Investigation Of Early Suicide-Related Symptoms In A Non-Suicidal Depressed Patient Population After Escitalopram Administration: A Pilot Study

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Citation

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Abstract

Background: The efficacy of selective serotonin reuptake inhibitors (SSRIs) is well established in the treatment of major depression. However, an important delay in the onset of global action relative to placebo is described within the first weeks after their administration. Little is known about the experience over time on specific and suicide-related symptoms. Aims: This study aimed at investigating the experience over time of escitalopram on depression-related symptoms that are also associated with increased risk for suicidal behaviour. Methods: In an 8-week prospective uncontrolled open-label design, escitalopram was administered to 18 patients with a current major depressive episode. Mood, state anxiety, state anger and hopelessness were assessed at baseline and after 2, 4 and 8 weeks of treatment with escitalopram in a flexible dose regimen up to 20 mg. Results: Mood ($p < 0.001$), state anxiety ($p = 0.002$), state anger ($p = 0.002$) and hopelessness ($p = 0.002$) significantly improved after 8 weeks of treatment with escitalopram. However, symptom improvement varied over time. Mood and anger significantly improved after 2 weeks of treatment, whereas significant reductions of state anxiety and hopelessness were noticed only by the end of the study.Conclusions: This study underlines the early beneficial experience of treatment with escitalopram on mood and different suicide-related symptoms in a non-suicidal depressed patient group.

INTRODUCTION

The efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of major depression is well established. This is reflected in most international guidelines such as NICE (National Institute for Health and Clinical Excellence, ([1])) and APA (American Psychiatric Association, ([2])), which recommend their use in the treatment of depression. The underlying mode of action is based on blocking the serotonin transporter, thereby increasing the synaptic availability of serotonin, which is thought to reduce symptoms of depression.

However, despite the rapid inhibition of serotonin transporters in vitro and in vivo by SSRIs, a delayed onset of action relative to placebo is well demonstrated. Statistically significant benefits versus placebo are first often reported after several weeks. Although the causes of this delay remain unclear, several hypotheses have been put forward. Acutely enhanced synaptic serotonin levels may lead to adaptive down regulation and desensitization of postsynaptic serotonergic receptors over time ([3]). The negative feedback loop installed by the presynaptic 5-HT(1A) receptors may also explain the delay ([4]). Further, antidepressants may activate not only second messenger systems leading to the activation of transcription factors such as cAMP response element-binding protein (CREB), but also may activate neurotrophic pathways and increase hippocampal neurogenesis ([5]).

Despite the well-documented delayed onset of action, clinical experience shows that depressed patients may report early improvement in symptoms shortly after initiation of antidepressant treatment ([6]). Recent research supports this clinical experience, demonstrating symptomatic improvement in mood by the end of the first week after use of SSRIs ([7]). Unfortunately, these studies focus mostly on mood and less on other depression-related symptoms, such as anxiety, hopelessness, impulsivity or anger ([8, 9, 10]). Early symptom improvement is of clinical importance because of its association with positive outcome and the relationship

between serotonergic dysfunction and suicidal behaviour ([11]). Depressed mood combined with feelings of hopelessness and anxiety strongly increases the risk for suicidal behaviour ([12]). Moreover, hopelessness is regarded as one of the best predictors of suicide in a depressed patient population ([13, 14, 15, 16]). Further, anger and impulsive behaviour increase the risk for suicide ([17, 16]). Anger may not only directly increase deliberated self-harm, but also may indirectly lead to a variety of negative outcomes such as poor evaluation by others, lowered self-esteem, interpersonal conflicts and occupational maladjustment, which in turn may function as important triggers for suicidal acts ([18, 19, 20]). In particular, anger-irritability may be associated with impulsive suicides ([19]). These findings are somehow in contrast with the recent warning by the Food and Drug Administration reporting an increased risk of suicidal thinking, feeling and behaviour especially in children and adolescents and in the early treatment phase with SSRIs, although there is also risk in not using antidepressant medication ([21, 22]).

The present study aimed to investigate the experience over time of the SSRI escitalopram early on in treatment. Hereby, treatment experiences were studied not only for mood but also for other depression-related symptoms. Special attention was paid to symptoms which are repeatedly reported to be associated with suicidal behaviour and suicide, such as anxiety, anger and hopelessness. The current study was part of a larger longitudinal study of behavioural, affective and cognitive functions and brain metabolism in depressed patients before and after treatment with escitalopram.

METHODS

PARTICIPANTS

This study investigated the effects of the administration of escitalopram during an 8-week prospective open-label design in patients who were diagnosed with a current major depressive episode (MDE). Participants of the study were recruited at the inpatient and outpatient services of the University Department of Psychiatry of the University Hospital of Ghent, Belgium. The first 18 patients participating were selected out of the before mentioned larger longitudinal study.

Inclusion criteria were (a) having a current major depressive episode (MDE), according to DSM-IV-TR criteria ([23]), (b) age between 18 and 65 years, and (c) having a score >25 on the Montgomery Åsberg Depression Rating Scale (MADRS) ([24, 25]). Patients were excluded from the study if they were diagnosed with bipolar disorder, if they suffered from severe suicidal behaviour requiring law forced treatment or closed facility treatment, if they had a concurrent medical illness, if they had an IQ <80 or cognitive dysfunction due to trauma capitis or dementia, if they were pregnant, lactating or in childbearing age without taking any contraceptive measures. All psychopharmacological treatments were stopped at least one week before the start of the study. Patients were allowed to take lorazepam 1 mg or zolpidem 10 mg during the study for insomnia. None of the patients were taking fluoxetine before inclusion. Patients could only participate in the study after giving their written informed consent. The study was approved by the ethical committee of the University Hospital of Ghent in accordance with the principles of the Declaration of Helsinki.

ASSESSMENT INSTRUMENTS

Patients were assessed by a psychiatrist using the Mini International Neuropsychiatric Interview, Dutch version 5.0.0., (section A to O) ([26]) and the MADRS. At baseline, the patients completed the following self-report scales: Beck Depression Inventory II (BDI-II) ([27, 28]), the Spielberger State Anxiety Inventory (STAI) ([29, 30]), the Spielberger State Anger Inventory (STAXI) ([31, 32]) and the Beck Hopelessness Scale (BHS) ([33]). All self-report questionnaires were re-administered at 2, 4 and 8 weeks after initiating treatment with escitalopram and at the same time patients were assessed by a psychiatrist using the MADRS.

The MADRS is a widely used clinician-rated depression scale designed to differentiate medication from placebo effect during treatment. It consists of 10 items, 9 of which are based upon patient report, with one additional clinician-rated item about the patient's sadness. Items are rated on a 0-6 scale, yielding a total maximum score of 60, with higher scores indicating a greater depressive symptomatology ([24]). The Dutch version of the MADRS has acceptable validity, good reliability and good internal consistency ([25]). In this study, Cronbach alpha reliability before treatment was 0.78. In this study, remission on MADRS was defined as a score 10 and treatment response as ≥50% improvement from baseline ([34]).

The BDI-II is a self-report questionnaire designed to assess the severity of the depression in order to monitor change over time. The BDI-II contains 21 item sets, each with a series of four statements (0-3) that describe symptom

severity along an ordinal continuum, varying from 0 to 63 ([27]). The Dutch translation of the BDI-II shows high internal consistency ([28]). In this study, Cronbach alpha reliability before treatment was 0.88. In this study, remission and treatment response were defined as a BDI score < 9 and as ≥ 50% improvement in BDI scores, respectively.

The STAI is a 20-item (1-4) self-report questionnaire designed to assess state and trait anxiety. Total scores vary from 20 to 80. For both state and trait anxiety, internal consistency is high. For trait anxiety, test-retest reliability is relatively high, whereas for state anxiety the stability coefficient tends to be low, as expected ([29, 30]). In this study, Cronbach alpha reliability of STAI state before treatment was 0.93.

The STAXI is a 10-item (1-4) self-report questionnaire that measures state and trait anger. Total scores vary from 10 to 40. Internal consistency and validity are high ([31, 32]). In this study, Cronbach alpha reliability of STAXI state before treatment was 0.93.

The BHS is a 20-item self-report questionnaire which assesses statements about the future that the subject rates as true or false. Total score ranges from 0 to 20, with a score higher than 8 indicating levels of hopelessness associated with an increased risk of suicide ([33]). The scale has excellent internal consistency and test-retest reliability. The concurrent validity is well established across a wide variety of samples. In this study, Cronbach alpha reliability before treatment was 0.70.

PHARMACOLOGICAL TREATMENT

At baseline, treatment with escitalopram was started in a flexible dose regimen up to 20 mg, with elevating the dose according to clinical condition. Escitalopram is a potent and highly selective inhibitor of the serotonin transporter protein, with high affinity for serotonin reuptake sites and low affinity for noradrenalin and dopamine reuptake sites. It is an effective and generally well-tolerated treatment for moderate-to-severe major depressive episodes ([35]). Side effects of the medication were registered on an adverse event form at every visit.

STATISTICS

Descriptive analyses were used to investigate the demographical and psychopathological characteristics of the study population. Non-parametric statistics (Wilcoxon signed-rank test) were used to compare scores at different time points. To correct for multiple comparisons with respect to the baseline measurements for all scales, a Bonferroni-type correction is applied and statistic significance was set at $p < 0.005$. The last-observation-carried-forward (LOCF) procedure was used in case of drop-outs before study termination.

RESULTS

SAMPLE DESCRIPTION

A total of 18 patients (4 men, 14 women, all Caucasian) participated in the study. Socio-demographic characteristics of the sample are described in Table 1. The mean age of the total sample was 33.3 (SD 10.6) years, while the mean education level was 13.2 (SD 2.1) years. At inclusion, the mean score on the MADRS was 30.4 (SD 5.5). Four patients (22.2%) withdrew from the study: one patient stopped just after inclusion, and one patient discontinued the medication after 4 weeks, for both it was their own decision. Two other patients (one at week 1 and one at week 2) were withdrawn because they required medication that was not allowed in the study protocol. No significant differences in gender, age, level of education and scores on MADRS were found between dropouts and completers at inclusion.

Figure 1

Table 1. Socio-demographic and other baseline characteristics of the study population

	Included population	Completers
Number, n (%)	18 (100%)	14 (77.8%)
Age, mean (SD), yrs	33.3 (10.6)	34.6 (10.7)
Gender, Male, n (%)	4 (22.2%)	3 (21.4%)
Female, n (%)	14 (77.8%)	11 (78.6%)
Level of education, mean (SD), yrs	13.2 (2.1)	13.3 (2.3)
Concomitant use of a benzodiazepine at visit 1, n (%)	6 (33.3%)	5 (27.8%)

EFFECTS OF TREATMENT

All investigated variables including mood ($p < 0.001$), state anxiety ($p = 0.002$), state anger ($p = 0.002$) and hopelessness ($p = 0.002$) significantly improved after 8 weeks of treatment with escitalopram. However, the starting point of the significant decrease of symptoms varied between the different variables (see Table 2, figures 1-2).

Figure 2

Table 2. Changes in psychopathological characteristics during treatment

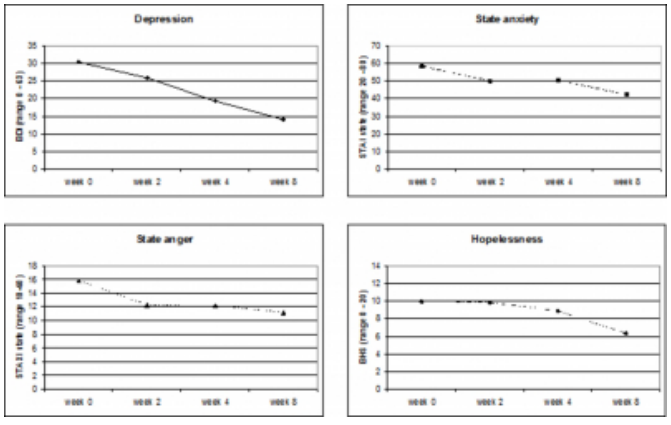
Scale	Week 0 (n = 18) M (SD)	Week 2 (n = 18) M (SD)	Week 4 (n = 18) M (SD)	Week 8 (n = 18) M (SD)	p-value
BDI	30.3 (10.6)	25.8 (13.6)	19.2 (9.7)	14.1 (11.7)	Week 0 to 2 = 0.012 Week 0 to 4 = 0.001 Week 0 to 8 < 0.001
MADRS	30.4 (5.5)	24.2 (10.4)	18.6 (9.8)	12.2 (10.7)	Week 0 to 2 = 0.002 Week 0 to 4 < 0.001 Week 0 to 8 < 0.001
STAI state	58.2 (10.8)	49.6 (11.7)	50.2 (12.4)	41.9 (11.6)	Week 0 to 2 = 0.006 Week 0 to 4 = 0.046 Week 0 to 8 = 0.002
STAXI state	15.8 (5.9)	12.2 (3.6)	12.1 (2.3)	11.2 (2.0)	Week 0 to 2 = 0.001 Week 0 to 4 = 0.009 Week 0 to 8 = 0.002
BHS	9.9 (3.5)	9.8 (3.6)	8.8 (3.6)	6.3 (3.0)	Week 0 to 2 = 0.867 Week 0 to 4 = 0.126 Week 0 to 8 = 0.002

BDI scores dropped significantly (p = 0.001) from an initial mean score of 30.3 (SD 10.6) at week 0 to a mean score of 19.2 (SD 9.7) at week 4. Treatment response rate measured on BDI-II at week 8 was 61.1 %, while the remission rate was 44.4 %.

In contrast to the self-reported mood (BDI-II), the clinician-rated MADRS total score decreased significantly (p = 0.002) from an initial mean score of 30.4 (SD 5.5) at week 0 to a mean score of 24.2 (SD 10.4) at week 2. The treatment response rate measured on the MADRS at week 8 was 77.8%, while the remission rate was 61.1%.

Figure 3

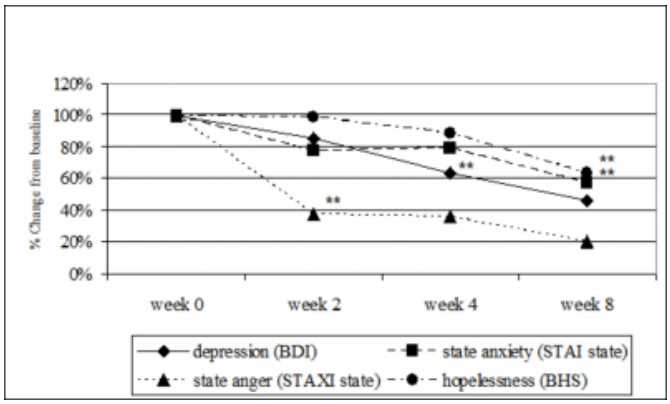
Figure 1. Changes in psychopathological characteristics during treatment



State anxiety was significantly reduced (p = 0.002) from an initial mean score of 58.2 (SD 10.8) at week 0 to a mean score of 41.9 (SD 11.6) at week 8. State anger decreased significantly (p = 0.001) from a mean score of 15.8 (SD 5.9) at week 0 to a mean score of 12.2 (SD 3.6) at week 2. This score was also the first score below the cut-off value of 13 reflecting a non-clinical status and 77.8% of the patients had a score within a non-clinical range at week 8. Hopelessness scores dropped significantly (p = 0.002) from an initial mean score of 9.9 (SD 3.5) at week 0 to a mean score of 6.3 (SD 3.0) at week 8.

Figure 4

Figure 2. Percentage of changes in psychopathological characteristics during treatment



 = p-value < 0.005

Finally, data on some additional suicide-related characteristics of the BDI-II were analysed. The item ‘hopelessness’ reduced significantly from a mean score of 1.7 (SD 0.8) at week 0 to a mean score of 0.6 (SD 0.7) at week 4 (p = 0.002) and a mean score of 0.6 (SD 0.7) at week 8 (p = 0.002). The item ‘suicidality’ reduced from a mean score of 0.8 (SD 0.8) at week 0 to a mean score of 0.4 (SD 0.6) at week 4 (p = 0.011) and to a mean score of 0.3 (SD 0.6) at week 8 (p = 0.013). The item of the MADRS about suicidality reduced significantly from a mean score of 1.8 (SD 0.6) at week 0 to a mean score of 0.8 (SD 1.1) at week 4 (p = 0.001) and a mean score of 0.6 at week 8 (p = 0.001).

OBSERVED CASES ANALYSIS

In order to check for a potential bias due to the use of the last observation measurements to replace missing data, these analyses were repeated using a reduced data set omitting participants with missing data. The results remained essentially the same with all findings remaining statistically significant.

TREATMENT DOSE AND SIDE EFFECTS

All patients received 10 mg of escitalopram at week 2, while the mean dose was 11.3 mg (SD 3.5) at week 4 and 12.0 mg (SD 4.1) at week 8. Reported side effects of the study medication were nausea (n = 2), increased sweating (n = 2),

akathisia (n = 1) and headache (n = 1). These complaints were mild and transient and were not reasons for withdrawing from the study.

DISCUSSION

In this 8-week prospective open-label study, treatment effects of escitalopram were examined in a depressed non-suicidal patient group. All investigated symptoms such as mood, state anxiety, state anger and hopelessness significantly improved after 8 weeks of treatment compared to baseline. However, symptom improvement varied over time: clinician-rated mood and anger significantly improved after 2 weeks of treatment, self-rated mood after 4 weeks, whereas significant reductions of state anxiety and hopelessness were reported only after 8 weeks. The statistically significant reductions were also clinically relevant. After the first significant reduction, the state anger score was below the cut-off value of 13 reflecting a non-clinical status, the BDI-II score reached the interval between 14 and 19, indicating only "possible or mild depression", the state anxiety score was within the range of the 7th decile for a non-clinical population and hopelessness score indicated only a "mild hopelessness". Suicidality did not increase.

First, the results of this study add further to the evidence suggesting that SSRIs do improve mood early on in treatment ([35, 6, 36]). A recent meta-analysis has suggested that SSRIs, including escitalopram, have observable beneficial effects on mood during the first week of treatment ([7]). The differences between clinician-rated mood, which improved at first measurement at week 2, and self-rated mood, which improved at week 4, may be explained, at least in part, by the possible biasing effect of the current mood on self-report ([37, 38]). Noteworthy, the remission rate measured on BDI-II at week 8 of 44.4 % is the same as revealed by the subanalysis of randomized controlled trials that involved patients randomized to citalopram (44%) done by the authors of a recent study ([39]).

Secondly, not only mood, but also the other symptoms improved, mostly to a non-clinical level, after 8 weeks of treatment with escitalopram. As for mood, this improvement occurred early on in treatment mainly for anger, and less for hopelessness, anxiety and suicidality. The significant reduction of these symptoms is of clinical interest since they all are associated with a decreased risk for suicidal behaviour and suicide ([35, 40]). The first period after initiating a treatment with antidepressants tends to be crucial in terms of suicidality. The risk of suicide in patients recovering from a major depressive episode may increase transiently as they develop the energy and capacity to act on self-destructive plans made earlier during the course of their illness. Therefore, an early decrease of these suicide-related characteristics may be important in the prevention of suicide in this initial treatment period.

The early reduction of anger may in particular be an important factor in reducing the risk of suicide. Anger has frequently been reported to be associated with suicidal behaviour and suicide ([41, 17, 16]). The responsiveness of anger and impulsive-aggressive behaviour to SSRI treatment has been the subject of extensive research. Anger and anger attacks disappeared significantly in depressed patients treated with an SSRI ([42, 43, 44, 45]). Fava and colleagues proposed the existence of a subtype of depressed patients who experience anger attacks that have a preferential treatment response to SSRIs ([46, 43]). However, more recent studies could not support this finding ([42, 46]). Nevertheless, it has been suggested that depressed patients with anger attacks may be distinct from those without anger attacks in terms of clinical correlates, personality features and biological characteristics, but not in terms of treatment response ([19]). Benazzi suggested major depressive disorder (MDD) with anger to be a midway between MDD without anger and bipolar II disorder ([47]).

Anger in depressed patients is not only associated with an increased risk of suicide, but may also play an important role in the interpersonal problems experienced by many depressed patients. Anger involves not only the experience of high-arousal negative feelings, but also often the attribution to blame others. As a result, expressing anger leads to social maladjustment which may further increase depressive feelings ([48, 49]). Dealing with angry feelings can also cause health problems as people might try to cope with this higher inner stress by unhealthy coping and problem-solving behaviour such as self-harm, alcohol or substance abuse ([50]). Therefore, the early reduction of anger is of importance to reduce interpersonal problems and co-morbidity in depressed patients.

Finally, the results of this study point to a differential time effect of escitalopram on the improvement of depressive symptoms. Mood and anger improved more rapidly than anxiety and hopelessness. Different explanations may be possible. Since some authors have argued that anger and mood share a similar theoretical background ([51]), it may be possible that the differences in time findings reflect

differences in underlying neurobiological pathways. The finding that all investigated symptoms improved during treatment with an SSRI, may suggest that the development of these symptoms is related to serotonergic dysfunction. The small sample size, increasing the risk of a type I error, may, however, also have contributed to these results. Additionally, differences in antidepressant response on symptom dimensions get more attention in recent studies and contribute to estimate the sources of residual variability in symptom change over time. The recent study "Genome Based Therapeutic Drugs for Depression" (GENDEP) used three symptom dimensions and proved more therapeutic effects of escitalopram on mood and cognitive symptoms, but less on neurovegetative symptoms, relative to the active comparator nortriptyline ([52]).

LIMITATIONS

Some potential limitations of the study should be addressed because they may limit the generalizability of our results. An important shortcoming of the study is the small sample size and the last-observation-carried-forward (LOCF) analysis to account for missing data. However, the lack of power of this study and the use of the LOCF analysis should rather have contributed to a negative bias favouring the delay in onset of action of antidepressants ([7]). For ethical reasons, it was not allowed to use a matched placebo-controlled condition. Due to the lack of matched controls, the improvements found in this study may be due to a placebo effect. However, one would expect that a placebo effect led to a more homogeneous and less differentiated pattern of symptom improvement. Notably, this study includes a higher number of female patients, so the findings could possibly be accounted only by this subgroup of subjects. Also, the lack of assessments at the first week after treatment initiation might be an additional limitation. Finally, another limitation is that the study has been mainly based on self-report with a possible biasing effect of the current mood.

CONCLUSION

This study underlines the beneficial impact early on in treatment of the SSRI escitalopram on mood and suicide-related symptoms in a non-suicidal depressed patient population. Further, a differential time impact of improvement was found for such symptoms. Further research is needed to replicate these findings in a larger, placebo-controlled sample and to investigate treatment impact of escitalopram in a patient group with severe suicidal symptoms.

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