

# Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder†

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## Background

Controversy exists over antidepressant use in rapid-cycling bipolar disorder.

## Aims

Exploratory analysis of safety and efficacy of fluoxetine v. lithium monotherapy in individuals with rapid- v. non-rapid-cycling bipolar II disorder.

## Method

Randomised, double-blind, placebo-controlled comparison of fluoxetine v. lithium monotherapy in patients initially stabilised on fluoxetine monotherapy (trial registration NCT00044616).

## Results

The proportion of participants with depressive relapse was similar between the rapid- and non-rapid-cycling groups

( $P=0.20$ ). The odds of relapse were similar between groups ( $P=0.36$ ). The hazard of relapse was similar between groups (hazard ratio 0.87, 95% CI 0.40–1.91). Change in mania rating scores was similar between groups ( $P=0.86$ ). There was no difference between groups in the rate of syndromal ( $P=0.27$ ) or subsyndromal ( $P=0.82$ ) hypomania.

## Conclusions

Depressive relapse and treatment-emergent mood conversion episode rates were similar for lithium and fluoxetine monotherapy and placebo during long-term, relapse-prevention therapy of rapid- and non-rapid-cycling bipolar II disorder.

## Declarations of interest

None.

Rapid-cycling bipolar disorder is associated with high morbidity and poor treatment outcome.<sup>1–7</sup> Some studies suggest an association between rapid cycling and antidepressant use,<sup>5,7–11</sup> although this has not been universally observed.<sup>12–18</sup> Controlled trials have reported good efficacy and low mood conversion rates during antidepressant use in bipolar II disorder.<sup>13,15,16,19–21</sup> We performed an exploratory analysis of a randomised, double-blind, placebo-controlled trial to examine the efficacy and mood conversion rate of long-term fluoxetine v. lithium monotherapy in patients with rapid- v. non-rapid-cycling bipolar II disorder who recovered from a major depressive episode during initial fluoxetine monotherapy (trial registration NCT00044616). We hypothesised that lithium monotherapy would provide greater relapse prevention with fewer treatment-emergent mood conversion episodes in patients with rapid- v. non-rapid-cycling bipolar II disorder.

## Method

### Participants

The participants were out-patients  $\geq 18$  years old with a DSM-IV<sup>22</sup> Axis I diagnosis of bipolar II disorder who recovered from a major depressive episode with a 17-item Hamilton Rating Scale for Depression (HRSD)<sup>23</sup> score  $\leq 8$ . A description of inclusion and exclusion criteria has been previously published.<sup>21</sup> Patients provided informed consent in accordance with the ethical standards of the Institutional Review Board of the University of Pennsylvania. The study was conducted using the Good Clinical Practice guidelines with oversight by the local Office of Human Research and independent Data & Safety Monitoring Board.

### Procedures

Psychiatric diagnosis was verified using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders format.<sup>24</sup> Estimates

of the number of prior syndromal depressive and hypomanic episodes (defined by DSM-IV criteria) and subsyndromal hypomanic episodes, were obtained. The participants' condition was classified as rapid cycling if they had an average of  $\geq 4$  affective episodes per year during the course of their illness:

$$\frac{(\text{Total number major depressive episode} + \text{hypomanic episodes} + \text{subsyndromal hypomanic episodes})}{\text{Total illness duration (in years)}}$$

Structured HRSD, Young Mania Rating Scale (YMRS)<sup>25</sup> and mood conversion measures were obtained as previously described.<sup>19–21</sup> Treatment-emergent hypomania was defined as: (a) syndromal hypomania meeting DSM-IV criteria of  $\geq 4$  symptoms lasting  $\geq 4$  days; (b) type I subsyndromal hypomania of  $\geq 4$  symptoms lasting  $\leq 3$  days; (c) type II subsyndromal hypomania of  $\leq 3$  symptoms lasting  $\geq 4$  days; and (d) type III subsyndromal hypomania of  $\leq 3$  symptoms lasting  $\leq 3$  days. Treatment-emergent depression was defined as: (a) major depressive episode meeting DSM-IV criteria plus a HRSD score  $\geq 14$ ; (b) type I minor depressive episode of  $\geq 5$  symptoms lasting  $< 14$  days or  $\leq 4$  symptoms lasting  $\geq 14$  days; (c) type II minor depressive episode of  $\geq 4$  symptoms lasting  $\geq 7$  days; and (d) type III minor depressive episode of  $\geq 4$  symptoms lasting  $< 7$  days. Patients experiencing a major depressive episode were discontinued from the study. Patients experiencing syndromal or subsyndromal hypomania, or subsyndromal depression underwent double-blind rescue therapy.<sup>21</sup>

### Treatment

Initial fluoxetine monotherapy 80 mg daily was administered up to 12 weeks. Patients with a final HRSD score  $\leq 8$  were randomised to long-term monotherapy with either fluoxetine

†See editorial, pp. 251–252, this issue.

10–40 mg daily, lithium 300–1200 mg daily (with a serum level of 0.5–1.5 mmol/l) or placebo for 50 weeks.

## Outcome

The HRSD, YMRS and mood conversion measures were obtained at baseline (i.e. randomisation) and during double-blind therapy, as previously described.<sup>21</sup> The primary outcome measure was the proportion of participants with rapid- *v.* non-rapid-cycling bipolar disorder with relapse or recurrence of a major depressive episode. Secondary outcomes included the hazard for depressive relapse, change over time in YMRS scores (in patients experiencing change in YMRS scores) and frequency of syndromal and subsyndromal mood conversion episodes.

## Sample size justification

The power estimate for the primary analysis has been previously described.<sup>21</sup> The current exploratory study was not powered to detect small to moderate differences in efficacy or mood conversion rates between rapid *v.* non-rapid-cycling groups.

## Statistical procedures

Exploratory analyses were conducted using Stata 11 on Windows, with two-sided tests of hypotheses and a *P*-value <0.05 for statistical significance. Proportions of participants with rapid- *v.* non-rapid-cycling bipolar disorder who discontinued treatment or had an increase in YMRS scores were compared using  $\chi^2$  and *t*-tests. Confidence intervals for proportions were based on the exact Binomial distribution.

Log rank tests were used to compare survival distributions to relapse for each treatment group by cycling status. Mean time to relapse was estimated. Logistic regression was used to estimate the odds of relapse. Cox regression was used to estimate the hazard ratio of relapse. Quasi-least squares (QLS) analysis was used to compare change in YMRS score using covariates of rapid cycling, time, and rapid cycling time. The largest intraparticipant change in YMRS scores (in patients experiencing a change in YMRS scores) was compared in participants with rapid- *v.* non-rapid-cycling bipolar disorder using a *t*-test.

## Results

### Enrolment

In total 167 people enrolled: 89 women with a mean age of 36.9 years (s.d.=12.7) and 78 men with a mean age of 37.9 years (s.d.=12.9). Cycling status was available for 166 patients (99.4%): 42 with rapid (25.3%) and 124 with non-rapid (74.7%). Overall, 37 participants with rapid- and 111 with non-rapid-cycling bipolar disorder received initial fluoxetine. Of these, 12 (32.4%, 95% CI 18.0–49.8) with rapid- *v.* 53 (47.7%, 95% CI 38.2–57.4) with non-rapid-cycling bipolar disorder discontinued treatment (*P*=0.10); whereas, 25 (67.6%, 95% CI 50.2–82.0) with rapid- *v.* 58 (52.3%, 95% CI 42.6–61.8) with non-rapid-cycling bipolar disorder recovered (*P*=0.10) (Fig. 1). Table 1 provides details of participant characteristics at the start of double-blind therapy.

### Depressive relapse

Relapse occurred in 9 (36.0%, 95% CI 18.0–57.5) in the rapid- *v.* 29 (51.8%, 95% CI 38.0–65.3) in the non-rapid-cycling group (*P*=0.20). The proportion of those with rapid-cycling bipolar disorder who relapsed was similar for fluoxetine (28.6%, 95% CI 13.2–48.7), lithium (34.6%, 95% CI 17.2–55.7) and

placebo (29.6%, 95% CI 13.8–50.2) (*P*=0.88). There was no significant difference between those in the rapid- *v.* non-rapid-cycling groups for the odds of relapse (odds ratio (OR)=0.6, 95% CI 0.2–1.8) (*P*=0.36) or for the hazard of relapse (hazard ratio 0.87, 95% CI 0.40–1.91).

### YMRS scores

The QLS analysis identified no significant difference in change over time in YMRS scores among treatment conditions, and no significant difference in change in YMRS scores among those in the rapid- *v.* non-rapid-cycling groups. The estimated regression coefficient for the rapid-cycling treatment duration was 0.0004 (*P*=0.86). The largest mean increase in YMRS score (for patients who experienced an increase) was 4.28 (s.d.=6.2) for those in the rapid- *v.* 3.3 (s.d.=4.2) for those in the non-rapid-cycling group (*P*=0.40).

### Mood conversion episodes

There was no significant difference in the proportion of those in the rapid- *v.* non-rapid-cycling groups with syndromal and/or subsyndromal hypomania (Table 2). There was a non-significant trend for a longer duration of hypomania in individuals in the rapid-cycling group (*P*=0.06), although this observation was based on only five episodes in two individuals in this group. There was also a significantly longer duration of type III subsyndromal hypomania in those in the rapid-cycling group (*P*=0.05), which was based on only two episodes (Table 3). There was no significant difference in the proportion of participants in the rapid- *v.* non-rapid-cycling groups with major or minor depressive episodes (Table 4). The duration of minor depressive episodes did not differ significantly between the two groups of patients (Table 5).

### Treatment discontinuation

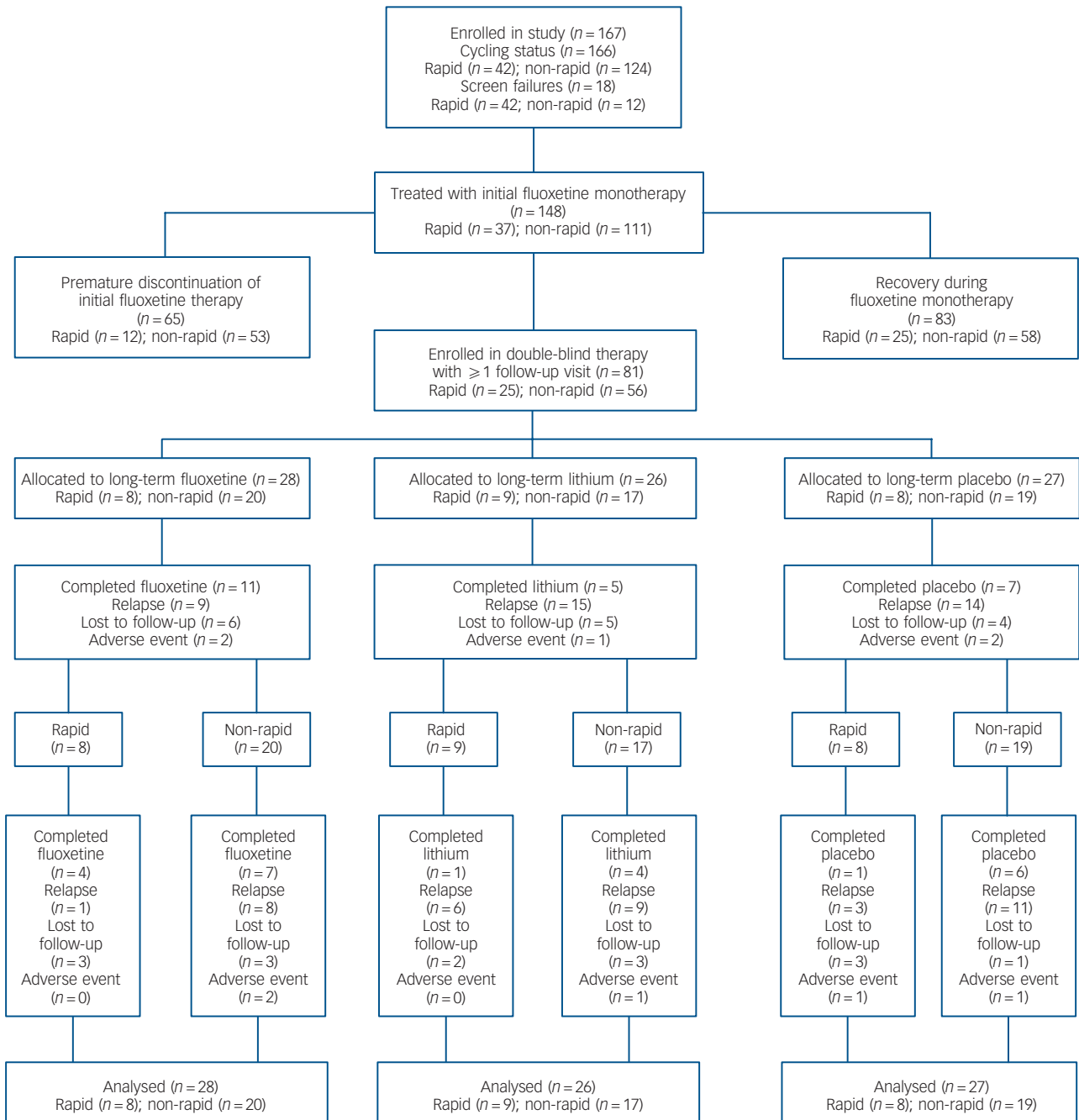
One participant (4.0%, 95% CI 0.1–20.4) in the rapid- *v.* 4 (5.4%, 95% CI 1.1–14.9) in the non-rapid-cycling group prematurely discontinued double-blind treatment because of an adverse event (*P*=0.60).

## Discussion

### Findings from other studies

Few double-blind, placebo-controlled trials have examined efficacy and safety of antidepressant *v.* mood stabiliser monotherapy in bipolar disorder. Leverich *et al*<sup>7</sup> found only a 23% sustained response rate without mood conversion episodes in patients with bipolar I and II disorder maintained on antidepressants (plus mood stabilisers). Schneck *et al*<sup>26</sup> followed 1191 individuals with bipolar disorder (356 rapid cycling) for 1 year and found a 34% recovery rate, with a 61% mood conversion rate during antidepressant therapy. A double-blind, placebo-controlled comparison of quetiapine *v.* paroxetine found no advantage for paroxetine *v.* placebo in bipolar depression,<sup>27</sup> whereas a recent meta-analysis of controlled studies found no advantage for antidepressants *per se* in treating bipolar depression.<sup>28</sup>

In contrast, a 5-year naturalistic study of 54 people with bipolar disorder found that antidepressants plus lithium maintained a response for an average of 17.2 months longer than if taking lithium alone, with a mood conversion rate of 14%.<sup>29</sup> A 1-year study of individuals with bipolar disorder who had recovered on antidepressants plus mood stabilisers (*n*=19) *v.* mood stabilisers alone (*n*=25) found a 32% and 68% depressive relapse rate, respectively (*P*=0.0065). Antidepressants produced a threefold lower risk of relapse.<sup>30</sup> A similar benefit from long-term



**Fig. 1** Flow chart of participants.

**Table 1** Characteristics of participants with rapid- v. non-rapid-cycling bipolar disorder at the start of double-blind therapy

Characteristic	Rapid-cycling group (n = 25)	Non-rapid-cycling group (n = 56)	P <sup>a</sup>
Male gender, % (n/N)	64.0 (16/25)	41.1 (23/56)	0.06
Age, years: mean (s.d.)	35.3 (10.0)	38.8 (12.8)	0.23
Illness duration, years: mean (s.d.)	17.2 (10.0)	20.0 (11.9)	0.32
Depressive episode duration, months: mean (s.d.)	13.3 (15.3)	4.0 (19.3)	0.87
Prior depressive episodes, mean (s.d.)	22.8 (43.7)	6.6 (6.4)	0.008
Prior hypomanic episodes, mean (s.d.)	45 (56.2)	9.0 (13.4)	<0.0005
Hamilton Rating Scale for Depression score baseline, mean (s.d.)	7.2 (6.1)	5.4 (4.0)	0.13
Young Mania Rating Scale score baseline, mean (s.d.)	1.3 (2.8)	0.8 (1.7)	0.27

a. P-values are from Student's t-test except for gender, which is from  $\chi^2$ .

**Table 2** Proportion of participants in the rapid- v. non-rapid-cycling group with treatment-emergent hypomania<sup>a</sup>

	Rapid-cycling group (n = 25)		Non-rapid-cycling group (n = 56)		P <sup>b</sup>
	n	% (95% exact CI)	n	% (95% exact CI)	
Hypomania	5	20.0 (6.8–40.7)	5	8.9 (3.0–19.6)	0.27
Type I subsyndromal	5	20.0 (6.8–40.7)	10	17.9 (8.9–30.4)	0.82
Type II subsyndromal	2	8.0 (1.0–26.0)	5	8.9 (3.0–19.6)	0.89
Type III subsyndromal	2	8.0 (1.0–26.0)	13	23.2 (13.0–36.4)	0.13
Hypomania or type I	10	40.0 (21.1–61.3)	15	26.8 (15.8–40.3)	0.30
Hypomania or type I or type II	11	44.0 (24.4–65.1)	18	32.1 (20.3–46.0)	0.33
Hypomania or type I or type II or type III	11	44.0 (24.4–65.1)	26	46.4 (33.0–60.3)	0.99

a. Some patients had more than one subsyndromal episode. Thus, the number of patients experiencing an episode shown in Table 2 may be smaller than the total number of episodes shown in Table 3.  
b. Fisher's exact test for comparison of rapid- v. non-rapid-cycling groups.

**Table 3** Duration of treatment-emergent hypomanic episodes (in days) in the rapid- v. non-rapid-cycling group<sup>a</sup>

	Rapid-cycling group		Non-rapid-cycling group		P <sup>b</sup>
	Mean (95% CI)	Episodes, n	Mean (95% CI)	Episodes, n	
Hypomania	23.2 (2.0 to 44.4)	5	5.8 (0.71 to 10.9)	5	0.06
Type I subsyndromal	2.6 (0.7 to 4.5)	5	5.8 (1.8 to 9.9)	11	0.27
Type II subsyndromal	9.0 (–16.4 to 34.4)	2	15.4 (6.8 to 24.3)	5	0.29
Type III subsyndromal	7.0 (–69.2 to 82.2)	2	2.3 (1.1 to 3.4)	16	0.05

a. Some patients had more than one subsyndromal episode. Thus, the number of patients experiencing an episode shown in Table 2 may be smaller than the total number of episodes shown in Table 3.  
b. P-value is for comparison of mean duration between groups.

**Table 4** Proportion of patients (with 95% exact CI) with a major or minor depressive episode

	Rapid-cycling group (n = 25)		Non-rapid-cycling group (n = 56)		P <sup>a</sup>
	n	% (95% exact CI)	n	% (95% exact CI)	
Major depressive episode	1	4.2 (0.1–20.4)	0	0 (0.0–6.4)	0.13
Type I minor depression	8	32.0 (14.9–53.5)	18	32.1 (20.3–46.0)	0.99
Type II minor depression	6	24.0 (9.4–45.1)	23	41.1 (28.1–55.0)	0.14
Type III minor depression	1	4.2 (0.1–20.4)	0	0 (0.0–6.4)	0.13
Major or type I minor depression	17	68.0 (46.5–85.1)	41	73.2 (59.7–84.2)	0.63
Major, type I or type II minor depression <sup>b</sup>	16	64.0 (42.5–82.0)	46	82.1 (69.6–91.1)	0.08
Major, type I, type II or type III minor depression <sup>b</sup>	16	64.0 (42.5–82.0)	46	82.1 (69.6–91.1)	0.08

a. Fisher's exact test for comparison of rapid- v. non-rapid-cycling groups.  
b. The same patients who experienced major, type I, type II or type III minor depressive episodes also experienced a type III minor depressive episode, resulting in similar values for the last two rows in Table 4.

**Table 5** Duration of treatment-emergent depressive episodes (in days) in the rapid- v. non-rapid-cycling group

Minor depression	Rapid-cycling group		Non-rapid-cycling group		P <sup>a</sup>
	Mean (95% CI)	Episodes, n	Mean (95% CI)	Episodes, n	
Type I	10.4 (3.9 to 17.0)	9	14.6 (4.3 to 24.9)	18	0.47
Type II	97.7 (–27.8 to 223.0)	12	14.7 (8.8 to 20.6)	27	0.10
Type III	3.0	1	0.0	0	–

a. P-value is for comparison of mean duration between groups.

antidepressant therapy was reported by Kupfer *et al*,<sup>15</sup> whereas a double-blind, placebo-controlled study of maintenance fluoxetine in individuals with bipolar II disorder who had recovered showed a clinically meaningful trend for fewer depressive relapses ( $P = 0.08$ ).<sup>19,20</sup> Finally, the primary analysis from the current study showed the estimated hazard for depressive relapse as 2.5 times greater during lithium v. fluoxetine monotherapy ( $P = 0.04$ ).<sup>21</sup>

## Limitations

Several caveats should be considered when interpreting the current findings. Results of this exploratory analysis are not definitive. The study was not powered to detect significant differences in efficacy or mania ratings between the rapid- v. non-rapid-cycling groups. The failure to identify significant differences in efficacy and safety

in the current analysis does not mean that differences do not exist. We note the limited sample size of the rapid- *v.* non-rapid-cycling group within each treatment condition. Larger samples would be needed to detect small differences in mood conversion rates between groups.

In the current study, patients were stabilised on fluoxetine prior to randomisation. This design methodology may have influenced the long-term efficacy and safety ratings in favour of fluoxetine, whereby patients randomised to fluoxetine were more likely to stay well and less likely to experience mood conversion episodes.

Our definition of rapid cycling differed from the DSM-IV definition and was based on an average of  $\geq 4$  affective episodes per year over the course of the illness (rather than  $\geq 4$  affective episodes in the preceding year). This difference may have resulted in a rapid-cycling cohort with fewer affective episodes.<sup>26</sup> Analysis of rapid cycling by DSM-IV criteria may have produced different results.

Finally, we limited our YMRS analysis to participants who experienced a change in YMRS scores over baseline in order to avoid averaging zero values from individuals with no change in YMRS scores. The frequency and severity of mood conversion episodes may have differed between groups had we used different threshold criteria for subsyndromal episodes, or if we employed a longer treatment duration. For example, Schneek *et al*<sup>26</sup> found a 61% mood conversion rate in patients with stabilised bipolar disorder during 1 year of antidepressant therapy, whereas Koukopoulos *et al*<sup>3</sup> reported rapid cycling in 88% of patients taking antidepressants in a 36-year naturalistic study. In contrast, the current study found no difference in the proportion of the patients in the rapid- *v.* non-rapid-cycling group in any treatment condition with increases in YMRS scores. Although it is possible that this low mood conversion rate resulted from the inclusion of more patients who were mildly ill with bipolar II disorder with a lower propensity for developing manic symptoms, the illness severity of the current patient cohort was similar to that of prior cohorts with bipolar II disorder in studies by us and others.<sup>7,10,11,15–17</sup>

## Implications

Although not definitive, these findings suggest that maintenance lithium or fluoxetine monotherapy are similar to placebo in preventing depressive relapse and treatment-emergent mood conversion episodes during long-term relapse-prevention therapy of rapid- and non-rapid-cycling bipolar II disorder. The findings call into question practice guideline recommendations to avoid maintenance antidepressants in patients with rapid- and non-rapid-cycling bipolar II disorder.<sup>31–34</sup>

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## reflection

### Karl Jaspers and human-based psychiatry

Michael Musalek

We live in an incredibly fast-moving scientific world: what was valid yesterday is outdated today and perhaps long-forgotten tomorrow. The same applies to psychiatry. In the increasingly swift stream of psychiatric knowledge, one work stands out as a sheer immovable rock: Karl Jaspers's *General Psychopathology*. What other medical work can lay claim to be just as topical and valid today as it was 100 years ago!

The quality of a scientific publication can be recognised by its impact on the world of research. With his work, Karl Jaspers not only succeeded in sending an unforgettable signal, he also created a source of strength for scientific research in psychiatry that even today has lost nothing of its power. This treasure trove of psychiatric knowledge also had an immeasurably strong impact on me personally. From the host of stimuli that I gained as a researcher and therapist, I would like to emphasise just two here: Jaspers's elaborations on 'phenomenological intuition' and those which led to the more than justified demand for a 'psychopathology of the sick human individual' rather than a 'psychopathology of human sickness'.

Jaspers's demand that a sick individual should be approached using phenomenological intuition with a view to gaining a deeper understanding of his state of sickness stands in stark contrast to the superficial registration of characteristics of disease and their insertion into diagnostic algorithms that is prevalent today and which is focused on increasing the reliability of data that have been collected. As well as repeatedly opening up a new understanding of the state of being mentally ill, this phenomenological intuition, this going far beyond a mere empathetic engagement to a Being-in-the-World-of-the-Other, also opened up possibilities for developing a special form of hospitality in everyday psychiatric routines. The patient is no longer viewed as a person on the opposite side of the table who simply has to be treated according to the latest therapeutic guidelines, but as an Other who is met in the diagnostic and therapeutic process on an equal footing in a genuine dialogue. The psychiatric treatment unit can thus become a meeting place that is characterised by lived reciprocal hospitality. The professional monologue, so rightly bemoaned by Michel Foucault, is replaced by a therapeutic dialogue that is based on reciprocity.

With the sentence: 'Psychopathology is concerned with the ill person as a whole, in so far as he suffers from psychic phenomena or those that are psychically determined', Karl Jaspers unequivocally tells us what our actual task as psychiatrists is. He stimulated me to think about a form of psychiatry which in recent years has been presented as human-based psychiatry. It is psychiatry based in postmodern maxims that overcome medical positivism and it permits the development and application of a multidimensional, differential-diagnostic process, which includes information not only about the patient's deficiencies, but above all information about their resources, thus opening the door for modular, resource-oriented treatment options. This kind of human-based psychiatry no longer aims just to make mental disorders disappear, but to enable patients to achieve a life that is as autonomous and happy as possible.

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