The message of the survival curves: I. Composite analysis of long-term treatment studies in bipolar disorder

Ede Frecska, Attila Istvan Kovacs, Petra Balla, Linda Falussy, Akos Ferencz and Zsofia Varga

Department of Psychiatry, University of Debrecen, Medical and Health Science Center, Debrecen

Rationale: There is a shortage of studies analyzing the time course of recurrent episodes and comparing effectiveness of long-term treatments in bipolar disorder. 'Number needed to treat' (NNT) analyses have been proven to be useful for clinically meaningful comparisons, but results vary considerably among studies. The survival curves of different trials also show a great variability preventing reliable conclusions on the time course of maintenance therapies. The variance of survival analyses on long-term medication management can be reduced with increasing the statistical power by combining the life-tables of individual studies. ***Methods:*** In this study the survival tables of 28 studies on maintenance treatment of bipolar disorder were reconstructed from the published diagrams, and the numbers of relapsed patients in the original studies were estimated for plotting composite survival curves of an inactive, mono- and combination therapy arm. The review was finally based on 5231 subjects. ***Results:*** The resulting composite diagrams indicate that within the first year 48% of patients on monotherapy, and 35% on combination therapy experienced recurrence of any affective episode ('early relapsers'). The rest of the patient population was affected by recurrences in a smaller rate over a more extended period of time ('late relapsers'). For a favorable outcome at 40 months of episode prevention in bipolar disorder the NNT was 6 for mono- and 3 for combination therapy. Log-rank analyses of the composite data supported the effectiveness of both medication protocols over placebo, and the superiority of drug combination over monotherapy; though there were some indications of decreased efficacy in the two treatment arms after extended maintenance. ***Conclusions:*** Composite analysis offers increased statistical power for studying the time course of survival data. Mood episodes in bipolar disorder are likely to recur early on and relapses in "real-life" can be more frequent than the rates published here. Our results favor combination therapy for the long-term management of bipolar disorder. Concerns are expressed that NNT analyses have significant limitations when applied to recurring events with cumulative deterioration instead of cases where cumulative improvement is expected over time.

(Neuropsychopharmacol Hung 2012; 14(3): 155-164; doi: 10.5706/nph201209001)

Keywords: bipolar disorder, cumulative survival rates, Kaplan-Meier analysis, life tables, maintenance, mood stabilizers, number needed to treat, recurrence

Bipolar disorder is a chronic, progressive condition which is recurrent in 80-90% of patients (Goodwin and Jamison, 1990; Kessing et al., 1998). Since the risk of relapse[1] persists for life after the onset (Angst et al., 2003), the majority of patients with mood disorder are prescribed long-term medication for hazard reduction. In spite of the maintenance treatment and almost regardless of patients' compliance, recurrence occurs in most of the cases. There are studies indicating that about half of the patients who take medication for maintenance relapse within the first year (Perlis et al., 2006).

Over the last two decades a number of placebo-controlled studies were conducted and established

[1] In this article we intend to use 'relapse' and 'recurrence' interchangebly, mostly for stylistic reasons: to avoide repetition of the same word within the same sentence or paragraph.

the superiority of mood stabilizers (such as lithium, some anticonvulsants and atypical antipsychotics) over placebo in preventing recurrence of mood episodes (see list of publications in Table 1). There is a smaller number of randomized, placebo controlled or naturalistic, observational trials which compare monotherapy against combination therapy in the long-term management of bipolar disorder (Table 1). While the results mostly favor combination treatment over monotherapy for relapse/recurrence prevention in bipolar disorder, the guidelines have usually taken a conservative approach in this direction, with the exception of rapid cycling where combination is the rule (Goodwin, 2009; Grunze et al., 2004).

The conclusions of the randomized and observational trials were mostly based on survival curves and focused on the statistical differences between the placebo and medication arms. What lies above and below the survival curves was less in their interest. Namely, what percent of patients receiving active treatment relapse in a given time period, and how many patients on placebo remain relapse-free within the same timeframe. Those numbers are essential to answer the question: what is the patients' number needed to treat (NNT) for the maintenance therapy of bipolar disorder. Since the number of patients remaining in a follow-up study is getting lower toward the end — and more so if the study lasts longer — the power of a NNT analysis is generally low and varies greatly from study to study (Popovic et al., 2011). The power of NNT analyses and the statistical comparison of the mono- vs. combination therapy would be increased by pooling the survival data of individual trials and plotting the summary of the observed frequency tables (resulting from Kaplan-Meier statistics) and/or the predicted frequency tables (calculated by a Cox proportional hazard analysis) in a composite diagram of the joint data. According to our knowledge, life-table analysis of this kind has not been published yet.

The aims of our study were the following (step-by-step): A) to review the literature of the maintenance therapy of bipolar disorder published during the last 15 years, B) to collect publications with survival plots presented, C) to analyze those plots and to generate composite curves for observed and predicted survival statistics of placebo, mono- and combination therapy arms, and D) to answer the following questions. 1) How many percent of bipolar patients receiving maintenance therapy relapse to an affective episode within the first year? 2) How many percent of bipolar patients without active maintenance treatment remain free of affective episodes after more than three years of follow up? 3) Does combination therapy decrease the risk of recurrence more than monotherapy? 4) What is the NNT for the relapse prevention of bipolar disorder and how reliable an index is that? 5) If patients have been maintained in stable condition for one year, what is the NNT for the continuation of a successful maintenance therapy to a given target date?

MATERIALS AND METHODS

For this analysis we were interested in studies using a placebo- or comparator medication-controlled, randomized or naturalistic design for long-term treatment of patients suffering from bipolar disorder and who had gone through stabilization before entering the maintenance phase. In particular, we sought trials that provided survival curves of the results which would permit estimation of the cumulative proportion of patients without recurrence plotted against the time to a new episode of any kind.

A comprehensive PubMed search of all English language articles published between the years 1997 and 2012 was conducted with different combination of all or less of the following keywords: 'bipolar', 'maintenance', 'long-term', 'Kaplan-Meier', 'survival'. To be accepted, studies had to have involved a minimum of 12 cases of bipolar disorder (I or II, diagnosed by criteria according to DSM-III-R, DSM-IV, ICD-9, or ICD-10) in one arm, a clinical stabilization by one or more mood stabilizer medication before maintenance treatment, at least 6 months long follow-up period under either blinded or open observation, and had to provide the plot of their survival analysis. Cases of cyclothymia, bipolar disorders NOS or schizoaffective type were rejected. The definition of recurrence of a new affective episode typically required rehospitalization or clinical worsening of the affective symptoms sufficiently severe to require pharmacologic intervention or electroconvulsive therapy as acute treatment. Publications presenting survival data separately on the recurrence of affective episodes (e.g., relapse to depression), trials focusing only on symptomatic relapse or discontinuation for any reason were excluded.

The selection process yielded a total of 28 pertinent studies summarized in Table 1. We also considered one study with discontinuation (Viguera et al., 2007) and incorporated it into our inactive arm. There were three studies (Colom et al., 2003; Lam et al., 2005; Meyer and Hautzinger, 2011) where the active

cohort included patients on a mood stabilizer with psychotherapy and the placebo group had standard pharmacotherapy alone. Only the latter was added to our active medication arm. As collected from the 28 accepted trials, our final composite analysis was based on 12 inactive groups (summed up in our placebo arm); 11 lithium, 5 valproate, 4 olanzapine, 3 lamotrigine, 2 quetiapine, 2 risperidone, 1 paliperidone, 1 aripiprazole, 1 carbamazepine, and 8 groups where participants were mixed regarding the administered mood stabilizer (all pooled into our monotherapy arm); and in a third arm we included 13 combination treatment groups, where usually lithium or valproic acid was combined with an atypical antipsychotic—except one study with lithium plus oxcarbazepine (Vieta et al., 2008).

The survival graphs of every pertinent study were analyzed in a computerized coordinate system and the X and Y axis values of the plots (time in months and the proportion of patients without recurrence, respectively) were converted into their numeric form. The majority of the publications with the exception of authors like Berwaerts et al. (2012), Geddes et al. (2010), Quiroz et al. (2010), Vieta et al. (2010) and Weisler et al. (2011) did not provide the 'subjects at risk table' or timing of the censored data (number of subjects lost to follow-up for other reason than the outcome criteria). Without that information the survival plots alone are not enough to reconstruct the original data sheet. Nevertheless, in this manner — for each accepted study — we were able to get an estimation of its calculated survival table with the cumulative proportions (those implicitly have the censored data), and replicas of the original survival curves were generated in order to check the accuracy of the restorative process.

While this way the shape of a survival curve (based on time and cumulative survival proportions) can be reproduced with good approximation, the raw number of patients at each time point is lacking. That would be necessary for statistical comparisons, since the composites of the survival curves were planned to be analyzed by log-rank test (IBM SPSS Statistics, Version 20) for a hypothesized difference between treatments. Without the knowledge of the correct number of subjects used in the original survival statistics (that is the 'number at risk' at each time point), we had to turn to a conservative estimate: our composite survival plots and log-rank statistical analysis were based on the total number of patients relapsed according to the outcome criteria during each trial, plus the number of patients remaining "survived" at the end. This number was used as sample size and got multiplied by the visually reconstructed cumulative proportions for the estimation of relapses at each time point (at every month).

Certainly, our approach resulted in the underestimation of the actual number of patients starting and relapsing in the original study, but we emphasize again that time course and NNT analyses were left grossly unaffected by this method. For the purpose of composite analysis a data sheet containing 5231 rows was generated from the (deflated) relapse numbers and "survivors" of each study. In Table 2 ten rows are sampled for illustration. The completed data file was entered into the statistical programs for further examination. The Kaplan-Meier analysis and the Cox regression model component of the IBM SPSS statistical package were used for calculating the composite observed and predicted survival tables, respectively. StataCorp Stata/SE program (Version 12) includes an option to plot the observed and predicted curves on the same graph. Confidence intervals (CIs) were visualized within the MedCalc statistical software (Version 12.2.1). 'Number needed to treat' and time analyses were based on the predicted cumulative proportions which are fairly independent of the participants' exact number.

RESULTS

Figure 1 shows the composite Kaplan-Meier survival curves for placebo, monotherapy (Mono), and combination therapy (Combo) arms with the corresponding 95% CIs. On Figure 2 the same observed values are plotted against the predicted survival data (darker lines) and it can be seen that the regression model fits the observed data (overall model fit: $ch^2=263.9$, df=2, $p<0.0001$). The composite survival curves cover a 40-month long follow-up period. The 'at risk' table below Figure 1 indicates that the number of patients is considerably decreased by the end of the observation period (more so in the individual studies), which has significant implication on the interpretation of NNT results (to be discussed later).

Overall log-rank test of equality of survival distributions for the different levels of treatment was highly significant ($chi^2=306.9$, df=2, $p<0.0001$). Both therapies were superior to placebo (or monotherapy: $chi^2=173.7$, df=1, $p<0.0001$; for combination therapy: $chi^2=283.3$, df=1, $p<0.0001$). Log-rank comparison between the two active treatment arms revealed statistical significance favoring combination ($chi^2=55.2$, df=1, $p<0.001$).

Table 1 Studies included in life-table analyses (N=28)

Study	Treatment	Diagnosis	Criteria	Index episode	Stabilization period	Duration (month)	Comments
Altamura et al. 2008	lithium, valproate, lamotrigine, quetiapine, lithium+quetiapine, valproate+quetiapine	BP I, II	DSM-IV	remission	min. 2 months	48	observational
Berwaerts et al. 2012	paliperidone, olanzapine, placebo	BP I	DSM-IV	manic, mixed	15 weeks	40	randomized
Bowden et al. 2000	lithium, valproate, placebo	BP I, II	DSM-III-R	manic	max. 3 months	12	randomized
Bowden et al. 2003	lithium, lamotrigine, placebo	BP I	DSM-IV	manic, hypomanic	8-16 weeks	18	randomized
Bowden et al. 2010	lit/val+ziprasidone, lit/val+placebo	BP I	DSM-IV	manic	min. 8 weeks	6	randomized
Calabrese et al. 2003	lithium, lamotrigine, placebo	BP I	DSM-IV	depressive	8-16 weeks	18	randomized
Colom et al. 2003	psychoeducation+TAU, TAU	BP I, II	DSM-IV	remission	min. 6 months	24	randomized
Geddes et al. 2010	lithium, valproate, lithium+valproate	BP I	DSM-IV	remission	min. 4 weeks	33	randomized
Gonzalez-Pinto et al. 2011	olanzapine mono., olanzapine comb.	BP I, II	DSM-IV ICD-10	manic, mixed	12 weeks	24	observational
Greil et al. 1997	lithium, carbamazepine	BP I, II	ICD-9	any episode	N/A	30	randomized
Keck et al. 2007	aripiprazole, placebo	BP I	DSM-IV	manic, mixed	6-18 weeks	23	randomized
Kessing et al. 2011	lithium, valproate	BP I, II	ICD-10	remission or any episode	N/A	144	observational
Lam et al. 2005	cognitive therapy+TAU, TAU	BP I	DSM-IV	remission	N/A	30	randomized
MacFadden et al. 2010	risperidon LAI+TAU placebo+TAU	BP I, II	DSM-IV	remission	min. 4 weeks	12	randomized
McElroy et al. 2008	valproate, lithium, placebo	BP I	DSM-III	manic, mixed	max. 3 months	12	randomized
Meyer and Hautzinger 2011	psychotherapy+TAU, TAU	BP I, II	DSM-IV	remission	2-4 weeks	40	randomized
Quiroz et al. 2010	risperidone LAI, placebo	BP I	DSM-IV	manic, mixed	6 months	24	randomized
Suppes et al. 2009	lit/val+quetiapine, lit/val+placebo	BP I	DSM-IV	any episode	12-36 weeks	24	randomized
Tohen et al. 2004	lit/val+olanzapine, lit/val+placebo	BP I	DSM-IV	manic, mixed	6 weeks	18	randomized
Tohen et al. 2005	lithium, olanzapine	BP I	DSM-IV	manic, mixed	6-12 weeks	12	randomized
Tohen et al. 2006	olanzapine, placebo	BP I	DSM-IV	manic, mixed	6-12 weeks	11	randomized
Vieta et al. 2006	gabapentin+TAU placebo+TAU	BP I, II	DSM-IV	remission	N/A	12	randomized

Vieta et al. 2008a	lithium+oxcarbazepine, lithium+placebo	BP I, II	DSM-IV	any episode	8-16 weeks	12	randomized
Vieta et al. 2008b	lit/val+quetiapine, lit/val+placebo	BP I	DSM-IV	any episode	12-36 weeks	24	randomized
Vieta et al. 2010	lithium+aripiprazole, valproate+aripiprazole	BP I, II	DSM-IV	manic	6 weeks	11	observational
Vieta et al. 2012	risperidone LAI, olanzapine, placebo	BP I	DSM-IV	manic, mixed	12 weeks	18	randomized
Viguera et al. 2007	discontinued TAU	BP I, II	DSM-IV	remission	min. 4 weeks	12	observational
Weisler et al. 2011	lithium, quetiapine, placebo	BP I	DSM-IV	any episode	24 weeks	24	randomized
Abbreviations: BP=bipolar, comb=combination treatment, lit=lithium, mono=monotherapy, TAU=treatment as usual, val=valproate							

Table 2 Sample of the generated data sheet

treatment	time	status	size
0	1	1	56
0	1	1	56
0	1	1	56
0	1	1	56
…	…	…	…
0	8	1	56
0	11	1	56
0	16	1	56
0	24	1	56
0	24	0	56
0	24	0	56

Each row represents one patient. Value 0 of the 'treatment' variable means that the subject belongs to the inactive treatment (placebo) arm. 'Time' values mean the months of the patient's relapse since baseline. If the subject terminated the study due to the outcome criteria (recurrence of any mood episode) 'status' is 1, else (censored) is 0 (e.g. lost to the study, or remained episode free at the end). 'Size' is the sample size (explained in the text).

It can be seen on the predicted survival curves that 48% of those patients who receive monotherapy and 35% of those who are on combination treatment relapse within the first year. During up to 2 years of follow-up the recurrence rate is 57% in the monotherapy group vs. 42% in the combination cohort. The composite analysis also reveals that at least 20% of subjects without active medication remain free of recurrent affective episodes up to 3 years. The survival curves have an inflection point at 12 months meaning that from that time point the recurrence rates decrease over time, and only 15% of patients on monotherapy and 14% of patients receiving combination treatment suffer recurrence during the following

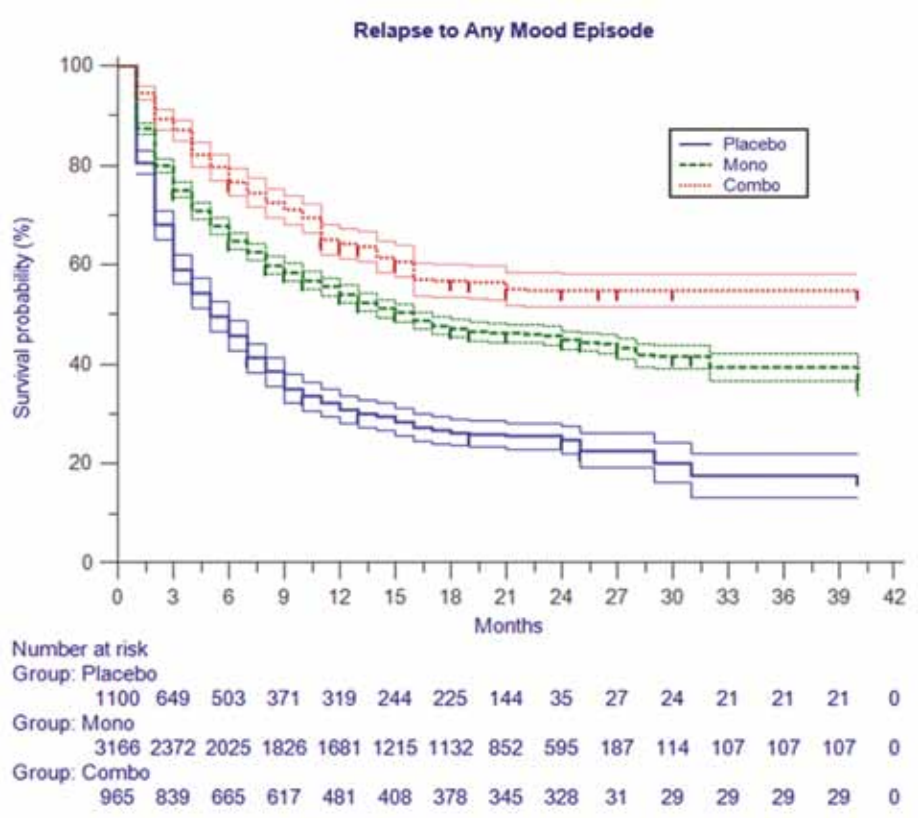

Figure 1 Composite Kaplan-Meier survival curves with 95% CIs

28 months. A comparable proportion, 14% of subjects in the inactive treatment arm experience recurrence throughout the same time period. Apparently, after the inflection point the three diagrams run parallel as reflected in the similar drop rates.

Using the SPSS generated predicted cumulative proportions we calculated NNTs with 95% CIs. The NNT with a target date of 40 months is 6 (CI=5.9-6.1) for monotherapy and 3 (CI=2.9-3.1) for combination treatment.

In case of patients who remain well during maintenance management, eventually the question may arise if the mood stabilizer should be stopped or whether it should be continued; and if so for how long and on what expense as expressed in the NNT. Especially so in situations, where the treatment arms are parallel to the placebo arm for the rest of the maintenance. In looking for answer to this question, we analyzed that group of patients who remained stable until 12 months and calculated NNTs for the continued relapse prevention between month 12 and 40. After one year follow-up, for extended stabilization with monotherapy the NNT is 14 (CI=10.4-25.4) vs. 8 (CI=6.7-9.4) of the combination treatment.

DISCUSSION

The authors are fully aware that the presented study is not a meta-analysis, and that term was decidedly avoided throughout the paper. A proper meta-analysis should be based on original numerical data and not on their visual reconstruction. The term of composite analysis was chosen which reflects more the intended goal than the applied method. The weakness of our study is not as much the graphical data restoration from published survival plots, as would appear at the first glance. It rather lies behind the deflation of the original sample those graphs were generated from, because most of the publications failed to detail

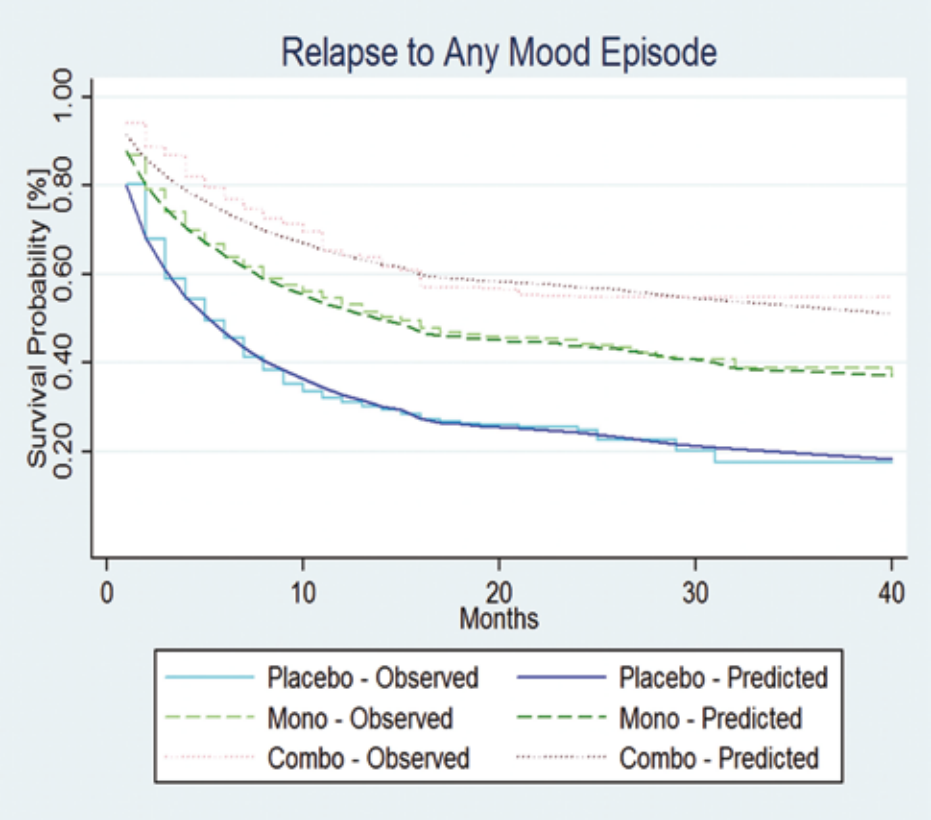

Figure 2 Observed and predicted composite survival curves

censored data, and omitted the 'at risk' numbers at each evaluation point.

The strength of our approach is that it can include almost every study with published survival plots or life-tables, since all original numerical data can hardly be collected successfully from the remote past. Moreover, every subjects of each enrolled study can be taken individually as member of one big study group, and can be "treated-as-in-one-trial" without the bias of group imbalances (Simpson's paradox) hindering many meta-analyses (Altman and Deeks, 2002). The different study durations don't matter at all: the "survivors" of shorter studies are simply censored out in the combined sample.

Due to the lack of timely censored original data, we lost information and statistical power. Equality between treatment arms cannot be tested reliably in this way, but non-equality can — with certain reservations. Furthermore, analyses based on the reconstructed cumulative proportions are fairly robust to the applied process. The presented composite analysis can offer a powerful tool for the examination of the time course of bipolar patients' maintenance treatment — a rare investigation in the literature.

We have raised a fair number of questions and despite the limitations we were able to answer them more accurately than any of the original studies. The proportion of patients relapsing during the first 2 years is remarkably close to the evaluation of Perlis et al. (2006). Our results also demonstrate that mood episodes in bipolar disorder are likely to recur in spite of guideline-based treatments. Since some of the included trials had a long stabilization period before the follow-up, the "real-life" relapse rates could even be higher after active episodes. Our results are not on par with the cautious recommendations of international guidelines regarding combination treatment for maintenance management. In our conclusion, combination therapy for relapse prevention of bipolar disorder has its advantages from early on.

The inflection point of the composite survival plots gives the idea that based on the time to recurrence in bipolar patients on maintenance can be classified into groups of 'early' and 'late relapsers'. It remains unclear if this classification is related to the natural course of the illness (that is 'late relapsers' are very slow cycling patients) or reflects different responsivity to the long-term therapy. Recognition of 'late responders' may help the individualization of maintenance mood stabilization. For example, in case of a childbearing 'late relapser' it is easier for the clinician to decide the discontinuation of pharmacotherapy for the duration of pregnancy.

Using NNT in relapse prevention means that it is directed at "deterioration", i.e. at groups with decreasing number of subjects over time as contrasted to its application for "improvement" with increasing number of responders of a relatively constant group size like in acute treatment protocols with a usually low number of drop-outs. Consequently, in cases like ours the statistical power of NNT analyses decrease on the course of the maintenance treatment, and may become meaningless after a too long follow-up period. Therefore, while our NNT results might be more reliable than those of small scale individual studies, yet they carry serious limitations. Moreover, if a NNT is calculated for a target date of — let's say — 40 months, then a case relapsed at 39 months is not included in the "needed" portion. Obviously, one cannot state that for that patient the maintenance treatment was "unneeded".

The most sensitive part of our findings is that the relapse rate slows down in the treatment arms and runs parallel with the placebo arm. This observation raises the question: is it possible that after a while the treatment arms just follow the placebo response? Well, that is not a 'non-equality' type issue like the others above, and a comprehensive meta-analysis using original data sheets is better suited to provide the correct answer.

Abbreviations: CI = confidence interval, DSM = Diagnostic and Statistical Manual, ICD = International Classification of Diseases, NNT = number needed to treat

Corresponding author: Ede Frecska, Department of Psychiatry, Debrecen University OEC, Nagyerdei krt. 98., Debrecen, 4012 Hungary.
e-mail: efrecska@hotmail.com

REFERENCES

1. Altamura, A. C., Mundo, E., Dell'Osso, B., Tacchini, G., Buoli, M., Calabrese, J. R. (2008) Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: a 4-year follow-up naturalistic study. J Affect Disord, 110:135-41.
2. Altman, D. G., Deeks, J. J. (2002) Meta-analysis, Simpson's paradox, and the number needed to treat. BMC Med Res Methodol, 2:3.
3. Angst, J., Gamma, A., Sellaro, R., Lavori, P. W., Zhang, H. (2003) Recurrence of bipolar disorders and major depression. A life-long perspective. Eur Arch Psychiatry Clin Neurosci, 253:236-40.
4. Berwaerts, J., Melkote, R., Nuamah, I., Lim, P. (2012) A randomized, placebo- and active-controlled study of paliperidone extended-release as maintenance treatment in patients with bipolar I disorder after an acute manic or mixed episode. J Affect Disord, 138:247-58.
5. Bowden, C. L., Calabrese, J. R., McElroy, S. L., Gyulai, L., Wassef, A., Petty, F., Pope, H. G., Chou, J. C. Y., Keck, P. E., Rhodes, L. J., Swann, A. C., Hirschfeld, R. M. A., Wozniak, P. J. (2000) A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch Gen Psychiatry, 57:481-9.
6. Bowden, C. L., Calabrese, J. R., Sachs, G., Yatham, L. N., Asghar, S. A., Hompland, M., Montgomery, P., Earl, N., Smoot, T. M., DeVeaugh-Geiss, J. (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry, 60:392-400.
7. Bowden, C. L., Vieta, E., Ice, K. S., Schwartz, J. H., Wang, P. P., Versavel, M. (2010) Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. J Clin Psychiatry. 71:130-7.
8. Calabrese, J. R., Bowden, C. L., Sachs, G., Yatham, L. N., Behnke, K., Mehtonen, O. P., Montgomery, P., Ascher, J., Paska, W., Earl, N., DeVeaugh-Geiss, J. (2003) A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry, 64:1013-24.
9. Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Goikolea, J. M., Bernabarre, A., Torrent, C., Comes, M., Corbella, B., Parramon, G., Corominas, J. (2003) A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. Arch Gen Psychiatry, 60:402-7.
10. Geddes, J. R., Goodwin, G. M., Rendell, J., Azorin, J. M., Cipriani, A., Ostacher, M. J., Morriss, R., Alder, N., Juszczak, E. (2010) Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet, 375:385-95.
11. Gonzalez-Pinto, A., Vieta, E., Reed, C., Novick, D., Barraco, A., Aguado, J., Haro, J. M. (2011) Effectiveness of olanzapine monotherapy and olanzapine combination treatment in the long term following acute mania – Results of a two year observational study in bipolar disorder. J Affect Disord, 131:320-9.
12. Goodwin, F. K., Jamison, K. R. (1990) Manic-Depressive Illness. Oxford University Press, New York.
13. Goodwin, G.M., Consensus Group of the British Association for Psychopharmacology (2009) Evidence-based guidelines for treating bipolar disorder: revised second edition--recommendations from the British Association for Psychopharmacology. J Psychopharmacol, 23:346-88.
14. Greil, W., Ludwig-Mayerhofer, W., Erazo, N., Schöchlin, C., Schmidt, S., Engel, R. R., Czernik, A., Giedke, H., Müller-

Oerlinghausen, B., Osterheider, M., Rudolf, G. A. E., Sauer, H., Tegeler, J., Wetterling, T. (1997) Lithium versus carbamazepine in the maintenance treatment of bipolar disorders – A randomised study. J Affect Disord, 43:151-61.

15. Grunze, H., Kasper, S., Goodwin, G., Bowden, C., Moller, H. J., WFSBP Task Force on Treatment Guidelines for Bipolar Disorders (2004) The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. World J Biol Psychiatry, 5:120-35.
16. Keck, P. E., Calabrese, J. R., McIntyre, R. S., McQuade, R. D., Carson, W. H., Eudicone, J. M., Carlson, W. H., Marcus, R. N., Sanchez, R. (2007) Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry, 68:1480-91.
17. Kessing, L. V., Andersen, P. K., Mortensen, P. B., Bolwig, T. G. (1998) Recurrence in affective disorder. 1 case register study. Br J Psychiatry 172:23-28.
18. Kessing, L. V., Hellmund, G., Geddes, J. R., Goodwin, G. M., Andersen, P. K. (2011) Valproate v. lithium in the treatment of bipolar disorder in clinical practice: observational nationwide register-based cohort study. Br J Psychiatry, 199:57-63.
19. Lam, D. H., Hayward, P., Watkins, E. R., Wright, K., Sham, P. (2005) Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. Am J Psychiatry, 162:324-9.
20. Macfadden, W., Alphs, L., Haskins, J. T., Turner, N., Turkoz, I., Bossie, C., Kujawa, M., Mahmoud, R. (2009) A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disord, 11:827-39.
21. McElroy, S. L., Bowden, C. L., Collins, M. A., Wozniak, P. J., Keck, P. E., Calabrese, J. R. (2008) Relationship of open acute mania treatment to blinded maintenance outcome in bipolar I disorder. J Affect Disord, 107:127-33.
22. Meyer, T. D., Hautzinger, M. (2011) Cognitive behaviour therapy and supportive therapy for bipolar disorders: relapse rates for treatment period and 2-year follow-up. Psychol Med, 42:1429-39.
23. Perlis, R. H., Ostacher, M. J., Patel, J. K., Marangell, L. B., Zhang, H., Wisniewski, S. R., Ketter, T. A., Miklowitz, D. J., Otto, M. W., Gyulai, L., Reilly-Harrington, N. A., Nierenberg, A. A., Sachs, G. S., Thase, M. E. (2006) Predictors of recurrence in bipolar disorder: primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). Am J Psychiatry, 163:217-24.
24. Popovic, D., Reinares, M., Amann, B., Salamero, M., Vieta, E. (2011) Number needed to treat analyses of drugs used for maintenance treatment of bipolar disorder. Psychopharmacology (Berl), 213:657-67.
25. Quiroz, J. A., Yatham, L. N., Palumbo, J. M., Karcher, K., Kushner, S., Kusumakar, V. (2010) Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry, 68:156-62.
26. Suppes, T., Vieta, E., Liu, S., Brecher, M., Paulsson, B. (2009) Maintenance treatment for patients with bipolar I disorder: results from a North American study of quetiapine in combination with lithium or divalproex. Am J Psychiatry, 166:476-88.
27. Tohen, M., Calabrese, J. R., Sachs, G. S., Banov, M. D., Detke, H. C., Risser, R., Baker, R. W., Chou, J. C. Y., Bowden, C. L. (2006) Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry, 163:247-56.
28. Tohen, M., Chengappa, K. N. R., Suppes, T., Baker, R. W., Zarate, C. A., Bowden, C. L., Sachs, G. S., Kupfer, D. J., Ghaemi, S. N., Feldman, P. D., Risser, R. C., Evans, A. R., Calabrese, J. R. (2004) Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry, 184:337-45.
29. Tohen, M., Greil, W., Calabrese, J. R., Sachs, G. S., Yatham, L. N., Oerlinghausen, B. M., Koukopoulos, A., Cassano, G. B., Grunze, H., Licht, R. W., Dell'Osso, L., Evans, A. R., Risser, R., Baker, R. W., Crane, H., Dossenbach, M. R., Bowden, C. L. (2005) Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry, 162:1281-90.
30. Vieta, E., Cruz, N., García-Campayo, J., de Arce, R., Crespo, J. M., Vallés, V., Pérez-Blanco, J., Roca, E., Olivares, J. M., Morígino, A., Fernández-Villamor, R., Comes, M. (2008a) A double-blind, randomized, placebo-controlled prophylaxis trial of oxcarbazepine as adjunctive treatment to lithium in the long-term treatment of bipolar I and II disorder. Int J Neuropsychopharmacol, 11:445-52.
31. 32. Vieta, E., Goikolea, J. M., Martinez-Arán, A., Comes, M., Verger, K., Masramon, X., Sanchez-Moreno, J., Colom, F. (2006) A double-blind, randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder. J Clin Psychiatry, 67:473-77.
32. Vieta, E., Montgomery, S., Sulaiman, A. H., Cordoba, R., Huberlant, B., Martinez, L., Schreiner, A. (2012) A randomized, double-blind, placebo-controlled trial to assess prevention of mood episodes with risperidone long-acting injectable in patients with bipolar I disorder. Eur Eur Neuropsychopharmacol, article in press.
33. Vieta, E., Owen, R., Baudelet, C., McQuade, R. D., Sanchez, R., Marcus, R. N. (2010) Assessment of safety, tolerability and effectiveness of adjunctive aripiprazole to lithium/valproate in bipolar mania: a 46-week, open-label extension following a 6-week double-blind study. Curr Med Res Opin, 26:1485-96.
34. Vieta, E., Suppes, T., Eggens, I., Persson, I., Paulsson, B., Brecher, M. (2008b) Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder. J Affect Disord, 109:251-63.
35. Viguera, A. C., Withfield, T., Baldessarini, R. J., Newport, D. J., Stowe, Z., Reminick, A., Cohen, L. S. (2007) Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry, 164:1817-24.
36. Weisler, R. H., Nolen, W. A., Neijber, A., Hellqvist, A., Paulsson, B. (2011) Continuation of quetiapine versus switching to placebo or lithium for maintenance treatment of bipolar I disorder. J Clin Psychiatry, 72:1452-64.

A túlélési görbék üzenete: I. A bipoláris zavar fenntartó kezeléseinek kompozit analízise

Bevezetés: A bipoláris affektív zavar hosszútávú kezelésének hatékonyságát összehasonlító, valamint a visszatérő epizódok időbeli lefolyását elemző tanulmány kevés született. A „number needed to treat" (NNT), ún. kezelési minimum analízisek jól értelmezhetőek a mindennapi gyakorlat számára, de az egyes vizsgálatok eredményei között jelentős eltérések vannak. A különböző tanulmányok túlélési görbéi szintén nagy változatosságot mutatnak, megnehezítve a megbízható következtetések levonását a profilaktikus terápia hatékonyságának időbeni lefutásáról. A hosszútávú gyógyszeres kezelések túlélési vizsgálatának statisztikai erejét növelheti az egyes vizsgálatok élettartam-táblázatainak összesítése. ***Módszerek:*** Munkánk során a bipoláris affektív zavar fenntartó kezelésével kapcsolatos 28 vizsgálat túlélési adatait rekonstruáltuk az irodalmakban megjelent diagramokból, majd az eredeti vizsgálatokban visszaesett betegek számát megbecsülve kompozit görbét szerkesztettünk gyógyszermentes, mono- és kombinált terápiás szárnnyal. ***Eredmények:*** Az elkészült kompozit görbék azt mutatják, hogy egy éven belül a monoterápiával kezelt betegek 48%-ánál és a kombinált készítményekkel kezelt betegek 35%-ánál valamelyik affektív epizód ismételten megjelenik (korai visszaesők). A betegek fennmaradó csoportja ritkább visszaesési gyakoriságot mutat hosszútávon (késői visszaesők). A 0-40. hónapra vonatkoztatott NNT értéke monoterápia esetében 6, kombinációs kezelés esetében 3 volt. A log-rank összehasonlító teszt mindkét kezelési mód szignifikáns előnyét mutatta ki placebóhoz viszonyítva és egymáshoz képest is, a kombinációs kezelés fölényével, bár utalnak adatok a hatékonyság csökkenésére mindkét aktív szárnyban a fenntartó kezelés hosszútávú folytatása során. ***Következtetések:*** A kompozit analízis növelheti a statisztikai megbízhatóságot a túlélési adatok időbeli lefolyásának vizsgálatához. Bipoláris zavarban az ismételt epizódok viszonylag hamar visszatérnek. Adataink a kombinációs kezelés előnyét támasztják alá a bipoláris betegség fenntartó kezelésében. Kihangsúlyozzuk, hogy a kezelési minimum (NNT) analízisek eredményei kevésbé megbízhatóak akkor, amikor a vizsgált személyek száma fokozatosan csökken a vizsgálat folyamán.

Kulcsszavak: bipoláris zavar, élettartam-táblázat, fenntartó kezelés, hangulatstabilizálók, Kaplan-Meier analízis, kezelési minimum, kumulatív túlélési arány, visszaesés