TREATMENT FOR DEPRESSION IN PATIENTS WHO HAVE SUFFERED FROM EARLY LIFE STRESS

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SUMMARY

Background: People with Major Depressive Disorder (MDD) are far more likely to suffer from Early Life Stress (ELS) than the average population. This typically increases severity of symptoms, and often leads to treatment resistance. This study set out to examine which treatments work best to treat depression in patients who have suffered from ELS, as well as possible interactions between ELS and antidepressant effects in therapies.

Method: A literature review was conducted in July 2020 using the databases Embase, PsychInfo, and MEDLINE. The search looked for clinical trials treating MDD with psychotherapies and pharmacotherapies with patients who suffered from ELS. Data regarding demographics, comorbidities, measurement tools, and outcomes (generally response rates and remission) were extracted. The data was compared according to treatment types.

Results: Cognitive Behavioural Therapy (CBT) had the best evidence for treating MDD in people with ELS. There was some mixed evidence for Interpersonal Therapy, SSRIs, and SNRIs as suitable treatments for MDD. There was also very promising but limited evidence for Cognitive Behavioural Analysis of System Therapy and combination treatments (pharmacotherapy and psychotherapy together). Nefazodone (a SARI) had the weakest evidence.

Conclusions: CBT was the most effective treatment for MDD with ELS. However, more research needs to be conducted to ascertain a proper hierarchy of treatments, particularly with combination treatments.

Key words: *major depressive disorder - early life stress – psychotherapy - pharmacotherapy*

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INTRODUCTION

Affective disorders are one of the leading causes of disability worldwide, and depression alone is said to affect over 260 million people globally (James et al. 2018). According to the same report, depressive disorders (alongside low back pain and headache disorders) were the leading cause of disability in 2017. Given that depression is one of the most common affective disorders, it is crucial to examine it further, delving into the specific populations that it may affect and how these populations can be affected by it.

Defining Early Life Stress

One of these populations is comprised of people who have suffered from early life stress (ELS). However, a potential problem with identifying this group comes about when attempting to define ELS. First, it is hard to establish what "early life" constitutes. Particularly, people react to stressors differently according to the point in which they are in their life, and as such may show varying levels of resilience according to whether they faced an adverse experience in early childhood or adolescence (Cassidy & Mohr 2001).

Furthermore, there are many different adverse experiences of different severities which may have varying detrimental effects of different degrees on psychiatric conditions, particularly depression (Nikkheslat et al. 2020). A review by Carr (2013) found that the most prominent forms of ELS linked to mood disorders were physical abuse, sexual abuse, and neglect (this review has the highest evidence for unspecified neglect, although other research generally points more heavily towards emotional neglect; Wiersma et al. 2009). This same review also found emotional abuse to be heavily linked with personality disorders and schizophrenia, and physical neglect to be heavily linked with personality disorders. This is important because of the high comorbidity between specific personality disorders (mainly borderline personality disorder, or BPD) and depression (Farabaugh et al. 2005).

Another issue with defining ELS lies within the fact that people have varying levels of resilience that are recently beginning to be understood beyond the socio-cultural aspects and more into the neurocognitive level (Baratta & Maier 2019, Fallon et al. 2019, Raghavan & Sandanapitchai 2019). As such, different stressors and ostensibly traumatic phenomena may or may not produce a traumatic response in the person. One way to circumvent this problem would be to define ELS as having suffered from something (in early life) that has led to trauma.

Nonetheless, this method is perhaps idiosyncratic to a fault, insofar as it becomes incredibly difficult to assess trauma in such a way (Marton 2016). To do this, the best-developed tools are those that either measure the outcomes of trauma, generally in the form of related disorders (such as Post-Traumatic Stress Disorder, or

PTSD), or to identify exposure to potentially traumatic experiences (which, again, overlooks differences in resilience). Moreover, though there are ways to measure the extent to which a potentially traumatic event may have impacted someone, there is significant heterogeneity in measurement tools, and it is increasingly challenging to determine and isolate how that experience could have led to psychological, affective, biological, and social impairments (Marton 2016).

Consequently, most research on trauma and ELS generally focuses on previous exposure to adverse experiences that could be traumatising (Copeland et al. 2018). Although the DSM (American Psychiatric Association 2013) defines a traumatic event (specifically in its diagnostic criteria for PTSD) as one that is life-threatening or violent, some other events could lead to trauma (Copeland et al. 2018). For example, sexual abuse, harassment, bullying, emotional neglect, physical neglect, and parental loss have all been linked to lower functioning later in life and worse outcomes with psychiatric conditions (Carr et al. 2013).

The final problem with defining ELS (and consequently, how to measure it) lies within the age boundaries. As previously stated, the extent to which one can be affected by a traumatic event may be dependent on the stage of development in which they find themselves (Cassidy & Mohr, 2001). Moreover, the type of trauma or adverse experience may interact with the age factor (Lamp 2013). For example, parental loss or neglect could lead to an attachment disorder if it occurs when the child is very young (American Psychiatric Association 2013). Furthermore, a parental loss could not be as traumatising for a teenager who lives by him or herself, and/or someone who has had more time to develop the tools necessary to overcome challenging situations. Finally, sexual abuse can be processed very differently by a victim according to the victim's age (Cassidy & Mohr 2001).

Ultimately, ELS is very hard to define, mostly because of its different effects and types. Arriving at a definition of it that is both sufficiently idiosyncratic to accurately reflect people's experiences and sufficiently parsimonious so that accurate research can be performed is nothing short of challenging. Nevertheless, research has generally shown that, though the effects may be different, there are considerable commonalities in its repercussions (Carr et al. 2013), and there are many measuring tools that can allow for them to be studied together, such as the Childhood Trauma Questionnaire (CTQ; Bernstein et al. 2003). In addition, although divergent stages of development can account for some differences in the development of trauma and different repercussions following ELS, it is also true that the effects are not entirely dissimilar, and generally, early life adverse experiences across different parts of the development will have similar consequences later on in life (Cassidy & Mohr 2001, Lamp 2013).

As such, this paper defines Early Life Stress as any adverse experience or experiences occurring prior to adulthood that could traumatise someone. ELS was thus examined in the forms of physical abuse and neglect, emotional abuse and neglect, sexual abuse, early parental loss, and exposure to violence. Instances such as bullying or repeated verbal abuse are considered emotional abuse, and acts of sexual violence, rape, sexual harassment, and so on are considered sexual abuse. There is also a caveat that when appropriate, specific stressful life events that do not fit into these definitions could be considered a type of ELS according to the situation, but it is important to note that the measurement of these is far less clearly defined. With this definition in mind, it then becomes essential to examine ELS can affect those with depression.

ELS, Depression, and Treatment Outcomes

Early Life Stress has been generally shown to have an adverse effect on treatment outcomes for depression. A meta-analysis and review by Nanni et al. (2012) found that depressed patients generally had far poorer treatment outcomes if they suffered from ELS, both in terms of remission and mere treatment response (both of these generally defined by a significant decrease in observer-rated symptoms, mainly using a scale). Moreover, depressive symptomatology is more magnified within this population, which could somewhat explain why they are generally less responsive to treatment (Kim et al. 2013). Unsurprisingly, this specific population (people with depression who suffered from ELS) are far more likely to become treatment-resistant (generally defined as showing no response to two or more treatments) than depressed patients without ELS (Tunnard et al. 2014, Carr 2013).

As such, it is of paramount importance that we thoroughly examine the best treatments for depressed people who have suffered from ELS. Given that depressed patients with ELS suffer more and are generally more treatment-resistant, it is hard to develop treatments that could work very well for this population. Consequently, this paper sets out to systematically review the literature on treatments for people who suffer from Major Depressive Disorder (MDD, the most common form of clinical depression) and who have also suffered from Early Life Stress.

METHOD

Inclusion Criteria

To be included in the analysis, studies had to have participants with a primary clinical diagnosis of Major Depressive Disorder. The studies had to reliably assess ELS in a way consistent with the definition of childhood maltreatment and/or adverse life events prior to age 18 and include these measurements in their analysis. The

study must have examined a way to specifically treat depression that involved pharmacotherapy and/or evidence-based or well-described psychotherapy. All participants must have been human and 18 years or older at the time of participation in their study. The study has to have been written in Catalan, English, Portuguese, or Spanish. Studies had to be clinical trials published by the 16th of July, 2020.

Exclusion Criteria

Exclusion criteria for this review included cross-sectional or correlational research, exclusively epidemiological research, literature reviews, and non-clinical trials. Studies not written in Catalan, English, Portuguese, or Spanish were excluded. Studies using participants with Bipolar Disorders, with a history of manic/hypomanic episodes, or with a primary diagnosis of another affective disorder or disorder that could better explain affective symptoms were excluded. Studies using participants under 18 were excluded, as well as studies that used non-human participants or samples. Furthermore, studies that did not measure and analyse the role and/or interaction of ELS, MDD, and treatments were excluded.

Study Identification

To search for studies, the following databases were used: MEDLINE, PsychInfo, and Embase. Filters including languages, age and human population were applied according to the inclusion and exclusion criteria. Overall, a total of 13 studies were included in this analysis.

Data Extraction

A Microsoft Excel sheet was created to extract data. Each of the selected studies was assigned a row, and then data was systemically extracted from it. This included participant numbers and demographic data, as well as locations of the studies. Data regarding comorbidities were also extracted. Data were then gathered regarding the interventions used to treat MDD, as well as control conditions and comparators. Data regarding the scales used to measure depression were also recorded. Then, reported outcome information was extracted. This included information regarding treatment response and overall remission, as generally grouped by treatment group. There were also columns made to assess findings regarding the effect of ELS on treatment outcome if at all reported. Final columns were made to add notes about methodology, results, and overall observations in each study.

RESULTS

13 total studies were observed to examine the relationship between ELS and MDD treatment outcome.

Table 1 presents general information about each study. Three of the studies analysed data from the same sample of sexually abused women who were treated with Interpersonal Therapy (IPT) or usual care (non-IPT evidence-based psychotherapies; Cort et al. 2012, Smith et al. 2012, Talbot et al. 2011). These were all kept in the data analysis because they can provide important information about this specific population and the effectiveness of certain treatments.

Demographic Data

The overall demographic data can be found in Table 1. The studies had an average of 334 participants, with a standard deviation of 330. All studies (except for Williams et al. 2016) were comprised of a predominantly female sample. Most studies had an age average either in their late 30s or early 40s. Furthermore, most studies took place in western or westernised countries (e.g. Canada, United States, and Italy), except for Xu et al. (2016), which took place in China.

There was more variability in terms of employment and income status, and 7 studies did not report on it at all (Harkness et al. 2012, Klein et al. 2009, Minelli et al. 2019, Nemeroff et al. 2003, Niciu et al. 2015, Williams et al. 2016, Xu et al. 2016). The three studies with the same population (Cort et al. 2012, Smith et al. 2012, Talbot et al. 2011) reported that the majority of their sample depended on public assistance for their income (59%) and that a large majority were unemployed (69%). Conversely, Docter et al. (2018) reported that a large majority of their sample (72%) were employed, and Miniati et al. (2010) also reported that their average participant was employed (specific number not given). Furthermore, Duberstein et al. (2018) reported that roughly 40% of their sample earned less than $10,000 (US Dollars) a year, and about 42% earned between $10,000 and $40,000. The rest either earned more than $40,000 (14%) or had missing data for this (4%) (Table 1).

Comorbidities

Data regarding comorbidities can be found in Table 2. There were 3 main comorbidities that were recorded: Posttraumatic Stress Disorder (PTSD), Borderline Personality Disorder (BPD), and anxiety disorders. The data displayed specifically refer to people with depression and ELS and excludes patients that do not fall under either (or both) of these conditions. Whenever data regarding comorbidities were gathered but not presented for participants suffering from MDD with ELS, NR (not reported) was put in its place. There was very high heterogeneity both in the range of comorbidities as well as in their reporting and exclusion based on a comorbid psychiatric diagnosis.

Table 1. Specific characteristics of clinical trials investigating the relationship between ELS and specific treatment outcomes in patients with Major Depressive Disorder

Study	Partici-pants (n)	Location	Female %	AA*	Interventions	Control Group	Scal**	Measure of ELS	MDD Diagnosis	Results
Nemeroff et al. 2003	681	USA (not specified)	65	43	CBASP SARI (Nefazodone) Combination	None	HDRS	CTS	SCID	Psychotherapy and combination worked best to treat depression with ELS.
Klein et al. 2009	808	USA	55	44	SSRI (sertraline, escitalopram) SNRI (Venlafaxine XR), NDRI (Buproprion XL), MAOI (Mirtazapine)	None	HDRS, IDS-SR	MOPS, CTQ,	SCID	Very poor remission out-comes of those with ELS compared to those without (32% and 44% respectively).
Miniati et al. 2010	312	USA (Pittsburgh) Italy (Pisa)	73	39	IPT, SSRI (Citalopram, Escitalopram)	None	HDRS, QIDS, MOODS-SR	Structured and Unstructured Clinical Interviews	SCID	People with ELS were more likely to require combination treatment, and generally had an earlier onset and longer duration of depression.
Talbot et al. 2011	70	USA (Rochester NY)	100	36	IPT	"Usual Care" (mix of non-ipt individual psychotherapies)	BDI, HDRS	Structured Clinical Interview	SCID	IPT was generally better in alleviating depressing symptomato-logy than usual care.
Cort et al. 2012	70	USA (Rochester NY)	100	36	IPT	"Usual Care" (mix of non-ipt individual psychotherapies)	BDI, HDRS	CTQ, TLEQ	SCID	Comorbid BPD and longer history of depression predict a more negative treatment outcome. No differences across subtypes of sexual abuse in predicting treatment out-comes.
Harkness et al. 2012	203	Canada (Toronto)	64	41	IPT, CBT, NDRI (Bupropion) SSRI (Citalopram, Fluoxetine, Fluvoxamine, Sertraline) MAOI (Phenelzine) SNRI (VenlafaxineXR)	None	HDRS	CECA, Standardised Interview for severity	SCID	ELS predicted worse treatment outcome in the IPT group, and generally predicted shorter time to recurrence.
Smith et al. 2012	70	USA (Rochester NY)	100	36	IPT	"Usual Care" (mix of non-ipt individual psychotherapies)	BDI, HDRS	Structured Clinical Interview	SCID	IPT was generally better in alleviating depressing symptomato-logy than usual care.
Niciu et al. 2015	50	USA (New Haven, CT)	60	43	CBT	None	BDI, HDRS	GPELS, ELTI, KLS	SCID	Only early parental loss predicted decreased response to antidepressants, other aspects of ELS did not.
Williams et al. 2016	1008	USA, Netherlands, Australia, New Zealand, South Africa	<50	NR	SSRI (Escitalo-pram, Sertraline) SNRI (VenlafaxineXR)	People without MDD	HDRS QIDS-SR	ELS-Q	Medical & medication history MINI HDRS	Abuse predicted worse response with sertraline than with escitalopram and venlafaxine.

*AA - Age Average;   ** Scal - Scales use for Symptom Severity;*

Notes: BDI: Beck Depression Inventory;   CBASP: Cognitive Behavioural Analysis of System Psychotherapy;   CBT: Cognitive Behavioural Therapy;   CECA: Childhood Experience of Care and Abuse (Structured Interview and Questionnaire);   CTQ: Childhood Trauma Questionnaire;   CTS: Childhood Trauma Survey;   ELS-Q: Early Life Stress Questionnaire;   ELTI: Early Life Trauma Inventory;   EMDR: Eye Movement Desensitization and Reprocessing;   GPELS: Global-Perceived Early Life Stress;   HDRS: Hamilton Depression Rating Scale;   IPT: Interpersonal Therapy;   KLS: Klein Loss Scale;   LES: Life Events Scale;   MADRS: Montgomery-Åsberg Depression Rating Scale;   MAOI: Monoamine Oxidase Inhibitor;   MCMI: Millon Clinical Multiaxial Inventory;   MINI: international neuropsychiatric interview;   MOODS-SR: Mood Spectrum Self-Report;   MOPS: Measure Of Parental Style;   NDRI: Norepinephrine/Noradrenaline and Dopamine Reuptake Inhibitor;   QIDS: Quick Inventory of Depressive Symptomatology;   SARI: Serotonin Antagonist and Reuptake Inhibitor;   SCID: Structured Clinical Interview for DSM Disorders;   SNRI: Serotonin and Norepinephrine/Noradrenaline Reuptake Inhibitor;   SSRI: Selective Serotonin Reuptake Inhibitor;   TLEQ: Traumatic Life Events Questionnaire;   TR-CBT : Trauma-Focused Cognitive Behavioural Therapy;   NR: Not Reported

Table 1. Continues

Study	Partici-pants (n)	Location	Fema-le %	AA*	Interventions	Control Group	Scal**	Measure of ELS	MDD Diagnosis	Results
Xu et al. 2016	281	China (Beijing, Nanjing, Changsha, Yangzhou, Huai'an)	59	39	SSRI, SNRI	None	HDRS	CTQ, LES	3 Psychiatrists	ELS did not have an effect on antidepressant response. There was a significant inter-action between ELS and a specific genotype in an SNP in a regression with treatment outcome as a DV.
Docter et al. 2018	604	Germany (not specified)	65	43	Group psycho-therapy, individual psycho-therapy, group support	None	QIDS-C	CTQ	QIDS-C, SCID	Individually, emotional neglect is somewhat negatively related to treatment outcome. However, as a whole, ELS was not found to be a significant predictor of treatment outcome.
Duberstein et al. 2018	161	USA (not specified)	100	30-39	IPT	"Usual Care" (mix of non-ipt individual psycho-therapies)	BDI, HDRS	Structured Clinical Interview	SCID, consensus diagnosis meeting between resea-rchers and clinicians	Similar effects between IPT and Usual Care (both effective), but IPT was better at treating traumatic symptoms and improving social function.
Minelli et al. 2019	22	Italy (Verona)	73	53	EMDR, TF-CBT	None	BDI, MADRS, MINI	CECA-Q, Holmes-Rahe Life Stress Inventory	SCID, MCMI	Generally better response to EMDR than TF-CBT, but both trauma focused psychotherapies seemed effective treatments for depression.

*AA - Age Average;   ** Scal - Scales use for Symptom Severity;*
Notes: BDI: Beck Depression Inventory;   CBASP: Cognitive Behavioural Analysis of System Psychotherapy;   CBT: Cognitive Behavioural Therapy;   CECA: Childhood Experience of Care and Abuse (Structured Interview and Questionnaire);   CECA-Q: Childhood Trauma Questionnaire;   CTS: Childhood Trauma Survey;   ELS-Q: Early Life Stress Questionnaire;   ELTI: Early Life Trauma Inventory;   EMDR: Eye Movement Desensitization and Reprocessing;   GPELS: Global-Perceived Early Life Stress;   HDRS: Hamilton Depression Rating Scale;   IPT: Interpersonal Therapy;   KLS: Klein Loss Scale;   LES: Life Events Scale;   MADRS: Montgomery-Åsberg Depression Rating Scale;   MAOI: Monoamine Oxidase Inhibitor;   MCMI: Millon Clinical Multiaxial Inventory;   MINI: mini international neuropsychiatric interview;   MOODS-SR: Mood Spectrum Self-Report;   MOPS: Measure Of Parental Style;   NDRI: Norepinephrine/Noradrenaline and Dopamine Reuptake Inhibitor;   QIDS: Quick inventory of Depressive Symptomatology;   SARI: Serotonin Antagonist and Reuptake Inhibitor;   SCID: Structured Clinical Interview for DSM Disorders;   SNRI: Serotonin and Norepinephrine/Noradrenaline Reuptake Inhibitor;   SSRI: Selective Serotonin Reuptake Inhibitor;   TLEQ: Traumatic Life Events Questionnaire;   TR-CBT: Trauma-Focused Cognitive Behavioural Therapy;   NR: Not Reported

Table 2. A display of the reported psychiatric comorbidities in the selected study samples

Study	Comorbid PTSD (%)	Comorbid BPD (%)	Comorbid Anxiety (%)
Nemeroff et al. 2003	Excluded	NR (59 any PD)	Excluded (33 history)
Klein et al. 2009	Excluded	Excluded	NR
Minitati et al. 2010	9	6	50
Talbot et al. 2011	66	37	86
Cort et al. 2012	66*	37	86*
Harkness et al. 2012	NR/NM	Excluded	NR/NM
Smith et al. 2012	66	37	86*
Niciu et al. 2015	NR/NM	NR/NM	NR/NM
Williams Et al. 2016	Excluded	NR/NM	NR/NM
Xu et al. 2016	NR/NM	NR	Excluded
Docter et al. 2018	NR/NM	NR	NR/NM
Duberstein et al. 2018	88	53	58
Minelli et al. 2019	41	Excluded	77

BPD: Borderline Personality Disorder; NM: Not Measured; NR: Not Reported; PD: Personality Disorder.
Numbers marked with an asterisk (*) were obtained from different papers, such as study protocols or different studies with the same participants. Fields were marked NR/NM when it was unclear whether a study failed to measure this comorbidity or whether it failed to report it after measuring.

Measurement Tools

Before reporting on the prevalence of different measurement tools, it is important to note that many of these, despite originating from the same tools, have different variations of each other. This is generally according to their length, whether they are self-reported or clinician-rated, or depending on whether the same tool has been updated into newer versions. Generally, these are all grouped under one name, but differences across these and their implications will be addressed in the discussion section. The most popular tool for diagnosing depression was the Structured Clinical Interview for DSM Disorders (SCID), the most popular one for assessing symptom severity was the Hamilton Depression Rating Scale (in this review referred to as HDRS, but also known as HAM-D and HRSD), and the most common tool for measuring ELS was the Childhood Trauma Questionnaire (CTQ).

Treatment Types

There were three main types of treatment: psychotherapy, pharmacotherapy, and combination groups. The most common psychotherapies used in the studies reviewed were IPT and CBT, which were present in 23% and 11% of the studies respectively. Trauma-focused CBT (found in Minelli et al. 2019) was generally regarded as CBT. Docter et al. (2018) used a wide variety of psychotherapies (see Table 1), though these were not overly explained and as such were classified as "Unspecified Psychotherapy." The most common antidepressants were SSRIs (Selective Serotonin Reuptake Inhibitors) and SNRIs (Serotonin and Norepinephrine/Noradrenaline Reuptake Inhibitors), and were present in 19% and 15% of the studies respectively. Docter et al. (2018) reported that pharmacotherapy was made available to participants, but they did not specify which drug types were used.

Four studies used combination treatments: Docter et al. (2018), Minelli et al. (2019), Miniati et al. (2010) and Nemeroff et al. (2003). Docter and Minelli did not analyse the effect that pharmacological treatment group had on outcome, though Minelli reported that there was no significant difference in pharmacological use across the two different treatment types (EMDR and TF-CBT). Nemeroff was the only study that specifically measured treatment outcome comparing the combination group to others. They used CBASP and Nefazodone, a drug of the SARI type.

Treatment Outcomes

It is challenging to compare treatment outcomes, even for the same therapies, when each study generally has its own comparators, outcome measures, and different measuring tools overall. It is important to note that most studies have regarded ELS as a binary variable (either having suffered from it or not). When possible, the differences in ELS subtypes were reported. The discussion provides a more critical analysis of different forms of ELS and how they may impact people differently. First, however, outcomes are presented for each treatment as reported in their respective studies, starting with psychotherapies, combinations, and then pharmacotherapies.

As previously stated, the most common type of psychotherapy was IPT. This is likely because three of the studies (Cort et al. 2012, Smith et al. 2012, Talbot et al. 2011) used data from the same trials with sexually abused women. These three studies in particular compared IPT to what they defined as "Usual Care/UC", which was defined as a mixture of non-IPT, evidence-based psychotherapies. Overall, they found that IPT was better at reducing depressive symptoms (Talbot et al. 2011) than UC was. However, they did not provide information regarding the percentage of responders or remitters under either condition.

Moreover, Smith et al. (2012) reports that sexually abused women developing insecure attachment styles, and that as a consequence have poorer outcomes in depression treatments. Then, they state that this relationship between attachment style and outcome is mediated (particularly in the IPT group) by the working alliance between patient/client and therapist. Duberstein et al. (2018) also state that IPT was better at improving social functioning, which could be related to Smith's et al. (2012) research on attachment models and working alliance. Unfortunately, however, Duberstein did not find that IPT or usual care (a similar comparator condition to the one previously described for the other studies) were significantly different from each other in reducing average depression severity. There were also no significant differences in remission rates.

The study by Miniati et al. (2010) did not compare the IPT group to any other one (they used IPT and SSRIs), but they did find that people with ELS generally required a combination of both treatments more so than those without ELS. Furthermore, Harkness et al. (2012) found that, amongst their three groups (IPT, CBT, and Antidepressants), IPT was generally the worse one judging by response rates (54%, 60%, and 72% respectively). Moreover, when grouped according to ELS, those who suffered from ELS were far less likely to respond to IPT than they were to CBT or Antidepressant medication. However, the latter is very heterogenous and was not then broken down according to antidepressant type.

Niciu et al. (2015) found that CBT was a significantly effective treatment for depressed patients with ELS, achieving an average 41% reduction of HDRS-reported symptoms and a response rate of 38%. Using the KLS, they also found a significant interaction between early parental loss and time in the effect of the treatment. The researchers found that having lost a parent would interact with the effect of time, so the antidepressant response to CBT was heightened. The group effect (early parental loss or not) did not significantly interact with antidepressant response. These last two findings were only applicable when measured with the HDRS, and the effect did not remain when using the BDI. Minelli et al. (2019) also found both TF-CBT and EMDR to be effective in reducing depressive symptoms (p<0.001) and found that EMDR produced a statistically more significant reduction in depressive symptomatology than TF-CBT, both using the MADRS and the BDI. There were no significant group differences in response rates.

Nemeroff et al. (2003) found that CBASP was an effective treatment for depressed people who suffered from ELS. CBASP produced larger response and remission rates in participants with ELS than in participants without, but it is not reported whether this difference is statistically significant. Nefazodone, a SARI, was conversely far worse at treating depression, both with and without ELS. In the condition without ELS, the combination treatment was far better at alleviating depressive symptomatology and increasing remission rates. However, in the condition with ELS, both combination and the CBASP group alone were far better at treating this group than Nefazodone.

Several studies have not been mentioned that focus exclusively on pharmacotherapy as treatments for depression with ELS. Klein et al. (2009) determined that, overall, SSRIs and SNRIs were not overly useful in treating depression with ELS (remission rates of 32% compared to 44% without ELS). However, they do not report whether this difference is significant. Overall, after several analyses, they determined that having suffered clinically significant abuse was significantly related to treatment outcome, in this case coded as treatment response.

Xu et al. (2016) had a more biological approach and determined that ELS significantly interacted with a single nucleotide polymorphism (SNP, with the name rs2171363) to affect antidepressant response. Specifically, this SNP was a significant predictor of antidepressant effect (as measured by response), and there was a significant interaction between it and ELS. They also state that it is too early to tell for what specifically that SNP may code, and as such, it becomes hard to draw a connection with the larger picture of the gene-environment interaction.

Williams et al. (2016) was the only one of these studies that compared the effect of the treatment group in treatment outcomes of depression. Overall, they found that a history of abuse predicted worse outcomes with Sertraline (SSRI) than with Escitalopram (SSRI) and Venlafaxine XR (SNRI). Furthermore, they found that people who had been abused between 4 and 7 years old were far less likely to respond to treatment at all or remit: response rates were 82% without abuse compared to 18% with, and remission rates were 84% and 16% without and with abuse respectively. They concluded that abuse (be it physical, emotional, or sexual) all could interact to create a worse antidepressant response.

The only study not yet addressed in treatment outcomes is that of Docter et al. (2018). Their methodology was somewhat mixed, and either did not record or did not report data according to treatment groups, so it is near impossible to determine precisely how ELS may have been affecting each treatment response or effect. Interestingly, however, they found that ELS was not generally associated with treatment response, except for the individual measure of emotional neglect, which was associated with poorer outcome. However, when put in a larger model, the effect of this variable became non-significant.

DISCUSSION

Demographics and Comorbidities

The first and perhaps most glaring result is the heterogeneity in the samples and measurements. There are significant discrepancies in sample sizes, employment/income status of participants, and gender of participants. Furthermore, there are lacking data regarding ethnicities of participants, making it difficult to

generalise. All but one study (Xu et al. 2016) were primarily conducted in countries said to have more westernised cultures (with the arguable exception of Williams et al. which has a study site in South Africa), and those who did report ethnicities generally reported that the majority of their sample was comprised of white women, which presented its own problems. For example, it is hard to ascertain the efficacy of IPT in treating depression with ELS, as 4 of the studies using IPT specifically used samples comprised of sexually abused women (Cort et al. 2012, Duberstein et al. 2018, Smith et al. 2012, Talbot et al. 2011). Research has shown that there are significant sex differences in processing trauma and that these may consequently affect antidepressant effects in treatment (Fallon et al. 2019, Helpman et al. 2017).

The data on comorbidities is also very mixed. It is particularly intriguing that Miniati et al. (2010) found such low comorbidity rates for PTSD and BPD, but then found higher ones (more consistent with the other studies) for anxiety disorders. This could, perhaps, be due to them excluding primary diagnoses of PTSD and/or BPD, but this is not strictly mentioned in their methodology. Given that these are not epidemiological studies, it would be inaccurate to draw conclusions regarding the actual comorbidity rates of these illnesses within this population. However, it is enough to infer that these other disorders are very likely to impact this population at a clinical level seriously. Other epidemiological studies and reviews have also stated high comorbidity across people with ELS in general and many psychiatric disorders, as well as with just depression (Carr et al. 2013, Farabaugh et al. 2005). Nevertheless, these often lack cross-cultural validity and are not entirely representative of a sample suffering specifically from MDD with ELS.

In addition, many of the studies in this review excluded patients with some of these comorbidities, and other subtypes of depression were often discriminated against in the selection process (e.g. psychotic symptoms or extreme symptom severity). Though these decisions are generally understandable and study-dependent, it does limit the extent to which one can generalise from these studies, especially considering that depressed patients with ELS are more likely to have more severe and treatment-resistant cases of depression (LeMoult et al. 2019, Schilling et al. 2014, Tunnard et al. 2014). All in all, however, it would appear as though comorbidity with PTSD, BPD, and Anxiety is something that must be taken seriously, as it is highly prevalent, and can even affect treatment outcomes (Coplan et al. 2015, Duberstein et al. 2018, Nanni et al. 2012).

Measurements

As previously mentioned, it is good that most studies use similar criteria and methods to both diagnose and assess symptom severity. The SCID has generally been shown to be fairly reliable and valid (First et al. 1996, First et al. 2004, Spitzer et al. 1994). Unfortunately, however, the studies that provided citations for their use of the SCID were for the original measures in the 90s, and as such did not provide validity or reliability estimates of their own in their use of the tool. Furthermore, all studies used DSM criteria (DSM-IV or DSM 5 according to when the study was conducted), which provides more consistent data regarding diagnosis. However, the DSM has previously been accused of being overly categorical (at least, compared to the ICD), making it better for more clear-cut research but perhaps less sensitive to more phenomenological approaches (Goldberg et al. 2009).

In terms of the HDRS, it is, fortunately, a very reliable and valid measurement tool (Hamilton 1986), and is used in many clinical trials worldwide (Nanni et al. 2012). Nevertheless, once again the studies in this review generally failed to provide their validity and reliability estimates, which is a lost opportunity, given that this could have provided information regarding whether the HDRS is equally valid and reliable in this population. Unfortunately, the HDRS is not sensitive to atypical symptoms and often measures different symptoms (like irritability and anxiety), so subtle changes in depressive symptomatology in this population may go overlooked and unaccounted for, especially considering that this population may exhibit slightly different symptomatology (LeMoult et al. 2019, Tunnard et al. 2014).

Measurements of ELS were very diverse, to the point where 16 different measures were used in only 13 studies (if we count each structured interview as its measure). Naturally, there lies a problem with most structured clinical interviews in this category: the researchers did not release all the questions, and as such may have asked about things that could not be as relevant to this review (according to our definition of Early Life Stress). Moreover, it is not clearly explained how they specifically extracted data and the sensitivity they may have given to each answer and question. As previously mentioned, there can be varying degrees of trauma (Fallon et al. 2019, Marton 2016): being the victim of a single incident of mild sexual harassment is unlikely to be as traumatising as being the repeated victim of sexual abuse throughout a longer timeframe. This is something that most, if not all, of the studies seemed to overlook: most of them merely addressed whether or not participants underwent a potentially traumatic experience (or more than one), but rarely measured how increasing degrees of trauma could affect treatment outcome. This is a shame, considering that specific measuring tools, like the CTQ, allow one to examine different trauma degrees (Bernstein & Fink 1998, Bernstein et al. 2003). However, the heterogeneity of the measurements can be beneficial, as there is a broader examination of different types of traumatic events that can be researched. Bearing all of these caveats in mind, it is important to then analyse the results with further critique of each study's methods (when relevant) to understand these data.

Interpretation of Outcomes

The IPT analysis was heavily biased by a lack of diversity in the samples, considering that 3 studies used the same one, and one more also used exclusively sexually abused women, which are not entirely representative of the target population. However, within these populations, it appears that it can be an effective treatment for depression, but mostly so in people with PTSD (or at least PTSD symptoms). IPT generally appeared to be fairly effective in improving social function, as well as reducing some of the stress and anxiety from the trauma (Duberstein et al. 2018). However, when compared to CBT and a group with optimised antidepressant medication, IPT seemed to be significantly worse than those at ameliorating depressive symptoms in a group with a broader definition of ELS (Harkness et al. 2012).

Because the first studies do not provide data regarding response or remission, it is hard to make a clear and fair comparison, so it is best to view these results as population or sample dependent. For groups with a broader definition of ELS outside of sexual abuse, it appears best to provide optimised antidepressant medication or CBT. Moreover, it is not entirely clear whether sex differences could play a role in treatment outcome in different groups in this population (e.g. higher rates of response in women than men treated with IPT). This could be the case and could remain consistent as well as shed some new light on sex differences that present themselves in depression (Hankin et al. 1998). However, it is also possible that these differences be explained better by depression severity or a sex and severity interaction (Thase et al. 2000).

CBT generally produced clearer results and consistently proved to be effective as a treatment when measured by both responders and remitters (Harkness et al. Niciu et al. 2015). CBT also appeared to be fairly effective in Minelli et al. (2019)'s study, albeit somewhat less so than EMDR. Nevertheless, this study has an abnormally small sample size when compared to the other studies (n=22, compared to an average of n= 334), and also reported that this was trauma-focused, without a description of how this specifically differed from standard CBT. Also, this study reported that participants also had pharmacological treatment as usual, with no differences in prescription rates across treatment groups (TF-CBT and EMDR). However, they do not report specifically measuring which types of antidepressants the patients took, nor did they group them according to antidepressant type.

Moreover, they did not report whether the medications had any significant interactions with other variables, which could ultimately play a role in producing an antidepressant response. As such, the results of this study are likely magnified, but their findings for CBT are generally consistent with the other studies. Unfortunately, this is the only study using EMDR to treat MDD in people with ELS in this review, so it is hard to ascertain the extent to which this result may be valid and can be extrapolated.

Nemeroff et al. (2003)'s study was fascinating and provided key information about the nature of this population's response to treatment. Nonetheless, it was the only study included in this review that used CBASP and Nefazodone, which makes it challenging to extrapolate its findings. CBASP was particularly developed for more chronic forms of depression (as often occurs with ELS), so it would make sense for it to be effective in this population sample (McCullough et al. 2014). However, this study is extremely popular, having achieved nearly 1000 citations (as of the time of this review), and appearing very frequently in most studies relating to the treatment of depression with ELS. Unfortunately, this has led to vast assumptions and over generalisations about the effects of psychotherapy and pharmacotherapy as wholes on treating this population (e.g. a throwaway line in Read et al. 2005, talking about how psychotherapies could be specifically helpful in treating this population). It is important to note that this study lacks replication and is only analysing one type of therapy and one type of antidepressant (which is relatively unpopular compared to SSRIs and SNRIs). As such, though the Nemeroff et al. (2003) study still holds a significant amount of validity, it is still very important to replicate these findings and truly analyse which treatments are ultimately best to treat this population. Unfortunately, there is limited evidence on the treatments used in this study, so the findings from it may not be entirely accurate or representative.

The evidence for pharmacotherapeutic interventions is mixed. Perhaps the study that provides the clearest comparison across treatments is that of Williams et al. (2016), which clearly outline how, of the drugs they tested, Escitalopram and Venlafaxine were the best ones to treat depression with ELS (compared to Sertraline). This at least provides some reference for which treatment types could be investigated further, at least in terms of effectiveness in treatment. However, this study was the only one that specifically looked at treatment outcome according to drug types and ELS. Studies like Docter et al. (2018) or Harkness et al. (2012) have generally just grouped antidepressants, and as such, it becomes impossible to discern which ones are the most effective. It would be interesting to conduct a multivariate analysis with Docter et al. (2018)'s data, to determine a hierarchy of treatments indeed (should one appear). This could also reveal whether ELS had any impact on the antidepressant effects of any specific treatments.

This could be similar to Xu et al. (2016)'s study, as it also found no effect of ELS directly on treatment outcome. However, Xu et al. (2016) did not even report which SSRI(s) or SNRI(s) they were using, so it becomes tough to determine what drug could be interacting (or not) to modulate the antidepressant effect. Furthermore, them reporting the specific drugs used could provide more insight into the interaction of ELS, the SNP site they identified, and treatment response. Unfortunately, that specific locus has not yet been

clearly and uniquely identified to any one function, so it also becomes hard to associate it to the aforementioned biological processes (Xu et al. 2016). It has, interestingly enough, been linked to studies in BPD and Anxiety (among others), and other mental health conditions, which could be linked to the high comorbidities explained before (Middledrop et al. 2010, Ni et al. 2009, Pérez-Rodríguez et al. 2010). Xu et al. could have investigated comorbidities further.

Implications

Overall, the results of this review are somewhat inconsistent and/or scattered. Nevertheless, they do generally seem to provide strong evidence for CBT as an effective treatment for depressed patients who have suffered from ELS (Harkness et al. 2012, Minelli et al. 2019, Niciu et al. 2015). There is also mixed evidence in favour of IPT (Duberstein et al. 2018, Harkness et al. 2018) and limited evidence in favour of CBASP and EMDR (Minelli et al. 2019, Nemeroff et al. 2003). There is also some limited evidence in favour of combination treatments (Docter et al. 2018, Nemeroff et al. 2003), but more research needs to be conducted to truly ascertain the optimal combination of psychotherapeutic and/or pharmacotherapeutic treatments. Based on the current evidence, it would be likely for this combination to be CBT and Escitalopram/Venlafaxine XR, which would be somewhat consistent with the National Institute for Health and Care Excellence (2017) guidelines.

Ultimately, this review has more research implications than treatment implications, as research in this area is probably not yet at the point in which there is sufficient understanding to create or modify official treatment guidelines. Research would also benefit from examining the specific subtypes of ELS and their severity to determine how exactly these two manifest themselves (if at all) in producing a specific antidepressant response (or lack thereof) with any given treatment. This could also provide further insight into aspects of resilience, and the role that resilience may or may not play in modulating (or mediating) the relationship between ELS and antidepressant response.

Limitations of this Review

The main limitation of this review is likely the lack of quantitative analysis. This was not conducted because of large heterogeneity in measurement tools of depressive symptomatology. A quantitative analysis could have reduced overall bias in the study. To adjust for this, each study was addressed equally in the results section when presenting their results, and comparisons across outcomes were only directly made when the outcome measures used the same scales or outcome measures (e.g. remission rates). Critique of studies and impact were explicitly made for the presented results whenever relevant. If, for example, a result was too abstract or irrele-

vant to the research question (examining the differential treatment outcomes between pharmacotherapies and psychotherapies in MDD with ELS), the specific result was either omitted or not explored in detail. As such, results more relevant to this review were explored further, both in terms of their explanations and their implications.

Another (aforementioned) limitation of this study is the large heterogeneity across the studies. The differences in sample sizes, locations, sex ratios, sample employment status, and measurement tools of the studies makes it hard to generalise across them. This is somewhat problematic because the evidence does suggest that race and income can be predictive of antidepressant treatment outcomes (Cientanni et al. 2019, Cort et al. 2012, Farrer et al. 2016). However, these findings are somewhat culture-specific and cannot be said to be universals (Bastos et al. 2017). Nevertheless, the socio-demographic variety does help illustrate that this is a heterogeneous population, one that can be comprised of people from different areas of the world and find themselves in vastly different predicaments.

Finally, as with any review, it is possible that this review was affected by publication bias, as non-significant findings with specific treatments may not have been published and therefore not found and included in the analysis.

CONCLUSION

This systematic literature review has looked at the differential outcomes of clinical trials treating Major Depressive Disorder in people who have suffered from Early Life Stress. Overall, there was the most substantial evidence for CBT as a treatment for depression, and mixed evidence for IPT, SSRIs, SNRIs. From here, research should focus on looking at specific combinations of clearly defined, evidence-based treatments, both psychotherapeutic and pharmacotherapeutic.

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