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Review

Antidepressant combination for major depression in incomplete responders—a systematic review

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ABSTRACT

Background: Antidepressant combination has been suggested as a strategy to increase treatment efficacy. The objective of this study was to perform a systematic review and meta-analysis of studies that assessed the effect of antidepressant combination for major depression in patients with incomplete response to an initial antidepressant.
Methods: Studies were retrieved from PubMed (1966–February, 2012), Cochrane Library (–February, 2012), Embase (1980–February, 2012), PsycINFO (1980–February, 2012), Lilacs (1982–February, 2012), clinical trials registry, thesis database (www.capes.gov.br), and secondary references. Included studies had an open label phase in which an initial antidepressant was used for the treatment of major depression and a double blind phase for the incomplete responders that compared monotherapy with the first antidepressant versus the association of a second antidepressant to the first one.
Results: Out of the 4,884 studies retrieved, only five satisfied the inclusion criteria. The total number of patients included was 483. Only two small trials reported benefits of adding a second antidepressant to the initial antidepressant. Dropouts due to side effects were not reported in three studies. Meta-analysis was not performed due to the small number of studies, the inconsistency in the direction of effect and the possible instability of effect size. Only limited kinds of combination, involving mianserin, mirtazapine and desipramine were studied. Some properties of the first two drugs such as the anxiolytic, sedative, and orexigenic effects, can mimic depression improvement.
Limitations: Publication bias cannot be ruled out. Only one study included a monotherapy arm with the antidepressant used for augmentation of the first antidepressant.
Conclusions: The practice of using a combination of antidepressants for major depression in incomplete responders is not warranted by the literature.

Contents

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1. Introduction

Antidepressants are a mainstay of the treatment of major depression. However the overall treatment outcome of depressed patients is usually far from optimal. Regardless of the initial choice of antidepressant, 30–50% of patients with a major depressive episode will not respond satisfactorily to adequate standard treatment (Bauer et al., 2007). Remission rates vary from 42% to 46% (Casacalenda et al., 2002; Smith et al., 2002) and about 30% of patients may not reach remission after multiple treatment trials (Rush et al., 2006). A review of four meta-analyses of efficacy trials submitted to the US Food and Drug Administration (FDA) suggests that antidepressants are only marginally efficacious compared with placebo and documents a profound publication bias that inflates their apparent efficacy (Pigott et al., 2010).

Antidepressant combination has been suggested as a strategy to increase treatment efficacy. There are two kinds of studies that evaluate antidepressant combination. One uses the combination from the beginning of treatment. We have published a systematic review and meta-analysis of this approach (Rocha et al., 2012). Another strategy is to add a second antidepressant to the treatment regimen of patients with persistent major depression despite adequate antidepressant monotherapy. However there are sparse data to support this strategy since the few trials that investigated this strategy have methodological flaws and involve small samples (Dodd et al., 2005; El-Mallakh et al., 2010; Rush, 2010; Thase, 2011). The larger studies about antidepressant combination in incomplete responders were conducted as part of the STAR*D trial but the lack of placebo control in these studies, among other drawbacks, prevents definite conclusions about the results. The objective of the present study was to perform a systematic review and meta-analysis of the combination of antidepressants versus a single antidepressant for the treatment of major depressive disorder with incomplete remission.

2. Material and methods

This systematic review was conducted at Instituto de Previdência dos Servidores do Estado de Minas Gerais, Faculdade da Saúde e Ecologia Humana, Faculdade de Medicina da Universidade Federal de Minas Gerais, and Faculdade de Ciências Médicas de Minas Gerais.

Studies were retrieved from the following sources: PubMed (1966 to February, 2012), Cochrane Library (until February, 2012), Excerpta Medica Database (Embase) (1980 to February, 2012), PsycINFO (1980 to February, 2012) and Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) (1982 to February, 2012). MeSH terms and filters for clinical trials were applied. There were no language limits. We also scanned secondary references, clinical trials registry (www.clinicaltrials.gov), a thesis database (www.capes.gov.br), and contacted experts in the field. In case of missing data, authors were contacted by email.

2.1. Criteria for considering studies in this review

2.1.1. Types of studies and interventions

Included studies were randomized controlled trials that had two phases. The first phase consisted of antidepressant monotherapy of patients with major depression. The second phase included only patients who persisted with major depression and compared two arms: continuation of monotherapy versus the addition of a second antidepressant to the first one. The monotherapy dosage could be kept the same or be increased.

2.1.2. Participants

Participants were adult out- or inpatients (aged 18–65 years) with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria.

2.1.3. Outcome measures

1 Remission defined as a subthreshold score on a depression scale, for example a score of 7 or less on the Hamilton 17-Item Depression Rating Scale (HDRS) or a score of 10 or less on the Montgomery–Asberg Depression Rating Scale (MADRS) (Keller 2003).
2 Response defined as a reduction of at least 50% in baseline symptoms on a depression scale (Keller 2003).
3 Safety
- Dropouts due to side effects.
- Number and severity of adverse events.

2.2. Data collection and quality analysis

2.2.1. Selection of trials

Two authors independently screened each abstract and decided if it potentially fulfilled inclusion criteria. In case of incomplete information in the abstract, the full text was assessed. After this first screening, all selected studies were evaluated. Any disagreement on the eligibility of a study was discussed with a third review author reaching a consensus.

2.2.2. Quality assessment

Quality assessment was evaluated according to recommendations of the Cochrane Collaboration Handbook (table 8.5 a) taking into account the following criteria: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (Higgins and Green 2008). The studies were classified as having low, unclear/moderate or high risk of bias.

2.2.3. Data extraction

Full data extraction of studies selected for inclusion in the review was performed independently by two authors using the