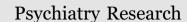
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Guilt, shame and expressed emotion in carers of people with long-term mental health difficulties: A systematic review



Psychiatry Research

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ABSTRACT

Expressed emotion (EE) is a global index of familial emotional climate, whose primary components are emotional over-involvement (EOI) and critical comments (CC)/hostility. There is a strong theoretical rationale for hypothesising that carers' guilt and shame may be differentially associated with their EOI and CC/hostility respectively. This systematic review investigates the magnitude of these theorised associations in carers of people with long-term mental health difficulties. Electronic searches (conducted in May 2016 across Medline, CINAHL, Embase, PsycINFO and ProQuest) were supplemented with iterative hand searches. Ten papers, reporting data from eight studies, were included. Risk of bias was assessed using a standardised checklist. Relevant data were extracted and synthesised narratively. EOI was positively associated with both guilt and shame, whereas CC/hostility was positively associated with shame. The strength of associations varied depending on whether or not guilt and shame were assessed within the context of the caring relationship. Based on these data, an argument can be made for the refinement, development and evaluation of systemic and individual interventions designed to target carers' guilt and shame. However, more research is needed to clarify the strength of these associations and their direction of effect before firm conclusions can be drawn.

1. Introduction

Expressed emotion (EE) is a global index of familial emotional climate, which encompasses family carers' attitudes, emotions and behaviours towards the person(s) to whom they provide care (Barrowclough and Hooley, 2003). Expressed emotion is usually defined in terms of its primary components: emotional over-involvement (EOI), critical comments (CC), and hostility (Barrowclough and Hooley, 2003). The term 'EOI' refers to overly self-sacrificing and/or intrusive behaviours and exaggerated emotional responses. Hostility and CC have a similar conceptual basis and often co-occur (Barrowclough and Hooley, 2003). As such, the term 'CC/hostility' is commonly used within the EE literature to refer to critical behaviour, character-focused statements and/or the presence or demonstration of negative attitudes towards service-users, including negative comments regarding their traits or personality (Barrowclough and Hooley, 2003).

Whilst not pathological in itself, EE is a robust predictor of prognosis across various psychiatric diagnoses (Butzlaff and Hooley, 1998; Weintraub et al., 2016). The negative association between EE, particularly EOI, and the mental health and well-being of carers is also widely noted (Brietborde et al., 2010; Jenkins and Karno, 1992). To this end, family interventions (FIs) have been developed to target and reduce aspects of EE whilst increasing carer support and raising awareness of factors contributing to EE (Pharoah et al., 2010). However, despite being recommended by clinical practice guidelines worldwide (American Psychiatric Association, 2004; Galletly et al., 2016; National Institute for Health and Care Excellence, 2014), FIs are poorly understood at the process level (Gracio et al., 2016). Furthermore, there exist a number of organisational, psychological and practical barriers to the dissemination and implementation of FIs within routine clinical practice (Bucci et al., 2016).

In an attempt to increase the precision and deliverability of current

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interventions, increasing research attention has focused on exploring both the psychological processes associated with EE and their mechanism of action (Barrowclough and Hooley, 2003). Cognitive approaches to understanding individual differences in carers' EE have mostly explored the utility of an attribution-based framework primarily focused on carers' attributions regarding the person affected by mental health difficulties (Barrowclough and Hooley, 2003; Kuipers et al., 2010). However, the attributions that carers make about their own roles in the development or maintenance of the illness are also likely to be of importance, as are the emotional states associated with such attributions (Jenkins and Karno, 1992; Robins and Schriber, 2009). Attributing one's own actions to internal, unstable and controllable causes is believed to engender guilt, whilst attributing them to internal. stable and uncontrollable causes is thought to result in shame (Tracy and Robins, 2006). This systematic review focuses on these two emotional states: guilt and shame.

Guilt and shame are self-evaluative emotions with distinct behavioural, affective and cognitive profiles (Tangney and Dearing, 2002; Tracy and Robins, 2006). Central to this distinction is the importance of the role of the self. Guilt reflects a judgement about one's behaviour or actions, resulting from the perception that a specific, transient and changeable aspect of one's behaviour has had a negative or undesirable effect upon another ('I did this bad thing'; Robins and Schriber, 2009). Guilt is thought to facilitate empathy and drive prosocial and reparative behaviours as a means of ameliorating feelings of responsibility for others' distress (Tangney and Tracy, 2012). To this end, guilt is often considered an adaptive emotion. However, guilt can become maladaptive when individuals develop an exaggerated or distorted sense of guilt for events that occur out of their control, or when reparation is not possible for a behaviour (Tangney and Tracy, 2012). As such, guilt may be an important factor to consider with respect to the development and maintenance of EOI. Carers experiencing guilt may engage in helpgiving behaviours driven by a desire to make amends for an illness or specific challenging behaviours or difficulties for which they feel responsible (Hatfield, 1981). However, although initially adaptive and reparative, these behaviours may become maladaptive if they are perceived by carers to be ineffective or if carers assume disproportionate levels of responsibility for service-users' difficulties or behaviours (Tangney and Tracy, 2012). To this end, guilt may both lead to, and maintain, EOI behaviours. However, guilt is unlikely to be associated with CC/hostility as these behaviours serve no reparative function (Tangney and Tracy, 2012).

In contrast to guilt, shame reflects an enduring and stable judgement about oneself or one's character, arising as a result of real or perceived negative evaluation from others and/or negative self-evaluation ('<u>1</u> did this bad thing'; Robins and Schriber, 2009). In keeping with this differentiation, shame is often considered to be a maladaptive emotion, as individuals often defend against the painful negative feelings of shame by externalising blame onto others in the form of defensive criticism, hostility and aggression (Brown, 2004; Tracy and Robins, 2006). Shame may therefore be an important consideration with respect to CC/hostility, as it may drive carers to engage in defensive, regulatory anger-driven behaviours designed to protect their social image (Gausel et al., 2016; Jenkins and Karno, 1992).

If empirical evidence supports the theorised links between guilt and shame and components of EE, then they may represent potential targets for intervention (Gilbert and Irons, 2005). However, no systematic examination and synthesis of the current evidence-base regarding the relationships between the constructs has been conducted. This systematic review aimed to address this gap by using systematic review methodology to examine the associations among guilt, shame, EOI and CC/hostility.

2. Methods

2.1. Search strategy

The conduct and reporting of this review adheres to the general principles recommended by the Centre for Reviews and Dissemination (CRD, 2009) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines⁴ (Stroup et al., 2000). After several scoping searches, five electronic databases (Medline, CINAHL, Scopus, PsycINFO and ProOuest) were searched for relevant published and unpublished literature from their inception until October 2015. Searches were devised in collaboration with an information specialist⁵ and contained no methodological search filters or disorder-specific keywords that would limit results to specific study designs or diagnostic groups. Table 1 details the search syntax used for each database. Conference proceedings and the authors' own files were then examined for additional relevant literature, followed by the reference lists of both included full-text studies and recent systematic reviews concerning the psychological factors associated with EE (Anastasiadou et al., 2014; Jansen et al., 2015). Finally, corresponding authors of included papers were contacted for information regarding studies in progress and unpublished research. Searches were repeated in October 2016 to identify any relevant new publications.

2.2. Study selection

Identified studies' titles and abstracts were simultaneously screened to assess their relevance to the review. Full-text copies of potentially relevant studies were then examined. Screening at both stages was done independently by two authors (MGC and JWR). Disagreement or uncertainty was resolved through consensus and the views of the wider research team were consulted where necessary. Studies were included if they: a) were published in English; b) reported data from family carers aged 18 years or over who provided care to relatives aged 18 years or over with long-term mental health difficulties; and c) reported quantitative data sufficient for computation of effect size(s) regarding the relationship(s) between guilt and/or shame and EOI and/or CC/ hostility. The term 'long-term mental health difficulty' was defined as any non-organic mental health difficulty of ≥six months' duration (Barrowclough et al., 1998); specific diagnoses were not used as inclusion/exclusion criteria as EE is associated with outcome across a range of mental health difficulties (Butzlaff and Hooley, 1998).

2.3. Assessment of risk of bias

Risk of bias in included studies was independently assessed by MGC and JWR using a tool adapted from the Agency for Healthcare Research and Quality (Taylor et al., 2015; Williams et al., 2010). This tool allows for risk of bias to be assessed in nine specific areas, thus enabling comparability of specific issues across included papers (Jüni et al., 1999). Disagreement or uncertainty was resolved through consensus and/or arbitration by a third reviewer (PJT). In line with CRD (2009) guidance, no study was excluded based on the findings of the assessment of risk of bias.

2.4. Data extraction and analysis

Relevant demographic, methodological and summary data were extracted using a standardised data extraction form by MGC and independently checked for accuracy by JWR. Disagreement or uncertainty was resolved through consensus and the views of the wider

⁴ A checklist designed to aid clear reporting of meta-analyses and systematic reviews of observational data.

 $^{^5\,\}mathrm{An}$ individual with expert knowledge in bibliographic databases and information retrieval.

Table 1

Database	Syntax
Medline and PsycINFO	(Expressed Emotion/OR Hostility/OR (critic* or hostile* or ((emotion* adj3 (express* or over-involv*)) or (critic* adj2 comment*)).tw.)) AND (Caregivers/or Family/OR (carer* or caregive* or famil* or relative* or relation* or caring).tw.) AND (Guilt/OR Shame/OR ((shame* or guilt* or self-blame*) OR ((self-conscious* or selfconscious or "self conscious") adj2 emotion) OR ((shame* or guilt*) adj2 pron*) OR (shame-pron* or guilt-pron*)).tw.)
CINAHL	(Expressed Emotion/OR Hostility/OR (critic* or hostile* or ((emotion* n3 (express* or over-involv*)) or (critic* n2 comment*)).tw.)) AND (Caregivers/or Family/OR (carer* or caregive* or famil* or relative* or relation* or caring).tw.) AND (Guilt/OR Shame/OR ((shame* or guilt* or self-blame*) OR ((self-conscious* or selfconscious or "self conscious") n2 emotion) OR ((shame* or guilt*) n2 pron*) OR (shame- pron* or guilt-pron*)).tw.)
Scopus	(Expressed Emotion/OR Hostility/OR (critic* or hostile* or ((emotion* w/3 (express* or over-involv*)) or (critic* w/2 comment*)).tw.)) AND (Caregivers/or Family/OR (carer* or caregive* or famil* or relative* or relation* or caring).tw.) AND (Guilt/OR Shame/OR ((shame* or guilt* or self-blame*) OR ((self-conscious* or selfconscious or "self conscious") w/2 emotion) OR ((shame* or guilt*) w/2 pron*) OR (shame-pron* or guilt-pron*)).tw.)
ProQuest Dissertations and Theses	Ab, ti((emotion* NEAR/3 (express* OR over-involv*)) OR (critic* NEAR/2 comment*)) AND (carer* OR caregiver* OR family* OR relative* OR relation* OR caring) AND ((sham* OR guil* OR self-blame*) OR ((self-conscious* OR selfconscious OR "self conscious") NEAR/2 emotion) OR ((shame* OR guilt*) NEAR/2 pron*) OR (shame-pron* OR guilt-pron*))

Search syntax.

research team were consulted where necessary. Authors were contacted, where relevant, regarding missing and/or unclear data. Data from studies presented in multiple publications were extracted and reported as a single study with all other relevant publications listed. Where studies reported multiple analyses, only data from: a) bivariate analyses examining relationships between guilt and/or shame and EOI and/or CC/hostility; and/or b) multivariate analyses in which the effects of other variables on the aforementioned associations were controlled for, were extracted. In the latter case, only data from the most complex models were extracted. Individual study data, including quality assessment, were subsequently organised into structured tables and analysed narratively. Heterogeneity in study methodology precluded meta-analysis.

3. Results

3.1. Number of studies identified and included

The search strategy identified 3004 unique records, from which 10 publications, reporting data from eight studies, were identified for inclusion (Bentsen et al., 1998; Brookfield, 2008; Keith, 2011; McMurrich, 2008; McMurrich and Johnson, 2009; Messham, 2014; Peterson and Docherty, 2004; Wasserman, 2010; Wasserman et al., 2012; Weisman de Mamani, 2010).⁶ The flow of information from identification to inclusion of studies is summarised in Fig. 1 (Moher et al., 2009).

3.2. Characteristics of included studies

The main characteristics of the included studies are displayed in Table 2. All studies were conducted in developed countries and employed a cross-sectional design. Studies reported data from 483 participants caring for 410 service-users. Participants were primarily female and middle-aged, and provided an average of 42.60 h of care per week; mean duration of caregiving was reported by two studies (Keith, 2011; Messham, 2014), with values ranging from 14.00 to 15.16 years. Service-users' characteristics ranged across studies and are outlined in Table 2.

3.3. Assessment of guilt and shame

Shame and guilt were measured in different ways (Table 3). Four studies, reported in five publications (Bentsen et al., 1998; Brookfield, 2008; McMurrich, 2008; McMurrich and Johnson, 2009; Weisman de Mamani, 2010), assessed a trait-like proneness to experiencing guilt or shame irrespective of a particular context or trigger. The remainder (Keith, 2011; Messham, 2014; Peterson and Docherty, 2004; Wasserman, 2010; Wasserman et al., 2012) assessed contextualised care-specific guilt and/or shame (i.e. guilt and/or shame in direct response to caring for someone with a mental health difficulty). Although participants' average levels of guilt and shame varied between studies (Table 3), the majority of studies did not report normative data for a carer sample, making further interpretation difficult. Correlations between guilt and shame were reported in five studies, reported in six publications, r=0.51-0.67 (Brookfield, 2008; Keith, 2011; McMurrich, 2008; McMurrich and Johnson, 2009; Messham, 2014; Wasserman, 2010; Wasserman et al., 2012).

3.4. Assessment of EOI and CC/hostility

All studies considered EOI and/or CC/hostility as outcome variables (Table 3). Broadly, there was a bifurcation in how EOI and CC/ hostility were measured. Five studies, reported in six publications (Bentsen et al., 1998; McMurrich, 2008; McMurrich and Johnson, 2009; Peterson and Docherty, 2004; Wasserman, 2010; Wasserman et al., 2012; Weisman de Mamani, 2010), assessed EE using coding schemes such as the CFI (Vaughn and Leff, 1976), abbreviated CFI (Mueser et al., 1992) or the Five Minute Speech Sample (FMSS; Magaña et al., 1986), in which frequency of utterances deemed to be of a critical, hostile or emotionally-over involved nature are determined from carers' speech samples. The remainder (Brookfield, 2008; Keith, 2011; Messham, 2014) used the self-report Family Questionnaire (FQ; Weidermann et al., 2002), in which participants' levels of EOI and CC/ hostility are quantified based on carers' responses to a range of carerelated statements. As with guilt and shame, participants' average levels of EOI and CC/hostility differed between studies. Six studies, reported in seven publications, explored gender differences in participants' EOI and CC/hostility scores; females' EOI scores were higher than males' in three studies, reported in four publications (Brookfield, 2008; Peterson and Docherty, 2004; Wasserman, 2010; Wasserman et al., 2012), whilst the remainder noted no difference in scores based on participants' gender (Keith, 2011; Messham, 2014; Weisman de Mamani, 2010).

⁶ Given the broad and exploratory nature of our review, no disorder-specific keywords were included in the search so as not to limit the findings to a particular patient population. This resulted in identification of a large number of non-mental health related citations, which largely accounts for the dramatic drop in numbers from screening to assessment of potentially-relevant full-text papers shown in Fig. 1.

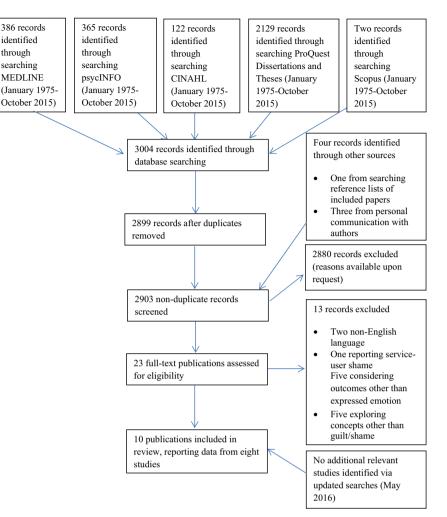


Fig. 1. Flow-chart of included studies.

3.5. Results of assessment of risk of bias

The results of the assessment of risk of bias are presented in Table 4. The most common methodological limitations related to study design, selection/description of participants, assessment of guilt and shame, blinding of assessors and appropriateness of statistical analyses, including justification of sample sizes. First, the cross-sectional nature of the included studies made it impossible to determine the direction of effect with regards to the association between variables. Second, demographic data for both carers and service-users were commonly under-reported, and most studies recruited carers from mental health settings and/or specialist carer support agencies, thus introducing a potential selection bias in that these samples reflected a subset of carers who were in receipt of services. Third, several studies assessed shame and/or guilt using measures with questionable or unknown psychometric data and poor discriminant validity. Furthermore, three of the eight studies used the self-report FQ, which may be more susceptible to self-report bias than coding schemes (van Humbeek et al., 2002). Fourth, the majority of studies either failed to recruit enough participants to meet the requirements of their own a priori sample size calculations or failed to justify their sample size in terms of power, which may have potentially resulted in inflated Type I error rates. Finally, most studies did not a) control for potentially confounding demographic variables (e.g. amount of weekly care provision); b) control for the potential covariance between guilt and shame (Tangney and Dearing, 2002); and/or c) fully account for nonindependent or nested data (i.e. data from multiple relatives per patient) in statistical analyses looking at predictors and correlates of

EOI and CC/hostility.

3.6. Main findings: EOI

3.6.1. Association between EOI and guilt

Six studies examined the association between EOI and guilt (Bentsen et al., 1998; Brookfield, 2008; Keith, 2011; Messham, 2014; Peterson and Docherty, 2004; Weisman de Mamani, 2010). Collectively, data indicated mixed support for the theorised positive association between the constructs (Table 5). However, the effects of measurement approaches on these relationships were noted.

Moderate to large positive associations (r=0.45-0.55; Cohen, 1988) were found between EOI and care-specific quilt when the former was assessed using the self-report FO (Keith, 2011; Messham, 2014). Carespecific guilt remained a significant predictor of EOI when the effects of shame and service-users' diagnoses were controlled for, although the strength of the association lessened slightly (Keith, 2011; Messham, 2014). However, divergent findings emerged regarding the association between care-specific guilt and EOI when EOI was assessed using coding schemes such as the CFI or the FMSS. Peterson and Docherty (2004) noted a small negative association between the constructs (r=-0.22), whilst Wasserman et al. (2010, 2012) found care-specific guilt not to predict EOI after controlling for hours of weekly contact and service-users' primary language and gender. However, it is important to note the relatively limited range of EOI scores between and within participants in both studies, which may have influenced the findings.

Irrespective of approach taken to assess EOI, no association was

	Study cha	Study characteristics		Part	icipant ch	Participant characteristics	S				
Author	Design	Location	Sampling method	=	Male, n (%)	Age, mean (SD)	Ethnicity, n (%)	Weekly contact (h), mean (SD)	% living with SU	Relation to SU, n (%)	SU diagnosis, n (%)
Bentsen et al. (1998)	Cross- sectional	Norway	Consecutive sampling	69	32 (46.37)	56.5 (n/s) n/s	s/u	26 (20.4)	71.0	Mother: 34 (49.28), father: 29 (42.03), spouse/partner; sibling: each 3 (4.34)	Schizophrenia: 32 (68.09); schizoaffective disorder/ schizobhreniform disorder/BD: $n \ln s^{\circ}$
Brookfield (2008)	Cross- sectional	UK	Convenience sampling	58	12 (20.69)	58 (13.5)	n/s	56 (n/s) ^b	s/u	Mother: 28 (48.28), father: 11 (18.97), sibling: 3 (5.17), spous/partner: 13 (22.41), daughter; son; friend: each 1 (1.72)	Schizophrenia: 30 (53.57), BD: 11 (19.64), depression: 8 (14.29); PD: 2 (3.57), OCD; PTSD; schizoaffective disorder: each 1 (1.79) ^c
Keith (2011)	Cross- sectional	UK	Convenience sampling	60	48 (80.00)	57 (9.9)	s/u	59 (31)	s/u	Mother: 31 (51.67), spouse/partner: 20 (33.33), father; daughter: each 2 (3.3.), sister: son: each 1 (1.67)	n/s
McMurrich (2008, 2009)	Cross- sectional	USA	Convenience sampling	42 ^d	13 (30.95)	s/u	Caucasian: 28 (73.68), Hispanic: 8 (21.05), AA: 2 (5.26) ^e	s/u	60.7	Parent: 4 (14.29), sibling: 1 (3.57), child: BD: 28 (100.00) ^b 15 (53.57) spouse: 8 (28.57) ^f	BD: 28 (100.00) ^b
Messham (2014)	Cross- sectional	UK	Convenience sampling	12	13 (18.31)	56 (14.2)	s/u	29.5 (31.2)	s/u	Mother: 35 (49.30), father: 6 (8.45), spouse/partner: 13 (18.31), sibling: 9 (12.68), offspring: 7 (9.86), grandparent: 1 (1.41)	SSD: 30 (42.3), PD: 11 (15.5), BD: 10 (14.1), anxiety: 9 (12.7), depression: 16 (22.5), OCD; PTSD: each 2 (2.8), n/s: 3 (4.2) ⁶
Peterson and Docherty (2004)	Cross- sectional	USA	s/u	54	27 (50.00)	61.8 (7.8)	61.8 (7.8) Caucasian: n/s (78)	s/u	s/u	Mother; father: each 27 (50.00)	Schizophrenia: 27 (100.00) ^h
Wasserman (2010), Wasserman et al. (2012)	Cross- sectional	USA	Convenience sampling	72	21 (29.17)	53.4 (14.2)	Hispanic: 37 (51.39), Caucasian: 21 (29.17), AA: 13 (18.06), other: 1 (1.39)	s/u	s/u	Mother: 34 (47.22), partner/spouse; sibling: each 9 (12.50), father: 7 (9.72), friend: 5 (6.94), offspring: 3 (4.17), aun/ uncle; cousin: each 2 (2.78), grandparent: 1 (1.39)	SSD: 72 (100.00)
Weisman de Mamani (2010)	Cross- sectional	USA	Consecutive sampling	57	17 (29.82)	54.3 (14.3)	Caucasian: 20 (35.09), Hispanic: 21 (36.84), AA: 16 (28.07)	s/u	n/s	n/s	SSD: 57 (100.00)

Note: data reported to two decimal places where possible; AA=African American; BD=bi-polar cusoruer, u_1, s -...., deviation; SSD=schizophrenia spectrum disorders; SU=service-user; UK=United Kingdom; USA=United States of America. ^a n=47. ^b n=55. ^c n=56. ^d Although 42 participants were recruited, only 38 returned complete datasets for analysis. ^e n=38. ^f n=28. ^g n > 71 as some participants recorded more than one diagnosis per service-user. ^h n=27.

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Table 2Main characteristics of included studies.

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Predictor and outcome variables.

Study	Predictor variable(s)	Method of assessing shame/guilt	Main findings: shame/guilt	Outcome variable(s)	Method of assessing EE	errry et a
Bentsen et al. (1998)	Guilt-proneness	RMGI ^a	 Hostility-guilt subscale: M=3.5 (SD 0.8) Guilty-conscience subscale: M=2.9 (SD 0.7) 	EOI; CC; hostility	Abbreviated CFI	High CC: $n=16$ (23.19%) Hostile: $n=10$ (14.49%) High EOI: $n=40$ (57.97%) High EOI and CC: $n=9$ (13.04%) High EOI and CC: $n=9$ (13.04%)
Brookfield (2008)	Guilt and shame-proneness	TOSCA-3S	 Shame-pronenees subscale: M=33.8 (SD 8.0, range 18–50) Guilt-proneness subscale: M=46.8 (SD 5.2; range 30–55) 	EOI; CC/hostility	P	• Low EE: $n=16$ (27.59%) • High EE: $n = 42$ (72.41%) 1. High CC/hostility only: $n=7$ (16.67%) 2. High EOI only: $n=5$ (11.91%) 3. High CC/hostility and high EOI: n = 30 (71.43%) • Total EE scale: $M=54.2$ (SD 8.4; range $31-67$) • CC subscale: $M=25.2$ (SD 5.5; range $12-27$) • CO subscale: $M=29.0$ (SD 5.1; remote $12-27$)
Keith (2011)	Guilt- and shame- proneness	TOSCA-3S	TOSCA-3S: • Shame-proneness subscale: M =34.1 (SD 8.2, range 12-47) • Guilt-proneness subscale: M =47.6 (SD 4.3, range 37-55)	EOI	PQ	 I. (18, 33%) I. (18, 33%) High EE: n=41 (18, 33%) High EE: n=49 (81.67%) I. High CC/hostility only: n=2 (4.08%) 2. High EOI only: n=17 (34.70%) 3. High CC/hostility and kich FOI
	Care-specific guilt and shame	CARES	 Care-specific shame subscale: M=31.1 (SD 7.4, range 16-46) Care-specific guilt subscale: M=38.3 (SD 8.7, range 13-54) 			 A. Tagan CV, Jussey and Jugar CO. Total EE scale: M=54.4 (SD 9.4, range 36-71) CC subscale: M=24.3 (SD 6.6, range 11-37) EOI subscale: M=30.0 (SD 4.7, monor effort 27)
McMurrich (2008), McMurrich and Johnson (2009)	Guilt and shame-proneness	TOSCA-3	 Shame-proneness subscale: M=43.3 (SD 10.0) Guilt-proneness subscale: M=64.8 (SD 6.7) 	Number of CC	FMSS	• CC: <i>M</i> =0.4 (<i>SD</i> 0.8)
Messham (2014)	Care-specific guilt and shame	TOSCA-3S [°]	 TOSCA-3S: Shame-pronenees subscale: M=34.1 (SD 6.9, range 20-49) Guilt-proneness subscale: M=46.5 (SD 4.5, erange 27-55) 	EOI; CC/hostility	PQ	 Low EE: n=6 (8.45%) High EE: n=65 (91.55%) I. High CC/hostility only: n=9 (13.85%) Ligh EOI only: n=10 (15.38%) High CC/hostility and high EOI:
Peterson and Docherty (2004)	Care-specific guilt	CARES-R CFI	 CARENENE: Manue subscale: M=42.2 (SD 15.1, range 19-79) Care-specific guilt subscale: M=47.6 (SD 13.7, range 21-77) Self-blame statements, M=1.2 (SD 0.6) 	EOI; CC/hostility	CFI	$\begin{array}{l} \begin{array}{l} \begin{array}{l} \mbox{meab} (JU, SU'95) \\ \mbox{CC} (SUBACCE) \\ \mbox{CC} (SUBACE) \\ \mb$

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Table 3 (continued)						
Study	Predictor variable(s)	Method of assessing shame/guilt	Main findings: shame/guilt	Outcome variable(s)	Method of assessing Main findings: EE EE	Main findings: EE
						n=5 (20.83%) ● CC subscale: M=5.1 (SD 4.7) ● EOI subscale: M=1.9 (SD 1.3)
Wasserman (2010), Wasserman et al. (2012)	Care-specific guilt and shame	SESS	 Care-specific shame subscale, M=2.2 (SD EOI; CC/hostility 1.9) 	EOI; CC/hostility	FMSS	 Low EE: n=49 (68.10%), High EE: n=19 (26.39%)^d HIGH EE: n=10 (26.39%)^d
			• care-speame gunt subscale, <i>M</i> =1.8 (30) 1.5)			1. High CC/nostility: $n=8 (47.37\%)$ 2. High EOI: $n=11 (57.90\%)$ were high EOI ^e
Weisman de Mamani (2010)	Guilt and shame-proneness TOSCA	TOSCA	 Shame-proneness subscale, M=46.3 (SD EOI; CC/hostility 11.9) Guilt-proneness subscale, M=62.0 (SD 6.9) 	EOI; CC/hostility	CFI	 Low EE: n=38 (66.67%) High EE: n=19 (33.33%) CC subscale: M=3.8 (SD 3.8)
						• EOI subscale: $M=1.9$ (SD 1.1)
Note: data renorted to two significant	figures where nossible: CARES=	€Caring and Related Emotions S	Note- data renoted to two simificant formes where nossible. CARES=Carins and Related Emotions Scale (Keith 2011). CARES.R=Carins and Related Emotions Scale- Revised (Messham 2014). CC=critical comments. CFI=Camberwall Family	Emotions Scale- Revised	1 (Messham, 2014): CC=critic	al comments: CFI≡Camberwell Familv

Note: data reported to two significant figures where possible; CARES-Caring and Related Emotions Scale (Keith, 2011); CARES-R=Caring and Related Emotions Scale- Revised (Messham, 2014); CC=critical comments; CFI=Camberwell Family Interview (Vaughn and Leff, 1976); EE=expressed emotion; EOI=emotional over-involvement; FMSS=Five Minute Speech Sample (Magaña et al., 1986); FQ=Family Questionnaire (Weidermann et al., 2002); M=mean; RMGI=Revised Mosher Guilt Inventory (Mosher, 1998); SESS=Self-Directed Emotions for Schizophrenia Scale (Weisman de Mamani et al., 2007); *SD*=standard deviation; TOSCA=Test of Self-Conscious Affect (Tangney et al., 1989); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000a); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 (Tangney et al., 2000b); TOSCA-3=Test of Self-Conscious Affect Version 3 - short form (Tangney et al., 2000b).

^a The hostility-guilt and guilty-conscience subscales used only. ^b Proportion classified as high EE not stated.

 $^{\rm c}$ TOSCA-3S data not considered in further analyses. $^{\rm d}$ Data only available for 68 carers. $^{\rm e}$ Number designated as high CC/hostility and high EOI not stated.

Table 4

Assessment of risk of bias.

Author(s)	Unbiased selection of cohort?	Sample size calculation?	Adequate description of cohort?	Validated method for assessing guilt/ shame?	Validated method for assessing EE?	Outcome assessors blind to predictor variables?	Missing data minimal?	Missing data Confounders minimal? controlled for?	Appropriate analyses?
Bentsen et al. (1998)	Partially	n/s	Yes	Partially	Partially	n/s	n/s	Yes	Partially
Brookfield (2008)	Partially	Partially	Yes	Yes	Yes	n/a	Yes	No	Partially
Keith (2011)	Partially	Partially	Partially	Partially	Yes	n/a	Yes	No	Partially
McMurrich (2008), McMurrich	Partially	Partially	Partially	Yes	Yes	n/s	Yes	No	Partially
and Johnson (2009)									
Messham (2014)	Partially	Yes	Partially	Partially	Yes	n/a	Yes	Yes	Partially
Peterson and Docherty (2004)	Partially	n/s	Yes	No	Yes	Yes	n/a	No	Partially
Wasserman (2010),	Yes	n/s	Partially	No	Yes	n/s	n/s	Partially	Partially
Wasserman et al. (2012)									
Weisman de Mamani (2010)	Partially	n/s	Yes	Partially	Yes	n/s	n/s	No	Partially

Note: EE=expressed emotion; n/s=not stated; n/a=not applicable.

Predictor variable Author	Author	Method of assessing	Bivariate analyses		Multivariate analyses		
		EOI	Statistical analysis Effect size	Effect size	Statistical analysis	Control variables	Effect size
Guilt-proneness	Bentsen et al. (1998)	Coding scheme	s/u		Logistic regression	'Standard control variables' ^a	n/s but not statistically significant ^b OR=29.0* ^c
	Brookfield (2008) Keith (2011)	Self-report measure Self-report measure	Pearson's correlation Pearson's correlation	r=0.21 r=0.08	Multiple linear regression n/s	Emotional empathy	β=0.35
	Weisman de Mamani (2010)	Coding scheme	Pearson's correlation	r = -0.16	Partial correlation	Shame-proneness	r=0.07
Care-specific guilt	Keith (2011)	Self-report measure	Pearson's correlation	$r=0.55^{*}$	Multiple linear regression	Care-specific shame	β=0.15**
	Messham (2014) Peterson and Docherty (2004)	Self-report measure Coding scheme	Pearson's correlation <i>t</i> -test ^d	r=0.45 r=-0.22	Hierarchical multiple regression n/s	Diagnosis; care-specific shame	β=0.12
	Wasserman (2010); Wasserman et al. (2012)	Coding scheme	s/u		Block-entry binary logistic regression	Weekly contact; SU language; SU gender	n/s but not statistically significant
Shame-proneness	Brookfield (2008)	Self-report measure	Pearson's correlation	$r=0.39^{\circ}$	Multiple linear regression	Emotional empathy; guilt- proneness	β=0.35
	Keith (2011)	Self-report measure		r=0.35	n/s		* r c c
Care-specific shame	Weisman ue Mamain (2010) Keith (2011)	Count scheme Self-report measure	Pearson's correlation Pearson's correlation	$r=0.59^{\circ}$	rarual correlation Multiple linear regression	Gunt-proneness Care-specific guilt	β=0.41
	Messham (2014)	Self-report measure	Pearson's correlation	$r=0.51^{\circ}$	Multiple linear regression	Diagnosis; care-specific guilt	β=0.41

p < 0.05.
 ^a i. b kind of relatives, socio-economic status, service-users' gender, illness duration, amount of face-to-face contact between carer and service-user, Positive and Negative Syndrome Scale components.
 ^b Guilty-conscience subscale.
 ^c Hostility-guilt subscale; significant findings for males only.
 ^c Values calculated from *t*-values; n/s=not stated; OR=odds ratio; SU=service-user.

Table 5 Main findings (EOI).

Predictor variable Author	Author	of assessing (CC/ Bivariate analyses		Multivariate analyses		
		HOSTING	Statistical analysis	Effect size	Statistical analysis	Control variables	Effect size
Guilt-proneness	Bentsen et al. (1998) ^a	Coding scheme	Logistic regression	Hostility: <i>OR</i> =0.40 ^b	Logistic regression	'Standard control variables' ^c	n/s but not statistically significant ^d
			Logistic regression	CC: n/s but not statistically significant	Logistic regression	Carers' mental health	OR=0.10 ^{*a}
	Bentsen et al. (1998) ^e	Coding scheme	Logistic regression	Hostility: n/s but not statistically significant	n/a		
			Logistic regression	CC: n/s*	Logistic regression	'Standard control variables' ^c	n/s but not statistically significant
	Brookfield (2008)	Self-report measure	Pearson's correlation	n/s but not statistically significant	n/s)
	McMurrich (2008) McMurrich and Johnson (2009)	Coding scheme	Pearson's correlation	r=0.17	Multiple linear regression	Depression; shame- proneness	β=0.01
	Weisman de Mamani (2010)	Coding scheme	Pearson's correlation	r = -0.02	Partial correlation	Shame-proneness	r=0.03
Care-specific guilt	Messham (2014)	Self-report measure	Pearson's correlation	$r=0.29^{*}$	Multiple linear regression	Care-specific shame	β=0.01
	Peterson and Docherty (2004)	Coding scheme	t-test ^f	r=0.06	n/s		
Shame-proneness	Brookfield (2008)	Self-report measure	Pearson's correlation	$r=0.26^{*}$	n/s		
	McMurrich (2008) McMurrich and Johnson (2009)	Coding scheme	Pearson's correlation	r=0.21	Multiple linear regression	Depression; guilt- proneness	β=0.01
	Weisman de Mamani (2010)	Coding scheme	Pearson's correlation	r = -0.11	Partial correlation	Guilt-proneness	r = -0.00
Care-specific shame	Messham (2014)	Self-report measure	Pearson's correlation	r=0.45	Multiple linear regression	Care-specific guilt	β=0.44
	Wasserman (2010), Wasserman	Coding scheme		n/s	Block-entry binary logistic	Type of relative	n/s but not statistically
	et al. (2012)				regression		significant

^b Revised Moher Guilt Inventory scores dichotomised for analysis.
 ^b Revised Moher Guilt Inventory scores dichotomised for analysis.
 ^c i.e. kind of relative, relative, relatives, socio-economic status, gender of service-user, illness duration, amount of face-to-face contact between carer and service-user, Positive and Negative Syndrome Scale components.
 ^d Hostility-guilt scale scores dichotomised at 3.70.
 ^e Guilty-conscience subscale.
 ^f Values calculated from t-values; CC=critical comments; n/s=not stated; OR=odds ratio.
 ^p < 0.05.

Table 6Main findings (CC/hostility).

noted between EOI and *guilt-proneness*, even after controlling for the effects of variables such as emotional empathy (Brookfield, 2008) and shame-proneness (Weisman de Mamani, 2010). The only exception to this was Bentsen et al. (1998), who found a positive association between male participants' EOI and guilt-proneness scores (using the hostility-guilt subscale of the RMGI), after controlling for the effects of demographic variables such as service-users' diagnoses and carers' ages. However, the credibility of these data are unclear, given that the researchers did not adjust for the effects of multiple testing, which may have increased the risk of Type I errors (Kline, 1999).

3.6.2. Association between EOI and shame

Four studies considered the association between EOI and shame (Table 5; Brookfield, 2008; Keith, 2011; Messham, 2014; Weisman de Mamani, 2010). Medium to large positive associations (r=0.35-0.59; Cohen, 1988) were noted between EOI and shame in three studies (Brookfield, 2008; Keith, 2011; Messham, 2014). Effect sizes were, on average, larger across studies using measures of care-specific shame than across studies using measures of shame-proneness. Shame remained a significant predictor of EOI when additional variables were controlled for, including guilt, emotional empathy and service-users' diagnoses (Brookfield, 2008; Keith, 2011; Messham, 2014), indicating that 'guilt-free' shame may be an important factor to consider with respect to EOI. Only one study's findings diverged from those above; Weisman de Mamani (2010) found a moderate negative association between EOI and shame-proneness (r=-0.34), which persisted after controlling for the effects of guilt-proneness (r=-0.31). However, it is possible that this divergence may be due to the limited number and proportion (n=19; 33.3%) of participants classed as high EOI in this study compared with the others.

3.7. Main findings: CC/hostility

3.7.1. Association between CC/hostility and guilt

Six studies, reported in seven publications, explored the association between CC/hostility and guilt (Table 6; Bentsen et al., 1998; Brookfield, 2008; McMurrich, 2008; McMurrich and Johnson, 2009; Messham, 2014; Peterson and Docherty, 2004; Weisman de Mamani, 2010). Five studies, reported in six publications, reported limited to no association between the constructs (Brookfield, 2008; McMurrich, 2008; McMurrich and Johnson, 2009; Messham, 2014; Peterson and Docherty, 2004; Weisman de Mamani, 2010), even when the effects of variables such as carers' mental health and shame were controlled for (McMurrich, 2008; McMurrich and Johnson, 2009; Weisman de Mamani, 2010). Findings were consistent across studies using measures of care-specific guilt and those using measures of guilt-proneness (Table 6). The only exception to these data was reported by Bentsen et al. (1998), who found the hostility-guilt and guilty-conscience subscales of the RMGI to significantly predict hostility and CC respectively. However, although the guilty-conscience subscale continued to significantly predict CC when the effects of carers' mental health were controlled for, the aforementioned methodological and analytical limitations associated with this study have implications for the weight that should be placed on Bentsen et al.'s (1998) data.

3.7.2. Association between CC/hostility and shame

Five studies, reported in seven publications, explored the association between CC/hostility and shame (Table 6; Brookfield, 2008; McMurrich, 2008; McMurrich and Johnson, 2009; Messham, 2014; Wasserman, 2010; Wasserman et al., 2012; Weisman de Mamani, 2010). Small to moderate positive associations (r=0.26–0.45; Cohen, 1988) were noted between the constructs when the self-report FQ was used to assess CC/hostility (Brookfield, 2008; Messham, 2014), which persisted when controlling for the effects of care-specific guilt (Messham, 2014). Effect sizes were greater when measures of carerelated shame were used rather than measures of shame-proneness. Conversely, no associations were observed when CC/hostility was coded using the CFI or FMSS, even after controlling for the effects of carer-specific variables including relationship with the service-user and levels of depression and guilt (McMurrich, 2008; McMurrich and Johnson, 2009; Wasserman, 2010; Wasserman et al., 2012; Weisman de Mamani, 2010). However, it is possible that the heterogeneity in findings may be in part due to these studies' small sample sizes and limited range of outcome data (McMurrich, 2008; McMurrich and Johnson, 2009; Wasserman, 2010; Wasserman et al., 2012), together with their frequent use of the (relatively insensitive) FMSS (van Humbeek et al., 2002).

4. Discussion

This systematic review investigated the magnitude of the associations between guilt and shame and components of EE in carers of people with long-term mental health difficulties. Narrative synthesis of included studies indicated that EOI was positively associated with both shame and guilt, whilst CC/hostility was positively associated with shame but not guilt.

Turning first to EOI. Guilt was theorised to be positively associated with EOI, given its potential role in motivating reparative behaviours in an attempt to ameliorate feelings of personal responsibility (Tracy and Robins, 2006). At the broadest level, when guilt was treated as a unidimensional construct, there was only minimal support for the theorised positive association between guilt and EOI. However, a strong positive association was found between the constructs when measures of care-specific guilt were used, which persisted when the effects of shame were controlled for. Collectively, these data lend support for the notion that, in order for guilt to have a salient impact on EOI, it must be associated directly with caring for and/or having a relative with mental health difficulties (Myers, 2010). This is perhaps unsurprising, given that guilt is context-specific (i.e. dependent on a specific event or behaviour for which an individual makes reparation; Gilbert, 1998; Tangney and Dearing, 2002). However, the crosssectional nature of included studies meant that it was not possible to determine whether guilt is a consequence or cause of emotionally overinvolved behaviour (Hatfield, 1981).

Data also indicated a relationship between shame and EOI; strong positive associations were noted between the constructs, irrespective of whether measures assessed shame-proneness or care-specific shame. These associations persisted after partialling for the effects of guilt, indicating that the observed associations between shame and EOI were not merely reflective of the shared variance between shame and guilt. This finding is of particular importance as it suggests that both the trait-like aspect of shame-proneness and guilt and shame specifically related to caring for someone with mental health difficulties may all be important factors to consider with respect to EOI, and to a roughly equal extent. The positive association between shame and EOI observed in this review is consistent with the notion that carers who experience shame within the context of their own, or service users', perceived characterological deficits may engage in well-intentioned but maladaptive emotionally over-involved behaviours in an attempt to promote a positive self-image (Allpress et al., 2014; Gausel et al., 2016; Lickel et al., 2007). However, the cross-sectional nature of included studies meant that it was not possible to firmly support or refute this hypothesis without further research (Allpress et al., 2014; Gausel et al., 2016; Gilbert, 1998; Hatfield, 1981; Lickel et al., 2007).

Turning next to CC/hostility. The theorised positive relationship between shame and CC/hostility was supported when CC/hostility was assessed using self-report measures but not when coding schemes were used. Although these findings may reflect common method variance, these data tentatively support the notion that shame may drive carers to engage in defensive, regulatory anger-driven behaviours focused specifically on behaviours and symptoms which are shame-eliciting (Jenkins and Karno, 1992). Furthermore, they suggest that both shame-proneness *and* shame specifically related to caring for a relative with a mental health difficulty may each be important factors to consider with respect to CC/hostility. However, the divergence in findings between studies using coding schemes and those using self-report measures warrants further investigation.

In contrast to shame, guilt was not theorised to be related to CC/ hostility due to its hypothesised function in promoting reparative behaviours (Tangney and Dearing, 2002). This was supported by the reviewed literature. The consistency in findings irrespective of the measurement approaches adopted by individual studies indicates the robustness of these findings, and militates against considering guilt as an important factor with respect to CC/hostility (Hatfield, 1981).

4.1. Methodological limitations and implications for research

Collectively, data appear to support the importance of considering carers' self-conscious emotions as potential contributors to their EE, and provide support for a shift away from considering EE as a response to symptomatology and instead toward considering the potential contribution of interpersonal and intrapsychic processes (Campbell et al., 2013). However, is it important to consider the limitations of both the review process itself and the included studies before drawing firm conclusions regarding the clinical significance or utility of these findings. With respect to the former, both published and unpublished data were searched and included in this review in an attempt to minimise the chances of missing key studies and avoid perpetuating the publication bias common to psychological research (Ferguson and Brannick, 2012). However, only citations written in English were considered for inclusion, which may have resulted in a language, selection or cultural bias, particularly considering that base-levels of guilt, shame and EE vary between cultures (Weisman de Mamani et al., 2007), as do the topics and actions that engender guilt and shame (Sznycer et al., 2012). In addition, methodological heterogeneity precluded meta-analysis, which may have allowed for more in-depth analysis of pooled study data than narrative synthesis alone.

More problematic is the potential impact of the methodological limitations of included studies. First, it was not possible to determine the causal direction of the effects noted in this review, nor examine the mechanism(s) by which constructs may be linked. Second, differences in the strength and significance of relationships were noted as a function of the measurement approaches taken to assess both guilt and shame, and EE. This likely reflects the conceptual ambiguity surrounding guilt and shame (Kim et al., 2011), but may have implications for the interpretation of the effects noted in this review. Furthermore, variation was often noticed in participants' average levels of EOI and CC/hostility, which likely influenced the comparability of samples and generalisability of findings. Finally, all studies were conducted in Western societies, using predominantly middle aged, female participants who were largely in receipt of services. Duration of caring and amount of weekly contact between carers and service-users was frequently under-reported, and gender differences in participants' EOI and CC/hostility were observed, but not controlled for, in several of the included studies. As such, the generalisability of these findings beyond the samples studied in the included papers is unclear.

Future research should attempt to address the aforementioned limitations by adopting prospective, longitudinal designs and recruiting representative samples of carers to minimise the possibility of selection bias and/or polarisation of responses. Ideally, guilt and shame should be assessed within the context of the caring relationship by supplementing self-report measures with well-established psychometric properties within a carer population with paralinguistic assessment⁷ (Tracy and Robins, 2007). This approach may be particularly valuable given research suggesting that carers are often unaware of shameful

feelings (Ryan, 1993). Furthermore, rather than relying solely on EOI and CC/hostility as indices of EE, researchers may wish to also consider investigating the potential influence of positive affect by incorporating indices of warmth and positive comments into their investigations. These components of EE are often conspicuous by their absence within the EE literature, but may provide additional information to supplement the findings of this review (Burbach, 2013). Given the small sample sizes of the studies included in this review, researchers should ensure analyses are adequately powered and may wish to consider controlling for the effects of variables such as gender and amount of weekly contact in analyses. Future research should also aim to investigate the potential influence of culture and ethnicity on the findings observed in this review, particularly in light of recent preliminary data suggesting that high EE is associated with better outcomes for African American families (Gurak and Weisman de Mamani, 2015). Examination of the psychological processes associated with the development of both EE and care-specific guilt and shame, together with reciprocal causation between the variables, would also be welcomed. This may help to provide insight into why some carers may be more susceptible to care-specific guilt and shame than others, as well as illuminating the factors that reduce vulnerability to guilt and shame (Lobban and Barrowclough, 2015). Currently, the direction of the association between shame or guilt and EE is unclear and either direction (or a reciprocal association) is equally theoretically plausible. Whilst we have discussed how shame and guilt may contribute to EE, engagement in critical, hostile or emotionally over-involved caring behaviours may well generate a subsequent appraisal of these actions, which may induce further shame (e.g. where critical behaviour is appraised as a sign of personal inferiority) or guilt. This is clearly an area which warrants further investigation. Attachment theory, and the related capacity of mentalisation, may form non-pathologising theoretical frameworks for future research, particularly given the relational nature of guilt, shame and EE (Jenkins and Karno, 1992; Tangney and Dearing, 2002).

4.2. Clinical implications

The aforementioned limitations notwithstanding, the findings of this review have potential implications for clinicians working with carers and their families. At present, FIs are largely outcome- rather than process-driven, and their efficacy is often evaluated against symptom-driven outcomes, such as relapse rates (Bucci et al., 2016). We argue that FIs should instead focus on identifying and modifying the underlying psychological processes associated with high EE, as these processes are likely to transcend diagnostic categories and influence the outcome of FIs. Specifically, the findings of this review indicate the importance of considering specific drivers of guilt and shame when working with carers displaying high EE. To this end, therapists may wish to consider sensitively placing more emphasis on the behavioural and psychological sequela of guilt and shame when assessing, formulating and intervening to alleviate carers' and families' difficulties. Therapists may wish to incorporate principles from compassion focused therapy (CFT), an integrated psychotherapeutic approach developed to help individuals prone to experiencing shame and self-criticism to build the capacity to experience compassion, to aid with this task (Gilbert and Irons, 2005). Individual and family interventions designed to reduce carers' guilt, shame, self-blame and burden (Weisman de Mamani and Suro, 2016) and/or those that focus on the role of carers' behaviours in the process of recovery (Lobban and Barrowclough, 2015) may also provide useful starting points for practitioners. Should the hypothesis that a reduction in guilt and shame may also result in a change in EE behaviours be correct, then targeted interventions focused, in part, upon carers' guilt and shame may have positive outcomes for both carers and service-users (Hatfield, 1981). Furthermore, adoption of a process-driven nosology may allow for existing FIs to be enhanced, and may facilitate the development and

⁷ Analysis of aspects of spoken communication that do not involve words.

outcome testing of further interventions.

5. Conclusions

The findings of this review extend current understandings of the relationships between carers' EE and their guilt and shame by lending support for the importance of considering both guilt and shame as potential contributors to carers' EE. Whilst caution must be taken when generalising these findings to clinical practice, data indicate that a focus on self-conscious emotions may be beneficial when delivering effective individual and family interventions for carers with high EE. However, the methodological limitations of the included studies, coupled with the limited research available, means that more high-quality research is needed before firm conclusions can be drawn regarding the clinical significance or utility of these findings.

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