelin Dichotomy" (Craddock and Owen, 2010) fail to adequately acknowledge this point. The current operational and systematic approach to clinical observation has the flaws and weaknesses inherent in clinical methods, but has provided a standard framework for classification and worldwide communication (APA, 2000; WHO, 1992).

Medicine is informed and defined by patients and populations. The most elegant example of the study of a population of patients that has guided the course of medicine is the Framingham Heart Study (Levy and Brink, 2005). In this study 5038 individuals from the village of Framingham MA were enrolled in 1948 and studied in detail for the emergence of cardiac disease. Longitudinal studies were the cohesive spine of this project, enabling risk and protective factors to be determined. A major portion of current medical recommendations related to cardiac health derived from this study. This seminal study is now in the third generation of follow-up and the implications of the research reach into several dimensions, including the social networks and the implications of changing risk patterns and outcomes. The Tecumseh study is another example of clinical studies at the population level. Over 8000 individuals from an entire community were engaged (Francis, 1961) and evaluated over time for the emergence with a wide range of clinical assessments encompassing respiratory, metabolic and temperamental features (Sen et al., 2003).

An undercurrent of longitudinal assessments among individuals with psychiatric illnesses persisted throughout decades. The essence of the mid-twentieth century revival of the ideas of Kraepelin was based on combination of the phenomenology and course of disease (Feighner et al., 1972). There were emerging studies that, while not prospectively longitudinal in design, used follow-up (or "follow-back") strategies for review, sometimes decades later to determine the outcomes in several domains (Winokur, 1975). Designs emerged in the 1970s to study the course of depressive disease, such as the NIMH Collaborative Study of Depression (Elkin et al., 1985) and the Camberwell Collaborative Study of Depression (Bebbington et al., 1988). Their ascertainment and follow-up at specific intervals continued for over 25 years in some cases. In bipolar research the clinically focused research by Jules Angst, began in the late 1950s and the outcomes of bipolar individuals followed for many years (Angst et al., 2003). Schizophrenia (Hegarty et al., 1994) and personality disorders (Gunderson et al., 2000) have followed similar longitudinal strategies.

Published longitudinal studies have, in general, focused to a considerable degree on clinical outcomes such as the rates of suicide or comorbidities. These initiatives have generally not formed the basis of genetic studies. The search for genetic susceptibilities has focused primarily on one-time assessments and diagnoses made using a structured interview augmented by medical records (Smoller et al., 2013). Follow-up has been limited. The combination of longitudinal *and* genetic strategies generally has been absent. This review is not a comprehensive review of all longitudinal studies in psychiatric disorders; studies with a genetic element familiar to the authors were included for discussion to emphasize and exemplify the importance of integrating longitudinal studies in etiological research.

Genetic research has identified susceptibility loci for many psychiatric disorders, however each of these loci contributes only a very small amount of the variance to the illness (Lee et al., 2013). It is clear that there is a complex interaction between environmental influences and the biology and that only with detailed information on the environment and the moderators of the course of illness will there be a comprehensive understanding of the interaction between biology and environment (Craddock et al., 2009). This will lead to improved knowledge of etiology, form the foundation for valid nosological classifications and subsequently improve "personalized" or tailored treatment options for the individual.

2. Longitudinal studies in bipolar disorder

The longitudinal study of bipolar disorder was pioneered by Jules Angst with research among individuals with bipolar disorders originating from his clinical work in Zurich (Angst et al., 1979; Angst and Preisig, 1995). The data from the Angst group informed on the overall frequency of episodes, 0.4 episodes per year in bipolar disorder compared to 0.2 episodes per year among patients with recurrent major depression. The investigators interpreted these data to support the need for ongoing maintenance and preventative therapy (Angst et al., 2003). Over 40 years of follow-up found that 11% of participants died by suicide and that long-term medication management decreased this suicide rate considerably (Angst et al., 2005). A Zurich Cohort Study was established to characterize clinical features related to mood disorders, such as the epidemiology of hypomania and bipolar II disorder (Angst, 1998); these data contributed to the emerging discussion on the bipolar spectrum, the frequency of which has been found to be in the range of 5% (Merikangas et al., 2007).

3. Stanley Foundation Bipolar Network

The Stanley Foundation Bipolar Network (SFBN) involved five international collaborative sites and monitored 908 patients over a period of 7 years and ended in 2002 (Leverich et al., 2001; Suppes et al., 2005). This collaborative contributed considerably to the clinical knowledge base on bipolar disorder during its active collection and analyses. As illustrations, the delay in diagnosis was approximately 10 years from onset of first symptoms, the course of the illness indicated that the disorder was increasing in relative severity over time with a moderate to severe impact on functioning in over half of the patients, and two-thirds of individuals had ongoing chronic symptoms between episodes (Suppes et al., 2001). Several studies of comorbidity and treatment trials were done with this cohort (McElroy et al., 2002; Post et al., 2003a, 2003b; Suppes et al., 2002). The SFBN became the Bipolar Collaborative Network (Post et al., 2006) and analyses of the data continues to contribute to the discussion of the course and risk factors in bipolar disorder (Miller et al., 2014; Post et al., 2014a, 2014b). While there are no specific genomic studies for the collection from the SFBN, many of the samples were subsequently included in genomic research (Drexhage et al., 2010; Padmos et al., 2008, 2009). The successes of the SFBN are many and productivity in analyses continues. Nevertheless, the