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Research report

Do young adults with bipolar disorder benefit from early intervention? ☆

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ABSTRACT

Background: It is unknown whether young adults with bipolar disorder are able to benefit from early intervention combining optimised pharmacological treatment and group psychoeducation. The aim of the present report was to compare the effects of early intervention among patients with bipolar disorder aged 18–25 years to that of patients aged 26 years or older.
Methods: Patients were randomised to early treatment in a specialised outpatient mood disorder clinic versus standard care. The primary outcome was risk of psychiatric re-hospitalisation.
Results: A total of 158 patients with mania/bipolar disorder were included among whom 29 (18.4%) were between 18 and 25 years and 129 patients were 26 years or older. For both age groups, the point estimate of the hazard ratio of re-hospitalisation was insignificantly decreased for patients treated in the mood disorder clinic versus standard treatment but more so for patients between 18 and 25 years (HR 0.33, 95% CI 0.10–1.07; $p=0.064$) than for patients 26 years or older (HR 0.68, 95% CI 0.40–1.14, $p=0.14$). Younger adults treated in the mood disorder clinic used mood stabilisers and antipsychotics more in contrast to those treated in standard care. The differences between the estimates of effects did not reach significance in tests of interactions ($p>0.2$).
Limitations: The study was based on a post hoc subgroup analysis and due to the small number of patients aged 18–25 years, type II errors cannot be excluded.
Conclusions: Although not statistically different, the observed differences of the point estimates was surprisingly larger for young adults suggesting that young adults with bipolar disorder may benefit even more than older adults from early intervention combining pharmacological treatment and group psychoeducation.

1. Introduction

Bipolar disorder may on average have a progressive course of illness with poor long-term outcomes. The risk of relapse of episodes is high and increases with the number of previous episodes (Kessing et al., 2004a, 2004b). A large proportion of patients do not recover to previous psychosocial function (Tohen et al., 2000; Conus et al., 2006) and develop sustainable cognitive impairment (Torres et al., 2007) and even dementia in the long run (Kessing and Nilsson, 2003). Early combined pharmacological and psychological intervention in bipolar disorder has recently attracted much interest and has been suggested to improve long-term outcomes (Berk et al., 2007, 2009; Macneil et al., 2011, 2012a, 2012b) but only one randomised clinical trial has specifically investigated the effects of such interventions in the early stages of bipolar disorder (Kessing et al., 2013). In that randomized clinical trial, we recently showed that early intervention in a specialised mood disorder clinic combining optimised pharmacological treatment and group psychoeducation significantly reduced psychiatric re-hospitalisation, increased use of mood stabilisers and antipsychotics, and increased patient satisfaction compared with treatment in standard care (Kessing et al., 2013).

☆ **Trial registration** ClinicalTrials.gov: ID: NCT00253071.

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Early onset bipolar disorder has been associated with greater severity, high level of comorbidity including substance abuse, resistance to mood-stabilisers and poorer long-term outcome including disturbed interpersonal relationships, academic failure, high rates of suicide attempts and completions, and multiple hospitalisations (see review by Leboyer et al. (Leboyer et al., 2005)). Consequently, it has been discussed whether young adolescents and adults are able to benefit from early intervention (Berk et al., 2007) facing challenges such as interference of illness with age-specific educational, social and psychological development (Berk et al., 2007) as well as poor insight (Robinson et al., 2009), poor adherence to treatment (Gonzalez-Pinto et al., 2010; Bates et al., 2010) and higher comorbidity with alcohol and other substance use (Conus et al., 2006) compared to older adults (Berk et al., 2007). It has, however, never been investigated in any trial whether younger patients benefit less or more from early intervention compared to older adults. Patients included in our early intervention trial (Kessing et al., 2013) had a rather high age at inclusion in the trial with a median age of 35.6 years, but 18.4% of the patients were between 18 and 25 years of age. Overall, age of the patients was in accordance with findings in observational studies recruiting patients following first hospitalisation (mean age 31.4+12.9 and 38.4+12.6 years, respectively (Khalsa et al., 2008; Perugi et al., 2000)). The clinical impression was that younger patients benefitted from the treatment programme in the mood disorder clinic.

The aim of the present report was to compare the effects of early intervention combining optimised pharmacological treatment and group psychoeducation among patients with bipolar disorder aged 18–25 years to that of patients aged 26 years or older. It should be emphasised that the original trial was not designed to test whether age at inclusion interact with the intervention effect, so this study represents a post hoc subgroup analysis. The trial design was pragmatic with very few exclusion criteria and investigated the effect among patients following psychiatric hospitalisation in The Capital Region of Denmark for the first, second or third time with a diagnosis of mania or bipolar disorder. This pragmatic design was chosen to obtain a high generalisability of the results from the trial to clinical settings regarding patients early in the course of bipolar disorders (Zwarenstein et al., 2008).

2. Methods

The trial protocol has been described in detail elsewhere (Kessing et al., 2013, 2011). In short, the trial included a total of 158 patients who were discharged from their first, second, or third hospitalisation from an inpatient psychiatric ward with an ICD-10 diagnosis of single manic episode or bipolar disorder (ICD-10 code: F 30.1–31.6) as the primary diagnosis. Patients were recruited from seven psychiatric wards in The Capital Region of Denmark during a period from December 2005 to December 2009. The vast majority suffered from a bipolar I disorder. Comorbidity with alcohol or substance abuse and other psychiatric disorders were allowed. The only exclusion criteria were moderate or severe dementia, poor understanding of Danish, or any kind of commitment. Patients were randomised 1:1 to the intervention group or the control group at the end of the index hospitalisation while still in hospital. The Copenhagen Trial Unit conducted randomisation centrally according to a computer generated allocation sequence to secure allocation concealment. Allocation was stratified for psychiatric centre and number of previous hospitalisations before the index hospitalisation (0 or >1). The randomisation was carried out with a block size of 20 unknown to the investigators. The primary outcome measure was psychiatric re-admission based on public register data (Mors et al., 2011) using blinding for intervention. All other outcomes were based on a questionnaire mailed to patients 1 and 2 years after randomisation and were assessed without blinding to the intervention. The questionnaire included formalised questions on mood symptoms, satisfaction with care and the use of mood stabilisers (lithium or anticonvulsants), atypical antipsychotics, and/or antidepressants. For each variable, data on questionnaires were combined for the 1 and the 2 years responses into one combined measure.

Patients in the experimental intervention group were treated in a specialised outpatient mood disorder clinic, The Copenhagen Affective disorder Clinic, the Capital Region of Denmark at the Psychiatric Centre Copenhagen, Copenhagen University Hospital, Rigshospitalet. The staff in the outpatient mood disorder clinic consists of full time specialists in psychiatry with specific clinical experience and knowledge on diagnosis and treatment of bipolar disorders as well as certified psychologists, nurses, and a social worker with experience in bipolar disorders. The clinic offers combined intervention with evidence based pharmacological treatment and group psychoeducation. Manuals for psychoeducation were developed, tested, and revised in a pilot phase with inclusion of approximately 30 patients. The intervention programme lasted 2 years. According to the protocol, a medical doctor evaluated all patients in the clinic as early as possible following discharge from inpatient hospitalisation and no later than 2 weeks after discharge as this is a vulnerable period. Prior course of illness and effect of treatment was carefully recorded and diagnosis and treatment plans were re-evaluated and current pharmacological treatment adjusted in accordance with clinical status and with an approach very similar to the revised recommendations from the British Association for Psychopharmacology that was published in 2009 (Goodwin, 2009). Thus, focus was on treatment with mood stabilisers, mainly lithium, valproate, lamotrigine, and atypical antipsychotics (for further details see Kessing et al. (2013)). Antidepressants were only employed when remission could not be obtained in other ways and in that case mainly SSRI's combined with one or two mood stabilisers (Goodwin, 2009).

The psychological intervention has been described in details elsewhere (Kessing et al., 2013, 2011). Patients participated in three different sequential group sessions. The first group was a settling-in group for patients just discharged from hospitalisation with the aim of obtaining at least partly remission (scores on Hamilton Depression Rating Scale-17 items <14 and on Young Mania Rating Scale <14), i.e., typically for some months up to half a year. When stable, the patients were transferred to the second group, a psychoeducation group for 1½ h intervention every week for 12 consecutive weeks followed by three additional booster sessions. In the psychoeducation group focus was on knowledge and acceptance of suffering from a bipolar disorder, identifying depressive and manic symptoms from normal reactions, personal identity in relation to suffering from a bipolar disorder, risk situations, stress management, the need for sustained pharmacological maintenance treatment, adverse effects to treatment, and identification of individual early warning signs of upcoming depressive and manic episodes. In addition, in some sessions cognitive behavioural therapeutic approaches were included focusing on cognitive distortions in identity and behaviour and to some extent on inter-individual conflicts. Finally, patients joined a 3–6 months discharge group that was a preparation for re-referral either to the general practitioner, a private psychiatrist, or to the community psychiatric centre. Six to eight patients and two therapists (psychiatrist and psychologist or nurse) participated in each group.

The control group was offered standard care consisting of the standard outpatient mental health service routines in The Capital Region of Denmark, i.e., treatment at the general practitioner,

a private psychiatrist, the local community mental health centre or at a local psychiatrist associated with the discharging ward. Participation in the trial had no influence on the treatment offered to these patients. Psychopharmacological treatment in the control group, compared with treatment in the mood disorder clinic, is likely more based on the preferences of the individual physician than on national and international guidelines. Psychosocial treatment elements like group psychoeducation or individual psychoeducation was not systematically offered, and contact with family was provided more infrequently and in a less intensive, non-systematic way as compared with the mood disorder clinic.

2.1. Statistical analysis

Regarding the primary outcome, time to the first re-hospitalisation was estimated in a Kaplan–Meier plot, censoring at the date of death or emigration or end of study December 31th, 2011. The difference in cumulated prevention of re-hospitalisation in the intervention and in the control group was tested in a log-rank test. Hazard ratios (HRs) were calculated in Cox' regression models. First order interaction between intervention and age group was tested with tests of interaction. *P*-values less than 0.05 were regarded as statistically significant. SPSS 19.0 was used for the statistical analyses.

3. Results

A total of 158 patients were included in the trial with an ICD-10 diagnosis of a single manic episode or bipolar disorder (F 30.1–31.6) at discharge from their first, second, or third psychiatric hospitalisation during the study period from December 1, 2005 to December 1, 2009.

Among these 158 patients, 29 (18.4%) were between 18 and 25 years, among whom 14 were randomised to treatment in the mood disorder clinic and 15 to standard treatment, and 129 patients were 26 years or older, among whom 58 were randomised to treatment in the mood disorder clinic and 71 to standard treatment. Table 1 presents baseline characteristics of the four groups of patients. Patients in standard care were treated at the local community mental health centre (56.5%), a private psychiatrist (24.7%), a local psychiatrist associated with the discharging ward (15.3%), or at the general practitioner (3.5%).

The interventions in principle started at the date of discharge from the index hospitalisation as patients before discharge were randomised to receive treatment in the mood disorder clinic versus standard treatment. Register-based data on re-hospitalisation and death was 100% complete, i.e., available for all 158 patients. No patient was lost to follow-up and no patient was excluded post-randomisation from the analyses.

All patients were followed to the first event, a re-admission at psychiatric hospital, or to the date of death or emigration or to the end of study on December 31th, 2011, whatever came first. One patient died and three patients emigrated during follow-up – all these patients were treated in the mood disorder clinic.

The follow-up period from the discharge date following randomisation was between 0 and 6 years with an average follow-up of 2.5 years (SD 1.7 years). In Fig. 1, it can be seen from the Kaplan–Meier curves that the rates of first psychiatric re-admission did not differ for the 29 patients aged 18 and 25 years and the 129 patients 26 years or older ($\chi^2=0.22$, d.f.=1, $p=0.6$). Similarly, there were no significant differences in rates of re-admission between

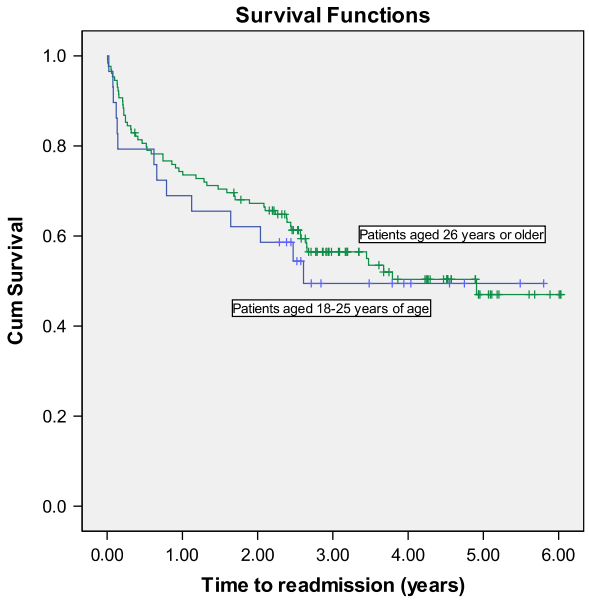

Fig. 1. Time to re-admission for patients aged 18–25 years versus patients 26 years or older ($N=158$).

Table 1
Baseline characteristics according to age of patients in the early intervention affective disorder trial.

	Age 18–25 $N=29$		**Age 26 or older** $N=129$	
	Mood disorder clinic	Standard care	Mood disorder clinic	Standard care
N	14	15	58	71
Mean age at randomisation (SD) (range)	22.6 (2.0) (18.0–25.9)	22.5 (1.8) (19.2–25.0)	41.5 (10.7) (26.3–63.0)	40.5 (10.8) (26.0–68.3)
Sex				
Female (%)	9 (64.3)	11 (73.3)	35 (60.3)	31 (43.7)
11 or more years of education (%)	9 (64.3)	7 (46.7)	43 (79.9)	42 (64.6)
Number of patients with or without previous admission before index hospitalisation				
Without (%)	6 (42.9)	9 (60.0)	35 (60.3)	31 (43.7)
With (%)	8 (57.1)	6 (40.0)	23 (39.7)	40 (56.3)
Centre				
Hvidovre (%)	3 (21.4)	5 (33.3)	21 (36.2)	25 (35.2)
Rigshospitalet (%)	6 (42.9)	5 (33.3)	19 (32.8)	20 (28.2)
Bispebjerg (%)	1 (7.1)	3 (20.0)	5 (8.6)	4 (5.6)
Others (%)	4 (28.6)	2 (13.3)	13 (22.4)	22 (31.0)

younger and older patients among those treated in the mood disorder clinic ($\chi^2=0.29$, d.f.=1, $p=0.6$) or among those treated in standard care ($\chi^2=1.46$, d.f.=1, $p=0.2$).

Fig. 2 presents rate ratios of psychiatric re-admissions for the four groups of patients according to age and randomisation status. The figure illustrates two findings: (1) time to readmission was increased for younger as well as older patients treated in the mood disorder clinic compared to patients treated in standard care; (2) among patients treated in the mood disorder clinic younger patients had increased time to readmission compared to older patients whereas the opposite was the case among patients treated in standard care, here younger patients had shorter time to readmission. However, results from Cox regression models showed that there was no significant interaction of age category on the associations between randomisation status and the rates of readmission ($\chi^2=1.20$, d.f.=1, $p=0.2$).

Table 2 presents comparisons of time to readmission for younger patients and older patients, respectively. For patients aged 18–25 years, time to readmission did not differ significantly for patients treated in the mood disorder clinic as compared to those treated in standard care (HR 0.33, 95% CI 0.10–1.07; $p=0.064$). A total of 4 (28.6%) of patients treated in the mood disorder clinic were re-admitted in contrast to 10 (71.4%) of patients treated with standard care (Table 2). Similarly for patients 26 years or older, time to readmission and number of patients readmitted was not statistically significant decreased for patients treated in the mood disorder clinic compared to those treated with standard care (HR 0.68, 95% CI 0.40–1.14; $p=0.14$).

For younger patients, the duration of first re-hospitalisation following randomisation was shorter for patients treated in the mood disorder clinic compared with standard care; however, the difference was not statistically significant ($p=0.3$; mood disorder clinic versus standard care: median (quartiles) 3.5 days (1.3–11.0) versus 8.5 days (2.0–44.3)). Regarding younger patients, those treated in the mood disorder clinic experienced a statistically significant decreased number of total re-hospitalisations following randomisation ($p=0.04$); mood disorder clinic versus standard care: median (quartiles) 0 (0–1) versus 1 (0–4). Further for younger patients, the cumulated duration of all hospitalisations following randomisation was significantly shorter for patients treated in the mood disorder clinic ($p=0.03$; mood disorder clinic versus standard care: median (quartiles) 17.0 days (4.8–93.0) versus 69.0 days (28.8–132.5)). Although these figures regarding patients 26 years or older were also numerically decreased for patients treated in the mood disorder clinic versus those treated with standard care, none of these differences reached statistical significance (results not presented).

The response rates regarding questionnaires on consumed medication were relatively good ranging from 79% for antidepressants, 86% for antipsychotics, to 93% for mood stabilisers (lithium or anticonvulsant). The use of antidepressants, antipsychotics or mood stabilisers did not differ for patients aged 18–25 years and patients 26 years or older (all $p>0.2$). As can be seen from Table 3, patients treated in the mood disorder clinic reported to use mood stabilisers (significantly) and antipsychotics (borderline significantly) more frequently compared with patients treated in standard care and additionally, the odds for using mood stabilisers and antipsychotics for patients treated in the mood disorder clinic versus standard care were substantially higher for patients aged 18–25 years than for older patients (OR=5.6–5.5 compared to OR=2.3–2.6). Nevertheless, results from Cox regression models showed that these figures did not differ significantly, as there was no statistical significant interaction of age category on the associations between randomisation status and adherence to any kind of medication (all $p>0.2$).

There was no difference in the use of antidepressants in any of the age groups.

Too few patients fulfilled the questionnaires regarding mood symptoms as well as satisfaction with care making comparisons between the four groups meaningless.

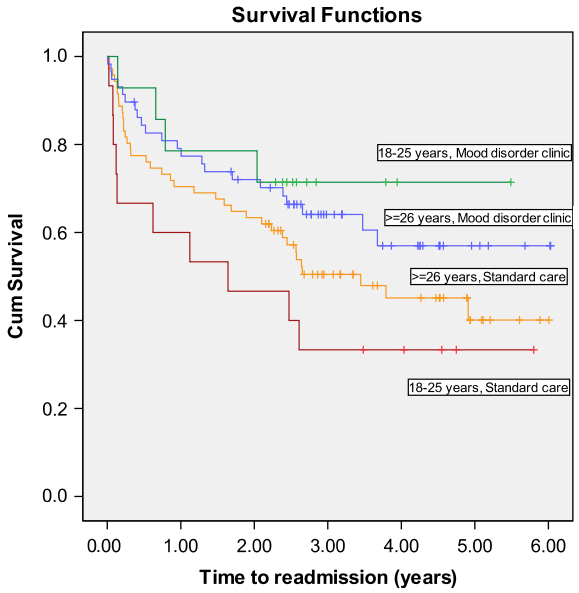

Fig. 2. Time to re-admission for patients aged 18–25 years and patients 26 years or older treated in the mood disorder clinic versus standard outpatient care ($N=158$).

4. Discussion

We have previously reported the main results from this randomised trial showing that treatment in the specialised mood disorder clinic combining pharmacological treatment and group

Table 2
Comparison of time to re-admission for patients treated in the mood disorder clinic versus standard treatment according to age at inclusion in the early intervention affective disorder trial.

Treatment	No. of patients	No. of re-admissions (%)	No. of events censored due to death or end of trial (%)	Mean years of post-randomisation survival time (95% confidence interval)	Log rank test		
					χ^2	d.f.	p
18–25 years							
The mood disorder clinic	14	4 (28.6)	10 (71.4)	4.2 (3.1–5.3)	3.77	1	0.05
Standard treatment	15	10 (71.4)	5 (28.6)	2.5 (1.3–3.8)			
26 years or older							
The mood disorder clinic	58	22 (37.9)	36 (62.1)	4.1 (3.4–4.7)	2.16	1	0.14
Standard treatment	71	37 (52.1)	34 (47.9)	3.4 (2.8–4.0)			

Table 3
Comparisons of use of mood stabilisers, antipsychotics and antidepressants for patients treated in the mood disorder clinic versus standard treatment according to age at inclusion in the Early Intervention Affective Disorder Trial (18–25 years compared to 26 years or older).

Treatment	Use of mood stabiliser %	OR (95% CI) p	Use of antipsychotic %	OR (95% CI) p	Use of antidepressant %	OR (95% CI) p
18–25 years						
The mood disorder clinic	71.4	5.6 (1.1–29.4) $p=0.04$	50.0	5.5 (0.8–36.2) $p=0.08$	22.2	0.7 (0.1–5.0) $p=0.7$
Standard treatment	30.8		15.4		28.6	
26 years or older						
The mood disorder clinic	66.7	2.6 (1.2–5.6) $p=0.01$	40.0	2.3 (1.0–5.6) $p=0.06$	46.3	1.4 (0.6–3.1) $p=0.4$
Standard treatment	43.1		22.4		38.1	

psychoeducation early in the course of bipolar disorder significantly reduces psychiatric re-hospitalisations and increase the use of mood stabilisers and antipsychotics compared with treatment in standard care. Surprisingly, we found in the present post hoc subgroup analysis of the data that young patients aged 18–25 years may benefit more from treatment in the mood disorder clinic compared with standard care compared to patients aged 26 years or older. For younger patients, the point estimate of the rate ratio of re-hospitalisation decreased 67% and the use of mood stabilisers and antipsychotics increased around 5 times whereas for older patients, the point estimate of the rate ratio of re-hospitalisation decreased 32% and the use of mood stabilisers and antipsychotics increased 2–2.5 times. However, it should be emphasised that the study was not originally designed to test whether age at inclusion interacts with the intervention effect and it should be noted that due to the small number of patients aged 18–25 years ($N=29$) a number of these estimates had rather wide confidence intervals and most comparisons did not reach statistical significance. Nevertheless, the observed differences of the point estimates in the effect of combined pharmacological treatment and group psychoeducation was surprisingly larger for patients aged 18–25 years for as well readmission and medication adherence as outcomes.

4.1. Limitations

The present report is dealing with post hoc subgroup analyses of relatively few patients which increase the risks of random errors both observing spurious differences when there in fact is none and observing no differences when there in fact is some. Such analyses shall be considered only as exploratory analyses (Oxman and Guyatt, 1992, 1993). On the other hand, we want to inform the ongoing debate having postulated that young patients would not benefit from early intervention combining pharmacological treatment and group psychoeducation with real life data.

It should be emphasised that patients included in the trial suffered from the most severe bipolar disorder leading to psychiatric hospitalisation. Consequently, as patients were recruited following their first hospitalisations, the median age of 35.6 years at inclusion in the study was rather high although with a substantial variation. This relatively high age of the sample of bipolar patients is also found in other studies recruiting patients following the first hospitalisation (mean age 31.4+12.9 (Khalsa et al., 2008) and 38.4+12.6 years (Perugi et al., 2000)). It is possible that a proportion of the patients in our sample got treatment for depressive episodes or even milder to moderate manic episodes in a period before hospitalisation. We have no information on such potential episodes and it cannot be excluded that patients aged 26 years or older may have had more such milder episodes prior to their first hospitalisation and that this may have added to decrease their benefits from treatment in the mood disorder clinic.

Further, we have no data on educational, social and psychological development, the level of insight, or the prevalence of comorbidity, which have been suggested to constitute important challenges especially among younger patients. These issues have to be investigated in future studies, but in post hoc subgroup analysis of data from the Barcelona group, patients with comorbid personality disorders also benefitted from psychoeducation (Colom et al., 2004).

Patients in the experimental group received a well-defined intervention programme combining evidence-based pharmacological treatment and manualised group psychoeducation (Kessing et al., 2013). On the other hand, it is likely that the patients in the control group received very different interventions and that these interventions varied between broad, competent and prolonged service to shorter and sporadic treatment offers. Patients were mainly treated in community psychiatric centres (56.5%) and to a lesser extent at private specialists in psychiatry (24.7%) or a local psychiatrist associated with the discharging ward (15.3%).

Time to (re)hospitalisation as an outcome has been criticised as reductionistic; however, it benefits from being consistently recorded and may have high face validity as admission to hospital reflects serious relapse of the illness (Burns, 2009).

4.2. Generalisability

Pragmatic randomized clinical trials as the present trial are designed to measure effectiveness; that is whether an intervention works when used in usual conditions of care. To ensure applicability in the wide range of usual care settings, pragmatic trials should include all kinds of participants to whom the intervention may be offered in the real world, if its effectiveness is established. The trial included patients suffering from bipolar disorder with all kinds of symptoms and comorbidities and used very few exclusion criteria.

5. Perspectives

Patients may benefit more from early intervention combining pharmacological treatment and group psychoeducation versus standard care when aged 18–25 years compared to older patients (see Fig. 2, although none of these differences reached statistical significance). This was the case according to the primary outcome of psychiatric re-hospitalisation as well as for the secondary outcomes of use of mood stabilisers and antipsychotics. There were no differences in the use of antidepressants (see Table 3). Thus, younger patients in the mood disorder clinic more often reported using mood stabilisers and atypical antipsychotics than older patients whereas the opposite was the case for patients treated in standard care; here younger patients used mood stabilisers and antipsychotics less than older patients. Mainly using mood stabilisers and antipsychotics is in accordance with the recommendations from the British Association for

Psychopharmacology (Goodwin, 2009). Thus, compared to younger patients treated in standard care, younger patients in the mood disorder clinic adhered substantially more to medication in ways recommended in current guidelines.

There are a number of challenges related to young adulthood such as interference of illness with age-specific educational, social and psychological development, problems with insight into an illness that may interfere with identity, and possible comorbidity with alcohol and other substance use (Conus et al., 2006; Berk et al., 2007). Despite these challenges we found indications that younger adults may potentially benefit more from early combined pharmacological and psychological treatment. Overall these findings are in accordance with suggestions that the effect of medication and psychological treatment is more pronounced when initiated early in the course of illness (Berk et al., 2010): treatment with lithium (Franchini et al., 1999; Swann et al., 1999; Post et al., 2003), group psychoeducation to patients (Vieta et al., 2009), group psychoeducation to caregivers (Reinares et al., 2010) and cognitive behavioural therapy (Scott et al., 2006) may be most effective when provided early. Findings from the present trial may suggest that also among young patients aged 18–25 years, the first episodes in bipolar disorder offer an important opportunity to provide psychological intervention and individual effective maintenance pharmacological treatment and improve outcome. Consequently, this should be tested in a larger randomised trial on early intervention in young patients with bipolar disorder.

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Conflict of interest

Lars Vedel Kessing has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, AstraZeneca, Pfizer, Wyeth, Servier, Janssen-Cilag.

Hanne Vibe Hansen, Ellen Margrethe Christensen, Henrik Dam, Christian Gluud and Jørn Wetterslev have no conflicts of interests.

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