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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 Clinical Trials.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.

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