Longitudinal research on bipolar disorders

PAOLA SALVATORE, MAURICIO TOHEN, HARI-MANDIR KAUR KHALSA, CHRISTOPHER BAETHGE, LEONARDO TONDO, ROSS J. BALDESSARINI

Abstract. Longitudinal assessment of the course of major psychiatric disorders has been advanced by studies from onset, but only rarely have large numbers of patients with a range of psychotic and major affective disorders been studied simultaneously and systematically from illness-onset. The decade-long McLean-Harvard First Episode Project & International Consortium for Bipolar Disorder Research has systematically followed-up large numbers of patients with DSM-IV bipolar or psychotic disorders from first-hospitalization. Major findings among patients with bipolar I disorder include: [a] full functional recovery from initial episodes was uncommon, and full symptomatic recovery, much slower than early syndromal recovery; [b] risks of relapse, recurrence, and switching were very high in the first two years; [c] most early morbidity was depressive-dysphoric, as reported in mid-course; [d] initial depression or mixed-states predicted more later depressive and overall morbidity, whereas initial mania or psychosis predicted later mania and a better prognosis; [e] based on within-subject modeling, most patients did not show progressive cycling over time, and illness-course was rather chaotic within and among patients; [f] treatment-latency or episode-counts were unassociated with responsiveness to long-term mood-stabilizing treatment; [g] very high rates of suicidal behavior and accidents occurred early; [h] early substance-use comorbidity associated with anxiety; [i] factor-analysis of prodromal symptoms predicted bipolar disorder much better than non-affective psychotic disorders. Project findings indicate that the course of bipolar I disorder is much less favorable than had been believed formerly, despite clinical treatment with modern mood-stabilizing and other treatments.

INTRODUCTION

Longitudinal studies of psychotic disorders

Many studies have sought to define the course of major psychiatric disorders and identify outcome predictors. Most have involved patients considered to have schizophrenia, usually in mid-course, and very few have compared mood and nonaffective psychotic disorders, or followed patients prospectively from illness-onset (Beiser *et al.*, 1988; Erickson *et al.*, 1989; Leff *et al.*, 1992; Tohen *et al.*, 1990a; Bromet *et al.*, 1996; Craig *et al.*, 1997). Such studies have yielded inconsistent findings, owing in part to mixing subjects who differ diagnostically, by illness-duration, and in effects of uncontrolled treatments (Zis & Goodwin, 1979; Tohen, 1991). The complexity and risk of confounding under such conditions has encouraged prospective studies of first-episode patients in early or prodromal phases of illness. Most first-episode studies involve patients diagnosed with early (Jones & Tarrant, 1999; McGorry *et al.*, 2000; Cannon *et al.*, 2001; Gaebel *et al.*, 2001; Hollis 2003), or established schizophrenia (Kane *et al.*, 1982; Biehl *et al.*, 1986; Schubart *et al.*, 1986; McCreadie *et al.*, 1989; Johnstone *et al.*, 1990; Tohen *et al.*, 1990b; 1992a; 1996; Tohen 1991; Leff *et al.*, 1992; Ram *et al.*, 1992; Ventura *et al.*, 1992; Lieberman *et al.*, 1993; Bromet *et al.*, 1996; Varma *et al.*, 1996; Craig *et al.*, 1997; Gupta *et al.*, 1997; Lay *et al.*, 1997). There have been far fewer first-episode follow-up studies of patients diagnosed with bipolar disorder (Tohen *et al.*, 1990b, 2000a,b; Fennig *et al.*, 1996; Strakowski *et al.*, 1998; Conus *et al.*, 2004; 2006; Schimmelmann *et al.*, 2005), or other types of psychotic disorders (Pillmann *et al.*, 2002; Schimmelmann *et al.*, 2005; Abe *et al.*, 2006; Emsley *et al.*, 2006; 2007).

Follow-up studies beginning early in the evolution of chronic or recurrent illnesses, and comparisons of affective vs. non-affective psychotic syndromes promise early identification of specific disorders, of clinical or biological factors associated with vulnerability or early morbidity, and may predict later illness-course and outcome (McGorry *et al.*, 1998; Tohen *et al.*, 2003; Meagher *et al.*, 2004). Early studies are much less likely to be confounded by effects of chronic illness and disability, artifacts of altered life-styles, institutionalization, poor nutrition, or changes produced by long-term treatment or effects of commonly comorbid substance abuse.

Address for correspondence: Dr. P. Salvatore, Centre Building, Office G07B, McLean Hospital, 115 Mill St., Belmont MA 02478 (USA).
Fax: 1-617-855-3479
E-mail: psalvatore@mclean.harvard.edu

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Longitudinal studies in bipolar disorder

Mapping the course of bipolar disorders systematically from onset, through their typically complex and variable patterns of recurrence is a critical research challenge (Goodwin & Jamison, 1990; Kessler *et al.*, 1997; Akiskal *et al.*, 2000; Geddes & Goodwin, 2001; Strakowski *et al.*, 2001; Tohen & Angst, 2002). Documenting the course of bipolar disorders requires reliable and clinically meaningful definitions of specific phases of illness, ideally based on operational criteria that facilitate comparisons across studies and support generalization of findings (Tohen *et al.*, 1990a,b; 1992a,b; Keller *et al.*, 1993; Winokur *et al.*, 1994; Keck *et al.*, 1995; Strakowski *et al.*, 2001; Chengappa *et al.*, 2005; Conus *et al.*, 2006; Harvey, 2006; McIntyre *et al.*, 2006; Shi *et al.*, 2006).

Bipolar disorders not only have high risks of multiple recurrences as well as sustained morbidity, but also very high rates of comorbidity with substance-use and anxiety disorders, variable disability, and premature mortality from extraordinarily high suicide rates as well as adverse outcomes of medical illness (Tsuang *et al.*, 1980; Goodwin & Jamison, 1990; Tondo *et al.*, 2003a; Fenn *et al.*, 2005). To develop and implement sound and evidence-based clinical and public policies for treating bipolar disorder patients with scarce resources, much more information is required concerning their course and morbidity, ideally as early as possible to facilitate predictions.

Longitudinal studies in bipolar disorder have included patients who vary greatly in the stages of their illnesses and numbers of prior episodes. Moreover, following subjects only in midcourse of illness risks enriching research samples with relatively unstable, poor-prognosis patients (Keller *et al.*, 1986;1987; Keck *et al.*, 1998; Bauer *et al.*, 2001; Goldberg & Harrow, 2004; Nehra *et al.*, 2006; Green, 2006; Keck, 2006). Very few studies have enrolled bipolar disorder patients from first-episodes (Tohen *et al.*, 1990b; Husted *et al.*, 1995; Fennig *et al.*, 1996; Strakowski *et al.*, 1998; Conus *et al.*, 2004; 2006; Schimmelmann *et al.*, 2005), and even fewer have followed subjects prospectively from prodromal phases preceding major episodes meeting contemporary clinical or research diagnostic criteria (Thompson *et al.*, 2003; Amminger *et al.*, 2006). Even among first-episode studies, very few have involved large numbers of subjects followed-up systematically over many years (Strakowski *et al.*, 1998; Tohen *et al.*, 2003; Conus *et al.*, 2004; Schimmelmann *et al.*, 2005).

Most longitudinal studies of bipolar-disorder patients have focused on initial syndromal outcomes, later recurrence frequency, or cycle-length (Tsuang *et al.*, 1981; Black *et al.*, 1988; Winokur & Kadrmas, 1989; Harrow *et al.*, 1990; Coryell *et al.*, 1993; 1995; Winokur *et al.*, 1994; Goldberg *et al.*, 1995; Kessing *et al.*, 1998; 1999; 2004; Angst & Sellaro, 2000; Angst *et al.*, 2003). Emerging improvements include operationally-defined measures of recovery based on modern diagnostic criteria, and distinction of syndromal from symptomatic or functional recovery (Keller *et al.*, 1986; Tohen & Goodwin, 1995; Keck *et al.*, 1998; Tohen *et al.*, 1992a,b; 2000a, b; 2003; Strakowski *et al.*, 1998).

Recent longitudinal studies of bipolar disorder patients have challenged some traditional views of manic-depressive illnesses as disorders of favorable prognosis, in contrast to schizophrenia and other chronic, nonaffective psychotic disorders (Tohen *et al.*, 1990a; Harrow *et al.*, 1990; Coryell *et al.*, 1990; 1995; Gitlin *et al.*, 1995; Goldberg *et al.*, 1995; Keck *et al.*, 1998). Even with access to modern mood-stabilizing and other treatments, most bipolar disorder patients experience high levels of morbidity, accounting for more than 40% of weeks of long-term follow-up, most of which is accounted for by depressive-dysthimic illness (Judd *et al.*, 2002; Post *et al.*, 2003; Baldessarini *et al.*, 2004b; Joffe *et al.*, 2004). Potentially more favorably, other findings challenge the proposal first made by Kraepelin that manic-depressive disorders are typically progressive, with routinely shortening wellness-intervals between increasingly frequent recurrences (Roy-Byrne *et al.*, 1985; Haghighat, 1996; Turvey *et al.*, 1999; Baldessarini *et al.*, 2004a). Still other studies find evidence that latency from illness-onset to long-term prophylactic treatment and pretreatment recurrence counts do not necessarily limit response to long-term treatment with mood-stabilizers (Baethge *et al.*, 2003; Bratti *et al.*, 2003; Baldessarini *et al.*, in press).

The McLean-Harvard First-Episode Project

Given this background indicating the need for additional longitudinal assessments of patients with bipolar I and other disorders evaluated longitudinally from onset by standardized methods over long periods, we organized the McLean-Harvard First Episode Project in the late 1980s, led by Mauricio Tohen. This project has followed patients presenting with first-lifetime manic or psychotic illnesses, prospectively and systematically, to clarify the future course of illnesses from early stages, and to characterize such patients before potential artifacts associated with prolonged illness and treatment have intervened (Tohen *et al.*, 1990a,b; 1992a,b; 2000a,b). In this naturalistic investigation, treatment was managed by treating physicians and not controlled by the investigators, although we collected information about treatment systematically.

The study cohort includes nearly 400 subjects who presented in a first-lifetime episode of psychotic illness in 1989-1995 at McLean Hospital in Belmont, Massachusetts, the largest psychiatric teaching hospital affiliated with Harvard Medical School. Diagnosis was based on a best-estimate procedure at intake and again at 24 months, using all available information (SCID-P, clinical records, and interviews of family members and primary clinicians; Tohen *et al.*, 2000a,b). Approximately 300 subjects met SCID-based DSM-IV criteria (updated, as required, from DSM-IIIR) for major affective disorders with psychotic features, including bipolar disorder and major depressive disorder; others were diagnosed with non-affective psychotic disorders including schizophrenia, delusional, schizophreniform, brief, or unspecified psychotic disorders. The sample is broadly inclusive of disorders, socioeconomic backgrounds, presentations, and outcomes.

In addition to detailed information about first symptoms, syndromes, and treatments obtained from subjects and family members, demographic and many clinical variables were recorded at baseline, including medical, psychiatric, and substance use comorbidity history, premorbid and current occupational and residential status. Symptoms and their severity at intake and during follow-up were rated with a version of the *Brief Psychiatric Rating Scale* [BPRS] expanded to 35 items to include symptoms of affective as well as psychotic disorders, as well as a range of other standard clinical rating instruments (Tohen *et al.*, 2000a,b; 2003). Data obtained during regular follow-up interviews included changes in social and demographic status, and details concerning the week-by-week course of the primary and comorbid disorders, with best-estimates of new diagnoses and approximate initial and final weeks of illness recurrences and major exacerbations. We also collected a comprehensive, systematic, and detailed inventory of specific psychopathological features present in prodromal, symptomatic, and recovered phases, supported by the 100-item *Manual for the Assessment and Documentation of Psychopathology* (AMDP; Guy & Ban, 1982) and 66-item *Bonn Scale for Assessment of Basic Symptoms* (BSABS; Gross *et al.*, 1987; Klosterkötter *et al.*, 2001).

Major Findings

Our First Episode Project involves the largest reported sample of DSM-IV bipolar I disorder patients (N=173) followed-up prospectively and systematically under naturalistic conditions through nearly five years after first-lifetime psychiatric hospitalization. Patient-recruitment (72%) and retention (87%) were high, and the naturalistic conditions permit realistic evaluation of contemporary clinical outcomes with reasonable expectation of generalizability, at least to patients with mental illnesses requiring early hospitalization.

Impact of duration of initial hospitalization

Administrative and economically driven changes in length-of-hospitalization in the 1990s led to gradual shortening, from approximately six weeks initially to 1–2 weeks by the mid-1990s, and even shorter stays currently. With shortening hospitalization, average annual improvements in expanded-BPRS ratings of morbidity between admission and discharge also declined across diagnostic groups. When patients were assessed at six and 12 months later, their clinical status and level of improvement were remarkably little affected. This finding suggests that clinical improvement initiated in the hospital continued during ambulatory aftercare, but with unmeasured impact of rising average residual morbidity on patients, their families and communities (Tohen *et al.*, 2003; Baldessarini *et al.*, in preparation).

Recovery from index manic or mixed bipolar disorder episodes

For bipolar I patients, *syndromal recovery* from index first-episodes of mania or mixed-states was relatively rapid (median, 5.6 weeks), and 98% no longer met DSM-IV diagnostic criteria for an acute major illness episode by 24 months following their first-lifetime hospitalization. Syndromal recovery was earlier after relatively brief initial hospitalization, among women, and with lower initial depression ratings, use of lithium, and non-use of antidepressants, suggesting an unfavorable impact of depressive features. As expected (Chengappa *et al.*, 2005), full *symptomatic* recovery was much less often achieved: only 72% of patients were symptomatically well at 24 months.

Even more strikingly, recovery of within-subject premorbid *functional* levels, based on assessments of occupational status and level of independent living, was not attained by 61% of bipolar I patients at six months, nor by 57% even by 24 months, when only 43% had returned to baseline functioning; another 13% achieved functional recovery within the first year and lost it by two years (Tohen *et al.*, 2003). Functional recovery at two years was more likely among older patients and after shorter initial hospitalization. These low rates of functional recovery early in the course of bipolar I disorder were unexpected, and indicate high levels of symptomatic

morbidity and dysfunction very early in this supposedly "good-prognosis" disorder, despite clinical application of modern treatments. They also accord closely with other findings, in which only 35% of initially first-mania patients were functionally recovered by 12 months (Strakowski *et al.*, 1998).

Early risks of new illness episodes in bipolar disorder patients

We considered the risk and timing of new episodes of illness in the bipolar I disorder patients involving *relapses* (return to full syndromal illness of the same type) or *switches* (new episodes of major depression) without full initial recovery from index manic episodes sustained for at least two months, as well as *recurrences* (new episodes of illness of any polarity). Relapses, switches, or recurrences occurred in 57% of bipolar I patients within two years of intake (Tondo *et al.*, 2003b; Harvey, 2006; Shi *et al.*, 2006). These risks are consistent with reported failure-rates of 39%–52%/year during various maintenance treatments in bipolar I patients (Gitlin *et al.*, 1995; Goldberg *et al.*, 1995; Baldessarini *et al.*, 2000; 2002; Maj *et al.*, 2001; Tondo *et al.*, 2001; Tsai *et al.*, 2001; Judd *et al.*, 2002).

Several factors differentially predicted new episodes of *mania*, including initial mood-congruent psychotic features, low premorbid occupational status, and lack of prominent initial depressive features. New major *depression* was associated with higher occupational achievement (possibly related to early demoralization), initial mixed-dysphoric states, and psychiatric or medical comorbidity. Other studies have found that mixed-dysphoric index episodes (Keller *et al.*, 1986; Tohen *et al.*, 1990b), comorbidity (Tohen *et al.*, 1990b; Goldberg *et al.*, 1995), and psychotic features (Tohen *et al.*, 1990b; 1992b; Coryell *et al.*, 1990; Fennig *et al.*, 1996; Carlson *et al.*, 2000; Tsai *et al.*, 2001) associated with poorer outcomes in bipolar disorder patients. We also noted somewhat earlier recovery and longer stability among those treated with lithium, and least favorable outcomes among those given an antidepressant (Tohen *et al.*, 2003). Overall, these initial findings from the very beginnings of bipolar I disorder, encourage earlier case-finding and intervention, with much greater emphasis on depression and functional recovery during close and continuous clinical aftercare.

Early morbidity during follow-up of bipolar disorder patients

Morbidity during long-term follow-up was very similar to that reported in mid-course studies (Judd *et al.*, 2002; Post *et al.*, 2003; Joffe *et al.*, 2004), in that depression-dysthymia-dysphoria were dominant mood-states, accounting for nearly 30% of weeks of follow-up, despite use of modern mood-stabilizing and antidepressant treatments (Baldessarini *et al.*, 2004b). The remarkably consistent mid-course and early longitudinal observations indicate that bipolar *depressive illness* remains a major unsolved problem. This phase of bipolar illness is of particular significance in that it is associated with substance abuse, disability, and premature mortality due to suicide or medical illnesses (Tondo *et al.*, 2003a; Baldessarini *et al.*, 2006; Carney & Jones, 2006; Newcomer, 2006). Moreover, it remains the least well studied type of depressive illness, for which very few treatments are proved safe and effective (Ghaemi *et al.*, 2003; 2004; Baldessarini, 2005; Goodnick, 2007).

We also found that the polarity of the initial episode in bipolar I disorder illness strongly predicted the type and amount of later morbidity: those starting in depressive or mixed-dysphoric states were more ill overall, and spent much more time later in depressive-dysphoric illness, whereas those who began in mania spent more time manic-hypomanic or psychotic.

Course of early bipolar disorder

Our review of research on the course of bipolar and other forms of manic-depressive disorders over the past century found highly inconsistent evidence for Kraepelin's proposed course-progression or increasing cycling-rate over time, even when the methods employed avoided the problem of enriching subsamples involving high recurrence counts with patients who cycle more rapidly than others (Oepen *et al.*, 2004; Salvatore *et al.*, in preparation).

We also assessed the course of bipolar I disorder among the first-episode bipolar disorder patients by a within-subject regression method to generate individual slope functions (cycle-length vs. episode count). We found a virtually random distribution of slopes, with increasing cycling rate in only 30%–40% of subjects (Baldessarini *et al.*, 2004a; in preparation). This finding may reflect effects of modern treatments, but it is consistent with other studies finding that acceleration of cycling occurs in only a minority of manic-depressive patients (Salvatore *et al.*, in preparation).

Lack of a routinely worsening course of bipolar illness over time accords with other findings of our Research Consortium concerning effects of illness-history on treatment-response. Findings from published studies as well as original research support the conclu-

sion that, although prolonged untreated morbidity can have a devastating impact on bipolar disorder patients, evidence that response to eventual long-term mood-stabilizing treatment is compromised by either delay of treatment or more previous recurrences was lacking (Baethge *et al.*, 2003; Bratti *et al.*, 2003; Baldessarini *et al.*, in press).

Suicidal risk in early bipolar disorder

Since depression is the dominant morbidity in early and later phases of bipolar disorder, as noted, we have been particularly interested in risks of suicidal behaviors early in the course of the illness. Early suicidal behavior as well as accidents were strongly associated with the excess of depressive morbidity found early in the course of treated bipolar disorder (Khalsa *et al.*, in press). A majority (59%) of first-episode bipolar I disorder patients were suicidal at some time during an average of 4.2 years at risk (14.0%/year: suicidal ideation at 9.8%/year, attempts at 4.2%/year, and suicides at 0.11%/year). This observed suicide rate is 10-times above the US general population incidence (0.011%/year), and the rate of attempts (4.2%/year) is 14-times above the estimated general population attempt rate (ca. 0.3%/year; Baldessarini *et al.*, 2006). Adding risk of accidents increases the total observed rate of violent fatalities to 0.22%/year. The rate of accidental deaths alone (0.11%/year) is three-times above the current US national rate of 0.037%/year. Moreover, 60% of accidents were associated with suicidality, suggesting a crucial subgroup among recent-onset bipolar I disorder patients at particularly high risk of violent self-injury or death.

Risk-factors found to be independently associated with violence, based on multivariate analysis, included greater mixed-dysphoric morbidity, presenting manic (accidents) or mixed episodes (suicidality), more time manic in follow-up (accidents), alcohol abuse, and previous suicide attempts (suicides and attempts). Similar suicidal risk factors have been identified previously, but later in the mid-course of bipolar disorders (Tsai *et al.*, 2001; Tondo *et al.*, 2003a; Dunner, 2004; Slama *et al.*, 2004; Baldessarini *et al.*, 2006).

In parallel collaborative studies within our Research Consortium found not only that suicidal risk was much higher among bipolar than recurrent major depression outpatients, but also that nearly one-third of suicidal acts in bipolar I and II disorder patients occurred within the *first year* of illness (Tondo *et al.*, 2003a; in review).

Early substance abuse in bipolar disorder

We evaluated the early emergence of substance-use comorbidity among bipolar I patients and found anxiety symptoms to be strongly associated with abuse of alcohol and other central depressants, as well as evidence that abuse of alcohol tends to precede and coincide with depression, and that abuse of stimulants tends to coincide with or follow mania (Baethge *et al.*, 2005; 2006).

Early prodromal symptoms of psychotic and bipolar disorders

We recently analyzed patterns of early symptoms among a broad range of first-episode patients later proving to have DSM-IV psychotic affective or non-affective disorders, using factor-analytic methods (Salvatore *et al.*, 2007). Clusters of early symptoms predicted later separation between affective and nonaffective disorders, generally, but relatively poorly distinguished particular *nonaffective* disorders. Psychopathological features of early morbidity in psychotic disorders were statistically well accommodated by four "Factors" associated with particular prodromal symptom-clusters: Factor I was considered to represent *mania with psychosis*; II a *mixed depressive-agitated* state; III an *excited-hallucinatory-delusional* state; IV a *disorganized-catatonic-autistic* state. Factors I and III were associated with mania, Factor II with major depression or bipolar mixed-state, Factor III was *less* likely to be found in association with delusional disorder, and Factor IV was positively associated with major depression and *negatively* with mania. Based on final diagnostic categorizations after two years of follow-up and consideration of all available data, *presence* of Factors I and II predicted later affective diagnoses, whereas *absence* of Factor I features predicted non-affective diagnoses, and no Factor predicted later schizoaffective diagnoses. This dimensional approach to psychopathology appears to be effective in identifying and subtyping affective psychotic disorders early in their clinical evolution, whereas nonaffective-schizoaffective conditions appear to be more complex or unstable entities.

CONCLUSIONS

This summary of recent research findings from the McLean-Harvard First Episode Project and International Consortium for Bipolar Disorder Research yields several insights concerning the course of bipolar I disorder in patients followed for several years from illness onset.

These include verification that full symptomatic recovery of first-lifetime manic or mixed-state episodes was much slower, and less likely, than early syndromal recovery. In addition, only a minority of first-episode bipolar disorder patients attained functional recovery to premorbid baseline levels of occupation and independent living, even after two years from onset. Risks of relapse, switching and recurrence were very high early in the course of bipolar disorder, despite access to modern clinical treatments. In accord with recent longitudinal studies of bipolar disorder patients in mid-course, most early morbidity was depressive-dysphoric. Moreover, initial depression or mixed states predicted slower recovery, later depressive illness, and greater overall morbidity, whereas initial mania or psychosis predicted later mania and better prognosis.

Based on within-subject analysis, the distribution of illness course-trends was nearly random. Only a minority of patients showed progressive cycle-acceleration, a nearly equal proportion showed slowing, and most showed a random pattern as episode counts rose. We also found that treatment delay and episode-counts were unpredictive of responsiveness to long-term mood-stabilizing treatment, as measured by morbidity *during* treatment. Moreover, apparently greater *relative* improvement of morbidity by earlier intervention may reflect an artifact of greater morbidity proximal to the start of maintenance treatment.

A particularly important finding is that suicidal behavior and accidents were prevalent within the first several years of bipolar illness, including a third of long-term suicidal acts within the first year of illness. Substance-use comorbidity, a risk factor for suicide and attempts in bipolar disorder patients, also emerged early, particularly in association with anxiety, and with a strong association of depression with alcohol-abuse. These several findings are particularly ominous in that latency to diagnosis and establishment of long-term prophylactic treatment in bipolar disorder patients is typically delayed by 5–10 years: clearly, earlier diagnosis and intervention are required. Earlier diagnosis and prognosis may be supported by analyses of prodomal and other early symptom-patterns.

In short, findings from the past decade of studies in the First-Episode Project and the International Consortium for Bipolar Disorder Research based at McLean Hospital and Harvard Medical School indicate that the nature and course of bipolar I disorder are much less favorable than had been proposed formerly, despite access to effective mood-stabilizing and other treatments. Our findings strongly encourage earlier diagnosis of bipolar disorder and long-term protective treatment interventions aimed at limiting morbidity, dysfunction, and mortality associated with this prevalent, often disabling, and life-threatening disorder.

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