Dropout Prevalence and Associated Factors in Randomized Clinical Trials of Adolescents Treated for Depression: Systematic Review and Meta-Analysis

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ABSTRACT

Purpose: Depression currently affects 350 million people, and its prevalence among adolescents is 4% to 8%. Adolescents who abandon antidepressant treatment or drop out of clinical trials are less likely to recover or experience a remission of symptoms because they are not being followed up by a medical team. The objective of this study was to analyze the dropout rates of randomized clinical trials of depressed adolescents receiving treatment with antidepressant drugs and the factors associated with nonadherence by summarizing this information in a systematic review and meta-analysis.

Methods: Articles were retrieved from MEDLINE, EMBASE, Cochrane, Clinical Trial, PsycINFO, and Web of Science using the MeSH terms “depressive disorder,” “randomized trials,” and “adolescents.” The evaluation of study quality was performed by using the Cochrane Handbook for Systematic Reviews of Interventions and the Jadad scale.

Findings: The final sample included 50 articles, of which 44 presented dropout rates. The overall dropout prevalence was 23% (95% CI, 20–27; P < 0.0001). Participants aged ≥16 years, those treated with serotonin norepinephrine reuptake inhibitors, and those receiving medication only exhibited the highest dropout prevalence, respectively (33% [95% CI, 27-39], 45% [95% CI, 31-64], and 15% [95% CI, 13-17]). The adverse effects most associated with dropout were attempted suicide followed by mania, skin rash, and headache. Problems relating to clinical trials and family arbitration were also related with dropout.

Implications: Serotonin/norepinephrine reuptake inhibitor treatment, adolescent age ≥16 years, and receiving medication were the only factors demonstrating a higher association with dropout rates. Selective serotonin reuptake inhibitors were linked to the lowest prevalence, probably due to fewer perceived problems with related adverse effects and higher efficacy in adolescents. Cognitive-behavioral therapy combined with pharmacotherapy produced a lower nonadherence prevalence; this approach can be an alternative to avoid dropouts and relapse. Prospero identifier: CRD42014013475. (Clin Ther. 2017;xxx-xxx) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: adolescents, antidepressant, depressive disorder, dropout.

INTRODUCTION

Depression is the leading cause of disability and the third leading cause of death among adolescents worldwide. It is estimated that by 2020, depression will rank first in disability-adjusted life years. The prevalence ranges from 4% to 8% among adolescents and 8% to 12% among adults. Each year, there are >90,000 suicides and 4 million attempted suicides among adolescents.

Several treatments are available for depression, and antidepressant drug therapy has proven effective for the treatment of symptoms. Adherence to treatment is critical because it prevents relapse and suicide, improves quality of life and development, and
prevents the wasting of financial resources. Complications of nonadherence to treatment can lead to the adolescent’s withdrawal from social and family life, poor academic performance, changes in weight, substance abuse, risky sexual behavior, conduct problems, and suicide, among other issues. The annual direct costs for the treatment of depression in several countries range from $244.09 to $2488.52 per capita, and indirect costs range from $94.14 to $5360.99. Nonadherent individuals may generate an even greater negative economic impact.

Lack of adherence among adolescents occurs for many reasons, including the disease itself, the medication, the physician-patient relationship, family issues, and the characteristics of adolescence. The desire to be accepted in certain groups, the need for independence, and oppositional behavior are also unique to adolescence and may hinder adherence, as these factors are at odds with good pharmacotherapeutic compliance.

Dropout of any treatment type limits the effectiveness of treatment and causes damage to adolescents’ health and development. It is difficult to study the lack of adherence to depression treatment because depression itself decreases an individual’s motivation to continually follow medical recommendations. In contrast to regular care, participation in a clinical trial involves closer monitoring of the patient by the medical team, as they are following up study participants for treatment outcomes as well as adherence and its causes. The identification of factors associated with dropping out of drug treatment among depressive adolescents is important so that better clinical trials can be designed to prevent dropouts and improve quality of care.

Because clinical trials constitute the ideal research format to report efficacy of treatments, they are also a good source of information regarding rates of nonadherence and its causes. Several randomized clinical trials of adolescents being treated for depression have reported dropout rates, but the data were not summarized in a systematic review or meta-analysis, and the factors associated with dropout are still poorly reported or not reported. The goal of the present study therefore was to report dropout rates and factors related to dropout among adolescents treated for depression in randomized clinical trials.

**MATERIALS AND METHODS**

**Protocol and Registration**

This systematic review is in accordance with the rules of Preferred Reporting Items for Systematic Review and Meta-Analyses.

**Eligibility Criteria**

Studies using the following criteria were eligible for inclusion: randomized controlled trials, drug treatment for depression, and depressed adolescents. Only studies published in the English language were included.

**Source of Information**

The studies were accessed from MEDLINE (accessed through PubMed), EMBASE, Cochrane-Central Clinical Trial Registries, Central Register of Controlled Trials, Lilacs, PsychINFO, and Web of Science. The cutoff date for the article search was December 2014, with no prior time criteria established. In addition, eligible studies were screened for in the references of accessed articles and through Google Scholar.

**Search**

The initial search used the PubMed MeSH terms “randomized trials,” “depressive disorder” (defined as an affective disorder manifested by either a dysphoric mood or loss of interest or pleasure in usual activities; the mood disturbance is prominent and relatively persistent), and “adolescent” (defined as a person 13–18 years of age). The strategy used with regard to the search engines is described in the Table.

**Study Selection**

Initially, article titles and abstracts were independently evaluated by 2 expert reviewers (A.I.R. and M. C.B.) for inclusion criteria. When abstracts did not provide enough information, their articles were accessed in full. Disagreement between the expert reviewers was discussed with a third reviewer (T.C.M.).

The selected studies were evaluated in terms of the following information: year of publication, study location and time, size of the overall sample and subgroups, mean age, number of female participants, type of intervention, general dropout and dropout according to subgroups, and factors associated with the dropout rate. If any of this information was not available, the authors were contacted by e-mail to...
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