Review

Duration of untreated illness and outcomes in unipolar depression: A systematic review and meta-analysis

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A B S T R A C T

Background: To systematically review evidence of the effects of the duration of untreated depression on the clinical outcomes of patients suffering from Unipolar Major Depression.
Methods: A systematic review and meta-analysis of the evidence of duration of untreated depression and the effect it has on clinical outcomes in Unipolar Major Depression. Data used to this purpose were obtained from a literature search of the MEDLINE, Psychoinfo and Embase databases. Comparable data extracted from studies were entered and analysed using Cochrane Collaboration's Review Manager software Version 5.2.
Results: Ten studies were identified as meeting the inclusion criteria. Only three studies reported comparable data and were consequently used for the meta-analysis. Pooled data indicates the overall positive effect of shorter duration of untreated illness both in a patient's response to treatment (RR 1.70) and remission (RR 1.65).

Other studies which were not included in the meta-analysis confirmed the importance of reducing delays in the treatment of depression in order to prevent the risk of worse outcomes and chronicity, in particular in patients presenting with a first episode of depression. Data regarding the association between the duration of untreated episode in recurrent depression and clinical outcomes are less evident.
Limitations: The heterogeneity of the selected studies was cause for limitations with regard to the carrying out of adequate meta-analysis.
Conclusions: There is evidence highlighting the importance of a reduced no-treatment interval for patients suffering Unipolar Depression. In particular, there is emphasis on the first episode of depression corresponding to the notion of reducing the duration of untreated illness.

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1. Introduction

Depression is a seriously disabling public health issue of very high prevalence worldwide (Kessler et al., 2003). Major Depressive Disorder has a 12-month prevalence of more than 5% and can occur at almost any age (Kessler et al., 2007, Cuijpers et al., 2012). Despite this high prevalence less than half of depressed patients are recognised and treated (Tylee and Jones, 2005), and the majority of those recognised report considerable delay before eventually seeking treatment. The proportional treatment contact in the year of onset ranges from 28% to 47% (Wang et al., 2005, Wang et al., 2007) and the median duration of delay in treatment ranges from 2 to 8 years (Wang et al., 2005, Wang et al., 2007).

The duration of untreated illness (DUI) – defined as the interval between the onset of a patient's first psychiatric episode and that patient's first appropriate treatment (Dell'Osso and Altamura, 2010) – is being increasingly investigated as a predictor of the clinical outcomes of psychiatric disorders.

The majority of international studies to date have focused on the possible role of the DUI on the clinical outcomes and the course of schizophrenia and psychotic disorders. The evidence from such studies shows that a long duration of untreated psychosis is the strongest predictor of relapse and poor outcomes (McGorry et al., 2000; Harris et al., 2005; Perkins et al., 2005; Marshall et al., 2005; Barnes et al., 2008; Hill et al., 2012).

The identification of these results stimulated a worldwide implementation of specific services aimed at the treatment of early psychosis (Lloyd-Evans et al., 2011; Ghio et al., 2012; McGorry, 2012). However, fewer studies have addressed the implication of the duration of untreated illness (DUI) on the clinical outcomes of mood disorders, even though the period between a patient's first episode of mood disorder and his/her first treatment is now known to be among the longest. The dearth of studies of this type could depend on several reasons: the poor reliability of a patient's self-reporting affective states after several years of illness evolution; the higher prevalence of mild to moderate episodes with spontaneous recovery which can lead to issues such as underestimating long-term outcomes; the variability of the pathways to care sought by depressed patients, which makes the implementation of studies difficult due to the diversity in research settings; and, finally, the increasing difficulty when it comes to defining the period of untreated illness in patients suffering from recurrent illnesses.

This last point raised is crucial to highlighting the distinction between the duration of untreated illness (DUI) and the duration of untreated episode (DUE). After the first episode of depression, the concept of DUI is replaced by the concept of DUE due to recurring depressive episodes. The DUE differs in interpretation both from a biological point of view (due to the possibility of neurobiological changes during the course of a patient's depressive episodes) and clinical point of view (it is very difficult, for example, to establish the DUE in patients suffering from recurrent depression who are undergoing maintenance treatment).

Despite the aforementioned confounding factors some studies indicate that a longer duration of untreated depression is associated with a reduction in the possibility of symptomatic remission and an increase in the likelihood of recurring episodes (Baldwin, 2011).

No systematic reviews on the clinical importance of the duration of untreated depression in Unipolar Depression had been conducted prior to this investigation.

The present study provides a systematic review and meta-analysis of all available empirical investigations on the relationship between the duration of untreated depression and clinical outcomes in relation to Unipolar Major Depression.

2. Methods

2.1. Literature search and study selection

Literature searches (last update: January 2013) were performed using the available information from the MEDLINE, Psychoinfo and Embase databases. The keywords and Medical Subject Heading terms entered were: untreated depression and outcomes, duration of untreated depression and outcomes, duration of untreated illness and depression, untreated depression.

Additional works were also identified using the reference lists of retrieved articles.

Studies were then selected in accordance with the following criteria:

(a) included patients with Unipolar Major Depression according to standardised diagnostic criteria;
(b) investigated the relationship between DUE or DUI and clinical outcomes; and
(c) compared patients with shorter and longer duration of untreated depression.

Duration of untreated episode (DUE) was defined as the interval between the onset of an episode of major depression and the first adequate treatment (de Diego-Adeliño et al., 2010). Duration of untreated illness (DUI) was defined as the interval between the first lifetime onset of symptoms of depression (not necessarily satisfying all five of the nine items for an episode of major depression according to DSM-IV) and the first adequate treatment (Dell'Osso and Altamura, 2010).

Since we expected to identify few studies specifically focused on duration of untreated depression and outcomes in Unipolar Major Depression, we included all of the study types (randomized clinical trial, clinical trial, observational studies) which met our selection criteria.

The algorithm and the results of the study search and selection are detailed in the PRISMA flow diagram (Moher et al., 2009) shown in Fig. 1.

2.2. Types of outcome measures

The main outcomes investigated were response and/or remission in relation to the time elapsed from the onset of adequate treatment, as measured by standardised rating scales for depression.

Additional factors related to outcomes were also considered, such as the number and duration of a patient's hospitalisations, the number of suicide attempts, and evidence of recurrent episodes of depression and functional impairments.

2.3. Data extraction

Two reviewers independently assessed the title and abstract of each retrieved citation for eligibility against our inclusion criteria. For all potentially eligible citations, we retrieved the full-text