Prophylaxis Latency and Outcome in Bipolar Disorders

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Objective: To analyze new and reviewed findings to evaluate relations between treatment response and latency from onset of bipolar disorder (BD) to the start of mood-stabilizer prophylaxis.

Method: We analyzed our own new data and added findings from research reports identified by computerized searching.

Results: We found 11 relevant studies, involving 1485 adult patients diagnosed primarily with BD. Reported latency to prophylaxis averaged 9.6 years (SD 1.3), and follow-up in treatment averaged 5.4 years (SD 3.1). Greater illness intensity and shorter treatment latency were closely associated, resulting in a greater apparent reduction in morbidity with earlier treatment. However, this finding was not sustained after correction for pretreatment morbidity, and treatment latency did not predict morbidity during treatment. Therefore, assessments based on improvement with treatment, or without correction for pretreatment morbidity, can be misleading.

Conclusions: Available evidence does not support the proposal that delayed prophylaxis may limit response to prophylactic treatment in BD and related disorders.

(Can J Psychiatry 2003;48:449–457)

Information on funding and support and on author affiliations appears at the end of the article.

Clinical Implication

Pharmacologic prophylaxis in bipolar disorder (BD) appears to be similarly effective at early and later stages of adult BD. Nevertheless, it is important clinically to intervene early to limit untreated morbidity.

Limitation

Available studies of this topic are naturalistic and uncontrolled.

Key Words: *anticonvulsants, bipolar disorder, delayed prophylaxis, kindling, latency, lithium, major affective disorder, outcome, prophylaxis, response, treatment*

Patients diagnosed with bipolar disorders (BDs) often experience prolonged latency from illness onset to the start of sustained, long-term prophylaxis (1–4). This may represent a particularly critical period in the natural history of these disorders (5–9). A widely considered hypothesis is that kindling-like phenomena or behavioural sensitization occurs in BD, as reflected in increasingly severe or more rapidly recurring illness episodes over time (5,6). Often cited in support of this concept is evidence that in major affective illnesses the cycle length (that is, the time from the start of an episode to the start of the next) and the intervals of relative wellness between acute episodes may undergo progressive shortening, particularly without treatment (10–12).

The kindling hypothesis of progressive worsening in major affective disorders arises from an animal model of secondarily generalized epilepsy following initially minor and localized, experimentally induced seizures (6,13). This phenomenon is sometimes taken as a nonhomologous model for mood disorders. The model suggests that untreated affective illness may lead to pathophysiological changes in brain tissue of untreated patients. Some neuroradiological and postmortem neuropathological findings have been interpreted as supporting this hypothesis. They include structural changes in brain imaging and postmortem neuropathological changes in the brain tissue of BD patients, as well as suggestions that mood stabilizers may prevent or reverse such changes (7,14–16).

The time between onset of BD illness and the start of prophylactic treatment can be characterized in various ways, such as elapsed time, episode counts, their relation (that is, episodes per time), or other measures of illness intensity. All these measures can be inaccurate when based on incomplete medical records and potentially faulty patient or family recollections about these clinically complex episodic illnesses (17,18). Hospitalization can be a more reliable parameter, but it does not take into account milder episodes. Moreover, neither episode nor hospitalization counts consider subsyndromal illness, which is often a major component of long-term morbidity in BD (19). It is also possible that pathophysiological mechanisms in BD may persist even in the absence of acute episodes or subsyndromal symptoms, suggesting consideration of time rather than illness events. For example, persistent dysregulation of hypothalamo–pituitary–adrenal (HPA) function (20), as well as phase advances in circadian motility rhythms (P Salvatore, personal communication, March, 2003), can persist in BD patients, independent of depression or mania.

Further, it seems plausible to expect that, if BD episodes tend to increase in frequency or become more severe over time, the disorder may also become less treatment-responsive and that earlier prophylaxis may therefore yield superior benefits and clinical outcomes (8,9). However, whether delay of prophylactic treatment in BD leads to inferior treatment response or outcome remains uncertain. To address this question empirically, we reviewed new data from our own studies as well as published reports on the effects of prophylaxis latency on response and outcome in patients with BD and related disorders.

Methods

We analyzed new data from our own naturalistic studies carried out in 2 large outpatient clinics for affective disorders in Berlin and Sardinia. Details of the clinical settings, patient characteristics, and diagnostic and clinical assessment methods are detailed elsewhere (2,3). Statistical analyses presented used Statview-5 statistical software (21).

In addition, we retrieved relevant research literature using a Medline-based computerized search from 1966 to April 30, 2003. The search terms were as follows: affective, bipolar, manic-depressive, mood disorder, long-term treatment, maintenance, prophylaxis, duration of illness, delay, latency, lithium, anticonvulsants, antiepileptic drugs, carbamazepine, and valproate. We checked references cited in retrieved papers and recent reviews for further contributions. We included studies if they examined the significance of the time between illness onset and first use of any form of long-term (that is, 6 months or longer) mood-stabilizer treatment in BD or in BD plus other related disorders. We excluded studies if they reported on short-term treatment of acute episodes. We decided against a quality rating of the studies and against using quantitative metaanalytic techniques, since the studies varied highly in methods and outcome parameters.

Results

Within our search period, we identified 11 studies published between 1967 and 2003 (3,8,9,22–29) that provided relevant information (Table 1). They involved 1485 patients, with an average of 135 subjects per study (range 29 to 450). Reported age at illness onset averaged 30.5 years (SD 1.4); latency from onset to start of maintenance treatment averaged 9.58 years (SD 1.32); and prophylaxis or follow-up averaged 5.36 years (SD 3.09) (range 1 to 11 years; means are weighted by number of subjects per study). All studies ascertained the time from illness onset to the start of sustained maintenance therapy retrospectively, and methods of acquiring outcome data during treatment varied. Table 1 summarizes diagnostic and other methods. Several studies (8,9,22,23) included some recurrent unipolar or schizoaffective disorder patients with the BD subjects and did not report each diagnostic group separately (Table 1).

Only 3/11 studies reviewed found a significant association between shorter latency and a better outcome of long-term prophylactic treatment with a mood stabilizer. Two of these studies involved some of the same subjects (8,9), and the third study found the effect only with some outcomes (28). Paradoxically, another study reported that longer latency was associated with better response (25). Most studies (7/11), however, found no relation between longer treatment latency and reduced benefits of long-term treatment (3,22–24,26,27,29).

Among the 3 studies reporting superior outcomes with shorter treatment latency (8,9,28), that of Franchini and coworkers (8) investigated the illness course of 270 BD and recurrent major depression patients. With earlier treatment, they found relatively greater sparing of morbidity (that is, reduced episode frequency during vs before treatment) among quartiles based on treatment latency. This finding was supported in a later report on 61 similar patients (9), 30 of whom were included in the earlier report (8). The association of latency and improvement was not corrected for the correlation found between more severe pretreatment illness and treatment latency. Moreover, episode frequency during treatment appeared not to differ among latency groups (8). The third seemingly positive study evaluated 56 BD I patients for retrospective and current morbidity, without prospective follow-up (28). Hospitalization rate, risk of suicide attempts, and social functioning during the previous year were all less favourable when prophylaxis had been started later. However, the morbidity measures provided include periods before

Table 1 Studies of relations between treatment latency and outcome in bipolar and related disorders

Study	Cases *n*	Onset age	Latency (years)	Treated (years)	Latency effects[a]	Study methods and comments
Baastrup and others[b] (22)	88	NR	10.3	2.5	None	Clinical diagnosis: mixed (BD + MDD), women only; lithium with serum assay; shorter latency associated with more severe pretreatment illness. Outcome: treated illness.
Bouman and others (23)	104	29.9	10.2	4.4	None	DSM-III: mixed MAD (BD + MDD + SzAD); lithium with serum assay. Outcome: change in morbidity; more episodes, but not latency, predicted better response.
Maj and others (24)	53	29.8	11.2	7.5	None	RDC: BD, highly selected, patients stable on lithium (with serum assays) 5 years. Outcome: subjects with recurrences *n* = 8) had a ligher latency. This finding was not sustained in multivariate logistic regression; some morbidity measures were greater with earlier treatment.
Kusalic and Engelsman (25)	29	29.7	11.2	2.0	Longer better	DSM-III-R: BD I; lithium with serum assay. Outcome in treatment: categorical (responder or better nonresponder).
Kulhara and others (26)	118	NR	8.4	11.1	None	ICD-9: BD I (men/women = 2.5); mostly retrospective; lithium with serum assay. Outcome: change in treated morbidity; no effect of latency or episode count.
Franchini and others[c] (8)	270	32.9	10.2	4.7	Shorter better	DSM-IV: mixed MAD (BD + MDD); lithium with serum assay. Outcome: change in episode rate; confound of shorter latency with more severe pretreatment morbidity not controlled.
Seretti and others (9)	61	31.0	11.3	4.5	Shorter better	SADS: mixed MAD (BD + MDD); overlaps Franchini sample; lithium with serum assay. Outcome: change in episode rate; higher melancholia scores with shorter latency.
Garcia-Lopez and others (27)	139	28.8	12.7	7.6	None	BD (clinical diagnosis): lithium and long-term adjuncts. Outcome: any relapse and, episodes per year nonsignificant correlation with recurrence rate (r = 0.16); results not controlled for pretreatment illness severity.
Goldberg and Ernst (28)	56	31.7	9.8	1.0	Shorter better	DSM-IV: BD I; various medicines; retrospective, cross-sectional; latency shorter with greater better Illness-severity. Outcomes: hospitalization, suicide attempts, social function better with shorter reatment-latency.
Baethge and others (3)	147	31.9	9.3	7.7	None	DSM-III-R: BD I; lithium (88%) or CBZ with serum assays; latency shorter with greater illness severity (controlled for). Outcomes: % time ill severity, time well, change of time in hospital; outcomes unrelated to treatment, latency or prior episode count.
Baldessarini and others (2,29)	450	28.9	7.8	4.2	None	DSM-IV: BD I and II; lithium (86%) or CBZ with serum assays; illness more severe with shorter latency. Outcomes: % time ill, episodes yearly during treatment; outcomes unrelated to latency with diagnostic group or treatment.

BD = bipolar disorder, CBZ = carbamazepine; MAD = recurrent major affective disorders; MDD = recurrent major depressive disorder; NR = not reported; SzAD = schizoaffective disorder; SADS = Schedule for Affective Disorders and Schizophrenia; = associated with

The 11 studies include 1485 subjects (discounting approximately 30 patients in 2 studies [8,9]).

Weighted average (SD): onset-age = 30.5 (1.4) years, latency = 9.58 (1.32) years; treatment follow-up time averaged 5.36 (3.09) years, indicating that age at the start of treatment was approximately 40.1 years.

[a]Effect of latency on outcome, as defined in study methods and comments.

[b]Latency and time treated are estimated: latency, from groups: short (0–5 years: *n* = 26), intermediate (6–14 years: *n* = 31), and long (15 years: *n* = 31).

[c]Latency and treated follow-up time are not specified, but are estimated from data reported.

Table 2 Relation of treatment latency to morbidity before and during prophylactic treatment and its change in patients with major affective disorder

		Correlations with morbidity					
		Before treatment		During treatment		Change (before–during)	
Subgroup	*n*	r_s	*P*	r_s	*P*	r_s	*P*
Diagnostic groups							
Bipolar I	475	–0.185	< 0.0001	–0.001	0.986	–0.215	< 0.0001
Bipolar II	157	0.143	0.075	0.123	0.125	–0.092	0.253
Schizoaffective	49	–0.784	< 0.0001	–0.198	0.170	–0.567	< 0.0001
Major depressive	69	–0.721	< 0.0001	0.293	0.016	–0.675	< 0.0001
Sex							
Women	461	–0.203	< 0.0001	–0.019	0.407	–0.212	< 0.0001
Men	289	–0.234	< 0.0001	0.072	0.219	–0.285	< 0.0001
All patients	750	–0.213	< 0.0001	0.018	0.606	–0.234	< 0.0001

Morbidity before treatment is approximate yearly days of hospitalization; morbidity during treatment is the estimated percentage of days ill; change in morbidity is episodes yearly before–minus–during treatment. Note that morbidity before starting maintenance treatment is inversely proportional to treatment latency, leading to a potentially misleadingly greater change in morbidity (especially in schizoaffective disorder and major depression patients, and least among bipolar II patients) but that morbidity during treatment is unrelated to treatment latency in any group, except for a relatively weak correlation among nonbipolar major depression patients that was not sustained in multivariate regression (not shown). Correlations are by nonparametric (Spearman) rank methods, since time and morbidity measures are nonnormally distributed. Analyses are based on previous reports (2,3,28–30) and unpublished data.

and during long-term treatment, which confounds interpretation of the results.

In addition, Maj and coworkers studied late loss of treatment response and reported that, among 53 lithium-treated BD patients who had been stable for 5 years, 8 had started lithium treatment somewhat later than the others and experienced 2 or more relapses in the following 5 years (24). However, a multivariate analysis disconfirmed this suggestive finding in a small and unusual sample. Moreover, the 8 late-relapsing subjects had other unfavourable outcome predictors, including more subsyndromal affective morbidity and substance abuse during the first 5 years of treatment (22). Also, Garcia-López and colleagues found a weak, nonsignificant correlation between longer treatment latency and a higher relapse rate during a period of prophylaxis and an apparently short time of lithium discontinuation (27). This finding was uncontrolled for pretreatment illness severity. Finally, the single study finding that longer treatment latency predicted a better outcome involved only 29 BD I patients (25). Of these, only 6 were considered nonresponders, leaving the significance of the association between treatment latency and outcome unclear.

Among studies providing data regarding pretreatment illness severity (3,8,9,22–24,29), all show an association between more severe illness and earlier start of prophylaxis (although only for some measures in 1 study [24]). Our studies (2,3,29–31) quantified such relations and found highly significant correlations with treatment latency (nonparametric Spearman r_s, all $P < 0.0001$): 0.58 for pretreatment hospitalization rate (3), 0.66 for pretreatment episodes yearly (2), and 0.67 for pretreatment percentage of time ill (2,29). However, none of our studies found a relation between treatment latency and response when pretreatment illness severity was controlled for in the statistical analysis (3) or when only morbidity during long-term treatment was considered (2,3,29).

For further analysis, we also pooled data from our studies (2,3,30,31, and unpublished data). These studies involved 750 patients with BD and related disorders ($n = 475$ BD I, $n = 157$ BD II, $n = 69$ recurrent major depressive, and $n = 49$ schizoaffective). Almost all cases were treated in monotherapy (652 with lithium, 59 with carbamazepine or divalproex, 20 with an antipsychotic, and 19 with an antidepressant) for a mean of 5.03 years (SD 5.30). By diagnosis, treatment latency ranked as follows: major depression (mean 11.2 years, SD 11.1) = schizoaffective (mean 10.9 years, SD 10.6) = BD II (mean 9.8 years, SD 8.8) > BD I (mean 7.6 years, SD 8.2); $F_{3,746} = 6.28$, $P = 0.003$ overall, with BD I shorter than all others by post hoc testing. Latency averaged 9.2 years (SD 9.0) in women and 7.5 years (SD 8.5) in men; $F_{1,748} = 6.47$, $P = 0.01$. There were strong correlations between greater pretreatment morbidity (that is, episodes yearly, hospitalizations yearly, hospitalized days yearly, or

Table 3 Relation of treatment latency and morbidity before or during long-term maintenance treatment in bipolar and schizoaffective disorder patients

			Treatment-latency categories	
Study	Sample	Measures	Shortest	Longest
Baethge and others	Berlin	Cases (BD I + SzAD + MDD)	75	75
(3,30,31,unpublished data)		Treatment latency (years)[a]	2.2	15.3
		Morbidity during treatment	12.0 (SD 20.0)	19.0 (SD 33.0)
Baldessarini and others (2,29)	Sardinia	Cases (BD I + BD II)	85	365
		Treatment latency (years)[c]	1.5	> 1.5
		% time ill before[d]	81.0 (SD 24.6)	38.4 (SD 27.0)
		% time ill during treatment	21.1 (SD 24.9)	24.3 (SD 27.7)

Disorders: BD = bipolar (type I or II); MDD = recurrent major depressive; SzAD = schizoaffective

[a]Based on lowest vs highest quartile of latency from first hospitalization to start of prophylaxis with lithium or carbamazepine

[b]Morbidity index: % of days ill during treatment severity factor (t_{148} = 1.63, P = 0.104)

[c]Years from illness onset to start of long-term maintenance treatment (lithium or carbamazepine): short (1.5) = 0.74 (SD 0.40) vs long (1.5) = 9.39 (SD 8.31) years

[d]By nonparametric Mann–Whitney U-test: z = 10.4, P < 0.0001; other contrasts differ nonsignificantly

Table 4 Effect of adjustment for pretreatment morbidity in multivariate analysis of effects of factors on response to prophylactic treatment in 147 bipolar disorder patients

	Pretreatment hospitalization			
	Excluded		Included	
Factors		P		P
Treatment latency	–0.473	< 0.001	0.003	0.925
Pretreatment episodes[a]	0.062	0.449	–0.012	0.611
Pretreatment hospital days yearly	—	—	0.961	< 0.001
Age at start of treatment	–0.360	0.654	–0.008	0.747
Familial mood disorders	0.094	0.219	0.043	0.057
Medicine type[b]	0.008	0.921	0.003	0.902
Sex	0.002	0.975	0.010	0.664

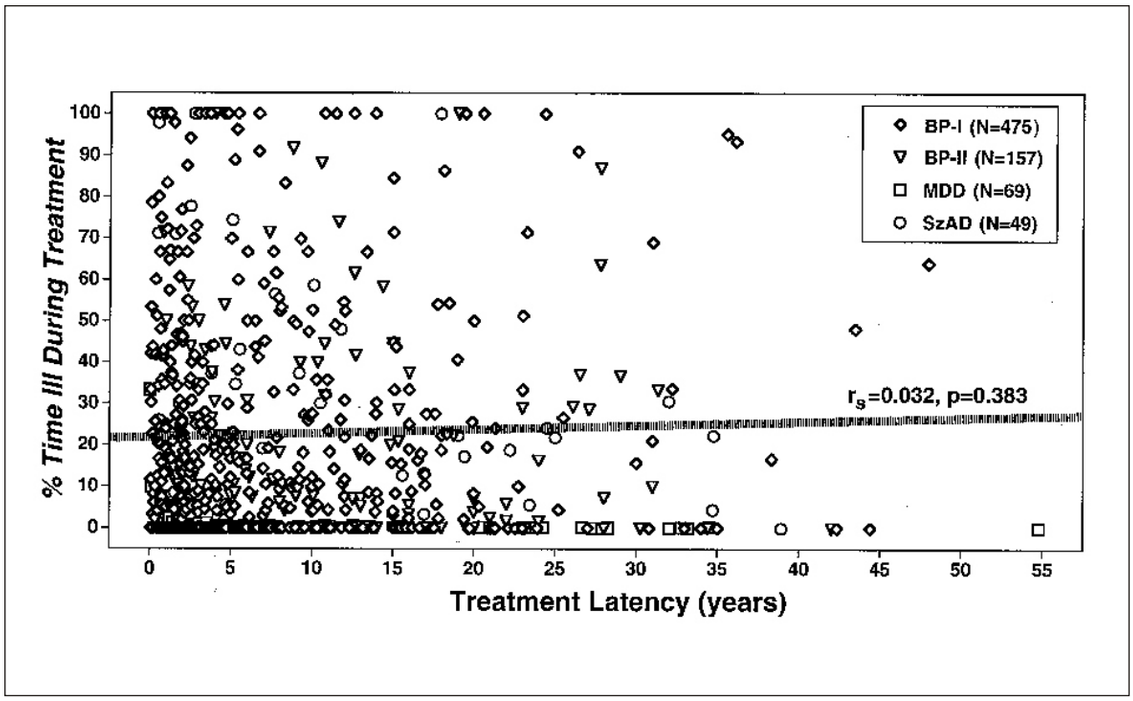
Analysis is based on logistic regression, showing the effect of including and excluding pretreatment as a morbidity measure (hospitalization days yearly). Excluding pretreatment morbidity leads to the impression that morbidity (index reflecting reduction in time in hospital) during maintenance treatment is significantly inferior with longer treatment latency. However, this conclusion is misleading, since latency and pretreatment morbidity are strongly inversely correlated, so that including pretreatment morbidity leads to a nonsignificant relation between latency and treatment response but a strong correlation between reduced morbidity during treatment and pretreatment morbidity. Both models highly significantly fit the data overall (both P < 0.001). (Based on a previously reported study [3]).

[a]Episodes documented by hospitalization

[b]Treated with lithium (n = 130) or carbamazepine (n = 17)

approximate percentage of days ill yearly) and shorter treatment latency (Table 2). This correlation accounted for an apparently greater relative change in morbidity (by all the pretreatment measures just listed) before vs during treatment. Correlations of pretreatment morbidity and its improvement with treatment were strongest among patients with schizoaffective disorder and unipolar depression, less strong among BD I patients, and weakest (nonsignificant) in BD II patients (Table 2). In contrast to changes in morbidity during vs before treatment, there were no robust relations for morbidity during prophylaxis and treatment latency, either overall or for any subgroup (that is, for patients with bipolar, unipolar depressive, and schizoaffective disorders), save for a suggestive bivariate relation for patients with unipolar major

Figure 1 Relation of approximate proportion of time ill during long-term maintenance treatment (% time ill) to treatment latency (averaging 8.58 [SD 8.85] years) among 750 Sardinia (*n* = 451) (2,27) and Berlin (*n* = 299) (3,28,29, unpublished data) patients (*n* = 461 women, 289 men) diagnosed with DSM-III-R or DSM-IV bipolar I (diamonds; *n* = 475), bipolar II (inverted triangles; *n* = 157), schizoaffective (squares; *n* = 49), or major depressive (circles; *n* = 69) disorders, treated for an average of 5.03 (SD 5.30) years with lithium (*n* = 652), an anticonvulsant (mainly carbamazepine; *n* = 91), or an antidepressant (*n* = 7) alone



The nonparametric correlation is nonsignificant overall (r_s = 0.019, P = 0.606), as well as for each treatment, diagnostic group (except for major depression patients) and sex considered separately (see Table 4).

depression—a relation that was not sustained in multivariate analysis (not shown).

The lack of relation between treatment latency and treatment response is further illustrated by our analysis of subsamples of extreme latencies. These include the shortest and longest quartiles in our Berlin samples (3,30,31, and unpublished data on unipolar depression patients; Table 3) and less than or equal to 1.5 years vs more than 1.5 years in our Sardinian subsamples (2,29; Table 3). Even at these extremes of maintenance-therapy delay, the differences in morbidity during treatment in both studies were very small (3.2% and 7.0% of time ill, respectively). Moreover, based on pooled data from all these studies (2,3,29–31, and unpublished), 253 patients with no detected morbidity during maintenance treatment and 112 who were ill 50% or more of the time showed virtually no difference in average treatment latency (8.29 years, SD 9.03 vs 8.57 years, SD 9.22, respectively; nonparametric Mann–Whitney *U*-test $z = 0.16$, $P = 0.798$).

A misleading interpretation of greater changes in morbidity with shorter treatment delay can also be avoided by using multivariate logistic regression methods, with control of pretreatment morbidity. Partial modelling using data for 147 BD I patients treated with lithium or carbamazepine, taken from one of our studies (3), produced a highly significant (but misleading) association between improvement in morbidity (that is, change in days yearly in hospital before-minus-during prophylactic treatment) and treatment latency. However, we found this association only when we excluded pretreatment morbidity (defined as hospitalized days yearly prior to initiation of prophylaxis) from the model, whereas no relation to latency was found when we included pretreatment morbidity. As well, whether we included pretreatment morbidity among the independent factors or not, this modelling found no relation between the stated measure of treatment response and pretreatment episode count, sex, age at the start of treatment, or family history. Similarly, this modelling found no relation between the stated measure of treatment response and whether treatment was with lithium or carbamazepine (Table 4).

Finally, based on pooled data from our studies of 750 patients with BD and related disorders (2,3,29–31, and unpublished), we provide an illustrative figure (Figure 1) to indicate the lack of relation between treatment latency and morbidity during prophylactic treatment, as well as enormous variance in treated morbidity among individual patients (coefficient of variation = SD / mean percentage of time ill = 128%; range 0% to 100%).

Discussion

Several noteworthy observations emerged from this study. First, the time from onset or first diagnosis of BD and related syndromes to first long-term prophylactic treatment with a mood stabilizer was remarkably long. Delay averaged 9.6 years, and was shortest among BD I patients, especially men. Longer latency to sustained mood-stabilizing treatment among patients with mainly depressive illnesses (that is, unipolar and BD II disorders), and in women, probably reflects more compelling clinical presentations among men displaying mania.

Second, more severe illness before starting prophylaxis was strongly associated with earlier treatment, leading to an apparent association of greater relative improvement following shorter delay. This relation likely reflects clinical decision making, with earlier interventions for more compelling indications. In addition, very prolonged prophylaxis latency probably reflects apparent dilution of finite morbidity in these recurring disorders over many years at risk, producing low estimates of morbidity over time. Of some importance, the strong inverse relation of morbid intensity and treatment latency implies, and produced, greater relative decreases in several measures of morbidity before vs during treatment. However, unless analyses are controlled for pretreatment morbidity (Table 4) or only morbidity during treatment is considered, one can easily be misled into concluding that earlier intervention produces a superior response. The evident error of such an interpretation is illustrated by the lack of correlation between treatment latency and several measures of morbidity during prophylaxis (Figure 1, Tables 2 and 3).

The present findings add further strong support to this conclusion, made earlier with respect to treatment latency specifically (2,3,29–31) and to the number of episodes (and associated latency) before prophylactic treatment (32). We recommend that assessments of the relations between pretreatment morbidity or illness duration and treatment effectiveness either consider only morbidity during treatment or control statistically for the potentially misleading effects of pretreatment morbidity, particularly when changes in morbidity are taken as the measure of treatment effectiveness. We found that studies suggesting that shorter (or longer) treatment latency may predict a better treatment outcome did not control for the relation of pretreatment morbidity to treatment latency (8,9,25,28).

It is sobering to realize that nearly a decade may elapse before prophylactic treatment is started in disorders characterized by multiple recurrences with high rates of morbidity, comorbidity, disability, and premature mortality, especially given the availability of effective treatments (33; Table 1). The observed average prophylaxis latency of 9.3 years (Table 1) may actually be even longer, since illness onset is often dated from first diagnosis rather than first symptomatic presentation, and the studies considered here did not address effects of intervention in the very first months of symptoms. Moreover, many cases of BD II are misdiagnosed and potentially mistreated as cases of recurrent non-BD major depression, and cases starting in childhood or adolescence may be difficult to recognize as BD (34). An indication of this diagnostic problem is that the mean onset age in the studies we reviewed was 31 years, whereas a review of early-onset BD suggested a median onset age of about 20 years (35). Egeland and coworkers found high reliability for most of the onset-age criteria for BD encountered in this study, but these researchers also found that initial symptoms typically precede first diagnosis or treatment by substantial periods of time (35). The inclusion of some studies using broadly defined subtypes of manic-depressive illness further contributes to the relatively older onset age reported here: it is well known that non-BD depressive illnesses have an older average onset age (10,31).

In addition to a lack of support for the proposition that early intervention in BD and related disorders leads to superior prophylaxis efficacy, the present analysis also gives reason to remain skeptical about the widely accepted view that BD may tend to have a progressive course, especially without treatment (8,9,10,36). Several studies have not supported this finding, and it is vulnerable to a common but evidently underappreciated sampling artifact that can yield overrepresentation of patients with faster average cycling times as the episode count rises (37,38).

Finally, for comparison with proposed effects of kindling in BD (36), we searched for studies of the effects of delayed anticonvulsant treatment in epileptic patients. We found 4 such studies (39–42). These reports involved 1121 epilepsy patients, almost all of whom had generalized tonic-clonic attacks, some with secondary generalization from more limited initial ictal events. Latency to anticonvulsant treatment averaged 7.7 years (SD 1.7), and sustained treatment lasted 1.7 years (SD 1.2). In all 4 studies identified, there was no relation between treatment latency and effectiveness of anticonvulsant therapy (39–42).

In conclusion, the studies we considered are subject to the limitations of naturalistic clinical investigations. No study randomly assigned patients to early vs late treatment, nor would such studies be considered ethically feasible. Despite their limitations, the findings of this study offer little support for the concept that an hypothesized progressive worsening tendency in BD also implies that earlier intervention regularly yields superior treatment effectiveness. This provocative conclusion is scientifically interesting as well as clinically optimistic. However, it would be irresponsible not to reemphasize an obvious clinical point: to limit the often devastating and potentially lethal impact of these highly prevalent and treatment-responsive disorders, early diagnosis and intervention for BD and other forms of recurrent major affective disorders are greatly to be preferred and vigorously pursued.

Acknowledgement

The authors are grateful to Edward Bromfield, MD, Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, for expert advice concerning treatment of epilepsy.

Funding and Support

This study was supported by the Max Kade Foundation (Dr Baethge), the Bruce J Anderson Foundation and the McLean Private Donors Psychopharmacology and Bipolar Disorder Research Fund (Dr Baldessarini), and the Stanley Research Institute and the National Association for Research on Schizophrenia and Affective Disorders (NARSAD) (Dr Tondo).

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Manuscript received and accepted May 2003.

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Résumé : Attente et résultat de la prophylaxie dans les troubles bipolaires

Objectif : Analyser les nouveaux résultats et d'autres déjà étudiés pour évaluer les relations entre la réponse au traitement et le temps d'attente, de l'apparition d'un trouble bipolaire (TB) au début d'une prophylaxie avec régulateur de l'humeur.

Méthode : Nous avons analysé nos propres données et avons ajouté des résultats d'autres études de recherche trouvées par une recherche électronique.

Résultats : Nous avons trouvé 11 études pertinentes concernant 1 485 patients adultes ayant principalement reçu un diagnostic de TB. Le temps d'attente déclaré avant une prophylaxie était en moyenne de 9,6 ans (ET 1,3), et le suivi du traitement était en moyenne de 5,4 ans (ET 3,1). Une plus grande intensité de la maladie et un temps d'attente du traitement plus court étaient étroitement associés, ce qui donnait une plus grande réduction apparente de la morbidité pour le traitement précoce. Toutefois, ce résultat n'était pas appuyé après correction pour la morbidité pré-traitement, et le temps d'attente du traitement ne prédisait pas la morbidité durant le traitement. Par conséquent, les évaluations fondées sur l'amélioration avec le traitement, ou sans correction pour la morbidité pré-traitement peuvent être trompeuses.

Conclusions : Les données probantes disponibles n'appuient pas la proposition selon laquelle le délai de la prophylaxie peut limiter la réponse au traitement prophylactique dans le TB et les troubles connexes.