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Comparison of the effects of escitalopram and nortriptyline on painful symptoms in patients with major depression

Jan Jaracz, Ph.D.,M.D. [a,*], Karolina Gattner, M.D. [a], Jerzy Moczko, Ph.D.,M.D. [b], Joanna Hauser, Ph.D.,M.D. [c]

[a] Department of Adult Psychiatry, Poznań University of Medical Sciences, ul. Szpitalna 27/33 60-572 Poznań, Poland
[b] Department of Computer Science and Statistics Poznań University of Medical Sciences ul. Dąbrowskiego 79 60-529 Poznań, Poland
[c] Department of Psychiatric Genetics, Poznan University of Medical Sciences, ul. Szpitalna 27/33, 60-572 Poznań, Poland

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ABSTRACT

Objective: Unexplained painful physical symptoms are commonly reported by depressed patients. The evidence suggests that dual-action antidepressants are potent in relieving pain in depression. However, a direct comparison of the effects of selective serotonergic and selective noradrenergic antidepressants on painful symptoms has not been investigated so far.
Method: Sixty patients who participated in the Genome-based Therapeutic Drugs for Depression study with a diagnosis of moderate or severe episodes of depression according to the *International Classification of Diseases, 10th Revision,* and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria were involved. All the participants were randomly allocated to receive nortriptyline or escitalopram. The severity of depression was measured using the Montgomery–Åsberg Depression Rating Scale, the Hamilton Depression Rating Scale and the Beck Depression Inventory at weeks 0, 2, 4, 6 and 8. The intensity of pain was measured on the Visual Analog Scale at the same points of the study.
Results: At "week 0," 83.3% of the patients later randomized to treatment with escitalopram and 86.7% of those treated with nortriptyline reported at least one painful symptom. A significant decrease of pain intensity was observed after 2 weeks of treatment. The two groups did not differ in degree of pain reduction at weeks 2, 4, 6 and 8 in comparison to baseline values. A 50% reduction in pain intensity preceded the 50% reduction of depression severity. The intensity of pain at "week 0" did not differ in remitted or nonremitted patients at week 8.
Conclusion: Both selective serotonergic and selective noradrenergic antidepressants are equally effective in alleviations of painful physical symptoms of depression. The presence of painful symptoms before the onset of treatment did not determine the final response.

1. Introduction

Epidemiological data and clinical experience indicate that a significant proportion of patients with depression report unexplained painful physical symptoms (PPSs) unrelated to any general medical condition. Bair et al. [1], who reviewed 14 studies examining pain in depression, found that the mean prevalence of pain was 65% and ranged from 15% to 100%. Pain complaints were identified in participants of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study on the basis of one item, somatic pain, of the 30-item Inventory of depressive Symptomatology — Clinical Rating. Pain of at least mild intensity was reported by 77% of subjects [2]. Recent studies have confirmed a high prevalence of pain in depression. Aguera-Ortiz et al. (2011) [3] showed that 59.1% of patients with depression, attended by psychiatrists in their regular practice, reported significant pain, defined as intensity of pain >40 on the Visual Analogue Scale (VAS) in a range of 0–100. The high prevalence of pain in depression was confirmed in the prospective FINDER (Factors Influencing Depression Endpoints Research) study, and moderate to severe pain was detected in 56% of the patients before initiation of treatment with an antidepressant. One third of the patients continued to experience moderate to severe pain at 6-month follow- up [4].

Several implications of painful symptoms in depression have been suggested. Karp et al. (2005) [5] postulated that a higher level of pain at baseline predicts a longer time to remission and it may therefore be considered as a marker of a more difficult-to-treat depression. Furthermore, painful symptoms in depression are related to poor functional status (higher unemployment and pain-related functional limitations), frequent utilization of health care (at baseline and 1-year follow-up) [6] and a poorer quality of life [7].

There is growing evidence suggesting that the regulation of mood and pain processing may share a common neurobiological mechanism. According to the monoamine theory of the pathogenesis of depression, deficiencies in ascending serotonin and noradrenaline pathways are responsible for core symptoms of depression such as depressed mood, psychomotor retardation, and vegetative symptoms. Descending 5-HT and NA pathways play a crucial role in the modulation of nociceptive

* Corresponding author. Tel.: +48 61 8491 531.
E-mail address: jjjaracz@gmail.com (J. Jaracz).

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signals from the periphery to the higher cerebral centers. Alteration of suppression of ascending sensory input has been implicated in the pathophysiology of painful symptoms in depression [8]. Since both 5HT and NA are involved in descending inhibition of pain impulses, it has been postulated that those antidepressants which block the reuptake of both 5-HT and NA are more effective in reducing pain than drugs acting upon a single neurotransmitter. Considerable research has confirmed the efficacy of venlafaxine, milnacipram and duloxetine in fibromyalgia, neuropathy and other painful conditions [9–13]. These data led to the assumption that analogously dual-action antidepressants are more effective in reducing unexplained pain in depression than selective agents. On the assumption that the analgesic efficacy of different classes of antidepressants is not equivalent, the choice of antidepressant would appear to be an important issue due to the fact that the presence of painful physical symptoms has an impact on several aspects of prognosis in treatment of depression. In recent years, duloxetine, a potent dual-reuptake inhibitor of 5-HT and NA, has attracted the attention of investigators in regards to its effect on painful symptoms. Placebo-controlled, randomized studies have shown that duloxetine significantly reduces pain in depressed patients [14–16]. Goldstein et al. [17], on the basis of data from three trials, confirmed that duloxetine is effective in the amelioration of PPSs in depression. However, in one study, paroxetine 20 mg/day appeared to be comparably effective in reducing pain severity to duloxetine 80 mg/day at week 8.

The effects of duloxetine have been well documented, but the paucity of data regarding the efficacy of other antidepressants in reducing PPSs of depression is evident. Moreover, it has not been clearly elucidated whether selective serotonin reuptake inhibitors (SSRIs) are noninferior to noradrenaline reuptake inhibitors in reducing painful physical symptoms in depression. PPSs were defined as experience of pain which is unexplained by the presence of general medical conditions.

We carried out a randomized controlled noninferiority trial to compare the effects of the SSRI escitalopram and the potent noradrenaline reuptake inhibitor nortriptyline on PPSs in patients treated because of depressive episode. Noninferiority trials are intended to show that the effect of one treatment is not worse than another by a specified margin.

2. Subjects

Sixty patients (44 males and 16 females) with the diagnosis of a moderate or severe episode in the course of unipolar major depression were involved in this study. All patients met both the *International Classification of Diseases, 10th Revision* (World Health Organization, 1992), and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994), criteria. The diagnosis was confirmed using the Schedules for Human Assessment in Neuropsychiatry v.2.1 (WHO 1999). For 30 patients, it was a first (single) depressive episode and, for others, the second ($n = 17$) or third ($n = 7$). All the subjects were participants in the Genome-based Therapeutic Drugs for Depression (GENDEP) study, an open-label, part-randomized multicenter pharmacogenetic study with two active pharmacological treatment arms in one of involved centers [18–20]. Patients with no contradictions were randomly allocated to receive a flexible dosage of nortriptyline ($n = 30$), a tricyclic antidepressant which inhibits the reuptake of noradrenaline (50–150 mg daily), or escitalopram ($n = 30$), a selective inhibitor of the serotonin transporter (SSRI) (10–30 mg daily). The following exclusion criteria were established: a family history of schizophrenia; bipolar disorder in first-degree relatives; a personal history of schizophrenia, manic or hypomanic episode, mood incongruent psychotic symptoms, active substance dependence or primary organic disease; current treatment with an antipsychotic or a mood stabilizer; nonresponse to one medication and the presence of serious medical condition interfering with treatment. None of the patients were diagnosed with medical conditions associated with chronic pain. Participants who could not tolerate the initially allocated medication or who did not experience sufficient improvement despite adequate dosage were offered to change to the other medication. Participants who changed medication were then followed up using the same protocol as for the first antidepressant. Other psychotropic medications were not allowed, with the exception of the occasional use of hypnotics.

Before randomization (week 0) and every two weeks (week 2, 4, 6, 8) throughout the study, the severity of depression was measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) [21], the Hamilton Depression Rating Scale (HAMD-17) [22] and the self-report Beck Depression Inventory (BDI) [23].

The mean age of the patients receiving nortriptyline was 38.7 years (S.D.± 11.5), and of those receiving escitalopram, the mean age was 41.3 years (S.D.± 12.3). The demographic and clinical characteristics of patients are given in Table 1.

At day 0, severity of depression in both groups was much the same, according HAMD (26 vs. 25), MADRS (31.4 vs. 29.8) and BDI (32.9 vs. 29.9).

The intensity of pain was measured with the VAS, which has been used in several studies investigating pain in depression. The participants were asked to assess the severity of pain in their head, neck, chest, abdomen and extremities on a range of 0–10 cm and to mark down on VAS every day in the previous 2-week period. During consecutive visits, the mean scores of VAS and the number of painful symptoms were calculated. In the case of multiple pains, the mean VAS scores referring to particular body parts were added up.

All the patients gave their written informed consent, and the study protocol was approved by the local ethics board of Poznań University of Medical Sciences.

2.1. Statistical methods

The Mann–Whitney and Wilcoxon tests were used to compare pain and depression scores. Data were analyzed with Statistica version 11. This statistical analysis was verified using Hodges-Lehman, Klotz and Lapage tests. On the basis of available data, an equivalence margin of 1.5 cm on the VAS was prespecified [24]. For the purpose of estimation of power of Mann–Whitney test applied for statistical analysis in this study, we administer POWER & SAMPLE SIZE for TWO ORDERED MULTINOMIALS procedure from Cytel Studio Version 10.0.0 (Jan. 16, 2013) software (StatXact suite of statistical tests). Estimations were performed using both exact and asymptomatic methods assuming difference 1.5 cm in pain severity as clinically significant. According to both methods, the power was estimated as 92% and 91%, respectively.

3. Results

At "week 0," 83.3% of the patients randomized afterwards to treatment with escitalopram and 86.7% of those to treatment with nortriptyline reported at least one painful symptom. At this point in the study, the mean VAS score in the escitalopram group was 6.7 (S.D. 7.6), whereas in the nortriptyline group, it was slightly lower at 4.6 (S.D. 4.6). The most common location of pain at day 0 was head (ESC 80%, NOR 77% with headache), chest (ESC 30%, NOR 29%), abdomen (ESC 33%, NOR 30%), upper limbs (ESC and NOR 7%) and lower limbs (ESC and NOR

Table 1
Demographic and clinical characteristics of the groups

	Escitalopram ($n = 30$)		Nortriptyline ($n = 30$)		
	Mean	S.D.	Mean	S.D.	*P*
Age	41.3	12.3	38.7	11.5	NS
Duration of disease (years)	4.23	5.36	4.11	5.66	NS
Number of episodes	1 n=12 2–3 n=14 >3 n=4		1 n=18 2–3 n=8 >3 n=4		NS
HAMD	26	4.8	25	6.8	NS
MADRS	31.4	7.2	29.8	8.4	NS
BDI	32.9	9.0	29.9	10.6	NS