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**Psychoeducation and Online Mood Tracking for Patients with Bipolar Disorder: A  
Randomised Controlled Trial**

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## ABSTRACT

**Background.** Psychoeducation is an effective adjunct to medications in bipolar disorder (BD). Brief psychoeducational approaches have been shown to improve early identification of relapse. However, the optimal method of delivery of psychoeducation remains uncertain. Here, our objective was to compare a short therapist-facilitated vs. self-directed psychoeducational intervention for BD.

**Methods.** BD outpatients who were receiving medication-based treatment were randomly assigned to 5 psychoeducation sessions administered by a therapist (Facilitated Integrated Mood Management; FIMM; n=60), or self-administered psychoeducation (Manualized Integrated Mood Management; MIMM; n=61). Follow-up was based on patients' weekly responses to an electronic mood monitoring program over 12 months.

**Results.** Over follow-up, there were no group differences in weekly self-rated depression symptoms or relapse/readmission rates. However, knowledge of BD (assessed with the Oxford Bipolar Knowledge questionnaire (OBQ)) was greater in the FIMM than the MIMM group at 3 months. Greater illness knowledge at 3 months was related to a higher proportion of weeks well over 12 months.

**Limitations.** Features of the trial may have reduced the sensitivity to our psychoeducation approach, including that BD participants had been previously engaged in self-monitoring.

**Conclusions.** Improved OBQ score, while accelerated by a short course of therapist-administered psychoeducation (FIMM), was seen after both treatments. It was associated with better outcome assessed as weeks well. When developing and testing a new psychosocial intervention, studies should consider proximal outcomes (e.g., acquired knowledge) and their short-term impact on illness course in bipolar disorder.

**Key words:** Bipolar Disorder, Psychoeducation, self-monitoring, relapse, randomised controlled trial.

**Clinical trial registration:** ISRCTN 67300357(EUDRACT).

## 1. INTRODUCTION

Current treatment guidelines for bipolar disorder (BD) recommend combining pharmacological with psychosocial interventions ( Goodwin et al., 2016; Yatham et al., 2009). Psychoeducation appears to be a common element in most successful psychosocial interventions for BD (Miklowitz et al., 2012b; Vallarino et al., 2015); interventions based on psychoeducational approaches can enhance relapse prevention and improve medication adherence over periods of 1-2 years (Candini et al., 2013; Colom et al., 2003a; Colom et al., 2003b; Colom et al., 2005; Kessing et al., 2014). The brevity of most psychoeducational models makes them an economically attractive alternative. An intervention of 7-12 individual sessions to improve identification of early symptoms of relapse and facilitate help-seeking behaviour was associated with reduced rates of manic (but not depressive) relapse compared with treatment as usual over 12 months (Perry et al., 1999). In remitted patients, 6 sessions of group psychoeducation appeared to be as efficacious as 20 sessions of individual cognitive behaviour therapy (CBT) in terms of symptom burden and relapse likelihood (Parikh et al., 2012).

Whether psychoeducational interventions are best delivered by group, family, individual instruction, or self-direction, remains uncertain. In addition, in testing new approaches, it is unclear which outcomes will be most informative. Relapse is often difficult to define and usually requires prolonged follow-up. Additionally, a relapse may not indicate treatment failure in a patient who is otherwise well for the majority of weeks of follow-up.

The current study used a randomised design to compare the effects of a 5-session Facilitated Integrated Mood Management (FIMM) intervention against a self-administered Manualised Integrated Mood Management (MIMM) intervention. Our primary focus was on depressive and manic symptoms reported weekly by patients in both groups, collected electronically via the True Colours platform (Bopp et al., 2010; Miklowitz et al., 2012a). Our hypothesis was that the FIMM approach would be more effective than the self-administered MIMM approach in reducing mood symptoms, particularly depression. We also reasoned that increased knowledge of recommended actions when experiencing prodromal symptoms of relapse (e.g., contacting one's physician) would be an important correlate of any effects of FIMM or MIMM on symptoms. We used the Oxford Bipolar Knowledge Questionnaire (OBQ) to measure knowledge of illness at baseline and follow-up visits.

## **2. METHODS**

The relevant protocols were reviewed and approved by UK NHS Ethics Committees (REC references: OXTEXT-1, 11/SC/0068; OXTEXT-6, 10/H0604/13). Written informed consent was obtained from all participants.

### ***2.1 Participants***

Participants registered for research under an observational protocol (the OXTEXT-1 study: (Bourne et al., 2015)) were invited to take part in the OXTEXT-6 trial. As part of OXTEXT-1, participants had completed a diagnostic interview, adapted from the Mini International Neuropsychiatric Interview (Sheehan et al., 1998), conducted and audio-recorded by trained Research Assistants. OXTEXT-1 also included completion of a battery of cognitive tasks

(data to be published elsewhere; includes (Bourne et al., 2015)) and weekly assessment for depression and mania via the True Colours system (see Assessments, below). All diagnostic interviews were reviewed by a Research Psychiatrist for diagnostic confirmation using DSM-IV-TR criteria.

Eligibility criteria were (i) age 16 years or over; (ii) a diagnosis of DSM-IV-TR Bipolar I (BD I) or Bipolar II (BD II) disorder, but not in a current mood episode; (iii) current and reliable participation in True Colours mood monitoring for  $\geq 4$  weeks, with at least 3 out of 4 responses in the 4 weeks as a requirement for participation, (iv) a current patient of Oxford Health NHS Foundation Trust; (v) able to give informed consent; (vi) understanding of verbal and written English sufficient to participate in trial procedures; and (vi) a treating psychiatrist deemed a psychoeducational intervention with mood monitoring to be appropriate, and there was no need for more acute treatment.

## ***2.2 Study design***

The study was a two-arm RCT in which participants were randomised to engage with FIMM (standard medication management + weekly mood monitoring + 5 sessions of facilitator integrated mood management), or MIMM (standard medication management + weekly mood monitoring + a self-care manual with instructions regarding mood management). Medication and case management was provided by NHS teams.

## ***2.6 Treatment facilitators***

Nine female facilitators were involved in delivering the FIMM arm of the study. Six had formal clinical qualifications or professional registration as a therapist and 3 worked in mental health research with clinical populations.

Prior to the trial, all facilitators underwent a 6-hour workshop delivered by DJM (a specialist in psychological interventions for BD) that included guidance on how to use the FIMM manual with participants. During the trial, facilitators continued to receive regular support from DJM and JP (a consultant psychiatrist) through supervision and monitoring of individual session tapes. Feedback was given for audio-recorded FIMM sessions 2 and 5 for the facilitators' first two participants, as well as for additional sessions when requested by the facilitator. In cases where clinicians received below average fidelity ratings (below 4 on the 1-7 point scale of overall fidelity), they were given additional supervision until ratings improved.

## **2.4 Assessments**

### *Mood assessment*

All participants were asked to complete weekly, remote symptom assessments of depression and (hypo)mania via the True Colours system ([www.truecolours.nhs.uk](http://www.truecolours.nhs.uk)). In brief, True Colours is an online system which schedules and prompts (via email and/or text message) self-report questionnaires, as well as curating the collected data (an example email prompt as delivered by the True Colours system is provided in Supplemental Figure 1). The system provides a graphical representation (e.g. a line graph) of symptoms over time, and individuals can share access to their account with their treating clinicians.

As part of the current trial, participants were asked to submit weekly ratings of depression with the Quick Inventory of Depressive Symptomology patient-rated version (QIDS-SR16; Rush et al., 2003) and mood elevation with the Altman Self-Rating Mania scale (ASRM; Altman et al., 1997), both of which were implemented in the True Colours system. Symptom scores were extracted from the True Colours system for the week in which participants were randomised (week 0, or W0), and for the subsequent 52 weeks (i.e. W0 to W52).

### *The Oxford Bipolar Knowledge Questionnaire (OBQ)*

The OBQ was developed as a self-report measure of the knowledge and behaviour relevant to self-management in BD. It comprises 10 items, each with 4 statements, which ask about participants' knowledge of risk factors and early warning signs that may indicate mood changes, and behavioural plans, sleep/wake routines, and medicines that may promote mood stability. The full OBQ questionnaire is provided in Supplementary Information. Participants rated their level of agreement with each statement on a 3-point scale, scored as 0=disagree, 1=neither agree nor disagree and 2=agree. A higher total OBQ score (range 0-80) is indicative of better knowledge of bipolar mood management. Participants completed the questionnaire at baseline (during face-to-face assessments with a researcher) and again at 3 months and 12 months (with pen-and-paper questionnaires sent by post).

### **2.5 Randomisation**

A computerised system was used to randomise participants. Allocation was stratified by diagnostic subtype (BPI vs. BPPI) and whether patients were in full recovery (defined as 4 consecutive weeks with minimal or no mood symptoms [QIDS-SR16 <10 and ASRM ≤5]) or not at the time of randomisation.

### *FIMM*

The development of FIMM is described in (Miklowitz et al., 2012b). In brief, FIMM required use of the True Colours remote monitoring system and a (hardcopy) psychoeducational manual, together with 5x50-min. individual sessions with a facilitator. Sessions corresponded to each stage of the manual. These comprised of (1) identifying the relapse signature; (2) reviewing risk and protective factors; (3) daily rhythm and sleep/wake regulation; (4) the role of medications and substance/alcohol abuse; (5) finalising the mood management plan.

Participants randomised to FIMM received the study outline of the psychoeducation manual at randomisation and received a printed copy of each chapter from their facilitator over the following 5 face-to-face sessions. Facilitators were allocated on the basis of availability. The target was for all 5 FIMM sessions to be delivered face-to-face within 12 weeks from entering the study. If all 5 sessions had not been completed during the 12 week period, the participant was sent the remaining sections of the manual and further sessions were only conducted over the telephone. Follow-up phone calls, which aimed to provide support for the implementation of core mood management techniques and did not contain any novel therapeutic material, took place at weeks 15, 17, 21 and 29 for FIMM participants only. Guidance for facilitators for telephone follow-up sessions is included in the Supplementary Material.

### *MIMM*

The MIMM intervention involved independent use of the integrated mood management IMM manual only. The full, printed manual was provided at randomisation and participants received neither face-to-face nor telephone support from facilitators. Participants could work through the manual at their own pace during the 12-week treatment period. The psychoeducational content of the manual was otherwise identical to that used in FIMM, and contained the same 5-section structure.

### *Follow-up*

All participants received postal follow-up questionnaires at months 3, 6, 9 and 12 after randomisation. These asked about factors such as changes in treatment or hospital admissions, and were used to determine relapse status. Postal follow-up questionnaires at months 3 and 12 included the OBQ.



## **2.8 Treatment fidelity ratings**

The FIMM supervisors (DJM and JP) listened to audio recordings of sessions 2 and 5 for every third case assigned to the FIMM psychoeducation protocol. Fidelity ratings were based on a modified version of the Therapy Competence and Adherence Scales (Marvin et al., 2014; Weisman et al., 1998) consisting of 20 Likert-type (range 1–7) items covering the following domains: (i) effective provision of psychoeducation; (ii) explaining the mood monitoring strategies; (iii) assignment of homework; (iv) exploring prodromal symptoms; (v) developing prevention plans; and (vi) problem-solving about sleep/wake monitoring or medication non-adherence. The scales also covered non-specific factors (rapport and alliance-building skills, pacing, session command, taking a didactic stance, and addressing patients' emotional reactions). An overall 1 to 7 score summarizing fidelity across the domains was derived for each session.

## **2.8 Outcome measures**

The primary outcome was group difference in self-rated depressive symptoms (using the QIDS-SR16) over the 12-month follow-up period. Secondary outcomes included weekly ASRM (mania) scores, OBQ knowledge scores, and relapse, defined as new interventions for emergent mood symptoms and/or admission to inpatient care or intensive community treatment. A final secondary outcome was *proportion of weeks well*, defined as the number of weeks over the post-intervention follow-up (Weeks 14-52) where QIDS-SR16 scores < 10 and ASRM scores  $\leq 5$ , divided by the total number of weeks for which ratings were available. Proportion of weeks well has been shown to be sensitive to interventions in other studies of psychosocial treatment in bipolar disorder (Miklowitz et al., 2007).

## **2.10 Statistical Analysis**

Analysis of primary and secondary outcomes was conducted in SAS (version 9.3) on an intention-to-treat (ITT) basis. Weekly QIDS-SR16 scores were compared across treatment groups using a mixed effects analysis of variance model, after verifying the assumption that the relationship between QIDS-SR16 and time was linear over the 12-month study period. The model included a random intercept for each patient and fixed effects for group allocation, time as a random effect, and stratification factors used in the randomisation (i.e., diagnostic sub-group and whether participants were in full recovery or not).

ASRM scores were positively skewed, and inspection of the repeated ASRM data suggested falling values over time. Thus, we examined weekly ASRM scores (1) as repeated binary variables (i.e., whether ASRM was  $\leq 5$  or  $> 5$  at each time point) compared across groups using a linear mixed effects model for binary data, with calculation (odds ratios plus 95% confidence intervals) of the likelihood that scores in each group would be above the cut-off; and (2) as log-transformed continuous scores. We compared these continuous scores across groups using the linear mixed effects model described for the QIDS-SR16 (above).

OBQ questionnaire item scores were summed across all items to calculate a total score. We compared the two groups with a linear mixed effects model with OBQ scores at 3 and 12 months as the outcome, adjusting for baseline OBQ values as a covariate and incorporating a group by time interaction term. Finally, proportion of weeks well, and proportion of weeks without depression ( $\text{QIDS-SR16} < 10$ ) or mania ( $\text{ASRM} \leq 5$ ) were compared across treatment groups using analysis of covariance, with baseline clinical status (i.e., in recovery or not) as a covariate.

### **3. RESULTS**

#### ***3.1. Participant flow, drop-out, and compliance***

Out of 121 participants recruited, 60 participants were randomised to receive FIMM and 61 to MIMM (see Supplemental Figure 2 CONSORT diagram). In the intention-to-treat sample, 1 participant in the FIMM group withdrew 12 weeks after randomisation (having begun CBT in another program). Two participants withdrew from MIMM (1 participant withdrew one week after randomisation due to finding the manual overwhelming and another participant no longer wished to continue 10 weeks after randomisation). In the FIMM group, the majority (n=49; 82%) attended all 5 facilitated sessions. Overall response rate to weekly QIDS and ASRM prompts over the 52-week study period was similar for the FIMM and MIMM groups ( $t(119)=1.36, p=0.18$ ), with compliance at 76.6% (SD 22.9%) and 70.7% (24.6%) respectively.

### ***3.2.Participant demographics and clinical variables***

Demographics and clinical characteristics of the study groups and the overall sample are shown in Table 1. Participants in the FIMM and MIMM groups were well matched. A small but unbalanced number of participants were not taking medicines (7 vs. 1 for MIMM and FIMM, respectively).

**Table 1. Demographic and clinical characteristics of participants (Total N= 121). Values are numbers of cases (percentages in brackets) unless otherwise specified.**

	Group status		
	MIMM (N= 61)	FIMM (N=60)	Overall
<b>Diagnosis</b>			
BPI	40 (65.6%)	39 (65.0%)	79 (65.3%)
BPII	21 (34.4%)	21 (35.0%)	42 (34.7%)

<b>Mean age at assessment (SEM, range), years</b>	43 (2, 16-71)	45 (2, 18-76)	44 (1, 16-76)
<b>Female gender</b>	46 (75.4%)	42 (70.0%)	88 (72.7%)
<b>Ethnicity</b>			
Caucasian	58 (95.1%)	54 (90.0%)	112 (92.6%)
Non-Caucasian	3 (4.9%)	6 (10.0%)	9 (7.4%)
<b>Education level</b>			
Postgraduate	13 (21.3%)	15 (25.0%)	28 (23.1%)
Degree	17 (27.9%)	17 (28.3%)	34 (28.1%)
Highers/A-levels or equivalent	18 (29.5%)	18 (30.0%)	36 (29.8%)
GCSEs or equivalent	7 (11.5%)	6 (10.0%)	13 (10.7%)
CSEs or equivalent	3 (4.9%)	2 (3.3%)	5 (4.1%)
No qualification	3 (4.9%)	2 (3.3%)	5 (4.1%)
<b>QIDS score at baseline</b>	7.2	7.5	7.4
<b>(SEM, range)</b>	(0.7, 0.0-22.0)	(0.8, 0.0-24.0)	(0.5, 0.0-24.0)
<b>ALTMAN score at baseline</b>	3.4	2.8	3.1
<b>(SEM, range)</b>	(0.5, 0.0-18.0)	(0.5, 0.0-14.0)	(0.4, 0.0-18.0)
<b>Medication</b>			
Lithium	20 (32.8%)	27 (45.0%)	47 (38.8%)
Anticonvulsant	26 (42.6%)	27 (45.8%)	53 (44.2%)
Antipsychotic	31 (50.8%)	30 (50.0%)	61 (50.4%)
Antidepressant	19 (31.1%)	25 (41.7%)	44 (36.4%)
Anxiolytic	13 (22.0%)	10 (16.9%)	23 (19.5%)
Hypnotic	7 (11.5%)	3 (5.0%)	10 (8.3%)
Drug free	7 (11.5%)	1 (1.7%)	8 (6.6%)

<b>Age of illness onset</b>	20	20	20
<b>(SEM, range)</b>	(1.0, 6-45)	(1.3, 4-47)	(0.8, 4-47)
<b>Number of episodes</b>			
<5	2 (3%)	2 (3%)	4 (3%)
5-10	12 (20%)	8 (13%)	20 (17%)
11+	40 (66%)	46 (77%)	86 (71%)
Rapid cycling	8 (13%)	3 (5%)	11 (9%)

### ***3.3. Treatment Fidelity***

Recordings of 25 sessions from 20 FIMM participants were analysed. The mean overall fidelity rating was  $5.22 \pm 1.0$  (mean  $\pm$  S.D.), indicating a “good” level of adherence and competence. The mean rating of effectiveness in administering the psychoeducational material was  $5.43 \pm 1.08$ ; ‘session command’ averaged  $5.26 \pm 1.21$ . A single session was rated below the minimum fidelity threshold (4 on the overall fidelity scale).

### ***3.4. FIMM vs. MIMM***

#### ***QIDS-SR16 and ASRM scores***

There was no significant difference between FIMM and MIMM for QIDS-SR16 depression scores (treated dimensionally) over the 12 months following randomisation (adjusted mean difference 0.17, 95% confidence interval [CI] (-1.35, 1.69),  $p=0.83$ ). The coefficient for the slope was -0.0038 ( $p=0.29$ ), indicating no significant drop in scores over time.

The odds of scoring above 5 in the ASRM revealed no difference between the FIMM and MIMM groups (adjusted odds ratio 0.71, 95% CI (0.35, 1.41),  $p=0.32$ ) and the coefficient for the slope was -0.002 (on the log-odds scale,  $p=0.12$ ), indicating no significant effect of time.

When ASRM scores were considered continuously (rather than as a dichotomous outcome), however, there was a main effect of time ( $F[1, 5308]=4.88, p=0.03$ ) indicating improvement in mania/hypomania scores. There was also a treatment by time interaction ( $F[1,5308]=4.55, p=0.03$ ), indicating a steeper slope of change in mania scores in the FIMM group than the MIMM group.

#### *OBQ scores and Proportion of Weeks Well*

The FIMM and MIMM groups did not differ at baseline on OBQ scores ( $M_{\text{FIMM}}=58.11, SD=13.30; M_{\text{MIMM}}=57.14, SD=12.88$ ). OBQ scores increased from baseline to 3 months in both treatment conditions (Figure 1). With baseline OBQ scores covaried, FIMM was associated with a greater increase in OBQ scores than MIMM at 3 months ( $F[1,94]=9.82, p=0.002$ ; adjusted mean difference  $-.60, 95\% \text{ CI: } -0.98, -0.22$ ). There was no significant difference between FIMM and MIMM at 12 months in this model ( $F[1,74]=0.19, p=0.66$ ; adjusted mean difference,  $-0.08, 95\% \text{ CI: } -0.46, 0.29$ ).

Treatment condition was not associated with the proportion of weeks well over the post-intervention follow-up ( $\text{FIMM}=0.64\pm0.35, \text{MIMM}=0.57\pm0.36, F[1, 108]=0.98, p=0.32$ ). However, in a post-hoc analysis, higher OBQ scores at 3 months were associated with a greater proportion of weeks well during the post-treatment period (months 3 – 12;  $r(98)=0.34, p=0.0006$ ). This moderately sized association between OBQ scores at 3 months and proportion of weeks well was observed for the FIMM group ( $r(50)=0.38, p=0.006$ ) and to a lesser extent, the MIMM group, ( $r(48)=0.27, p=0.06$ ).

#### *Relapse*

Relapse was defined as intervention for a new/worsening mood episode; increased intensity of home treatment; or admission to hospital. Full self-reported relapse data over 12-month

follow-up was available for 73% (N=88) of the participants, and 56.8% of these (N=50) reported a relapse. Of these, 25 relapses were reported in the FIMM group, and 25 in the MIMM group ( $p>0.10$ ). Instances where participants reported a worsening of symptoms due to deliberate trial withdrawal of medication were not included as relapses in this analysis, but their inclusion (N=3) did not alter the pattern of results (27 relapses in the FIMM group vs. 26 in the MIMM group).

There were also no differences between FIMM and MIMM in rates of hospital admission (based on hospital records): 6 participants in each group were admitted to hospital. This rate corresponded to an overall readmission rate of 9.9% (12/121) over the 12 month period. For comparison, 121 patients were identified in the OXTEXT-1 cohort who had not received either the facilitator-aided or self-administered interventions, but did have access to True Colours. They were matched with trial participants by gender, age and diagnosis (bipolar type I or type II), and rates of readmission were obtained over a 12-month interval. These participants showed a similar readmission rate of 7.4% (9/121).

#### **4. DISCUSSION**

The trial demonstrates the feasibility of individual psychoeducation for bipolar patients using a simple manual focused on its key elements: prodromal signatures of relapse, risk and protective factors, daily rhythm and sleep/wake regulation, medication adherence, risks associated with substance/alcohol abuse, and a mood management/relapse prevention plan. Acceptability was good, with 82% of participants attending all FIMM sessions. Our hypothesis was that FIMM (a facilitator-based psychoeducational therapy) would be superior to MIMM (a self-education course) in reducing subsequent levels of depressive and manic/hypomanic symptoms. This hypothesis was only weakly supported. FIMM showed no superiority to MIMM in ameliorating depressive symptoms or reducing rates of relapse and

admission to hospital. There was evidence of a differential effect of FIMM on dimensional self-ratings of mania (ASRM scores), which decreased to a greater extent in FIMM than MIMM during the trial. Given the residual skewing of the transformed ASRM data, however, these findings are merely suggestive of a differential treatment effect.

Since there was no important difference between treatments, were both equally effective or equally ineffective? FIMM and MIMM increased understanding of psychoeducational principles at 3-month and 12-month follow-up. The increase in OBQ scores at 3 months was greater in patients receiving FIMM than in patients in the self-educated MIMM course, but knowledge scores converged between FIMM and MIMM at 12 months. Thus, psychoeducation did achieve its primary didactic objective of increasing knowledge of bipolar disorder, and FIMM was associated with an accelerated understanding of mood management strategies. Moreover, improved OBQ scores at 3 months were related to a greater proportion of weeks well over the follow-up period, a relationship that was numerically stronger in the FIMM compared to MIMM group. These findings suggest that increased knowledge of bipolar disorder may be associated with a more stable course of illness and that there was a benefit from psychoeducation delivered by either FIMM or MIMM. Table 2 summarizes cohort characteristics and outcomes (dichotomised for comparison purposes) for psychoeducation trials with designs comparable to our own. Trials that failed to find a difference between groups tended to have relatively higher proportions of patients with more prior episodes. A secondary analysis of the Barcelona study (Colom et al., 2003a) suggested that patients with 7 or more previous episodes were insensitive to psychoeducation. Meta-analysis of relapse prevention studies also identified large numbers of previous episodes as a negative predictive factor of the efficacy of psychoeducation and CBT (Scott et al., 2007) although this relationship was not confirmed in a further meta-analysis (Lam et al., 2009). In the present sample, over 80% of participants had more than 7 episodes.



## **Limitations of the present study**

Features of our trial methodology may have resulted in reduced sensitivity to some of the benefits of psychoeducation in BD. Patients were recruited from an observational programme (OXTEXT-1) that may have selectively enrolled participants who were engaged in treatment and compliant with medications and mood monitoring. They may have had high levels of pre-existing knowledge of the illness; indeed, OBQ scores appeared to be quite high at baseline (mean of 60 on a 0-80 scale) and many showed ceiling effects at follow-up. All patients were already enrolled in self-monitoring of mood using True Colours, which may have had an educational value in itself. FIMM might not be expected to readily outperform the active MIMM comparison given that both study arms involved good pharmacological management and self-monitoring of mood; this may be particularly true of effects on distal outcomes such as relapse or rehospitalisation. The FIMM group had additional follow-up telephone sessions with their facilitator after the initial 5 sessions. It is possible that these calls, which focused on implementing the mood management plan, may prove to be important for the longevity of treatment effects. Studies comparing in-person psychoeducational delivery models to telephone- or internet-based models will be informative when considering the costs of psychosocial programs.

Our sample had low rates of relapse and admission compared with studies that found an effect of psychoeducation on relapse (see Table 2). The rates in our randomized cohort were similar, however, to rates in a matched sample of patients who were completing True Colours monitoring but were not in the trial. Length of follow-up may have been too short to capture changes in hard outcomes like admission to hospital, especially when evaluated among patients receiving pharmacotherapy. Shorter term designs offer much potential for treatment innovation if proximal measures (e.g., increases in knowledge) can be shown to be valid mediators of the clinical effects of treatments. Possibly, novel psychoeducation protocols

should first be tested in relation to proximal targets with clinical relevance before moving on to harder outcomes such as recurrence rates.

New technologies such as smartphones are increasingly emerging as a potential method of tracking subjective (and objective) mood and functioning (eg. MONARCA; (Faurholt-Jepsen et al., 2015a; Faurholt-Jepsen et al., 2015b) and PSYCHE; (Paradiso et al., 2010; Valenza et al., 2013)), and may be relevant to the search for sensitive proximal measures of treatment/intervention response. Although these technologies are limited by the sensitivity of the instruments on which they are based (in the present study, the QIDS or Altman), electronic mood monitoring did not result in any appreciable loss of longitudinal data in the present study.

The choice of depressive symptoms as a primary outcome was somewhat arbitrary. The trial was designed at a time when relapse prevention had been a preferred primary, but we wished to maximize the potential for weekly data collection given our preliminary finding that self-monitoring of depressive symptoms was sensitive to change over time (Bopp et al. 2010). However, interventions comprised of shorter numbers of treatment sessions may not be sufficient to address disruptions in interpersonal relationships or low social support, which are key predictors of the course of depression in bipolar disorder (Miklowitz et al., 2008). It is therefore possible that shorter interventions, whilst cheaper, are unlikely to be effective in the better management of depressive symptoms in BD.

**Table 2.** *Comparison of trials of psychoeducation interventions for Bipolar Disorder.*

Study	Number of sessions	Sample size	Age	% sample at $\geq 7$ episodes	% Relapse rate (12 months)*	Clinical effect
Perry et al. (1999)	7 – 12	69	44.5	$\sim 50.0\%^1$	72.1%	+ve
Colom et al. (2003a)	21	120	34.0	45.8%	65.5%	+ve
Rea et al.(2003)	21	53	25.5	Low % <sup>2</sup>	49.1%	+ve
Castle et al. (2010)	12 – 15	84	42.1	NK	83.3%	+ve
Candini et al (Candini et al., 2013)	21	102	43.2	Low rates of previous hospitalization; episode history NK	20.0% hospitalization; relapse rate NK	+ve
Parikh et al. (2012)	6	204	40.9	$>70\%$	$<55.0\%$	NS
Pellegrinelli et al. (2013)	16	55	43.5	63.0%-80.0%	NA	NS
Lobban et al. (2010)	6	96	45.0	$\sim 80.0\%^3$	52.0%	NS
<i>Present study</i>	5	121	44.0	80.0%	42.0%	NS

NK = Not Known; NA = Not applicable; NS = Not Significant. +ve = positive

\*relapse rate linearly interpolated for 12 months where not available.

<sup>1</sup> Only median and range data available: 6 episodes (2-25) in the experimental arm and 5 episodes (2-17) in the control arm

<sup>2</sup> In this sample 40% had only one episode of mania and 60% had a history of multiple episodes of mania.

<sup>3</sup> Only median and range data available: 16 episodes (2 to 30+) in the experimental arm and 20 episodes (3 to 30+) in the control arm.

## Implications

Psychoeducation is a standard of care in the management of bipolar patients (Goodwin and Consensus Group of the British Association for Psychopharmacology, 2009; Goodwin et al. 2016). The most apparently successful interventions have delivered input over many sessions in a group or family focussed setting, the demands of which may limit both acceptability for patients and feasibility for application in routine clinical care. Our 5-session intervention was adequate for acquisition of knowledge, which was itself associated with symptomatic benefit (i.e., weeks well). The increased knowledge observed in both treatment groups, however, indicates that there is likely to be a place for both facilitated approaches and self-education in acquiring the knowledge necessary to self-manage bipolar disorder. The provision of MIMM as an online guide linked to the TrueColours system is being implemented and could be included in subsequent studies.

Most previous studies have based claims for efficacy of psychoeducation on relapse prevention. Assessing symptomatic relapse and hospitalization can be complex and requires lengthier periods of follow-up. There is a need to move to more proximal measures to shorten the assessment period and facilitate much needed innovation. The OBQ is an example of how such measures, sensitive to a brief intervention, can be developed.

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### **Author Contributions**

GMG, JRG, DJM, JR, JP, JS, CH and EH designed the study. GMG, JRG and MV prepared the statistical analysis plan. DJM trained the study facilitators. Both DJM and JP provided facilitators with ongoing support. ACB, LZA and HCM collected the data and prepared it for analysis. MV conducted the analysis. ACB, LZA and GMG drafted the manuscript with support from HCM. All authors contributed to subsequent versions of the report and approved the final version. The trial was part of a programme grant jointly led by GMG and JRG.

### **Declaration of interest**

Dr. Bilderbeck has received salaries from P1vital Ltd. Dr. Goodwin reports grants and personal fees from Servier, personal fees from Teva, personal fees from Otsuka, personal fees from Takeda, grants and personal fees from Lundbeck, personal fees from Eli Lilly, personal fees from Merck, personal fees from GlaxoSmithKline, personal fees from Astra Zeneca, and grants from P1vital during the conduct of the study. Dr. Miklowitz reports grants from American Foundation for Suicide Prevention

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## REFERENCES

- Altman, E.G., Hedeker, D., Peterson, J.L., Davis, J.M., 1997. The Altman Self-Rating Mania Scale. *Biological psychiatry* 42, 948-955.
- Bopp, J.M., Miklowitz, D.J., Goodwin, G.M., Stevens, W., Rendell, J.M., Geddes, J.R., 2010. The longitudinal course of bipolar disorder as revealed through weekly text messaging: a feasibility study. *Bipolar Disord* 12, 327-334.
- Bourne, C., Bilderbeck, A., Drennan, R., Atkinson, L., Price, J., Geddes, J.R., Goodwin, G.M., 2015. Verbal learning impairment in euthymic bipolar disorder: BDI v BDII. *Journal of affective disorders* 182, 95-100.
- Candini, V., Buizza, C., Ferrari, C., Caldera, M.T., Ermentini, R., Ghilardi, A., Nobili, G., Pioli, R., Sabaudo, M., Sacchetti, E., Saviotti, F.M., Seggioli, G., Zanini, A., de Girolamo, G., 2013. Is structured group psychoeducation for bipolar patients effective in ordinary mental health services? A controlled trial in Italy. *J Affect Disord* 151, 149-155.
- Castle, D., White, C., Chamberlain, J., Berk, M., Berk, L., Lauder, S., Murray, G., Schweitzer, I., Piterman, L., Gilbert, M., 2010. Group-based psychosocial intervention for bipolar disorder: randomised controlled trial. *The British journal of psychiatry : the journal of mental science* 196, 383-388.
- Colom, F., Vieta, E., Martinez-Aran, A., Reinares, M., Goikolea, J.M., Benabarre, A., Torrent, C., Comes, M., Corbella, B., Parramon, G., Corominas, J., 2003a. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Archives of general psychiatry* 60, 402-407.
- Colom, F., Vieta, E., Reinares, M., Martinez-Aran, A., Torrent, C., Goikolea, J.M., Gasto, C., 2003b. Psychoeducation efficacy in bipolar disorders: Beyond compliance enhancement. *Journal of Clinical Psychiatry* 64, 1101-1105.

Colom, F., Vieta, E., Sanchez-Moreno, J., Martinez-Aran, A., Reinares, M., Goikolea, J.M., Scott, J., 2005. Stabilizing the stabilizer: group psychoeducation enhances the stability of serum lithium levels. *Bipolar Disord* 7 Suppl 5, 32-36.

de Barros Pellegrinelli, K., de, O.C.L.F., Silval, K.I., Dias, V.V., Roso, M.C., Bandeira, M., Colom, F., Moreno, R.A., 2013. Efficacy of psychoeducation on symptomatic and functional recovery in bipolar disorder. *Acta Psychiatr Scand* 127, 153-158.

Faurholt-Jepsen, M., Frost, M., Ritz, C., Christensen, E.M., Jacoby, A.S., Mikkelsen, R.L., Knorr, U., Bardram, J.E., Vinberg, M., Kessing, L.V., 2015a. Daily electronic self-monitoring in bipolar disorder using smartphones - the MONARCA I trial: a randomized, placebo-controlled, single-blind, parallel group trial. *Psychological medicine* 45, 2691-2704.

Faurholt-Jepsen, M., Ritz, C., Frost, M., Mikkelsen, R.L., Margrethe Christensen, E., Bardram, J., Vinberg, M., Kessing, L.V., 2015b. Mood instability in bipolar disorder type I versus type II-continuous daily electronic self-monitoring of illness activity using smartphones. *Journal of affective disorders* 186, 342-349.

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. *Journal of psychopharmacology* 23, 346-388.

Goodwin, G.M., Haddad, P.M., Ferrier, I.N., Aronson, J.K., Barnes, T., Cipriani, A., Coghill, D.R., Fazel, S., Geddes, J.R., Grunze, H., Holmes, E.A., Howes, O., Hudson, S., Hunt, N., Jones, I., Macmillan, I.C., McAllister-Williams, H., Miklowitz, D.R., Morriss, R., Munafo, M., Paton, C., Saharkian, B.J., Saunders, K., Sinclair, J., Taylor, D., Vieta, E., Young, A.H., 2016. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. *Journal of psychopharmacology* 30, 495-553.

Kessing, L.V., Hansen, H.V., Christensen, E.M., Dam, H., Gluud, C., Wetterslev, J., Affective, E.I., 2014. Do young adults with bipolar disorder benefit from early intervention? *J Affect Disorders* 152, 403-408.



Lam, D.H., Burbeck, R., Wright, K., Pilling, S., 2009. Psychological therapies in bipolar disorder: the effect of illness history on relapse prevention - a systematic review. *Bipolar disorders* 11, 474-482.

Lobban, F., Taylor, L., Chandler, C., Tyler, E., Kinderman, P., Kolamunnage-Dona, R., Gamble, C., Peters, S., Pontin, E., Sellwood, W., Morriss, R.K., 2010. Enhanced relapse prevention for bipolar disorder by community mental health teams: cluster feasibility randomised trial. *The British journal of psychiatry : the journal of mental science* 196, 59-63.

Marvin, S.E., Miklowitz, D.J., O'Brien, M.P., Cannon, T.D., 2014. Family-focused therapy for individuals at clinical high risk for psychosis: Treatment fidelity within a multisite randomized trial. *Early Interv Psychia*, No Pagination Specified.

Miklowitz, D.J., Goodwin, G.M., Bauer, M.S., Geddes, J.R., 2008. Common and specific elements of psychosocial treatments for bipolar disorder: a survey of clinicians participating in randomized trials. *Journal of psychiatric practice* 14, 77-85.

Miklowitz, D.J., Otto, M.W., Frank, E., et al., 2007. Psychosocial treatments for bipolar depression: A 1-year randomized trial from the systematic treatment enhancement program. *Archives of general psychiatry* 64, 419-426.

Miklowitz, D.J., Price, J., Holmes, E.A., Rendell, J., Bell, S., Budge, K., Christensen, J., Wallace, J., Simon, J., Armstrong, N.M., McPeake, L., Goodwin, G.M., Geddes, J.R., 2012a. Facilitated Integrated Mood Management for adults with bipolar disorder. *Bipolar Disord* 14, 185-197.

Miklowitz, D.J., Price, J., Holmes, E.A., Rendell, J., Bell, S., Budge, K., Christensen, J., Wallace, J., Simon, J., Armstrong, N.M., McPeake, L., Goodwin, G.M., Geddes, J.R., 2012b. Facilitated Integrated Mood Management for adults with bipolar disorder. *Bipolar Disord* 14, 185-197.

Paradiso, R., Bianchi, A.M., Lau, K., Scilingo, E.P., 2010. PSYCHE: personalised monitoring systems for care in mental health. *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Annual Conference* 2010, 3602-3605.

Parikh, S.V., Zaretsky, A., Beaulieu, S., Yatham, L.N., Young, L.T., Patelis-Siotis, I., Macqueen, G.M., Levitt, A., Arenovich, T., Cervantes, P., Velyvis, V., Kennedy, S.H., Streiner, D.L., 2012. A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: a Canadian Network for Mood and Anxiety treatments (CANMAT) study [CME]. *The Journal of clinical psychiatry* 73, 803-810.

Parikh, S., Zaretsky, A., 2012. A randomized controlled trial of psychoeducation or cognitive-behavioural therapy in bipolar disorder: a CANMAT study. *European Neuropsychopharmacology* 22, S290-S290.

Perry, A., Tarrier, N., Morriss, R., McCarthy, E., Limb, K., 1999. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. *Bmj* 318, 149-153.

Rea, M.M., Tompson, M.C., Miklowitz, D.J., Goldstein, M.J., Hwang, S., Mintz, J., 2003. Family-focused treatment versus individual treatment for bipolar disorder: results of a randomized clinical trial. *J Consult Clin Psychol* 71, 482-492.

Rush, A.J., Trivedi, M.H., Ibrahim, H.M., Carmody, T.J., Arnow, B., Klein, D.N., Markowitz, J.C., Ninan, P.T., Kornstein, S., Manber, R., Thase, M.E., Kocsis, J.H., Keller, M.B., 2003. The 16-item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological psychiatry* 54, 573-583.

Scott, J., Colom, F., Vieta, E., 2007. A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum* 10, 123-129.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development

and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry* 59 Suppl 20, 22-33;quiz 34-57.

Valenza, G., Gentili, C., Lanata, A., Scilingo, E.P., 2013. Mood recognition in bipolar patients through the PSYCHE platform: preliminary evaluations and perspectives. *Artificial intelligence in medicine* 57, 49-58.

Vallarino, M., Henry, C., Etain, B., Gehue, L.J., Macneil, C., Scott, E.M., Barbato, A., Conus, P., Hlastala, S.A., Fristad, M., Miklowitz, D.J., Scott, J., 2015. An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. *Lancet Psychiat* 2, 548-563.

Weisman, A.G., Okazaki, S., Gregory, J., Tompson, M.C., Goldstein, M.J., Rea, M., Miklowitz, D.J., 1998. Evaluating therapist competency and adherence to behavioral family management with bipolar patients. *Fam Process* 37, 107-121.

Yatham, L.N., Kennedy, S.H., Schaffer, A., Parikh, S.V., Beaulieu, S., O'Donovan, C., MacQueen, G., McIntyre, R.S., Sharma, V., Ravindran, A., Young, L.T., Young, A.H., Alda, M., Milev, R., Vieta, E., Calabrese, J.R., Berk, M., Ha, K., Kapczinski, F., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2009. *Bipolar Disord*.11, pp.

Study	Number of sessions	Sample size	Age	% sample at $\geq 7$ episodes	% Relapse rate (12 months)*	Clinical effect
Perry et al. (1999)	7 – 12	69	44.5	$\sim 50.0\%^1$	72.1%	+ve
Colom et al. (2003a)	21	120	34.0	45.8%	65.5%	+ve
Rea et al.(2003)	21	53	25.5	Low % <sup>2</sup>	49.1%	+ve
Castle et al. (2010)	12 – 15	84	42.1	NK	83.3%	+ve
Candini et al (Candini et al., 2013)	21	102	43.2	Low rates of previous hospitalization; episode history NK	20.0% hospitalization; relapse rate NK	+ve
Parikh et al. (2012)	6	204	40.9	$>70\%$	$<55.0\%$	NS
Pellegrinelli et al. (2013)	16	55	43.5	63.0%-80.0%	NA	NS
Lobban et al. (2010)	6	96	45.0	$\sim 80.0\%^3$	52.0%	NS
<i>Present study</i>	5	121	44.0	80.0%	42.0%	NS

**Table 2. Comparison of trials of psychoeducation interventions for Bipolar Disorder.**

NK = Not Known; NA = Not applicable; NS = Not Significant. +ve = positive

\*relapse rate linearly interpolated for 12 months where not available.

<sup>1</sup> Only median and range data available: 6 episodes (2-25) in the experimental arm and 5 episodes (2-17) in the control arm

<sup>2</sup> In this sample 40% had only one episode of mania and 60% had a history of multiple episodes of mania.

<sup>3</sup> Only median and range data available: 16 episodes (2 to 30+) in the experimental arm and 20 episodes (3 to 30+) in the control arm.

## FIGURE LEGENDS

**Figure 1.** Box and whisker plot of median, 25th percentile, 75th percentile, and range of depressive symptoms as measured with the OBQ (Oxford Bipolar Knowledge Questionnaire) at baseline, 3 months, and 12 months follow-up, for 121 participants with bipolar disorder randomly assigned to the FIMM intervention (Facilitated Integrated Mood Management; n=60) or to the MIMM intervention (Manualized Integrated Mood Management; n=61). Black dots represent outliers. \*significant difference between treatment conditions at  $p<0.05$ .