



## Review

# Selective serotonin reuptake inhibitors and tricyclic antidepressants in the acute treatment of chronic depression and dysthymia: A systematic review and meta-analysis



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## ABSTRACT

**Introduction:** Chronic depression represents a substantial portion of depressive disorders and is associated with severe consequences. This review examined the efficacy and acceptability of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in the treatment of chronic depression. Additionally, the comparative effectiveness of the two types of antidepressants has been examined.

**Methods:** A systematic search was conducted in the following databases: CENTRAL, MEDLINE, EMBASE, ISI Web of Science, BIOSIS, PsycINFO, and CINAHL. Primary efficacy outcome was a response to treatment; primary acceptance outcome was dropping out of the study. Only randomized controlled trials were considered.

**Results:** We identified 20 studies with 22 relevant comparisons. 19 studies focused on samples with a majority of dysthymic patients. Both SSRIs and TCAs are efficacious in terms of response rates when compared to placebo (Benefit Ratio [BR]=1.49;  $p < 0.001$  for SSRIs and BR=1.74;  $p < 0.001$  for TCAs) and no statistically significant differences between the active drugs and placebo in terms of dropout rates could be found. No differences in effectiveness were found between SSRIs and TCAs in terms of response rates (BR=1.01;  $p=0.91$ ), yet, SSRIs showed statistically better acceptability in terms of dropout rates than TCAs (Odds Ratio [OR]=0.41;  $p=0.02$ ).

**Limitations:** The methodological quality of the primary studies was evaluated as unclear in many cases and more evidence is needed to assess the efficacy of SSRIs and TCAs in patients suffering from chronic forms of depression other than dysthymia.

**Conclusions:** This systematic review provides evidence for the efficacy of both SSRIs and TCAs in the treatment of chronic depression and showed a better acceptability of SSRIs.

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## 1. Introduction

Approximately 20% of all patients who experience a major depressive episode develop a chronic course (Gilmer et al., 2005) and approximately 47% of patients who are treated in mental health care facility suffer from some form of chronic depression (Torpey and Klein, 2008). Four subtypes of chronic depression are usually distinguished: (1) dysthymia, (2) chronic major depression, (3) recurrent major depression with incomplete remission between episodes, and (4) double depression (Klein, 2010). Dysthymic disorder is defined as a mild condition that is chronic and persistent for at least 2 years. A major depressive episode, chronic type, refers to a more severe condition that meets all criteria for major depression continuously for a minimum of 2 years. Patients who have recovered to the point where they no longer meet all criteria for a major depressive episode but continue to experience significant symptoms for a total duration of illness greater than 2 years are referred to as having recurrent major depression with incomplete remission during episodes. The superimposition of a major depressive episode on antecedent dysthymia is referred to as double depression (Klein, 2010).

Chronic depression is associated with increased functional impairment (Satyanarayana et al., 2009), increased health care utilization, and higher rates of hospitalization compared with non-chronic forms of depression (Berndt et al., 2000; Gilmer et al., 2005).

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are two groups of antidepressants often used as pharmacological interventions in the treatment of chronic depression. An increasing number of studies have assessed the efficacy and effectiveness of these two groups of antidepressants in the last several decades.

These studies have been partly summarized in current guidelines and systematic reviews. Meta-analytic findings regarding the treatment of dysthymic patients showed that both types of antidepressants are effective but highlighted the differential acceptability of the two drug groups (Lima et al., 2005). Accordingly, the practice guideline for the treatment of patients with major depressive disorder of the American Psychiatric Association (American Psychiatric Association, 2010) comes to the conclusion, that both types of antidepressants are effective in the treatment of dysthymia and may also be used for other forms of chronic depression. The national clinical practice guideline for the treatment and management of depression in adults of the National Institute for Health and Clinical Excellence (National Institute for Health and Clinical Excellence (NICE), 2009) further highlights that SSRIs are better tolerated than TCAs by patients suffering from subthreshold depressive symptoms (including dysthymia). In contrast to these findings, the superiority of antidepressants to placebo was questioned for mild to moderately depressed patients in a controversially discussed meta-analysis (Kirsch et al., 2008). Thus, it remains unclear how chronicity and severity of depression influence the effectiveness of antidepressants. A systematic review considering the whole spectrum (i.e., all subtypes) of chronic depressions is still missing.

The objectives of this systematic review are first to examine the efficacy and acceptability of SSRIs and TCAs in the treatment of chronic depression, and second, to assess the comparative effectiveness of the two types of antidepressants.

## 2. Methods

The methods and results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). Methods were specified a priori in a freely accessible review protocol, which included a detailed description of the methods, which are summarized briefly here (Kriston et al., 2010).

### 2.1. Eligibility criteria

Studies that were conducted in adults with a diagnosis of chronic major depression, dysthymia, double depression, or recurrent depression without complete remission between episodes were included. The diagnosis of depression had to rely on a formal classification system. Studies focusing on preselected samples (e.g., predefined comorbidities) of chronically depressed patients were excluded.

Pharmacological interventions that included the administration of either an SSRI or a TCA and that focused primarily on the treatment of depressive symptoms were considered. Only acute treatments (no maintenance or continuation treatments) were included. Somatic, psychotherapeutic, non-pharmacological, and organizational interventions were not considered.

The comparator treatment required either the administration of a pharmacological placebo or another antidepressant pharmacological intervention (SSRI or TCA).

Only studies that reported at least one outcome regarding the efficacy of the interventions and only randomized controlled trials (RCTs) were included.

### 2.2. Search strategy

An electronic database search was conducted in the following databases on January 18, 2010: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ISI Web of Science, BIOSIS, PsycINFO, and CINAHL. A disease component was combined (AND) with a design component for all searches: (((chron\$ adj3 depress\$) or dysthym\$ or (double adj1 depress\$) or (treatment adj1 resist\$ adj1 depress\$) or (non adj1 respon\$ adj3 depress\$) or (recurrent adj3 depress\$)).ab,ti,sh.) AND ((random\$ or rct).ab,ti. or random\$.sh.) (e.g., MEDLINE). No language restrictions were applied and all publications from 1970 forward were considered.

Additionally, all volumes of the Archives of General Psychiatry, the Journal of Consulting and Clinical Psychology, and the Journal of Affective Disorders were searched by hand beginning with the

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