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Research report

# The effect of prolonged duration of untreated depression on antidepressant treatment outcome

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ABSTRACT

*Background:* The duration of untreated illness has been considered a likely predictor of the course of psychotic disorders. However, there is only sparse data concerning the influence of treatment delay on the outcome of mood disorders. The present study aimed to assess the effect of prolonged untreated depression on the outcome of antidepressant treatment.

*Method:* Patients aged 18–70 years with recent onset of the first lifetime depressive episode were systematically recruited by the Danish Psychiatric Central Research Register during a 2-year period. A total number of 399 individuals out of 1006 potential participants in the Register were interviewed, and 270 fulfilled the inclusion criteria. The validity of the diagnosis, duration of untreated illness, remission on first-line antidepressant treatment and a number of covariates, including psychiatric co-morbidity, personality disorders and traits, stressful life events prior to onset, and family history of psychiatric illness, were assessed by structured interviews.

*Results:* The remission rate was significantly decreased among patients with six months or more of untreated depression as compared to patients who were treated with antidepressant medication earlier after onset (21.1% versus 33.7%, OR=0.5, 95% CI 0.3 to 0.9, $p=0.03$). The negative influence of a prolonged DUI on the outcome did not seem confounded by any of a wide range of demographic and clinical variables.

*Limitations:* The outcome was evaluated retrospectively. The findings cannot be generalized to patients outside hospital settings.

*Conclusion:* Initiation of antidepressant treatment more than six months after onset of first episode depression reduces the chance of obtaining remission. The results emphasize the importance of early recognition and treatment of patients suffering from depression.



## 1. Introduction

The duration of untreated illness (DUI), defined as the time interval between first onset of the illness and initiation of (pharmacological) treatment, has increasingly been considered to influence the clinical course of different psychiatric disorders (Dell'osso and Altamura, 2010), especially in schizophrenia and other psychotic disorders (Nordentoft et al., 2009). Similarly, knowledge of the potential consequences of postponing medical treatment of depression is of crucial importance, when the choice stands between antidepressants, other therapies or watchful waiting. Unfortunately, there is little evidence for the effect of DUI on the outcome of affective disorders. Scott et al. (1992) reported, that the length of the index episode prior to institution of antidepressant treatment was the most important predictor of time to recovery in a cohort of 55 patients with major depression. Gormley et al. (1999) replicated the findings of an association between the "no-treatment interval" of a depressive episode and the time to remission following antidepressant treatment ($N=83$). Later, Kisely et al. (2006) found a significant association between the duration of untreated symptoms and the overall psychiatric morbidity in a 12-month follow-up among 351 patients in primary care presenting with a range of psychiatric disorders (201 with major depression). However, the duration of untreated episode or untreated symptoms during recurrent depression is essentially different from the concept of DUI, generally defined as untreated first onset illness. Furthermore, a number of patients suffering from recurrent depression will be taking maintenance antidepressant medication; hence, the duration of untreated episode cannot be established in a meaningful way for those individuals. Only two small studies (de Diego-Adelino et al., 2010; Okuda et al., 2010)–including 83 and 133 patients, respectively–have recently provided preliminary evidence

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for a negative influence of prolonged DUI in the more strict sense (that is, the duration of untreated first episode depression) on the outcome of antidepressant treatment. In addition, Altamura et al. (2007, 2008) has reported an unfavourable effect of a longer DUI on the subsequent course of the illness (a higher number of recurrences, a longer total duration of illness and more frequent co-morbid axis I disorder).

The present study aimed to assess the influence of DUI on the remission rate following antidepressant treatment in a larger sample of patients suffering exclusively from first episode depression, investigating the hypothesis that longer DUI is associated with a poorer treatment outcome. Further, a broad range of demographic and clinical covariates were examined in order to detect potential associations with the DUI.

## 2. Method

### 2.1. Design

The present investigation is part of a study of gene–environment interactions on depression and antidepressant outcome. The sample and methodology of the study have been described in more details elsewhere (Bukh et al., 2010). In short, 401 in- and out-patients discharged from a psychiatric hospital in eastern Denmark (Zealand (Sjælland)) with the main diagnosis of a single depressive episode (ICD-10, code DF32-32.9) were sampled consecutively from the Danish Psychiatric Central Research Register every second month in a 2-year period from 2005 through 2007. Patients with organic, schizoaffective or non-affective psychotic disorders, or a history of recurrent depression, manic, hypomanic, or mixed state episodes were not included (see flowchart in Fig. 1 for further details). The Danish Psychiatric Central Research Register is a nation-wide registration of all psychiatric hospitalisations and outpatient contacts in Denmark (Munk-Jorgensen and Mortensen, 1997) comprising information on treatment settings, duration of contact to psychiatric care, and psychiatric diagnoses. Further inclusion criteria were treatment with antidepressant medication, age at discharge was 18 to 70 years, and Danish ethnicity. Since the present study was part of a study of gene–environment interactions, rather strict criteria were used for Danish ethnicity, which was established, when the patient as well as both parents were born in Denmark, and none of the grandparents were born outside Europe. Exclusion criteria were significant physical illness, dementia or mental retardation.

The participants were invited to the present study consecutively 2–3 months after discharge from inpatient treatment or completion of outpatient treatment. They completed the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck, 1975) and went through a number of standardized semi-structured interviews conducted after discharge by two experienced medical doctors (CB and JDB). Firstly, the clinical diagnoses reported to the Register were validated by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990) based on the interview with the patient and data from case reports. ICD-10 diagnoses were established for the episode leading to psychiatric hospital contact and for the lifetime

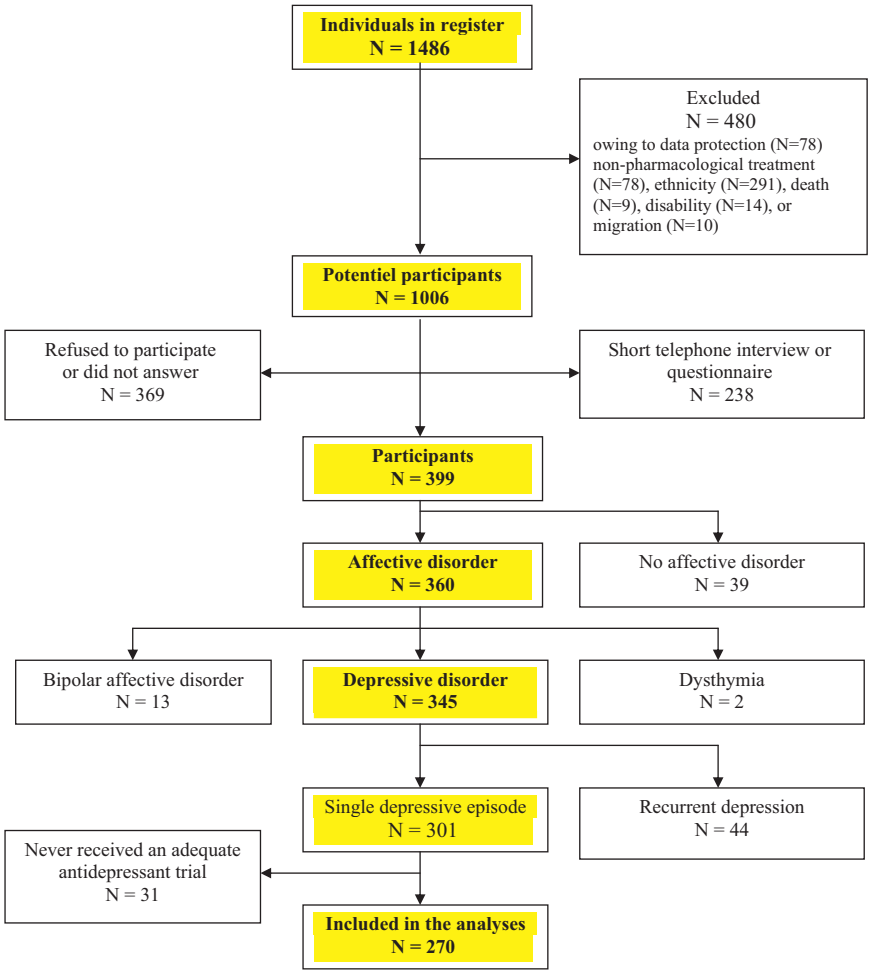


**Fig. 1.** Participants in the study.