AMERICAN PSYCHOPATHOLOGICAL ASSOCIATION

LONG-TERM OUTCOMES IN PSYCHOPATHOLOGY RESEARCH

Rethinking the Scientific Agenda

EDITED BY

Evelyn J. Bromet

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Long-Term Outcomes in Psychopathology Research

RETHINKING THE SCIENTIFIC AGENDA

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I dedicate this book to my parents, Max and Ruth Bromet, and to my mentors, Martin Harrow, Rudolf Moos, and Thomas Detre. This book is the final volume from the American Psychopathological Association (APPA). I am indebted to Joseph Zubin for introducing me to this esteemed organization. This book reflects his overall wisdom and critiques at prior APPA meetings, as well as the passing comment he made during his very last lecture when he chided the audience for presuming to know all of the questions and possible answers instead of being inquisitive, active listeners. The chapters in this book reflect that we have taken his words to heart.

Contents

Preface

As President of the American Psychopathological Association (APPA) in 2013, I had the honor of organizing the 103rd annual meeting on March 7–9. The meeting focused on examining what we have learned about the long-term course of illness and functioning of individuals treated for mental health and substance use disorders and the unexplored areas that require further attention. The stage for the meeting was set on the evening of March 6 with the screening of *Kings Park: Stories from an American Mental Institution*. Directed by Lucy Winer, this documentary film offers a personal narrative of the past and present history of the US mental health system. Lucy, a seasoned filmmaker, had been admitted to Kings Park Psychiatric Center in the late 1960s when she was seventeen years old, placed on the violent women's ward, and given a clinical diagnosis of schizophrenia. Thirty years later, she embarked on this film, offering viewers a disturbing history of how psychiatric patients were treated before deinstitutionalization and how they continue to be treated today. Indeed, the film concludes with interviews shot in the county jail. The personal tone of the question-and-answer period following the film was echoed throughout the meeting, and thus voices missing during past APPA meetings were encouraged and welcomed.

Like the authors of the chapters in this volume, I have devoted a considerable part of my career to outcomes research. The shape and focus of outcomes research continue to expand as breakthrough findings on antecedents, risk factors, effect modifiers, and outcomes are published and new technologies are developed. At times, however, major advances derive from modest sources. Indeed, the original breakthroughs came about through the remarkable narratives published by Kraepelin and Bleuler. Until recently, personal narratives and dialogues between investigators and study participants all but disappeared from clinical outcomes research. The pendulum is now swinging toward a more inclusive approach to research. In this regard, by starting the 2013 meeting with the screening of *Kings Park*, the APPA meeting added faces and voices who had not previously attended these meetings. By design, the meeting also included talks and critiques by experienced investigators who had publicly

disclosed their psychiatric narratives and, having sat on both sides of the table, offered unique perspectives on the research.

Part 1 of the current volume covers long-term studies of psychosis, bipolar disorder, depressive disorders, and substance use disorders and includes a commentary that synthesizes much of this research. Part 2 addresses some unresolved issues in case definition as reflected in the new *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), including Asperger's syndrome (dropped from DSM-5), disruptive mood dysregulation disorder (added to DSM-5), and post-traumatic stress disorder (PTSD; reconceptualized and redefined in DSM-5), along with a commentary on quantitative versus categorical/consensus classification. Part 3 addresses the concept of recovery in individuals with juvenile-onset depression, psychosis, and PTSD along with personal perspectives on recovery by a psychologist who had been diagnosed with schizophrenia and a social worker who designed and administered a recovery-oriented program. Part 4 covers three topics that have been significantly understudied: nonsuicidal self-injury, included in DSM-5 as a condition for further study but for which no long-term outcome studies exist; psychiatric genetics, which, with a few exceptions, is only beginning to make its way into longitudinal research; and brain imaging, which has enormous potential for understanding treatment response, remission, and recovery but is often conducted with small samples of convenience. The volume concludes with an Epilogue about research priorities, particularly for individuals with chronic and severe disorders. The Epilogue reflects the hope and optimism that can come about through partnerships among patients, families, and investigators.

Last, the conceptual platform for the meeting drew from the structure of Bach's *Goldberg Variations*. Published in 1741, the *Goldberg Variations* begin with an ethereal aria, followed by thirty variations, and ending with a repetition of the opening aria. It is almost impossible for a performer to play the aria exactly the same way after performing the variations. Even when the repetition of the aria is very similar, the experience for the listener is altered considerably. In the same way, the field began in large part with Kraepelin's and Bleuler's detailed descriptions of their patients' illness course. Their books have been followed by a multitude of follow-up studies. It is time for investigators to listen again to the aria—that is, to current narratives that are obscured by our structured measurements—and, having listened, to engage study participants in the research process itself.

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PART I

Findings from Long-Term Outcome Studies

1

Past and Future Directions in Psychosis Research

EVELYN J. BROMET

Overview

This chapter offers a series of observations about the changes in orientation and the findings of studies of long-term outcomes of individuals with schizophrenia and affective psychoses. Although we know considerably more about the short-term (under 5 years from first diagnosis) course and functioning of these individuals, there are many fewer long-term studies, especially having at least 10 years of follow-up. Several comprehensive reviews of the follow-up literature have been published.[1–9] The key purpose here is to synthesize the contributions of older and more recent studies and make suggestions for reshaping future research so that all stakeholders—scientists, patients, family members, and providers—have input into conceptualizing and operationalizing the "bio," "psycho," and "social" aspects of the biopsychosocial model. Prior to the early 1980s, when the World Health Organization (WHO) began the Determinants of Outcome of Severe Mental Disorders (DOSMED) study,[10] most longitudinal research findings were based on consecutive admission samples from single inpatient facilities.[3,8,11] Fewer than half of the patients in these studies were considered improved at follow-up.[3] DOSMED was a game changer for study design, but, as shown in this chapter, the refinements in sampling, diagnosis, and measurement, and the newly available psychiatric services and treatments, did not markedly alter the overall picture about clinical or social improvement. What is beginning to change, however, is the broadening of our perspective about risk factors and outcomes.[11] The chapter concludes with recommendations about domains of functioning and research partnerships that will enrich our understanding of the illness course and clinical, social, and cognitive outcomes of the millions of people who suffer from a psychotic illness.

Introduction: A Brief History

This chapter focuses on our understanding of the long-term course and outcomes of individuals with psychosis who were followed for at least 10 years after study enrollment. Prior to the mid-1980s, the typical method of case identification was through clinically diagnosed consecutive admissions to a single treatment facility.[3] There were also a handful of notable multisite studies, including the International Pilot Study of Schizophrenia[12] headed by the WHO and the Collaborative Study of the Psychobiology of Depression funded by National Institute of Mental Health (NIMH).[13] However, since illness onset had begun years earlier in the vast majority of patients in these studies, the design was not optimal for evaluating "change" in clinical or functioning domains. As Cohen and Cohen demonstrated,[14] consecutive admissions (i.e., prevalent samples) are biased toward poor outcomes. Moreover, comparisons of the findings among these studies are hampered by variations in their ratios of first to multiple admission cases;[8] the mix of patients with schizophrenia, schizoaffective disorder, affective psychoses, and other nonaffective psychotic conditions;[1] and the stage of the illness when the diagnosis was made.[15]

In spite of obvious shortcomings, there are many important findings from these studies that have stood the test of time. One example is the poorer outcomes of younger males with schizophrenia compared to older onset cases and to women. Other risk factors that were later confirmed include family history of schizophrenia, lower intelligence and education, co-occurring substance abuse, insidious onset, delay in treatment seeking, and nonadherence to treatment. Perhaps most striking of all is confirmation of the proportion of cases fitting each of the eight course types derived from the type of onset (acute vs. insidious), interim course (fluctuating vs. steady), and outcome (good vs. poor), first described by Bleueler[16] and Ciompi.[17] Thus, before the era of modern psychotropic medicines and deinstitutionalization, and before studies were designed with better sampling and diagnostic assessment methods, 40% of patients with schizophrenia were judged as having good outcome, thus challenging the belief that schizophrenia is a degenerative disease, as noted in Chapter 18. Remarkably, three recent studies of first-episode or recent onset psychosis conducted in different cultural settings found very similar results.[18–20]

Launched in the early 1980s, the DOSMED study represented the first large-scale paradigm shift in the design of psychopathology outcome studies.[10] Rather than consecutive admissions, DOSMED selected incident, or first-contact, cases. Rather than recruit from single facilities, typically hospitals, DOSMED searched for first-contact individuals in mental health programs, jails, and primary care settings, and among those seeking help from

nontraditional providers, like natural healers. Rather than rely on a clinical diagnosis, DOSMED recruited individuals with psychosis and administered a systematic and reproducible assessment procedure to diagnose study cases, thereby reducing misclassification. In these respects, DOSMED was a methodological and conceptual game-changer. Other studies soon followed DOSMED's lead, elaborating on the design[21] and adding new measurement domains.[22–24]

A goal of studies designed in the twenty-first century has been to assemble cohorts of people either at the earliest possible stage of psychosis or in the prodromal stage, before frank psychosis has set in.[25] As described in Chapter 12, these studies often had a dual goal of primary prevention along with early case identification of psychosis.[26–28] Surprisingly, the rates of good outcome and the risk factors associated with improvement were similar to those reported during the pre-DOSMED era. For example, rates of good outcome after 10 years of follow-up continued to be in the order of 40-45% in developed counties.[29] When outcome was defined more rigorously, however, the percent with favorable outcomes decreased considerably. In the most comprehensive review to date, Jääskeläinen and colleagues[2] refined the definition of recovery to include good clinical and social outcome, with one of these areas being sustained for at least 2 years. Among the nineteen first-episode schizophrenia studies with 10 or more years of follow-up, the range of recovery according to this definition was 0–37%, and the median was only 16%.

We note that in the Suffolk County[30] and Chicago[31] samples, patients with schizophrenia diagnoses had worse outcomes than those with psychotic mood disorders. For example, at the 10-year follow-up of the Suffolk County cohort, composed of first admissions with psychosis recruited from each of the inpatient facilities across the county, 14.2% of participants with schizophrenia versus 59.1% having other diagnoses had periods of remission as defined by Andreasen et al.[32] Moreover, while one-third of the cohort had global assessment of functioning (GAF) scores higher than 60, mirroring pre-DOSMED outcome rates, only 11.0% with schizophrenia compared to 51.3% with other disorders were in this range of GAF scores. In the 10-year follow-up of the AESOP cohort, Morgan and colleagues also reported significantly lower rates of recovery and remission in those with a nonaffective compared to an affective diagnosis.[20] Again, it is important to emphasize that the difference in outcome by diagnosis had been duly noted in pre-DOSMED studies.[33]

Clinicians' definitions of recovery are not equivalent to subjective feelings of well-being and life satisfaction. Hence, diagnostic differences in clinician-defined recovery may not necessarily correspond to comparisons using subjective evaluations.[34] The Suffolk County data illustrate this well. Although our clinician ratings of outcome showed significantly poorer

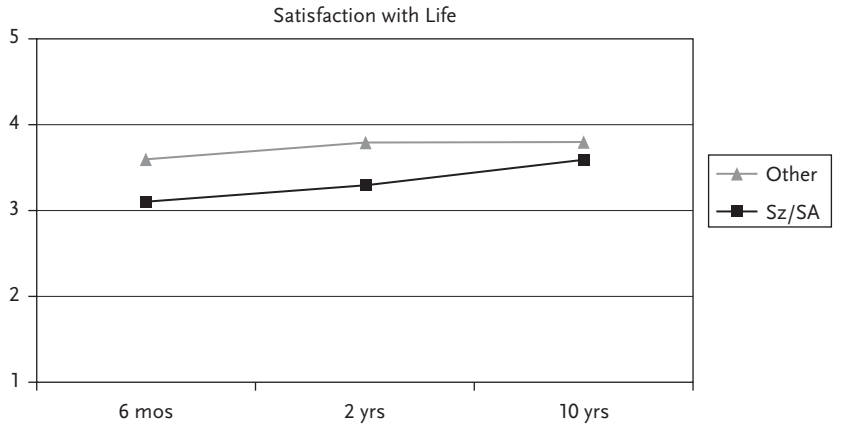

Figure 1.1 Ratings of life satisfaction by Suffolk County participants with schizophrenia/schizoaffective disorder (N = 117) and with other psychoses (N = 180).

functioning among participants with schizophrenia compared other psychoses,[30] we found little difference in life satisfaction measured with the Quality of Life Scale.[35] As shown in Figure 1.1, minor (although statistically significant) diagnostic differences were evident in the early phases of the follow-up, but by the 10-year mark, the two diagnostic groups basically converged (higher scores = better).

Predictors of Long-Term Outcomes

As noted earlier, consecutive admission studies consistently found several predictors of the poor outcome. The most consistently and most often studied were premorbid and school functioning, gender and age of onset, marital and socioeconomic status, delay in treatment (later referred to as *duration of untreated psychosis*), insidious outcome and blunted affect (later conceptualized as *negative symptoms*) early in the course, comorbid substance abuse, and nonadherence to medication treatment.[36,37] Nonadherence to treatment is associated with poor insight, side effects, and denial of illness and need for treatment.[36]

In spite of refinements in sampling and diagnosis, and in spite of deinstitutionalization and new pharmacologic and psychotherapy treatments, the recent studies of schizophrenia have mainly confirmed the predictors found during the pre-DOSMED (and pre-DSM-III) era.[38–40] For example, the 10-year follow-up of the Danish OPUS study found that the two most important predictors of full recovery were fewer negative symptoms at baseline and earlier

age of diagnosis.[39] Recent studies have integrated neurobiological measures in assessing response to treatment,[41] but, as noted in Chapters 16 and 17, genetic and imaging variables have rarely been included as predictors of outcomes in long-term follow-up investigations.

Epidemiologists separate risk factors into modifiable and nonmodifiable variables. Modifiable factors are of great interest to investigators wanting to design preventive interventions. The findings on duration of untreated psychosis and the profound importance of the premorbid and prodromal periods were pivotal issues behind the design of intervention programs for prodromal and pre-psychotic individuals.[42,43] These programs have three objectives.[43] The first is to improve the prodromal symptoms themselves. The second is to reduce the risk of psychosis. The third is to minimize duration of untreated psychosis through prompt recognition and pharmacological and psychological treatments. It remains to be seen whether the long-term outcomes of individuals participating in these programs are more favorable than those of patients identified at the time of their first episode of psychosis. The Personal Assessment and Crisis Evaluation (PACE) study in Melbourne, Australia, found that one-third patients transitioned to psychosis during a 15-year follow-up period, with the risk of transitioning being highest in the first 2 years.[44] The long-term outcome of "converters" in the first 2 years compared to both "nonconverters" and patients identified during their first psychotic episode is an important area of future research.

In the pre-DSM-III era, many patients given the diagnosis of schizophrenia would be classified today as having a mood disorder, either schizoaffective disorder, psychotic bipolar disorder, or major depression with psychotic features. Mood disorders investigators studying samples with psychosis have found that the predictors of poorer outcome include mood-incongruent delusions, initial depression (as opposed to mania) in bipolar disorder, greater severity of depressive symptoms, and poorer psychosocial functioning.[45,46] Goldberg and Harrow[47] also found that patients with bipolar disorder had poorer global outcome and occupational functioning than did those with psychotic depression, in large part because of the impact of recurrent depressive episodes during the follow-up.

In the search for novel prognostic indicators, several variables described in the pre-DOSMED era have recently been evaluated as risk factors for short- and long-term outcome: households characterized by high levels of expressed emotion,[48,49] childhood behavior problems,[50] exposure to traumatic events in childhood,[51] and inpatient experiences that were either highly distressing and traumatic (e.g., being put in restraints, being forced to take medication, being put in an isolation room).[52] Other variables in recent research were extensively tested in long-term studies conducted years ago, such as duration of untreated psychosis (originally labeled *delay in treatment*) and neurocognitive

impairments, although the scope and precision of newer neuropsychological test batteries have been expanded and enriched.

What Remains to Be Learned

Outcome studies have been designed using a top-down approach, with investigators deciding on the research question, the content of the assessments, the questions to be asked, the response options, and the definitions of what it means to function well or be recovered. As science becomes increasingly specialized and fragmented, it is important that outcome studies be designed to test integrated conceptual frameworks, such as the biopsychosocial model. Zubin and Spring[53] described such a comprehensive model in 1977, but their model was oriented toward onset rather than recovery. Recently, Yanos and Moos[54] provided an integrative model to explain the subjective (sense of well-being and personal growth) and objective functioning (engagement in school or work, social, and recreational activities) among people who live with psychotic illness. Their model considers the influences of enduring environmental resources, personal traits and symptoms, transitory experiences (including trauma and stigma), cognitive appraisal and insight, and coping mechanisms (including medication adherence). Yanos and Moos argued that an integrative conceptual model, such as the one they proposed, has both theoretical and practical value for designing meaningful interventions.

Individuals with psychotic disorders, their loved ones, and the clinicians who care for them are rarely included as active participants in the planning or execution of long-term outcome studies. Nor are they the first to learn about the findings and be given an opportunity to offer interpretations of the results, their practical value, and what might have been missing from the research. This absence of consumer and provider perspectives leaves us with several important gaps in knowledge. One area that has been the focus of important discussion by consumer groups, mental health advocates, and researchers is defining "recovery" and designing recovery-oriented treatment programs.[55] In a comprehensive review of recovery research, Leamy and colleagues[56] provide an empirically based conceptual framework that can serve as the basis for future studies of the effectiveness of recovery-oriented services.

Four other critical gaps in the long-term outcomes literature are important to note. One is the risk of incarceration. Although it is well known that substantial proportions of prison populations have severe mental illness,[57] very little is known about the risk of incarceration among individuals who develop a

psychotic disorder.[58] A second area is homelessness. Again, several studies have documented that a substantial percentage of homeless individuals have a serious mental illness, but only a handful of studies have examined the prevalence of and risk factors for homelessness among people who develop a psychotic disorder, and none of these studies addresses long-term outcome.[59] A third issue is malnutrition. People with severe mental illness frequently live on incomes that are inadequate to meet their daily needs. Although studies have shown that inadequate nutrition during pregnancy is a risk factor for schizophrenia in the offspring,[60] we have little or no information on the extent and effects of malnutrition among people living with mental disorders. This is surprising because there is a substantial body of research on early mortality[61] and on the high prevalence of obesity, diabetes, and cardiovascular disease in schizophrenia,[62–64] especially since the introduction of atypical antipsychotics. The fourth issue is oral health. Psychotropic medication, particularly when combined with smoking and alcohol use, causes severe dry mouth, which in turn leads directly to chronic oral health problems.[65–67] In spite of their impact on quality of life,[67] oral health problems have not yet been included as risk factors in long-term outcomes research.

Box 1.1 lists eleven elements for the next generation of long-term outcome studies that could broaden our understanding of the prognostic factors and outcomes of psychotic disorders. In many ways, these ideas reflect the philosophy and achievements of the consumer-driven recovery movement.[68] Taken one by one, these recommendations enhance the success of a long-term research study. Taken together, they enable studies to address the needs and goals of both researchers and stakeholders, thus expanding each study's potential contribution to science and society.

Conclusion

The WHO defines health as: "A state of complete physical, mental and social well-being, and not merely the absence of disease." Each of these concepts should be measured in long-term outcome studies of psychiatric disorders at each point along the developmental pathway. As psychiatry becomes ever more biologically focused and medicine becomes more specialized and fragmented, it is important to bear in mind that naturalistic, long-term outcome studies play a critical role in providing unbiased evidence about basic issues, such as (1) how people with different risk profiles and treatment exposures fare over time, (2) separating antecedents from consequences observed in neurobiological evaluations, (3) showing the evolution and temporal patterning of different

Box 1.1
Recommendations for the next generation of long-term outcome studies

1. Formulate hypotheses, methods, and dissemination plans together with all stakeholders (researchers, consumers, families, advocates, psychiatric, medical and dental providers).
2. Ensure that studies are cross-disciplinary, cross-cultural, and have cross-national capacity.
3. Lock away "we-they" mentality and replace it with mutual respect and gratitude.
4. Develop prospective hypotheses that address vulnerabilities and strengths.
5. Create methods for long-term engagement to minimize attrition.
6. Integrate a life-span approach into the timing of follow-up points and assessment goals.
7. Build in translational value from the start.
8. Designate mental health professionals as interviewers.
9. Listen to participants; include questions that do not have pre-set responses.
10. Incorporate personal narratives.
11. Consider all aspects of health.

domains of functioning, and (4) showing the effectiveness of personalized treatments in real-world settings.

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2

Course of Bipolar Disorder in Adults and Children

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Overview

During the past decade, the descriptive epidemiology of bipolar disorder (BD) has come to maturity. A proliferation of international studies has yielded aggregate lifetime prevalence rates of BD of 1–2% at the diagnostic level and 4–5% with expansion to the spectrum concept of bipolarity.[1,2] BD was the second ranking cause of disability, measured by days spent out of role per year, among a range of physical and mental health conditions assessed in the World Health Organization World Mental Health surveys,[3] and it is one of the leading causes of disability adjusted life years worldwide.[4] Most strikingly, one in every four or five persons with BD has a history of suicide attempts.[5] When taken together with the early age at onset and strong association with other mental disorders, these results provide further documentation of the individual and societal disability associated with this disorder.[2] However, despite these advances in our understanding of BD at the general population level, the vast majority of global evidence on the prevalence, impact, and correlates of BD is based on cross-sectional research that cannot provide information on the course or outcome of BD, particularly at the milder end of the spectrum, that is critical for a comprehensive depiction of the public health significance of BD. Characterization of the lifetime course of BD may inform our understanding of causes, prevention, and treatment to minimize its individual and societal impact.

The goals of this chapter are (1) to provide a summary of the findings from studies of the course and mortality of BD from clinical and community samples and (2) to summarize methodological challenges and future directions in interpreting aggregate findings on the course of BD.

Course of BD

Course in Adults

There have been a growing number of prospective studies of the course of BD in adults identified in treatment settings in the United States and Europe. Table 2.1 summarizes the methods and major findings of the ten prospective studies with greater than 1 year follow-up with direct assessments of patients. Many of these studies involved multicenter collaborative efforts in order to recruit large numbers of patients and increase the representativeness of the samples. These include the National Institutes of Mental Health (NIMH) Collaborative Depression Study (CSD),[6–8] the Stanley Foundation Bipolar Network (SFBN),[9] the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study,[10] and the European Mania in Bipolar Evaluation of Medication study (EMBLEM) that included investigators in four European countries (Denmark, Germany, Spain, and Switzerland),[11] and a number of other studies in the United States, Europe, and Australia.[12–19] The duration of follow-up ranged from 2 years in studies in Australia[19] and the STEP-BD study;[10] to 4 years in the EMBLEM study,[11] a recent Austrian BD sample,[12] and a systematic county-wide study of first episode psychotic BD patients;[13] to 7 years in the Stanley Foundation BP Course study;[9] and to several decades in the Collaborative Study of Depression in the United States,[6–8] a cohort of inpatients with BD in the United States,[14] and a Swiss hospital cohort that has now been followed for nearly half a decade.[15–17] The samples in these studies have generally been identified in specialty treatment settings, with some focusing solely on inpatients,[12–14,17,18] whereas others recruited broader samples of both inpatients and outpatients.[8–11,19] The study of first-episode psychosis in Suffolk County, New York, by Bromet et al.[13] has the only population-based sample of first-incident treated cases.

Rich information on the precursors and sequelae of BD has also been obtained from large population registries in Denmark,[20] Sweden,[21] and the Netherlands.[22] Although the lack of direct interview information precludes evaluation of specific clinical features of episodes, these studies can provide valuable data that complement clinical course studies through linked registries that provide data on premorbid risk factors, and correlates and indices of outcome and course. There are also a few prospective community studies, such as the Zurich Cohort Study[23] and the NEMESIS study,[24] that also investigated the longitudinal stability of mania/hypomania. More recently, Baek et al.[25] assessed the stability of unipolar mania in the 3-year follow-up of a large US community-based sample who participated in the National Epidemiologic Survey on Alcohol and Related Conditions.

Table 2.1 **Prospective studies of the course of bipolar disorder in adults and children**

Author	*Year*	*Site*	*N*	*Source*	*Duration*	*OUTCOMES*		
						Syndrome Recovery	*Recurrence/ Relapse*	*Functional Recovery*
ADULTS								
Tohen	2003	US	166	Inpt-1st	4 yrs	98%		43%
Bromet	2005	US	123	Inpt-1st	4 yrs	84%	61%	
Suppes	2005	US; Europe	908	Outpt	7 yrs	57%	43%	
Perlis	2006	US	1469	Inpt/outpt	2 yrs	58%	48%	
Angst	1995; 2003	Switzerland	210	Inpt	40 yrs	16%		
Solomon	2010	US	219	Inpt/outpt	25 yrs	75% 1 yr 89% 2 yrs	31–47%	
Haro	2011	Europe	1656	Inpt/Outpt	4 yrs	34%	68%	
Goldberg and Harrow	2011	US	46	Inpt	15 yr	77%		35%
Kulkarni	2012	Australia	222	Outpt	2 yr	91%	27%	
Simhandl	2014	Austria	300	Inpt	4 yrs		68%	
YOUTH								
Strober	1995	US	52	Inpt/Outpt	5 yrs	90%	42%	
Carlson	2002	US	123	Inpt	2 yrs			
Delbello	2007	US	71	Inpt	1 yr	86%	54%	41%
Geller	2008	US	115	Inpt/Outpt	8 yrs	73%		
Birmaher	2014	US	367	Outpt	4 yrs		22.30%	
Wozniak	2011	US	78	Inpt/Outpt	4 yrs	27%		

Clinical Outcome in Adults

The distinction between syndromic recovery, defined as the absence of the criteria at the level of the disorder, and symptomatic recovery, based on absence of significant levels of symptoms on a dimensional measure, has facilitated standardization of the assessment of course across studies.[26] The aggregate findings of the longitudinal studies of BD indicate generally high recovery rates, ranging from 58% to 60% to as high as 98%[27] after the acute episode. Substantial variability in recovery rates can be attributed to differential severity and length of follow-up, with higher recovery rates for briefer periods and higher remission rates for longer periods of follow-up. In general, studies found that between 60% and 90% of those with an initial episode of BD recover syndromally, whereas between 40% and 60% achieve full symptom remission at one or more follow-up interviews. In terms of recurrence, however, the longer term follow-up studies tend to reveal that more than half of those who remit eventually experience recurrence of episodes of BD.[8,10–13,17–19] Despite sex differences in some of the risk factors and consequences of BD, the majority of the studies of the course of BD did not detect important gender differences in patterns of course and outcome.[27,28]

Another source of variability in the course of BD is the lack of comparability in the duration of illness at the time of sample ascertainment; durations range from new onsets to more than 30 years since onset. In order to facilitate comparability of such samples, investigators have attempted to identify patients at the initial onset of manic episodes. The two systematic follow-up studies of adult patients exhibiting their first manic or psychotic episode[13,18] are the decade-long McLean-Harvard First Episode Project that systematically followed a large cohort of patients from first hospitalization with bipolar or psychotic affective and nonaffective disorders to the 6-year mark[28,29] and the Suffolk County study[13] that collected a systematic sample of all episodes of first-onset psychosis in a circumscribed geographic area.

Predictors of Course in Adults

The most potent predictor of course and outcome is prior history of the specific clinical features of mood disorders. One of the strongest correlates of recurrence and severity is early age of onset of mood disorder. An early age of onset is associated with long delays until first treatment and an overall more severe clinical picture with more frequent episodes, more comorbidity, rapid cycling, and fewer well days. Adolescent onset, although less severe than childhood onset, is associated with a lower likelihood of symptomatic and functional recovery than is adult onset.[27,30,31]

Clinical predictors of poor outcome were fairly consistent across studies, with the number of prior episodes and years with illness at study entry as the most discerning predictors of course. Cycling and mixed episodes were also consistently associated with recurrence.[9,32,33] Index depressive or mixed states tend to predict later depression, poorer treatment response, longer time to remission, and shorter time to relapse, whereas initial mania predicts later mania and an overall better prognosis.[31] Later manic episodes are also predicted by initial mood-congruent psychosis, lower occupational status before the index mood episode, higher degree of cognitive deficits, and initial manic presentation, whereas later depressive episodes are predicted by initial depressive or mixed episode, higher occupational status before index mood, and presence of comorbid disorders.[27] Although several studies found a decrease in the time between episodes as a function of number of subsequent episodes,[17,20] other studies did not confirm this reduction in interepisode length over time.[32]

Predictors of Remission in Adults

Predictors of functional remission/recovery include onset in adulthood, absence of a family history of BD, absence of comorbid disorders, and presentation with manic symptoms.[18,31,34] Conversely, those who had longer periods before remission and shorter periods before relapse were more likely to have a history of child psychopathology, greater symptom severity during index hospital visit, and an index depressive mood episode.[13,27,29] The effect of polarity and recurrence was inconsistent across studies, with some showing better course for manic episodes,[19,32] and others finding that depressive index episodes were associated with better course.[14,17] Treatment adherence and response are also predictors of remission in both adults[13] and youth.[35,36]

Functional Outcome in Adults

Whereas syndromic recovery is quite common, there is a large gap between clinical remission and functional outcomes in BD. Several of the first-episode studies systematically tracked quality of life and adjustment in occupational and social spheres. For example, Tohen and colleagues[18] found that people with BD had work impairment for more than 30% of a 4-year follow-up period. Several other studies also demonstrated the importance of occupational and social functioning as both a predictor and outcome of BD.[14,19] One explanation for the gap between symptomatic recovery and functional impairment could be attributable to risk factors such as lower socioeconomic status (SES), limited social support, and poor psychosocial adjustment prior to the index mood

episode that may be more chronic in nature and not ameliorated by pharmacologic treatment.[27,31] Nonremitting comorbid physical disorders may also explain residual impairment in those who have responded to treatment.[19] In addition, neurocognitive deficits that tend to persist despite symptomatic remission in BP may also contribute to impairment and disability.[27,31] For example, MacQueen[37] found a direct association between the number of episodes and decline in cognitive function and well-being. These findings underscore the urgent need to expand clinical trials and systematic studies of treatment to inclusion of functional impairment that could reduce the burden of this illness.

BD in Youth

The average age of the samples followed in studies of the course of BD, as shown in Table 2.1, is approximately forty, which reflects a major gap in knowledge about the disorder for younger cohorts. This is especially noteworthy because the average onset has been shown to occur before age twenty in both retrospective and prospective studies of BD. However, there are a growing number of prospective studies of children with BD identified in clinical samples[35,36,38–40] that serve to supplement the information derived from studies of adults with BD. The results of follow-up studies of youth yield remarkably similar findings to those of adults reviewed earlier. With one exception,[36] syndromal recovery occurs in the overwhelming majority of youth with BD, yet about half experience one or more recurrent episodes. Using a latent analysis approach to characterize the course of treated bipolar in adolescents, Birmaher and colleagues[38] identified four different longitudinal mood trajectories through latent transition analysis: "predominantly euthymic" (24.0%), "moderately euthymic" (34.6%), "ill with improving course" (19.1%), and "predominantly ill" (22.3%). This shows that a substantial proportion of youth with BD do remit over time. Predictors of course included age at onset of mood symptoms, lifetime family history of BD and substance abuse, manic symptoms, severity of depression, suicidality, subsyndromal mood episodes, and sexual abuse at baseline.

Several community studies have investigated the continuity of bipolar symptoms and disorders in youth identified in community samples, including the Early Developmental Study of Psychopathology[41] and the Oregon Adolescent Depression Project.[42] These studies tend to show that a large proportion of youth may meet criteria for manic or depressive episodes, but few meet the clinical significance criterion. Moreover, Tijssen and colleagues[41] showed that the persistence of symptoms, rather than their presence or absence, was the strongest predictor of transitions to clinically significant outcomes in early adulthood. There is an urgent need to conduct these studies on a larger scale