



## Hot Topic

## Major depressive disorder in breast cancer: A critical systematic review of pharmacological and psychotherapeutic clinical trials



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## ABSTRACT

**Background:** While women with breast cancer often face varying levels of psychological distress, there is a subgroup whose symptomatology reaches a threshold for diagnosis of major depressive disorder (MDD). Major depressive disorder is known to influence patient outcomes, such as health-related quality of life and treatment adherence. There are no systematic reviews that evaluate pharmacological and psychotherapeutic treatment trials for MDD among individuals with breast cancer.

**Methods:** Two authors independently searched MEDLINE, EMBASE, Cochrane and ClinicalTrials.gov databases through February 20, 2013 without language restrictions. Core journals, reference lists and citation tracking were also searched. Articles on breast cancer patients were included if they (1) included participants with a diagnosis of MDD; (2) investigated pharmacological or psychotherapeutic treatments for MDD compared to placebo or usual care in a randomized controlled trial (RCT).

**Results:** Two RCTs on antidepressant treatment met inclusion criteria. However, no RCTs investigating the effects of psychological treatments for MDD in breast cancer were identified. Notwithstanding the paucity of data investigating the effects of psychological treatments for MDD in breast cancer, numerous psychotherapeutic strategies targeting depressive symptoms were identified. Mianserin had significant antidepressant effects when compared to placebo in a 6-week, parallel-group, RCT of Stage I–II breast cancer in women with MDD. Desipramine and paroxetine were reported to be no more efficacious than placebo in a 6-week, RCT of Stage I–IV breast cancer in women with MDD.

**Conclusions:** The evidence reviewed herein underscores the paucity of data available to guide clinicians in treatment decisions for MDD in individuals with breast cancer. Therefore, the treatment of MDD in breast cancer is primarily based on clinical experience. Some antidepressants (for example, paroxetine) should be avoided in women concurrently taking tamoxifen due to relevant interactions involving the cytochrome CYP2D6.

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## Introduction

Breast cancer is the most frequent malignancy among women with an estimated 1.38 million new cases diagnosed worldwide in 2008, constituting 23% of all cancers [1]. Marked advances in

the detection and treatment of breast cancer has significantly improved prognoses with an estimated 89% surviving 5 years post-diagnosis [2].

Women face significant burden to adapt to the diagnosis of breast cancer [3]. A considerable number of women with breast cancer continue to suffer from psychological distress, which represents an unmet need in this clinical population [4]. While many experience some degree of distress, there is a subset of individuals that are diagnosed with major depressive disorder (MDD), affecting approximately 10–25% of women with breast cancer [5].

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Furthermore, the treatment of breast cancer may cause unintended consequences, such as the induction of menopausal symptoms (e.g., following chemotherapy or anti-estrogen treatment) [6], disrupted body image [7] and impaired sexual function [8], which are important sources of distress. The foregoing consequences are further complicated by the complex interplay of biological (e.g., reduction in estrogen function, genetic factors and inflammatory mechanisms [5,9,10]) and psychological factors involved in the pathogenesis of MDD in women with breast cancer [5]. Among women with breast cancer, MDD has been independently associated with impaired health-related quality of life [11]. Furthermore, MDD in breast cancer relates to other significant negative outcomes, such as diminished treatment adherence, impaired physical, cognitive and sexual functioning [4,5]. Notwithstanding the significant impact of MDD among individuals with breast cancer, MDD is often under-recognized and under-treated by health care providers [12].

The goal of health care providers is to develop specific means to identify clinically significant levels of depressive symptoms in patients with breast cancer, and once identified, to determine whether these symptoms warrant the need for further evaluation of underlying MDD [4].

The treatment of MDD in cancer patients requires pharmacological and/or psychotherapeutic management [4,13]. Previous systematic reviews have reported that psychotherapy may be effective for the treatment of depressive symptoms in breast cancer patients [14,15]. However, to date there are no systematic reviews on pharmacological and psychotherapeutic randomized clinical trials (RCTs) evaluating the treatment of MDD in individuals with breast cancer.

Therefore, the purpose of the present study is to perform a systematic review of the available antidepressant and psychotherapeutic RCTs for the treatment of MDD among women with breast cancer. The authors also propose further directions for research and the clinical management of MDD in breast cancer patients based on available evidence.

## Methods

### Search strategy

Articles for review were identified from the MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception to February 20, 2013. Two standardized searches were conducted: (1) the first sought RCTs of antidepressants for MDD in breast cancer (**Key Question #1**) and (2) the second search was for RCTs of psychotherapy for MDD in breast cancer (**Key Question #2**). Manual searches were performed on reference lists of included articles, previous relevant reviews and at ClinicalTrials.gov. We tracked citations of included articles and relevant reviews using Google Scholar. Authors were contacted to provide additional data when necessary and were also inquired about the availability of data for ongoing treatment protocols. The web sites of pharmaceutical companies were checked for additional data. The search strategies for Key Questions #1 and #2 are detailed in the [Supplementary Information S1 and S2](#), respectively. This study followed the recommendations of the *Preferred Items for Reporting of Systematic Reviews and Meta-Analyses* (PRISMA) statement [16].

### Identification of eligible studies

Eligible articles included studies in any language on breast cancer participants meeting Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD)

criteria for MDD based on a validated structured or semi-structured clinical interview (e.g., Structured Clinical Interview for DSM-IV [SCID-IV] [17], Composite International Diagnostic Interview [CIDI] [18], Diagnostic Interview Schedule [DIS] [19]) or a clinical interview. Participants of the RCTs were women with a histologically confirmed diagnosis of breast cancer at any stage of the illness. Study with mixed cancer populations were included if data on breast cancer participants were reported separately. For Key Question #1, included trials were RCTs of antidepressants compared against placebo. Trials had to be of 4-week duration or longer, involved the use of parallel (not crossover) design and employed oral formulations of antidepressants. For Key Question #2, included trials were RCTs which compared disparate psychotherapeutic approaches (e.g., cognitive therapy, group psychotherapy, mindfulness-based stress reduction etc.) to usual treatment, waiting list or another psychotherapeutic technique.

The primary end-points for both key questions were: changes from baseline to endpoint in total depression severity score as measured by a validated depression instrument (e.g., the Hamilton Depression Rating Scale [HDRS] [20], the Montgomery-Åsberg Depression Rating Scale [MADRS][21]) and response rates defined as a 50% or greater reduction in depression scores from baseline. For both key questions, trials encompassing participants with treatment-resistant depression or other depressive disorders including bipolar disorder, depression with psychotic features, dysthymic disorder, adjustment disorder, neurotic depression or minor depression were excluded.

Two investigators independently reviewed the articles for eligibility. If either deemed an article as potentially eligible based on title/abstract review, then a full-text review was performed. Final decisions regarding the eligibility were made by consensus following the full-text review.

### Evaluation of eligible studies

Two investigators (AFC and PMGS) independently extracted and entered the data in a standardized spreadsheet, which included information about the country of origin, assessment tool, population (e.g., stage of breast cancer), sample size, trial duration, drug treatment (for Key Question #1), psychotherapy modality (for Key Question #2) and outcomes of each trial. Discrepancies were resolved by consensus. Risk of bias of included studies was assessed with the Cochrane Risk of Bias tool [22]. Two investigators (AFC and PMGS) rated the risk of bias of each included study and discrepancies were resolved by consensus.

### Data presentation and synthesis

In studies included for Key Questions #1 and #2, when multiple depression outcomes were reported, the *a priori* defined outcome for each trial was considered valid, followed by observer-rated scales, then self-report instruments. Response rates of each included study were presented when available. We considered response rates at study completion.

## Results

### Key question #1: antidepressant RCTs for major depressive disorder in breast cancer

Of 677 citations, 659 were excluded after title/abstract review. Four additional articles were selected from other sources, leaving 22 articles selected for full-text review. Following consensus, two antidepressant RCTs were found eligible for Key Question #1 ([Fig. 1](#)). Characteristics of included studies are summarized in

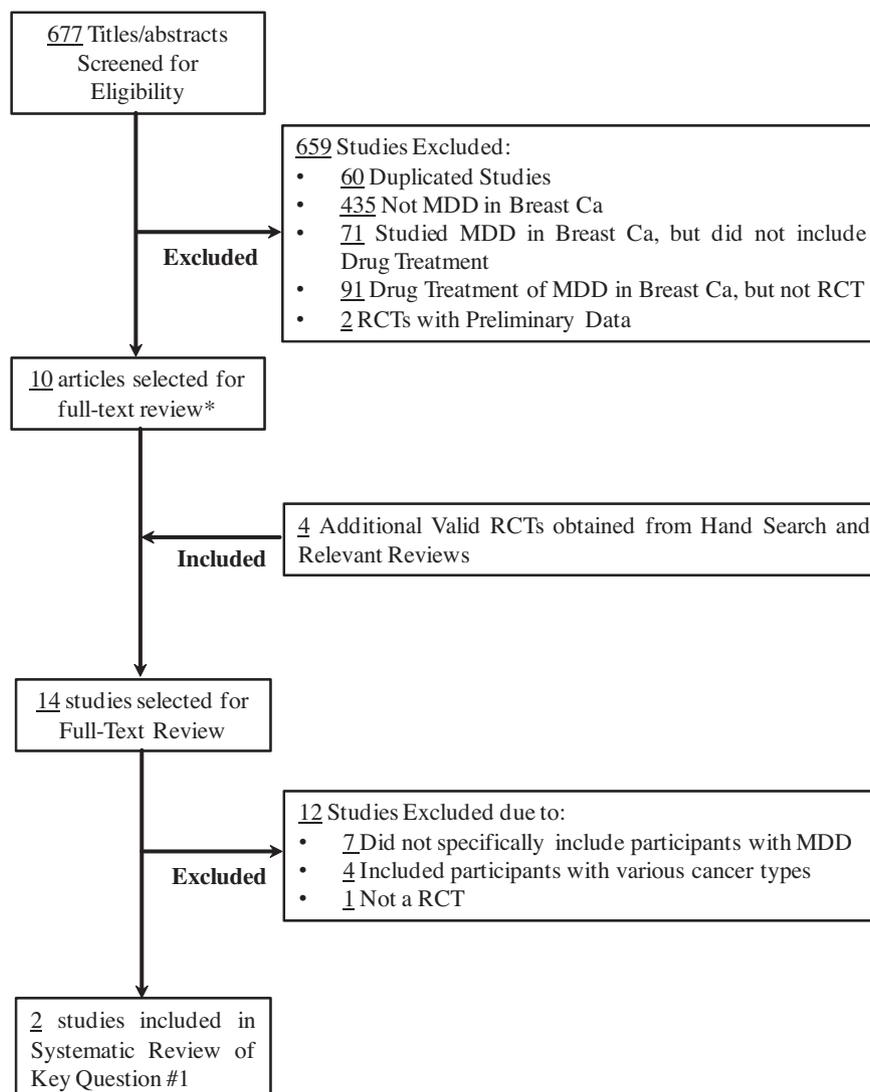
**Table 1.** Reasons for exclusion, as well as characteristics of trials which were not eligible following a full-text review, are presented in [Supplementary Material S3](#). Briefly, Van Heeringen and Zivkov performed a single center 6-week placebo-controlled RCT testing the effects of mianserin (final dose: 60 mg/day) in a sample of 55 women with stages I and II breast cancer undergoing radiation therapy [23]. A total of 28 participants were randomized to mianserin treatment, while 27 women received placebo. By the end of the trial the mianserin group had higher reductions in the Hamilton Depression Rating Scale (HDRS) than the placebo group. The final response rates also favored mianserin over placebo (Table 1). The final drop-out rate for the aforementioned trial was high (55% for the placebo group), and may represent a source of attrition bias. According to the guidelines proposed by the Cochrane Collaboration Group (Fig. 2 and [Supplementary Material S4](#)), the foregoing trial would be considered as having significant risk of bias. This trial was supported by NV Organon Oss, The Netherlands.

A 2-center, randomized, placebo-controlled study was designed to assess the efficacy and tolerability of paroxetine and desipramine for the treatment of depressive symptoms in women with breast cancer [24]. Outpatients with stage I-IV breast cancer who met DSM-IV criteria for a major depressive episode ( $n = 35$ ) were enrolled in this 6-week clinical trial and received paroxetine (20–40 mg/day,  $n = 13$ ), desipramine (25–125 mg/day,  $n = 11$ ) or

placebo ( $n = 11$ ). There were no differences in efficacy between treatment groups and placebo by the end of the trial (Table 1). Regarding tolerability, the drop-out rate by the end of the trial was high (40%) and 5 (14%) of the participants withdrew from the study due to minor treatment-emergent adverse effects (e.g., dry mouth, nausea, constipation). There were no statistically significant differences in drop-out rates between study arms. This trial was also deemed to have a significant risk of bias based on the guidelines proposed by the Cochrane Collaboration Group (Fig. 2 and [Supplementary Material S4](#)). No information on potential sponsorship bias was disclosed by the authors.

*Key question #2: psychotherapy RCTs for major depressive disorder in breast cancer*

Of the 1,149 retrieved citations, 1,102 were excluded following title/abstract screening. Eighteen additional studies were obtained from other sources, leaving 52 articles selected for full-text review (Fig. 3). Following consensus, no study met inclusion criteria for Key Question #2 (Fig. 3). Reasons for exclusion and characteristics of trials excluded following full-text review are presented in [Supplementary Material S5](#). Several trials excluded participants with a valid MDD diagnosis, while others included participants with



**Fig. 1.** PRISMA flow diagram for study selection process for Key Question #1.

**Table 1**  
Included studies for Key Question #1.

Study (Year) country	Study design	Population (inclusion criteria, stage)	Intervention groups (Dose) number of participants (N)			Duration	Outcomes related to depression	Dropout rate	Main results	Response rates
			A	B	C					
Musselman et al. (2006) USA	RCT, parallel groups	Women with breast cancer (stages I– IV) plus 17- item HDRS $\geq$ 14	Paroxetine (20– 40 mg) N = 13	Desipramine (25–125 mg) N = 11	Placebo N = 11	6 Weeks	HDRS	40%	No differences between placebo/treatment groups.	Paroxetine (38%)  Desipramine(45%) Placebo (55%) Mianserin (67.8%)
Van Heeringen et al. (1996) Belgium	RCT, parallel groups	Women with breast cancer (stages I–II) plus HDRS $\geq$ 16	Mianserin (30– 60 mg) N = 28	Placebo N = 27	–	6 Weeks	HDRS	38%	Statistically significant reduction of the HDRS scores on the treatment group. Higher dropout rate observed on Placebo group (55%)	Placebo (37%)

Notes: **HDRS** – Hamilton Depression Rating Scale; **RCT** – Randomized Controlled Trial

various cancer types and did not separately report outcomes for breast cancer samples (Fig. 3 and Supplementary Material S5).

We identified two psychotherapy trials that screened/assessed for MDD in women with breast cancer. In a study of 45 women with metastatic breast cancer, Savard et al. reported that eight weekly sessions of cognitive therapy (CT) and three booster sessions were superior to a wait-list-control (WLC) condition [25]. Inclusion criteria at baseline consisted of a Hospital Anxiety and Depression Scale (HADS) score  $\geq$  7 or a Beck Depression Inventory (BDI) score  $\geq$  15. Mean HDRS scores were 14.21 for the CT group and 14.40 for the WLC arm. In the CT arm, HDRS response rates were 73.3%, 50.0% and 79.6%, compared with a 16.7% response rate for the WLC arm. The analysis was limited to 21 CT participants and 16 WLC participants with post-treatment data. Furthermore, this trial included participants with a variety of other DSM-IV diagnoses (for example, anxiety disorder and adjustment disorders).

Another trial had assessed the efficacy of 6 weekly 90-min. group psychotherapy sessions for women with stages 0, I or II breast cancer as compared to a self-help group. The authors identified potential participants with DSM-III-R psychiatric diagnoses (according to the Structured Clinical Interview for DSM-III-R) [26]. However, the trial included participants without MDD. Notably, women assigned to the intervention group had significantly lower levels of depressive symptoms beginning immediately post-intervention and at 2-years follow-up.

## Discussion

One of the most relevant functions of systematic reviews is to identify areas with insufficient clinical evidence and where clinical trials are needed [27]. The results of the present systematic review highlight the paucity of RCTs evaluating the efficacy and tolerability of antidepressants for the treatment of MDD among women with breast cancer. Moreover, no RCTs for psychotherapeutic approaches were identified for this systematic review, emphasizing the dearth of data available to guide the treatment of MDD in breast cancer patients. Notwithstanding insufficient evidence for the use of antidepressants in this subpopulation, clinical guidelines recommend the use of antidepressants [13] based on their efficacy in treating depressive symptomatology in other clinical populations [28,29].

Advances in the treatment of breast cancer has led to significant increments in long-term survival rates [2]. Depressive symptoms are commonly viewed as prevalent manifestations associated with the diagnosis and treatment of breast cancer [30,31]. However, there is an urgent need to identify women with MDD who require pharmacological and/or combined treatments for their affective symptomatology.

This systematic review identified two eligible antidepressant RCTs for the treatment of MDD in breast cancer [23,24]. The results of these RCTs were mixed. Furthermore, these trials recruited relatively small samples and had a significant risk of bias. Therefore, it is difficult to derive definite conclusions regarding the efficacy and tolerability of antidepressants from the available literature. Several trials have investigated the secondary effects of antidepressants for the treatment of depressive symptoms among women with breast cancer. Roscoe et al. performed a multicenter randomized placebo-controlled trial to evaluate the efficacy of paroxetine (20 mg/day) for the treatment of depressive symptoms among women with breast cancer scheduled to receive at least four cycles of chemotherapy [32]. By the end of the trial, paroxetine was not effective for fatigue, but promoted a significant reduction in depressive symptoms. A 12-week, cross-over, RCT tested the efficacy and tolerability of sertraline (50 mg/day) for the treatment of hot flashes in a sample of women with early stage breast cancer who were also taking tamoxifen [33]. By the end of the trial, sertraline was effective for the alleviation of hot flashes, but no significant effects over placebo for depressive symptoms were observed. However, the relevance of these findings is questionable, since antidepressants do not seem to be effective for the treatment of milder depressive syndromes (i.e., minor depression) in both clinical and non-clinical populations [34]. Furthermore, even among patients with MDD, the efficacy of antidepressants may vary as a function of baseline symptom severity [35].

It should be emphasized that the use of antidepressants for the management of MDD in women with breast cancer may be associated with additional side effects and potential risks that require a personalized approach. For example, it has been reported that the majority of women with invasive breast cancer have tumors that express estrogen and/or progesterone receptors on the cell surfaces. Moreover, women with receptor-positive breast cancer are reported to obtain substantial benefit from treatment with tamoxifen and agents that decrease circulating levels of estrogen

	Random Sequence Generation	Allocation Concealment	Blinding of Participants/Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Musselman (2006)	?	⊖	⊖	⊖	⊕	⊕	⊖
Van Heeringen (1996)	?	⊖	⊖	⊖	⊖	⊕	⊖

Fig. 2. Risk of bias assessments for trials included in Key Question #1.

(e.g., aromatase inhibitors) [36]. Tamoxifen is considered a classical pro-drug that is converted to an active metabolite which is more potent when compared to the parent compound [37]. Tamoxifen is converted to endoxifen; mainly by a non-inducible cytochrome P450 enzyme that is coded by the most polymorphic

gene in the cytochrome P450 system: CYP2D6 [38]. Several serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are potent inhibitors of the CYP2D6 system (e.g., fluoxetine and paroxetine) [39]. The co-administration of these antidepressants with tamoxifen may cause clinically significant drug-drug interactions [40] and adversely influence outcomes [41]. A recent study investigated the effects of co-treatment with different SSRIs and venlafaxine on women being treated with tamoxifen for breast cancer using a population health care database [42]. Results indicated that the co-administration of paroxetine during tamoxifen treatment was independently associated with an increased risk of death from breast cancer, arguably as a result of its strong inhibitory activity on CYP2D6, which prevents the conversion of tamoxifen to its bioactive metabolite endoxifen [43]. Thus, large-scale, well-designed RCTs evaluating antidepressants for the treatment of MDD in breast cancer are needed to assess the clinical benefit-to-harm ratio in this subpopulation.

Psychosocial interventions are often recommended for the treatment of MDD in cancer patients. However, there is a paucity of data for the efficacy of these interventions, underscoring the necessity for more evidence-based interventions in this subpopulation [13]. Due to the complex and fluctuating nature of depressive symptoms and contributing medical and psychosocial factors, RCTs also need to estimate the efficacy and safety of psychotherapeutic

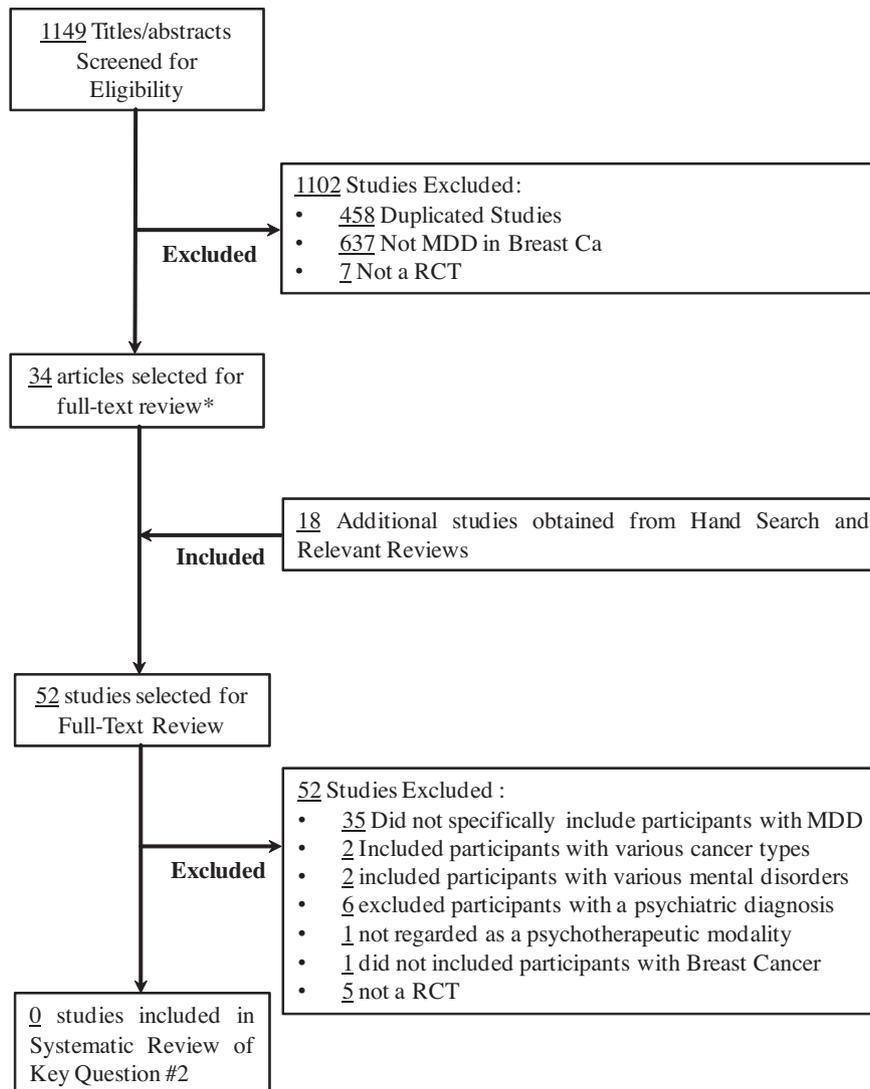


Fig. 3. PRISMA flow diagram for study selection process for Key Question #2.

modalities in this population. A previous meta-analysis indicated that psychotherapeutic interventions may improve depression and quality of life in breast cancer [15]. However, several small trials with varying methodological quality were included for the analysis. A separate systematic review and meta-analysis indicated that mindfulness-based stress reduction has a moderate-to-large effect size for the alleviation of depressive symptoms among breast cancer women [14]. However, this meta-analysis included non-randomized trials. Conversely, a recent Cochrane systematic review did not find consistent evidence to support the effectiveness of psychosocial interventions for depression in cancer in general [44]. In the present systematic review, we report significant variation across trial participants, mode of delivery, discipline of 'trained therapist' and intervention content among excluded trials, which further limits the interpretation of the available literature. The inclusion of underpowered studies with limited methodological quality may have biased the results of previous meta-analyses [45,46]. In the present systematic review, no psychotherapy RCT met inclusion criteria.

This review has several strengths: we performed a systematic search of articles and included studies with clearly defined criteria to minimize selection bias, and rigorous methods for data extraction were applied. Furthermore, we specifically included RCTs of MDD in breast cancer. This is important, because the severity of distress may moderate the effects of psychosocial interventions [47]. This study also has limitations. First, we did not attempt to include unpublished results by contacting relevant experts. However, we did make substantial efforts to find all relevant trials through inclusive search strategies and contacted authors of ongoing clinical trials to determine whether relevant results could be obtained. Secondly, in this systematic review we primarily focused on depression-related outcomes. The effects of intervention on other relevant outcomes, such as quality of life, cannot be inferred from our work.

Clinical experience suggests that psychosocial interventions and antidepressant pharmacotherapy in women with breast cancer may reduce their depressive symptoms. However, it is highly concerning that only two small RCTs of antidepressant treatment for MDD in breast cancer were identified, with mixed results. Furthermore, no RCTs for psychotherapeutic interventions met our inclusion criteria. The consequence is a lack of high quality evidence to guide the treatment of MDD in patients who have breast cancer. Whilst it is probably reasonable to use standard depression treatments in depressed breast cancer patients until more specific evidence is available, clinicians should be aware that the effectiveness and potential adverse effects of these treatments remain unclear in this patient group. The identification of treatment moderators is also an important step and may inform clinician selection for appropriate interventions in patients with MDD and breast cancer. Further evidence from well conducted randomized trials is urgently required to guide the treatment of MDD in breast cancer patients.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ctrv.2013.09.009>.

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