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Research paper

Residual symptoms and functionality in depressed outpatients: A one-year observational study in Switzerland with escitalopram

Rico Nil [a,*], Simone Lütolf [a], Erich Seifritz [b]

[a] Lundbeck (Switzerland) Ltd, Cherstrasse 4, CH 8152 Glattbrugg, Switzerland
[b] Department of Psychiatry, Psychotherapy and Psychosomatics, Hospital of Psychiatry University of Zurich, Zurich, Switzerland

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ABSTRACT

Background: Residual depressive symptoms are associated with a poor prognosis for relapse or recurrence and are recognized as impeding factors of functionality. Recovery to the pre-depression level of functioning should be the goal of treatment.
Aim: To evaluate outcomes in depressed outpatients treated with escitalopram regarding response, recovery, residual symptoms, functionality and ability to work over 48 weeks.
Method: 3278 outpatients were evaluated at weeks 8, 24 and 48. A simple questionnaire was used to rate severity of illness, impairment of functionality, treatment response, tolerability, presence and severity of residual symptoms, whether remission with residual symptoms or recovery was achieved, and to what degree the patient was able to work.
Results: Data over the full 48-week period were available for 75.8% of patients, for whom treatment response was rated as "very good" or "good" in 81%. However, only 42% of the completing patients achieved recovery without residual symptoms, while 41% were rated as remitters with residual symptoms. Lack of energy/motivation was the most common reported residual symptom and was present in 23.5% of patients at study end. Concentration difficulties were present in 15.8% and impaired sleep in 13.9% of patients. Complete inability to work decreased from 36% at baseline to 9% at week 48, while full-time working capacity increased from 37% to 62%.
Limitations: Non-controlled observational real life study using simple ratings rather than established rating scales.
Conclusion: $<50\%$ of patients completing a one-year antidepressant treatment regimen were rated as being symptomatically fully recovered, and $\approx 50\%$ still reported functional deficits.

1. Introduction

Major depression is a common, chronic disease characterized by recurring depressive episodes in most of the affected patients (Mann, 2005). However, the time between depressive episodes is often not completely symptom-free and the onset and end of the individual episodes are, therefore, not clear-cut (Möller, 2008). Prospective long-term studies of up to 12 years have shown that patients were symptomatic for most of the time and underwent periods with different levels of depressive symptom severity (Judd et al., 2008a,b; Kennedy et al., 2004). Incomplete remission or remission with residual symptoms was a common outcome of depression in a three-year follow-up study in primary care (Conradi et al., 2011). According to this study, more than two DSM-IV symptom clusters were present during the follow-up period after the resolution of the index major depressive episode. Cognitive problems, lack of energy and sleep problems were seen as the most dominating residual symptoms. Zajecka (2013) also described sustained fatigue without physical exertion as an important disabling factor. McIntyre et al. (2013) stressed the importance of cognitive impairment and memory dysfunction in depression and their impact on functioning and working capacity. Concerning the nature of residual symptoms, Paykel (2008) proposed that they may reflect persistence of the original disorder in a milder form and that these symptoms need pharmacological or non-pharmacological continuation treatment.

A negative impact of symptoms of depression on psychosocial functioning has been recognized and well described (Judd et al., 2000). In a review of the literature, Kennedy et al. (2007) concluded that psychosocial impairment persists even after remission from depression and that residual symptoms such as cognitive deficits may lead to psychosocial impairment over long periods of time. Functional and psychosocial disability was shown to depend on depressive symptom severity and, thus, varied with the course

* Corresponding author.
E-mail address: rcn@depressionen.ch (R. Nil).

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of depressive symptoms (Judd et al., 1998b, 2000). A comparison between groups of depressive patients differing in the time since their last depressive episode showed that the symptom level after more than 12 months since the previous episode was still higher than in a non-depressed control group (Mojtabai, 2001).

Although antidepressants have repeatedly been shown to be highly effective in preventing relapse or recurrence of depressive episodes once response or remission criteria were reached (Williams et al., 2009), less research has focused on the evolution and treatment of residual symptoms (Fava, 2006). The level of residual symptoms was not only shown to have prognostic value for the risk of relapse and recurrence (Judd et al., 1998a), but also to have a major impact on psychosocial functioning and capability to work (Kennedy et al., 2007).

Looking at randomized placebo-controlled clinical trials, a meta-analysis of escitalopram data in the acute treatment of depression over 8 weeks revealed that 53% of the patients fulfiled the remission criterion defined by a MADRS total score ≤ 12 (Kennedy et al., 2009). In a pooled patient analysis, Wade et al. (2009) evaluated remission rates after continuation treatment with escitalopram over 24 weeks using different criteria for remission. After applying the most stringent criterion of symptom-free remission (no single MADRS item score > 1), less than half of the patients (46.1%) had achieved remission at month 6. Among the remitters, reduced sleep, concentration difficulties, lassitude and inner tension were the MADRS items with the highest scores at month 6.

No observational long-term depression study under a defined pharmacotherapeutic treatment scheme has so far focused on residual symptoms and functionality. Complementary to the study by Conradi et al. (2011), who included patients under a variety of non-pharmacological treatments, the present observational study aimed to analyse long-term treatment outcomes over one year in a large group of primary care patients treated with escitalopram, which is the most prescribed antidepressant in Switzerland. The principle of an observational study was applied, prohibiting the use of standard scales or diagnostic interview techniques in order to reflect daily practice as closely as possible and to make the study feasible for many private practices. The focus was on remission with or without residual symptoms and the status of patient functionality and working capacity. Based on the studies by Conradi et al. (2011) who identified in a primary care patient sample fatigue, sleep problems and cognitive problems as the most important residual symptoms, which was confirmed in a review by Zajecka (2013), and the pattern of the remaining symptoms from the Wade et al. (2009) escitalopram analysis, the present study also explicitly assessed these three potential residual symptoms.

2. Methods

2.1. Patient recruitment

Patients aged 18 years and above were recruited from 556 general practitioners or office-based psychiatrists throughout Switzerland from September 2012 to December 2013. Patients were eligible if the treating physician had foreseen the need for long-term treatment with escitalopram for up to one year. The diagnosis was either depression or an anxiety disorder as described in the current product labelling, i.e., general anxiety disorder, panic disorder, social anxiety disorder or obsessive compulsive disorder. Patients with a double diagnosis of anxiety and depression were allowed to enter the study. The diagnosis was given at the discretion of the treating physician according to his routine clinical practice. The current product label was the only selection criterion for recruiting patients. The study was submitted to all relevant regional ethical review boards and was only started after having received approval. According to the local observational study procedures, patients were informed about the study and gave oral or written consent according to the requirements of the local ethics committee. Only anonymised data were recorded to fulfil data protection regulations.

2.2. Design

The present study was performed according to an open, observational (non-interventional) study design. The use of assessment scales or diagnostic interview techniques was avoided in order to strictly reflect clinical routine practice. Therefore, the participating investigators were asked to treat the patients according to their routine clinical practice and to conduct a baseline evaluation before treatment with escitalopram was initiated. The patients were to be evaluated around 8, 24 and 48 weeks after treatment began, whenever routine visits were normally scheduled. Across the whole patient sample, the median/average evaluation time points were at weeks 8/8, 24/25 and 49/51.

2.3. Assessment questionnaire

For feasibility reasons, a simple tick box questionnaire was used with the following assessments:

Baseline: gender, age, diagnosis, presence of co-morbidities, previous antidepressant treatments.

Co-medication, severity of illness (*mild, medium, severe*), functional disability (*none, mild, medium, severe,* with illustrative examples [physical, daily living, cognition, organisational]) and percentage of working capability including unpaid work (% of time put on sick leave by treating physician) was recorded at baseline and throughout the study. Working capacity was only assessed among patients younger than 66 years.

In addition, the following assessments were performed at the follow up visits: dose of escitalopram, potential discontinuation with reasons, therapeutic effect and tolerability using a four-point scale (*unsatisfactory, satisfactory, good, very good*), achievement of recovery or remission with residual symptoms including severity of residual symptoms (*mild, medium, severe*) and the presence of the three specific residual symptoms "*lack of energy/motivation*", "*concentration difficulties*" and "*impaired sleep*". In case of adverse events, a faxed form had to be filled out in order to fulfil reporting obligations on a continuous basis throughout the study.

2.4. Data entry and analysis

A data-scanning system (Canon–Image Formula DR-6030C) was used to automatically read all tick-box data and to import them into an Excel file. This file was completed by manually entering all remaining data. A series of plausibility checks was performed with the help of an external statistician. Whenever possible, queries were resolved by phone with the investigators before the database was closed and delivered to the statistician, who ran descriptive analyses using SPSS statistical package (IBM SPSS Statistics, Version 22). A separate safety report was prepared and submitted to the national authorities (Swissmedic). Generally, unless stated otherwise, data analyses are based on the observed cases (OC) dataset. Correlational analyses were calculated using 2-sided Kendall's Tau-b coefficients.