

**Psychological interventions for caregivers of people with bipolar disorder:
a systematic review and meta-analysis**

Dr Ella Baruch, University College London¹

Professor Nancy Pistrang, University College London

Professor Chris Barker, University College London

Version for UCL repository, dated 29 April 2018

Manuscript accepted for publication in the *Journal of Affective Disorders*. Please do not quote without authors' permission. The final article will be available, upon publication, via its doi: 10.1016/j.jad.2018.04.077

This research was based on the first author's 2017 thesis for the Doctorate in Clinical Psychology at University College London.

Address correspondence to Dr Ella Baruch: ella.baruch.14@ucl.ac.uk

¹ Department of Clinical, Educational and Health Psychology, University College London, 1-19 Torrington Place, London, WC1E 7HB. Email: ella.baruch.14@ucl.ac.uk. Tel: 020 8702 3100.

Abstract

Aims: Clinical guidelines recommend that psychological interventions be offered to caregivers of people with bipolar disorder. However, there is little clarity about the efficacy of such interventions. This review examined the efficacy of psychological interventions in improving caregiver-focused outcomes, including burden, psychological symptoms and knowledge.

Method: A systematic search for controlled trials was conducted using a combination of electronic database searches (PsycINFO, MEDLINE, and CENTRAL), and hand searches. Risk of bias was assessed using the Cochrane Collaboration tool. Outcomes were meta-analysed using Review Manager (RevMan).

Results: Nine studies met inclusion criteria. All meta-analyses compared psychoeducation to a control. At post-treatment there was a large effect of psychoeducation on burden ($g = -0.8$, 95% CI: -1.32, -0.27). However, there was high heterogeneity, confidence intervals were wide, and the effect was not maintained at follow-up. The apparent effect of psychoeducation on psychological symptoms was driven by a single outlying study. There was a very large effect on knowledge at post-treatment ($g = 2.60$, 95% CI: 1.39, 3.82) and follow-up ($g = 2.41$, 95% CI: 0.85, 3.98).

Limitations: There was considerable diversity in study methodology and quality. The number of included studies and sample sizes were small.

Conclusions: This review provides tentative meta-analytic evidence for the efficacy of psychoeducation in improving caregiver burden at post-treatment, and knowledge at post-treatment and follow-up. Services could consider offering psychoeducation as part of a multi-disciplinary package of care. However, more methodologically rigorous research is needed before clinical recommendations can be made with confidence.

Keywords: bipolar disorder; caregivers; systematic review; meta-analysis; psychoeducation.

Introduction

Caregivers of people with bipolar disorder can experience high levels of burden and significant psychological distress (Steele et al., 2010; Van der Voort et al., 2007). The majority report at least a moderate level of burden, with around 90% reporting high subjective burden in relation to their relative's symptoms (Perlick et al., 1999, 2007a). Caregiving is associated with increased risk of mental health problems, with up to 46% experiencing anxiety and depression (Steele et al., 2010). While clinical guidelines emphasise improving the experience of caregivers, there is a lack of clarity about the most effective ways to provide psychological support (NICE, 2014; National Collaborating Centre for Mental Health [NCCMH], 2014a).

Caregiver burden is a multidimensional concept, and there is considerable diversity in definition and operationalisation (Vella and Pai, 2012). Some definitions are based on a concept of global burden, defined as the emotional, social and financial stresses that caregiving imposes on the caregiver (Hoenig and Hamilton, 1967). Others distinguish between objective burden, which comprises the symptoms and behaviour of the patient and their consequences such as disruption of social, financial and occupational functioning; and subjective burden which refers to the psychological consequences of caregiving, such as distress and burnout (Cuijpers and Stam, 2000.; Schene, 1990).

Caregiving in bipolar disorder has been conceptualised within a 'stress-appraisal-coping' model (Chakrabarti and Gill, 2002; van der Voort et al., 2007). The level of burden and psychological symptoms experienced by caregivers may be linked to the severity of the patient's symptoms and the caregiver's level of social support (Perlick et al., 1999, 2007a, 2007b). However, caregiver appraisals may moderate the relationship between patient symptom severity and caregiver burden or psychological symptoms (Perlick et al., 1999; Steele et al., 2010). This may in part be due to how appraisals influence coping style (Chakrabarti and Gill, 2002; Perlick et al., 2007b). Lack of illness awareness (defined as understanding that symptoms are attributable to a mental illness requiring treatment) is associated with more frequent use of maladaptive coping strategies such as avoidance, and less frequent use of adaptive strategies such as positive communication (Chakrabarti and

Gill, 2002; Perlick et al., 2008). Appraisals of controllability are also linked to 'expressed emotion', defined as the expression of critical attitudes, hostility or emotional over-involvement (Leff and Vaughn, 1984; Wendel et al., 2000). This in turn is associated with negative patient outcomes such as increased relapse and symptom severity (Hooley, 2007; Kim and Miklowitz, 2004). However, research is predominantly cross-sectional, and the direction of causality between caregiver responses and illness severity is unclear (Hooley, 2007).

The 'stress-appraisal-coping' model implies the potential for interventions to reduce caregiver burden and psychological symptoms, through modification of appraisals and coping strategies and increasing social support. In accordance with this, NICE guidelines for bipolar disorder recommend psychological interventions to improve the experience of caregiving, including group psychoeducation and support groups (NICE, 2014). Support groups involve caregivers providing mutual support, and may be led by a peer or professional who facilitates interaction between group members. Psychoeducation may predominantly provide information about the nature, treatment and management of bipolar disorder, or can include more complex components such as increasing coping strategies, and teaching problem-solving and communication skills. The NICE guidelines do not explicitly recommend a particular type of psychological intervention, as the evidence that the recommendations are based on is described as being of low to moderate quality (NCCMH, 2014b). It is also important to note that the guidelines are based primarily on studies involving caregivers of people with psychosis and schizophrenia (NCCMH 2014a, 2014b).

There is some variation in how psychoeducational interventions are categorised in the literature (Oud et al., 2016; Reinares et al., 2016). However, a broad distinction can be made between interventions involving caregivers alone, such as group psychoeducation, and interventions involving caregivers and patients. Interventions involving caregivers and the index patient can be further sub-divided into those delivered in a group format, such as multi-family group psychoeducation and those delivered to individual families or dyads, such as family-focused therapy (Miklowitz & Goldstein, 1997). This is a modification of the Falloon

model of behavioural family therapy for schizophrenia (Falloon et al., 1984; Miklowitz and Goldstein, 1997). The primary aims are the reduction of expressed emotion and modification of associated appraisals, in order to reduce relapse (Miklowitz and Chung, 2016). However, there is a substantial overlap in the content of psychoeducational interventions, with many involving communication skills and problem-solving skills training, as well as basic psychoeducation (Reinares et al., 2016).

Despite the fact that psychological interventions often aim to improve caregiver outcomes through promoting coping strategies (Reinares et al., 2016), these are often not reported in reviews of the literature (e.g. Oud et al., 2016). To date there have been no reviews exclusively evaluating the impact of psychological interventions aiming to improve the experience of caregiving in bipolar disorder. In a wider review of family interventions for bipolar disorder, Reinares et al. (2016) reported that five trials of psychoeducation showed positive effects on caregiver knowledge, burden, and psychological symptoms, but did not meta-analyse study effects. A systematic review and meta-analysis of interventions for caregivers of those with severe mental illness found some evidence to support the efficacy of psychoeducation and support groups in improving the experience of caregiving (primarily operationalised within individual studies as burden) and reducing psychological symptoms (Yesufu-Udechuku et al., 2015). However, the review only evaluated interventions provided to caregivers alone, and was based predominantly on interventions for caregivers of people with psychosis. There were insufficient numbers of studies to meta-analyse findings for bipolar disorder.

The aim of the current review and meta-analysis is to critically evaluate and synthesise the impact of psychological interventions aiming to improve the experience of caregiving in bipolar disorder. The experience of caregiving is defined broadly as encompassing any carer-focused outcome, including burden, psychological symptoms or knowledge of bipolar disorder. This is the first review to focus exclusively on outcomes for caregivers of patients with bipolar disorder, and to use meta-analytic methods to synthesise study findings. Although there have been recent reviews in this area, new trials have been

published since this time, which enable the use of meta-analytic methods. In contrast to the most recent meta-analysis of caregiving (Yesufu-Udechuku et al., 2015), interventions involving caregivers alone and caregivers with the index patient will be included in the meta-analysis, thus increasing completeness and transparency of findings. In line with the literature on caregiving in bipolar disorder, the primary outcome variable will be caregiver burden. However, other relevant carer-focused outcomes, including psychological symptoms and knowledge of bipolar disorder, will also be synthesised. No reviews to date have evaluated the impact of psychological interventions on caregiver knowledge. Given that improving knowledge of bipolar disorder is a primary aim of psychoeducational interventions, and there has been found to be a relationship between illness awareness and coping style (Chakrabarti and Gill, 2002), this seems a significant gap in the literature. A further aim of the review is to assess the quality of the studies included in order to highlight possible areas for further research.

In summary, the review will address whether psychological interventions for caregivers are effective in:

1. reducing burden
2. Improving other caregiver-focused outcomes, including psychological symptoms and knowledge of bipolar disorder

Method

Inclusion criteria

Studies were selected based on the PICOS framework (Petticrew and Roberts, 2006):

- (1) *Population*. Informal caregivers of adults with a diagnosis of bipolar disorder. Caregivers included relatives, spouses, partners, friends or neighbours. Caregivers could be living with the person with bipolar or not. Where the study included caregivers or index patients under the age of 18, over 75% of caregivers and patients had to be

over the age of 18. Studies where the population had significant comorbidities, for example substance misuse, were excluded.

- (2) *Intervention*. Psychological interventions, including a psychological therapy, psychoeducational intervention, or support group aimed at improving the experience of caregiving. Interventions could involve the person with bipolar disorder as well as their caregiver, or caregivers alone. They could be delivered to individuals, couples, families or groups. They could be administered by any healthcare professional, such as psychologists, psychiatrists, family therapists and nurses.
- (3) *Comparator*. 'Treatment as usual', a waitlist control, or an alternative intervention, where this was clearly intended to be a control for the intervention of interest.
- (4) *Outcomes*. At least one quantitative caregiver-focused outcome, such as caregiver burden, psychological symptoms or knowledge. For studies where more than one diagnostic group took part, studies were included if disaggregated data were reported for caregivers of those with bipolar disorder.
- (5) *Study design*. Randomised and pseudo- randomised controlled trial design, with pre- and post- measures.
- (6) *Publication characteristics*. Primary research published in English in a peer-reviewed journal.

Search strategy

Four strategies were used to identify relevant studies:

- (1) The Ovid PsycINFO and Ovid MEDLINE databases were systematically searched on 12th October 2017. Search terms were developed for three main concepts: 'caregiver or family member', 'bipolar disorder', and 'psychological intervention' (see Supplementary Table 1). These were combined with Cochrane's highly sensitive search strategy for identifying randomised trials in Ovid MEDLINE (Higgins and Green, 2011). Terms referring specifically to drug trials ('placebo' and 'drug therapy') were removed. There is no equivalent Cochrane strategy for Ovid PsycINFO, so the MEDLINE strategy was adapted. Searches were conducted separately for each

concept as both a text word and medical subject heading ('MeSH') search, and then combined using the Boolean operator 'AND'. Studies were limited to those published in English in peer-reviewed journals.

(2) A broader search was conducted on the Cochrane Central Register of Controlled Trials (CENTRAL).

(3) Existing systematic reviews and meta-analyses were searched for further papers (Justo et al., 2007; Oud et al., 2016; Reinares et al., 2016; Yesufu-Udechuku et al., 2015.). Reviews were identified from the electronic searches and through searching the Cochrane database.

(4) The reference lists of identified studies were reviewed to identify any further papers.

Study selection

All studies were screened by title and abstract by EB. Ten percent of papers were cross-checked by CB, with inter-rater reliability calculated at 96%. If there was uncertainty whether a study met inclusion criteria, it was selected for full-text screening. Remaining studies were included or excluded after reviewing the full text. Where there was doubt over eligibility this was discussed among all three authors, and a consensus reached.

Data extraction

Data were extracted from the full text of studies that met inclusion criteria, and recorded in a data extraction form. Information extracted included study location, inclusion and exclusion criteria, participant characteristics, sample size, setting, nature and duration of the intervention and control, outcome measures, length of follow-up, and outcomes at post-treatment and follow-up. Where there were insufficient data reported to include studies in the meta-analysis, this was requested from study authors.

Assessment of risk of bias

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Higgins and Green, 2011). This assesses selection bias, which covers the method of random sequence generation and allocation concealment prior to assignment; performance bias, which covers blinding of participants and study personnel; detection bias, which covers

blinding of outcome assessors; attrition bias, which covers the level, nature and handling of incomplete outcome data; and reporting bias, which covers selective outcome reporting. Assessment was carried out by two reviewers independently (EB and CB), and any disagreement resolved through discussion. Review Manager (Revman) Version 5.3 was used to collate results.

Measures of treatment effect

RevMan was used to synthesise data and calculate overall estimates of treatment effect with 95% confidence intervals. Due to the heterogeneity of measures used, the standardised mean difference (SMD; Hedges' adjusted g ; Hedges, 1981) was used to standardise effect sizes using the following formula:

$$SMD_i = \frac{m_{1i} - m_{2i}}{s_i} \left(1 - \frac{3}{4N_i - 9} \right)$$

Hedges' g was used rather than Cohen's d (Cohen, 1988), as it adjusts for small sample bias (Borenstein et al., 2009). Effects were weighted by the inverse of variance. Random effects models were used to calculate composite effects. This approach takes into account the possibility of variability in population parameters among studies, thus allowing more robust conclusions to be drawn (Hunter and Schmidt, 2000). Given the likelihood of heterogeneity of behavioural, social and health science data, this approach also allows generalisation of meta-analytic findings (Field and Gillett, 2010; Hunter and Schmidt, 2000). Separate post-treatment comparisons were carried out for the three categories of outcome that emerged from the literature. Separate comparisons were carried out for follow-up data. In order to maintain consistency between studies, only follow-up periods of between six months and one year were included in the meta-analyses.

Visual inspection of forest plots and the associated chi-squared test were used to assess heterogeneity. As the chi-squared test has low power when studies have small sample sizes or are few in number, a threshold of .10 was used to determine statistical significance (Higgins and Green, 2011). As it can be argued that, due to methodological and clinical diversity, statistical heterogeneity is inevitable within a meta-analysis (Higgins et al.,

2003), inconsistency was also assessed using the I^2 statistic. An I^2 value of over 50% represents substantial heterogeneity and 75% high heterogeneity (Higgins and Green, 2011). In these cases reasons for heterogeneity were explored qualitatively. Reasons considered included clinical diversity, for example differences in participants and interventions, and methodological diversity, such as outcome measures and risk of bias. Where substantial heterogeneity was present, interpretation of results was based on confidence intervals rather than the average effect. As the meta-analysis included fewer than 10 studies, it was not appropriate to use funnel plots and associated significance tests and correction methods to assess publication bias (Higgins and Green, 2011).

Unit of analysis issues

In three-armed trials that included two active interventions and a control, the intervention that was more clearly focused on improving the experience of caregiving was treated as the intervention of interest, and included in the meta-analyses. Where studies reported results for subscales measuring both objective and subjective burden, which were not intended to be combined into a global burden score, subjective burden subscale scores were used in the meta-analysis, as this could be most reasonably be expected to change following an intervention.

Sensitivity analyses

The following sensitivity analyses were conducted in order to assess whether findings were robust to the methodological decisions made.

1. Separate comparisons were carried out for global burden, subjective burden, and objective burden, in order to assess the validity of combining global and subjective burden scores.
2. The influence of each study on the combined effect was assessed. It was reported where an outlying study had a substantial impact on heterogeneity, and reasons for this were considered.

Results

Study selection

Figure 1 shows the number of studies identified, examined and excluded at each stage. The combined electronic searches yielded 985 references; 318 duplicates were removed. A total of 667 references were screened and 653 excluded based on title and abstract. The most common reasons for exclusion were that bipolar disorder was not the main focus of the study, the study did not evaluate an intervention, or the study evaluated a drug treatment. Many studies were excluded based on multiple reasons. Fourteen references were screened and six excluded based on full-text screening. Reasons for exclusion are detailed in Figure 1. One additional eligible study was identified from the Cochrane database of randomised controlled trials. Hand searches of identified reviews and studies did not yield further eligible studies. The final number of studies included in the review was nine.

Description of studies.

The main characteristics of the nine included studies are summarised in Table 1. Studies were conducted in the United States (k=2), Europe (k=5), Brazil (k=1), and Australia (k=1). Six (67%) had been conducted since 2010. The most common constructs assessed were caregiver burden, psychological symptoms, and knowledge of bipolar disorder. Five studies also evaluated patient-focused outcomes, such as symptomatology and functioning. Eight studies were randomised controlled trials, and one had a pseudo-randomised design (Fiorillo et al., 2015). Eight had a two-arm trial design with one intervention arm and one control. One (Madigan et al., 2012) had a three-arm design, with two intervention arms and one control. The intervention that was more clearly focused on improving the experience of caregiving (psychoeducation) was treated as the intervention of interest. Four studies reported outcomes at post-treatment and follow-up, three at post-treatment only, and two at follow-up only.

Sample characteristics

For the majority of studies (k=7), only caregivers took part in the intervention. In two studies both caregivers and the index patient participated (Clarkin et al., 1990; Fiorillo et al., 2015), and in three patients' outcomes were reported but they did not participate. The

number of caregivers taking part ranged from 26 to 155 (median=46). The number of index patients participating or providing data ranged from 21 to 137 (median=40). One study did not report the number of caregivers participating or demographic features (Clarkin et al., 1990), and another did not report the number of patients participating (Madigan et al., 2012).

All studies recruited adult samples (mean age range of carers: 44.1- 53.3; mean age range of patients; 32.2- 47.1), aside from one (de Souza et al., 2016) which recruited caregivers aged 16 years or older and patients aged 16 to 35 years. The authors confirmed that all index patients and 52 (98%) of 53 caregivers were 18 or over. In all studies the majority of caregivers and patients were female (caregivers' range: 53%- 84%; patients' range: 63%- 67%). In the seven studies where the relationship between the caregiver and index patient was described, it was most common for caregivers to be parents (range: 28%- 71%) or spouses/partners (range: 6%- 100%) of the index patient. For the five studies which reported whether patients were diagnosed with type I or II bipolar disorder, the majority were diagnosed with type I bipolar disorder (range: 64%- 100%).

Intervention characteristics

All interventions were described as psychoeducational. Common components included education about the nature of bipolar disorder, triggers and warning signs, treatment, management, and the impact on and role of caregivers. Interventions aimed to teach coping strategies, communication skills, and problem-solving skills. The intervention reported by Perlick et al. (2010) placed a greater emphasis on reducing health risks associated with caregiving, and was more explicitly based on cognitive-behavioural principles. The psychoeducational family intervention reported by Fiorillo et al. (2015) was based on family-focused therapy (Miklowitz and Goldstein, 1997). The number of sessions ranged from 2 to 18, with durations ranging from 45 to 150 minutes. Five were delivered in a group format involving caregivers only, two through individual sessions with caregivers (de Souza et al., 2016; Perlick et al., 2010), and two through family sessions (Clarkin et al., 1990; Fiorillo et al., 2015). One intervention took place in an inpatient setting (Clarkin et al., 1990); the remainder took place in the community. Although seven studies reported that the

intervention was manualised, only two reported carrying out adherence checks (Hubbard et al., 2016; Perlick et al., 2010). Therapists discipline included psychology, psychiatry, family therapy, and nursing. Only two studies reported that therapists had received training and supervision (Fiorillo et al., 2015; Perlick et al., 2010).

Control or comparative intervention characteristics

Studies compared the active intervention to treatment as usual (k=5), a wait-list control (k=1), a wait-list control receiving treatment as usual (k=1), and no intervention (k=1). Treatment as usual included multidisciplinary care, pharmacological treatment, and informal contact between the caregiver and clinicians. A weakness of the included studies was that for the majority (k=8) the 'dosage' or therapeutic contact was lower than in the active arm. Five studies reported that the intervention arm also continued to receive treatment as usual. The comparative intervention reported in the only three-armed trial (Madigan et al., 2012) was 'solution-focused group psychotherapy', delivered to caregivers over five sessions. Intervention details and duration were not reported.

Outcome measures

Eight studies evaluated the impact of the intervention on caregiver burden. Three studies reported separate objective and subjective burden sub-scale scores, one reported only subjective burden scores, and four reported a global burden score. Five were self-report measures, and three assessor-rated. All measures had adequate to high reliability and validity, aside from one where this was not reported (Clarkin et al., 1990). Four studies evaluated the impact of the intervention on caregiver psychological symptoms; all measures were self-report and had good reliability and validity. Six studies evaluated the impact of the intervention on caregiver knowledge. Five measures were self-report and one assessor rated. One study reported high reliability of the measure (Hubbard et al., 2016), one adequate reliability (Kolostoumpis et al., 2015); the remaining four did not report reliability or validity. Other outcomes evaluated by individual studies included caregiver quality of life and self-esteem, health risk behaviour, psychosocial problems, social support, attitudes and

family relationships. These outcomes are reported in Table 1, but were not meta-analysed due to there being an insufficient number of studies.

Risk of bias

Figure 2 summarises risk of bias for individual studies. Supplementary figure 1 summarises risk of bias for all studies by domain. Five studies described an adequate method of random sequence generation, and were rated at low risk of bias. One study (Fiorillo et al., 2015) reported a consecutive allocation method, and so was rated a high risk. The remaining three studies were rated at unclear risk, as they did not clearly report the randomisation method. Two studies were rated at low risk of bias for allocation concealment, one at high risk due to use of consecutive allocation, and six were rated at unclear risk. All studies were at high risk of performance bias *per se*, as blinding of participants and personnel are not possible within psychoeducational interventions delivered face-to-face. Blinding of outcome assessors was clearly described in four studies and four used only self-report measures, and so were rated at low risk of detection bias. One study (Fiorillo et al., 2015) was rated at unclear risk, as it was not reported whether assessors were blinded.

Studies were rated at low risk of attrition bias if the level of attrition was unlikely to impact on the observed effect size (set at less than 20%) (Greenhalgh and Brown, 2014); if broadly equal numbers were retained in each group, reasons for attrition were given and were unlikely to be related to the true outcome; or if intention to treat (ITT) analyses were carried out (Higgins & Green, 2011). Six studies were rated as at low risk of bias. One study did not report whether attrition occurred (van Gent and Zwart, 1991), and so was rated at unclear risk of bias. The remaining two were rated at high risk of attrition bias for several of the above reasons.

The research protocol was only available for one study, which was rated at low risk of reporting bias due to reporting all pre-specified outcomes (Hubbard et al., 2016). Three studies were rated as at high risk of bias. Clarkin et al. (1990) did not report descriptive statistics, precluding inclusion in the meta-analysis. van Gent and Zwart (1991) did not report

statistics for non-significant findings. Perlick et al. (2010) measured both objective and subjective burden, but only reported subjective burden scores. The remaining five studies were rated as at unclear risk of bias as the research protocol was not available, and no clear statement was made that all measured outcomes had been reported.

Intervention effects

All meta-analyses were for psychoeducation compared to a control. One study did not report sufficient data to allow inclusion in the meta-analysis (Clarkin et al., 1990).² Only three studies reporting outcomes at follow-up between 6 months and one year were included in the relevant meta-analyses. The remaining follow-up periods of 1 month (Hubbard et al., 2016) and 2 years (Madigan et al., 2012) were too diverse to be meaningfully combined in the analyses. Unless otherwise stated estimates favour the intervention over the control where the standardised difference is negative ($g < 0$). Individual effects for a comparison between psychoeducation and an active intervention are summarised below.

Psychoeducation vs control: burden at post-treatment

The first meta-analysis examined the effect of psychoeducation on caregiver burden at post-treatment. Six studies were included, comprising 379 participants (see Figure 3). Overall, there was a large combined effect of the intervention, $g = -0.8$ (95% CI: -1.32, -0.27). However, confidence intervals were wide, ranging from a small to large effect, and there was evidence of high heterogeneity, $\chi^2(5) = 26.18$, $p < .001$, $I^2 = 81\%$.

The confidence intervals for four studies ranged from a small to large effect of psychoeducation, while one showed no effect (de Souza et al., 2016). Kolostoumpis et al. (2015) reported a substantially larger effect size than the other studies, and this appeared to be due to very small standard deviations for both the intervention (SD = 1.93) and control (SD = 2.16) (for example, compared to the values reported by Hubbard et al. (2016) for a

² The authors were contacted for this information, but were unable to provide it within the necessary timeframe.

scale with a similar range) [intervention SD = 9.12; control SD = 8.57].³ Excluding this study reduced heterogeneity to $I^2 = 43%$, $g = -0.56$ (95% CI: -0.90, -0.22), although confidence intervals remained wide.

As shown in Table 2, sensitivity analyses showed that the combined effect size differed quite substantially depending on the type of measure of burden used. The combined effect for global burden was large, with evidence of moderate heterogeneity. Confidence intervals were large but the lower bound was still compatible with a large effect. The combined effect for subjective burden was small to moderate, with low evidence of heterogeneity. Confidence intervals for objective burden were compatible with both a reduction and increase in burden, and there was evidence of substantial heterogeneity.

Psychoeducation vs control: burden at follow-up

Three studies were included in the meta-analysis of the effect of psychoeducation on caregiver burden at follow-up, comprising 137 participants (see Figure 4). Overall there was a large combined effect of the intervention, $g = -1.22$ (95% CI: -3.19, 0.75). However, confidence intervals were compatible with a reduction and increase in burden, and there was evidence of high heterogeneity, $\chi^2 (2) = 43.01$, $p < .001$, $I^2 = 95%$.

Psychoeducation vs control: psychological symptoms at post-treatment

Three studies were included in the meta-analysis of the effect of psychoeducation on caregiver psychological symptoms at post-treatment, comprising 155 participants (see Figure 5). Overall there was a large combined effect of the intervention, $g = -1.76$ (95% CI: -4.21, 0.70). However, again this was largely driven by the effect for Kolostoumpis et al. (2015). Confidence intervals were compatible with both a reduction and increase in symptoms, and there was evidence of high heterogeneity, $\chi^2 (2) = 70.78$, $p < .001$, $I^2 = 97%$. The substantially larger effect size reported by Kolostoumpis et al. (2015) may again have been due to very small standard deviations (intervention SD = 1.51; control SD = 1.89).

³ The authors were contacted for clarification about possible reasons for this, but did not respond. Other possible methodological reasons for the outlying effect are explored in the discussion section.

Excluding this effect reduced heterogeneity to $I^2 = 5\%$, $g = -0.42$ (95% CI: -0.90, 0.05).

However, confidence intervals ranged from no effect to a large effect of the intervention.

Psychoeducation vs control: psychological symptoms at follow-up

Two studies were included in the meta-analysis of the effect of psychoeducation on caregiver psychological symptoms at follow-up, comprising 101 participants (see Figure 6). Overall there was a very large combined effect of the intervention, $g = -2.44$ (95% CI: -5.91, 1.03). However, again this was driven by the large effect reported for Kolostoumpis et al. (2015). Confidence intervals were compatible with both a reduction and increase in symptoms, and there was evidence of high heterogeneity, $\chi^2 (1) = 32.94$, $p < .001$, $I^2 = 97\%$.

Psychoeducation vs control: knowledge at post-treatment

Four studies were included in the meta-analysis of the effect of psychoeducation on caregiver knowledge at post-treatment, comprising 183 participants (see Figure 7). All studies reported a combined score, with the exception of one study (van Gent and Zwart, 1991), which reported separate scores for knowledge of the illness, lithium and management strategies. For the purpose of the meta-analysis these were combined into a single mean and standard deviation for each group. Effect estimates favour the intervention over the control where the standardised difference is positive ($g > 0$).

All studies reported large effect sizes. There was a very large combined effect of the intervention, $g = 2.60$ (95% CI: 1.39, 3.82). Confidence intervals were wide, but the lower bound was compatible with a large effect. However, there was evidence of high heterogeneity, $\chi^2 (3) = 24.52$, $p < .001$, $I^2 = 88\%$. Excluding the substantially larger effect of Kolostoumpis et al. (2015) reduced heterogeneity to $I^2 = 0\%$, and the combined effect remained very large $g = 2.00$ (95% CI: 1.51, 2.49). However, reasons for the larger effect reported by Kolostoumpis et al. (2015) were unclear, as standard deviations were similar to those reported in another study for a scale with the same range (Reinares et al., 2004).

Psychoeducation vs control: knowledge at follow-up

Three studies were included in the meta-analysis of the effect of psychoeducation on caregiver knowledge at follow-up, comprising 127 participants (see Figure 8). Overall, there

was a very large combined effect of the intervention, $g = 2.41$ (95% CI: 0.85, 3.98). Although confidence intervals were wide, the lower bound was compatible with a large effect. There was evidence of high heterogeneity, $\chi^2(2) = 18.31$, $p < .001$, $I^2 = 89\%$. Excluding the substantially larger effect of Kolostoumpis et al. (2015) reduced heterogeneity to $I^2 = 0\%$, and the combined effect remained very large $g = 1.66$ (95% CI: 0.97, 2.34).

Comparison between psychoeducation and an active intervention

Madigan et al. (2012) was the only study to compare two active interventions: psychoeducation and solution-focused group psychotherapy. At one year follow-up, for knowledge confidence intervals ranged from no effect to a large effect in favour of solution-focused group psychotherapy, $g = 0.80$ (95% CI: 0.01, 1.59). For burden, $g = -0.40$ (95% CI: -1.17, 0.36) and psychological symptoms, $g = -0.37$ (95% CI: -1.13, 0.39), confidence intervals were compatible with both a superior and inferior effect of psychoeducation relative to solution-focused group psychotherapy.

Discussion

The review included nine studies, although only eight could be included in the meta-analyses. All interventions were psychoeducational. Seven were delivered to caregivers without the index patient; five in a group format, and two to individual caregivers. The remaining two studies evaluated family interventions, one in an inpatient setting (Clarkin et al., 1990) and one in an outpatient clinic (Fiorillo et al., 2015). This was an adaptation of family-focused therapy, based on the Falloon model of behavioural family therapy (Falloon et al., 1984; Miklowitz and Goldstein, 1997).

The current review provides some meta-analytic evidence for the efficacy of psychoeducation in reducing caregiver burden and improving knowledge of bipolar disorder. For psychoeducation compared to a control, there was evidence of a small to large effect on burden at post-treatment. When the outlying effect for Kolostoumpis et al. (2015) was removed from the analysis the combined effect remained moderate. However, sensitivity analyses showed that the effect varied according to the type of measure used; for studies

using a global burden measure the effect was large, the effect for subjective burden was small to moderate, and there was no effect for objective burden. It may be that psychoeducational interventions are unlikely to impact on the objective realities of caregiving, but do impact on caregivers' subjective experience. The results for burden at follow-up are inconclusive, as the large combined effect was predominantly driven by the effect reported by Kolostoumpis et al. (2015). It could be that contact with professionals and other caregivers reduces burden in the short-term, but interventions are not sufficient to sustain this in the long-term. However, further research is needed to clarify this.

There was a very large effect on knowledge at post-treatment and follow-up, and the effect remained large when Kolostoumpis et al. (2015) was removed from the analysis, which removed any statistical heterogeneity. However, due to lack of information about reliability and validity for the majority of measures used, these results should be interpreted with caution. Clinically, it is also not clear how much gaining knowledge enhances the experience of caregiving. However, theoretically within a stress-appraisal-coping model it seems plausible that greater knowledge could lead to more adaptive appraisals and coping strategies, and there is evidence to suggest that increased awareness of the illness is associated with more adaptive coping (Chakrabarti and Gill, 2002). The effect of psychoeducation on psychological symptoms at both post-treatment and follow-up was large, but these effects were primarily driven by a single outlying study, and due to the small number of studies included in these analyses it is difficult to interpret these results.

For all the meta-analyses, heterogeneity reduced substantially when the results of Kolostoumpis et al. (2015) were removed. Possible reasons for the outlying size of the effects are that the intervention was compared with pharmacotherapy alone rather than multi-disciplinary care, or the comparatively higher number of patients with a less severe Type 2 bipolar diagnosis (37%), which could have made it more possible for caregivers to assimilate and implement new strategies and information. The study was also at unclear risk of attrition bias, which could have led to overestimation of effects (Higgins and Green, 2011). As noted, the standard deviations were low compared to those reported in a study using a

scale with a similar range, but reasons for this were unclear. Only one study showed no effect on burden (de Souza et al., 2016). This study included caregivers of adults aged 16 to 35, and caregivers aged 16 or older. Although only one caregiver was below the age of 18 and the average age of caregivers was similar to that of other studies, it is likely that the average age of patients was considerably lower.⁴ It may be that the sample was representative of a different population to that of other studies. There is some evidence to support the efficacy of family-focused therapy for adolescents on patient outcomes (Frías et al., 2015). It may be that interventions with a greater emphasis on improving family functioning are also more effective in improving the experience of caregivers of young adults. The study was also one of the lower quality studies, and was rated at unclear or high risk of bias in three of five domains. This may have influenced findings, although bias is more commonly associated with over-estimation of effects (Higgins and Green, 2011).

The results summarised above are derived principally from comparisons between psychoeducation and a non-active control. It is important to note that one study (Madigan et al., 2012) found that when psychoeducation was compared to an active intervention (solution-focused group psychotherapy), there was no effect for burden or psychological symptoms, and a large effect for knowledge in favour of the comparator, although the lower bound of the confidence intervals was compatible with no effect. It may be that, although psychoeducation brings some benefits compared to a control, it is not superior to an intervention with a similar level of therapeutic contact. Given that this is the finding of a single study and few details were given about the comparative intervention, it is difficult to draw clear conclusions.

The findings of this review are in line with that of the most recent meta-analysis of caregiving in severe mental illness (Yesufu-Udechuku et al., 2015), which found a large effect of psychoeducation on the experience of caregiving (largely operationalised as burden) at post-treatment, but no effect for psychological symptoms. However, the current

⁴ This information was requested but was not available.

review found no effect for burden at follow-up, whereas large effects were reported by the previous review. This may be a function of the different diagnostic groups included, or differences in how follow-up periods were combined. The finding that there was a more robust combined effect for knowledge compared to burden or psychological symptoms is in line with a previous review of interventions for caregivers of people with psychosis (Lobban et al., 2013). This may reflect the fact that the majority of interventions appeared to place a greater emphasis on management of the illness and improving family-functioning, rather than improving caregiver distress or self-care. It may be that interventions continue to be informed predominantly by the expressed emotion and relapse-prevention literature, even when caregiver outcomes are reported within studies as primary or of equivalent importance to patient outcomes.

Limitations

Overall there was substantial heterogeneity between studies, confidence intervals were wide, and some of the included studies had substantial methodological limitations. It is therefore difficult to draw firm conclusions from the results of the meta-analyses. However, statistical heterogeneity seemed to be primarily driven by one study (Kolostoumpis et al., 2015), and aside from those reported by de Souza et al. (2016) study effects were consistently positive for burden and knowledge. The included studies were also fairly methodologically diverse in terms of study quality, mode of delivery, the nature of the comparator, and the severity and type of bipolar disorder. There was also diversity in terms of the measures used, for burden in particular. The number and duration of sessions was variable, and the length of follow-up was inconsistent, making it difficult to draw clear conclusions about long-term efficacy of interventions. However, there was fairly high consistency in terms of the content and aims of the intervention, demographic features of caregivers and patients, and exclusion criteria.

Three studies differed in particularly substantial ways, and difficult methodological decisions had to be made about their inclusion in the meta-analyses. The possible difference of the study population for de Souza et al. (2016) is outlined above. The inclusion criteria for

Pelick et al. (2010) differed in that only caregivers showing mental or physical health problems were included. Another (Fiorillo et al., 2015) was the only study to evaluate a family intervention and have a pseudo-randomised design. In order to increase transparency and completeness, these studies were included in the review, and it is also worth noting that the effects reported by two of these (Fiorillo et al., 2015; Perlick et al., 2010) were relatively consistent with that of other studies.

In an under-researched area it is of value to combine a relatively small number of studies with some methodological differences in order to gain a preliminary estimate of the efficacy of psychoeducational interventions (Claxton et al., 2017; Oud et al., 2016; Sin et al., 2017). However, it must be acknowledged that the results were limited by methodological and statistical heterogeneity, and the small number of studies included in the meta-analyses, particularly at follow-up and for psychological distress. A key finding of the review is therefore the need for further, more methodologically rigorous research and greater consistency in terms of study design (further outlined below).

Other limitations of the review include the fact that only databases holding published studies were searched, and it was not possible to assess publication bias. Given the wide confidence intervals for the majority of results, it may only have taken a few null findings to make the effects non-significant. Only English-language studies were included, which may have reduced generalisability, although studies were carried out in diverse locations. Generalisability may also be limited in that five of the studies used community samples, which could differ in significant ways from clinical populations. However, the inclusion of a quasi-randomised study carried out in mental health clinics (Fiorillo et al., 2015) may have increased external validity, and is in line with Cochrane guidance (Higgins and Green, 2011). The review as a whole may have been underpowered due to the small number of studies and small sample sizes, or conversely large effect sizes may have been due to chance small-study effects.

The studies included in the review had methodological weaknesses, and there is therefore a risk of biased findings. Two were rated as at high or unclear risk of bias in five of

the six domains. There was no clear link between individual study bias and effect size, aside from two studies at higher risk of bias reporting outlying effects, although these were in opposite directions. Other methodological weaknesses included the small sample size of the majority of studies, which may have led to lack of precision of estimates and increased heterogeneity. Lack of therapist fidelity may have influenced results; the majority did not report manualisation, adherence checks, or therapist training and supervision. The majority of measures of psychological symptoms and burden were reliable and valid, but this was not reported for the majority of measures of knowledge. The control condition was not well-specified for several studies, and four did not report whether the intervention arm continued to receive treatment as usual. Effects may therefore have reflected the influence of concurrent interventions. Overall, the results of the review should be approached with caution due to these limitations.

Implications for research and clinical practice

A key finding of the review is that the existing literature has considerable methodological limitations. Future research would therefore benefit from increased methodological rigour in terms of randomisation methods and allocation concealment. It would also be helpful for the nature of intervention and control conditions to be reported with greater clarity, and for trial protocols to be published and outcomes specified in advance. Studies with greater power and the use of reliable and valid measures are also needed in order to improve precision of findings.

In terms of addressing diversity between studies, it would be helpful for a consensus to be reached about the most meaningful outcomes to be targeted by interventions and the most valid measures, particularly in terms of burden. For example, it may be that interventions are unlikely to substantially improve objective burden, and measures of subjective burden should be used to evaluate efficacy. Qualitative research could be useful in exploring the needs of caregivers and their experiences of interventions. In particular, it could be helpful to explore how caregivers perceive the balance struck within interventions between improvement of illness-management and family functioning versus caregiver well-

being and coping. Greater homogeneity in terms of the length of follow-up would allow more robust conclusions to be drawn about long-term efficacy.

Future studies might compare family with caregiver-focused interventions. Trials of other interventions recommended in clinical guidelines (NICE, 2014), such as support groups, would help to increase understanding of the most effective support for caregivers. Given the finding that there was no effect of psychoeducation when compared to another psychotherapeutic intervention, further studies are needed which compare psychoeducation to an intervention with an equivalent level of therapeutic contact.

Despite the most prominent models of caregiving using a stress-appraisal-coping framework, only one study (Perlick et al., 2010) assessed the role of coping style as a mediator of treatment outcome, and found that change in caregiver depression was partially mediated by changes in avoidance coping. Future research could assess the role of appraisals, knowledge and coping style as mediators or moderators of treatment effect on burden and psychological symptoms. Other moderator variables could also be explored, such as patients' clinical severity and age, and whether the intervention is delivered in an individual, group or family format.

This review provides tentative evidence that psychoeducation is effective in reducing caregiver burden at post-treatment and improving knowledge at post-treatment and follow-up. Services could therefore consider offering psychoeducation as part of multi-disciplinary care for people with bipolar disorder and their families. Due to diversity in terms of the format of interventions and the small number of studies, it is not possible to recommend interventions involving patients over those involving caregivers alone, or a particular duration of treatment. The majority of interventions were delivered in a group format, although individual and family psychoeducation were also shown to be effective. The lack of an effect for psychological symptoms could suggest that more targeted interventions are needed to address the needs of caregivers experiencing greater levels of distress. Despite the lack of clarity about the most effective support for caregivers, the review certainly raises the

importance of assessing caregivers' needs, and offering appropriate support where this is required.

Acknowledgements

We thank Amanda Williams who provided consultation on carrying out the meta-analysis.

Table 1 *Study Characteristics*

Author (year) and country	Caregiver characteristics	Patient participation and characteristics	Intervention	Control/comparative treatment	Outcome: post-treatment	Outcome: follow-up
Clarkin et al. 1990 USA	Families of voluntary inpatients Demographics not reported	Participated in intervention N = 21 Female = 67% Age: <i>M</i> = 32.3	Psychoeducational inpatient family intervention plus standard multimodal hospital treatment Duration: At least 6 x 45-60 mins <i>n</i> = 12	Standard multimodal hospital treatment <i>n</i> = 9	Not reported	6 months: No between-group differences for burden, attitude to the patient or quality of life 18 months: Small improvement in attitude towards treatment in the intervention group
de Souza et al. 2016 Brazil	Volunteers from allied research study Total <i>N</i> = 53 Female = 79% Age: <i>M</i> = 44.1	NA	Individual psychoeducation. Duration: 6 x 90 minutes. <i>n</i> = 25	TAU <i>n</i> = 28	No between-group differences in subjective, burden, objective burden, self-esteem or quality of life	6 months: No between-group differences.
Fiorillo et al. 2015 Italy	Families of clinic attendees <i>N</i> = 155 Female = 54% Age: <i>M</i> = 51.9	Participated in intervention <i>N</i> = 137 Female = 63% Age: <i>M</i> = 47.1 Type I BD = 100%	Psychoeducational family intervention plus treatment as usual (TAU) Duration: 12-18 x 90 minutes. Caregiver <i>n</i> = 85. Patient <i>n</i> = 70	Wait list/TAU Caregiver <i>n</i> = 70 Patient <i>n</i> = 67	Greater improvement in subjective burden, objective burden and social support in the intervention group compared to the control.	Not reported.

Hubbard et al. 2016 Australia	Recruited through radio, clinics and university. Total <i>N</i> = 32 Female = 58% Age: <i>M</i> = 48.1	NA	Group psychoeducation Duration: 2 x 150 minutes <i>n</i> = 18	Wait list <i>n</i> = 14	Greater improvement in burden, knowledge and self-efficacy in the intervention group. No improvement in psychological symptoms.	One month Greater improvement in burden and knowledge from pre-intervention to follow-up, but not from post-intervention to follow-up in the intervention group.
Kolostoumpis et al., 2015 Greece	Recruited from nongovernmental organisation Caregivers <i>N</i> = 80 Female = 69% Age: <i>M</i> = 53.3 Patients: Type I BD = 64%	NA	Group psychoeducation plus standard pharmacotherapy Duration: 7 x 120 minutes <i>n</i> = 40	Standard pharmacotherapy <i>n</i> = 40	Greater improvement in knowledge, burden, and psychological symptoms in the intervention group.	Six month. Greater improvement in knowledge, burden, and psychological symptoms in the intervention group.
Madigan et al. 2012 Ireland	Recruited through media and mental health services.) Caregivers: <i>n</i> = 47 Female = 53% Age: <i>M</i> = 52.0	Patients provided data N not reported Female = 65% Age: <i>M</i> = 42 Type 1 BD = 100%	Group psychoeducation Duration: 5 x 120 minutes <i>n</i> = 18	1. TAU <i>n</i> = 10 2. Solution focused group psychotherapy Duration: 5 sessions (length not stated) <i>n</i> = 19	Not reported	1 year and 2 years. Geater improvement in burden, knowledge and psychological symptoms ⁵ in the psychoeducation group compared to the control. No differences between the two intervention groups.

⁵ Although Madigan et al. (2012) reported a statistically significant effect for psychological symptoms, the direct calculation of the confidence intervals for the effect within this meta-analysis showed that they overlapped zero (see figure 7).

Perlick et al. 2010 USA	Recruited from mental health services and support group. Caregivers: $n=43$ Female = 84% Age: $M=52.8$ Patients	Patients provided data $n=40$ Female = 63% Age $M=34.7$ Type 1 BD = 80%	Individual psychoeducation Duration: 12-15 x 45 mins $n=24$	Caregiver health education intervention delivered via DVD. Duration: 8-12 x 20-25 minutes. $n=19$	Greater reductions in burden, psychological symptoms, and health risk behaviour in the intervention group.	Not reported
Reinares et al. 2004 Spain	Recruited from outpatient clinic. Total $N=45$. Female = 76% Age: $M=48.5$	Patients did not participate Type 1 BD = 79%	Group psychoeducation Duration: 12 x 90 minute sessions. $n=30$	Standard pharmacological treatment. $n=15$	Greater improvement in subjective burden and knowledge in the intervention group. No differences in objective burden, patient relatedness or family relationships.	Not reported.
van Gent and Zwart 1991 The Netherlands	Recruited from outpatient clinic. Partners: $n=26$ Age: $M=48.5$	Patients provided data Patients: $n=26$ Age: $M=33.16$ Gender not reported	Group psychoeducation. Duration: 5 sessions. Session length not reported. $n=14$	No intervention. $n=12$	Greater improvement in knowledge in the intervention group. No differences in relationship problems or psychosocial problems.	6 months. Greater improvements in knowledge in the intervention group compared to the control were maintained.

Table 2

Sensitivity Analysis for Measures of Burden at Post-treatment

Measure of burden	Number of studies (author names and date)	Combined effect	95% Confidence Interval	Heterogeneity effect χ^2 (p)	Inconsistency I^2
Global burden	2 (Hubbard et al., 2016; Kolostoumpis et al., 2015)	-1.58	-2.20, -0.95	1.87 (p=0.17)	46%
Subjective burden	4 (de Souza et al. 2016; Fiorillo et al., 2015; Perlick et al., 2010; Reinares et al., 2004)	-0.47	-0.77, -0.16	3.96 (p=0.27)	24%
Objective burden	3 (de Souza et al. 2016; Fiorillo et al., 2015; 2010; Reinares et al., 2004)	-0.03	-0.46, 0.51	5.16 (p=0.08)	61%

References

1. Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H., 2009. Introduction to meta-analysis. John Wiley & Sons, Chichester.
2. Chakrabarti, S., Gill, S., 2002. Coping and its correlates among caregivers of patients with bipolar disorder: a preliminary study. *Bipolar Disord.* 4, 50–60.
doi:10.1034/j.1399-5618.2002.01167.x
3. Clarkin, J., Glick, I., Haas, G., 1990. A randomized clinical trial of inpatient family intervention V. Results for affective disorders. *J. Affect. Disord.* 18, 17-28.
4. Claxton, M., Onwumere, J., Fornells-Ambrojo., 2017. Do family interventions improve outcome in early psychosis? A systematic review and meta-analysis. *Front Psychiatry.* 8, 371.
5. Cohen, J., 1988. Statistical power analysis for the behavioural sciences, second ed. Lawrence Earlbaum Associates, Hillside. NJ.
6. Cuijpers, P., Stam, H., 2000. Burnout among relatives of psychiatric patients attending psychoeducational support groups. *Psychiatr. Serv.* 51, 375-9.
7. de Souza, M.S., da Silva, R.A., Molina, M.A.L., Jansen, K., de Lima Ferreira, L., Kelbert, E.F., Soares, J.M., de Mattos Souza, L.D., 2016. Six-session caregiver psychoeducation on bipolar disorder: Does it bring benefits to caregivers? *Int. J. Soc. Psychiatry* 62, 377–385. doi:10.1177/0020764016636909
8. Falloon, I. R., Boyd, J. L., & McGill, C. W., 1984. Family care of schizophrenia: A problem-solving approach to the treatment of mental illness. Guildford, New York.
9. Field, A.P., Gillett, R., 2010. How to do a meta-analysis. *Br. J. Math. Stat. Psychol.* 63, 665–694. doi:10.1348/000711010X502733
10. Fiorillo, A., Del Vecchio, V., Luciano, M., Sampogna, G., De Rosa, C., Malangone, C., ... Iapichino, S., 2015. Efficacy of psychoeducational family intervention for bipolar I disorder: a controlled, multicentric, real-world study. *J. Affect. Disord.* 172, 291-299.
11. Frías, Á., Palma, C., Farriols, N., 2015. Intervenciones psicosociales en el

- tratamiento de los jóvenes diagnosticados o con alto riesgo para el trastorno bipolar pediátrico: una revisión de la literatura. *Rev. Psiquiatr. Salud Ment.* 8, 146–156.
doi:10.1016/j.rpsm.2014.11.002
12. Greenhalgh, J & Brown, T, 2013. What tools do i use to quality assess my studies?, in: Boland, A., Cherry, G., Dickson, R. (Eds.), *Doing a systematic review: a student's guide* (pp. 61-84). Sage, London.
 13. Hedges, L. V., 1981. Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Behav Stat.* 6, 107-128.
 14. Higgins, J. P., Thompson, S. G., Deeks, J. J., Altman, D. G., 2003. Measuring inconsistency in meta-analyses. *Br Med J.* 327, 557.
 15. Higgins, J.P.T., Green, S., (2011). *Cochrane Handbook for Systematic*
 - a. *Reviews of Interventions Version 5.1.0 [updated March 2011].*
 16. <http://handbook.cochrane.org> (accessed 13 January 2018)
 17. Hoenig, J., Hamilton, M. W., 1967. The burden on the household in an extramural psychiatric service, in Freeman, H. (Ed.), *New aspects of the mental health services.* Pergamon., London, pp. 612-635.
 18. Hooley, J.M., 2007. Expressed emotion and relapse of psychopathology. *Annu. Rev. Clin. Psychol.* 3, 329–352. doi:10.1146/annurev.clinpsy.2.022305.095236
 19. Hubbard, A., McEvoy, P., Smith, L., Disorders, R.K., 2016. Brief group psychoeducation for caregivers of individuals with bipolar disorder: A randomized controlled trial. *J. Affect. Disord.* 200, 31-36
 20. Hunter, J.E., Schmidt, F.L., 2000. Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge. *Int. J. Sel. Assess.* 8, 275–292. doi:10.1111/1468-2389.00156
 21. Justo, L., Soares, B.G. de O., Calil, H., 2007. Family interventions for bipolar disorder. *Cochrane Database Syst. Rev.* doi:10.1002/14651858.CD005167.pub2
 22. Kim, E. Y., & Miklowitz, D. J., 2004. Expressed emotion as a predictor of outcome among bipolar patients undergoing family therapy. *J. Affect. Disord.* 82, 343-352.

23. Kolostoumpis, D., Bergiannaki, J.D., Peppou, L.E., Louki, E., Fousketaki, S., Patelakis, A., Economou, M.P., 2015. Effectiveness of relatives' psychoeducation on family outcomes in bipolar disorder. *Int. J. Ment. Health.* 44, 290–302.
doi:10.1080/00207411.2015.1076292
24. Leff, J., Vaughn, C., 1984. *Expressed emotion in families: Its significance for mental illness.* The Guildford Press, New York.
25. Lobban, F., Postlethwaite, A., Glentworth, D., Pinfold, V., Wainwright, L., Dunn, G., ... & Haddock, G., 2013. A systematic review of randomised controlled trials of interventions reporting outcomes for relatives of people with psychosis. *Clin Psychol Rev.* 33, 372-382.
26. Madigan, K., Egan, P., Brennan, D., Hill, S., Maguire, B., Horgan, F., ... & O'Callaghan, E. , 2012. A randomised controlled trial of carer-focussed multi-family group psychoeducation in bipolar disorder. *Eur Psychiatry*, 27, 281-284.
27. Miklowitz, D. J., Goldstein, M. J., 1997. *Bipolar disorder: A family-focused approach.* Guilford, New York.
28. Miklowitz, D.J., Chung, B., 2016. Family-focused therapy for bipolar disorder: reflections on 30 years of research. *Fam. Process* 55, 483–499.
doi:10.1111/famp.12237
29. NICE, 2014. *Bipolar disorder: the assessment and management of bipolar disorder in adults, children and young people in primary and secondary care.*
<https://www.nice.org.uk/guidance/cg185> (accessed 29/9/2017)
30. NCCMH, 2014a. *Bipolar Disorder: the Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care [full guideline].*
<https://www.nice.org.uk/guidance/cg185/evidence/full-guideline-pdf-193212829>
(accessed 29/9/2017)
31. NCCMH, 2014b. *Psychosis and schizophrenia in adults: treatment and management [full guideline].* <https://www.nice.org.uk/guidance/cg178/evidence/full-guideline-490503565> (accessed 29/9/2017)

32. Oud, M., Mayo-Wilson, E., Braidwood, R., Schulte, P., Jones, S. H., Morriss, R., ... & Kendall, T. (2016). Psychological interventions for adults with bipolar disorder: systematic review and meta-analysis. *Br J Psychiatry*. 208, 213-222.
33. Perlick, D., Clarkin, J. F., Sirey, J., Raue, P., Greenfield, S., Struening, E., & Rosenheck, R., 1999., Burden experienced by care-givers of persons with bipolar affective disorder. *Br J Psychiatry*. 175, 56-62.
34. Perlick, D.A., Rosenheck, R.A., Miklowitz, D.J., Chessick, C., Wolff, N., Kaczynski, R., Ostacher, M., Patel, J., Desai, R., 2007a. Prevalence and correlates of burden among caregivers of patients with bipolar disorder enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder. *Bipolar Disord*. 9, 262–273. doi:10.1111/j.1399-5618.2007.00365.x
35. Perlick, D. A., Miklowitz, D. J., Link, B. G., Struening, E., Kaczynski, R., Gonzalez, J., ... & Rosenheck, R. A., 2007b., Perceived stigma and depression among caregivers of patients with bipolar disorder. *Br J Psychiatry*.190, 535-536.
36. Perlick, D. A., Rosenheck, R. A., Miklowitz, D. J., Kaczynski, R., Link, B., Ketter, T., ... & STEP-BD Family Experience Collaborative Study Group. (2008). Caregiver burden and health in bipolar disorder: a cluster analytic approach. *J Nerv Ment Dis*. 196, 484.
37. Perlick, D.A., Miklowitz, D.J., Lopez, N., Chou, J., Kalvin, C., Adzhiashvili, V., Aronson, A., 2010. Family-focused treatment for caregivers of patients with bipolar disorder. *Bipolar Disord*. 12, 627–637. doi:10.1111/j.1399-5618.2010.00852.x
38. Petticrew, M. & Roberts, H., 2006. *Systematic Reviews in the Social Sciences: A Practical Guide*. Blackwell, Oxford.
39. Reinares, M., Vieta, E., Colom, F., Martinez-Aran, A., Torrent, C., Comes, M., ... & Sanchez-Moreno, J., 2004. Impact of a psychoeducational family intervention on caregivers of stabilized bipolar patients. *Psychotherap. Psychosom*. 73, 312-319.
40. Reinares, M., Bonnín, C.M., Hidalgo-Mazzei, D., Sánchez-Moreno, J., Colom, F., Vieta, E., 2016. The role of family interventions in bipolar disorder: A systematic

- review. *Clin. Psychol. Rev.* 43, 47–57. doi:10.1016/j.cpr.2015.11.010
41. Schene, A. H. (1990). Objective and subjective dimensions of family burden. *Psychiatr Epidemiol*, 25, 289-297.
42. Sin, J., Gillard, S., Spain, D., Cornelius, V., Chen, T. and Henderson, C., 2017. Effectiveness of psychoeducational interventions for family carers of people with psychosis: A systematic review and meta-analysis. *Clin Psychol Rev.* 56, 13-24.
43. Steele, A., Maruyama, N., Galynker, I., 2010. Psychiatric symptoms in caregivers of patients with bipolar disorder: A review. *J. Affect. Disord.* 121, 10–21. doi:10.1016/j.jad.2009.04.020
44. van der Voort, T.Y.G., Goossens, P.J.J., van der Bijl, J.J., 2007. Burden, coping and needs for support of caregivers for patients with a bipolar disorder: a systematic review. *J. Psychiatr. Ment. Health Nurs.* 14, 679–687. doi:10.1111/j.1365-2850.2007.01158.x
45. van Gent, E. M., & Zwart, F. M. (1991). Psychoeducation of partners of bipolar-manic patients. *J. Affect. Disord.*, 21, 15-18.
46. Vella, S. L., & Pai, N. (2012). The measurement of burden of care in serious mental illness: A qualitative review. *Aust N Z J Psychiatry.* 47, 222-234. doi: 10.1177/0004867412468494.
47. Wendel, J. S., Miklowitz, D. J., Richards, J. A., & George, E. L. (2000). Expressed emotion and attributions in the relatives of bipolar patients: An analysis of problem-solving interactions. *J Abnorm Psychol.* 109, 792.
48. Yesufu-Udechuku, A., Harrison, B., Mayo-Wilson, E., Young, N., Woodhams, P., Shiers, D., ... & Kendall, T. (2015). Interventions to improve the experience of caring for people with severe mental illness: systematic review and meta-analysis. *Br J Psychiatry.* 206, 268-274.