Generalized anxiety disorder: a study of integrated therapy

Disturbo d'ansia generalizzato: uno studio di terapia integrata

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Summary

Objectives

The aim of the present study was to evaluate the efficacy of duloxetine in generalized anxiety disorder and the its compatibility and synergy with non-pharmacological instruments.

Methods

This observational study was carried-out in 130 patients (80 women and 50 men) (Table I) with generalized anxiety disorder recruited among outpatients of the Operative Unit of Mental Health, district 13, ASL Caserta. The patients were subdivided into two cohorts: the first cohort was treated with duloxetine 30 mg/die (70 patients), the second with duloxetine 30 mg/die plus a group trained in stress control counseling (60 patients). They were assessed through the Hamilton Rating Scale for Anxiety (HAM-A) administered at the 1st, 2nd, 3rd, 4th, 5th, 6th, 8th, 10th, and 12th week of treatment, and the Anxiety Scale Questionnaire (ASQ) administered at T0, T_{30}, T_{60} and follow-up at T_{90} days.

Results

In the group treated with duloxetine (dulo) + stress control counseling (scc), the improvement was more rapid than the group treated only with dulo (Fig. 1); in the first 4 weeks, 65% of patients treated with dulo plus scc and 53% of patients treated with dulo alone responded to treatment significantly; while regarding remission, there were no statistically significant differences (Fig. 2). Dulo 30 mg + scc-treated patients also showed significantly greater improvements compared with dulo 30 mg-treated patients on each of the secondary efficacy measures (Fig. 3); with the scale ASQ, we observed that the sum score of A + B improved significantly in the first month of treatment, gradually stabilizing in the group treated with dulo plus scc (Fig. 4).

Conclusions

The results of this observational study suggest that duloxetine is effective and well tolerated at a dose of 30 mg/die for the treatment of GAD. Patients who received the drug plus the educational training group in stress control counseling have achieved a significant improvement, with reduced severity of anxiety symptoms and improving the overall performance, faster than the group treated only with the medication. These improvements were clinically significant, as indicated by the good response from the sustained improvement and remission rates at study endpoint. The clinical evidence that drugs inhibiting serotonin and norepinephrine reuptake (SNRIs) are particularly effective in treating the short, medium and long-term generalized anxiety disorder has recently found an experimental correlate at the neurochemical level. The ability of SNRIs to act simultaneously and more selectively on the serotonergic and noradrenergic transmission is certainly a peculiar property, fundamental in allowing these drugs to modulate the most efficient synthesis of trophic factors and the process of neurogenesis, the two most important phenomena associated functionally to neuroplasticity.

Key words

Generalized anxiety disorder • Integrated therapy • Duloxetine • Stress control counseling

Introduction

The Mental Health Operative Unit (UOSM), health district 13, comprises a population of about 90,000 inhabitants. Over a period of 20 years or so, an increasing population suffering from anxiety disorders was seen and with different psychopathological disorders.

An empirical assessment identifies, at present, a total of 800 people with anxiety disorders among a total of 5000 people assisted annually.

Among people with anxiety disorders, increased in recent years of diagnosis of generalized anxiety disorder.

Generalized Anxiety Disorder (GAD) is defined in DSM-IV-TR [1] as a pervasive and excessive concern, accompanied by a variety of somatic symptoms, causing a significant alteration of social or occupational functioning or marked distress in the patient.

Diagnostic criteria for Generalized Anxiety Disorder

The person indicates excessive anxiety and worry (apprehensive expectation), and persistent, occurring on most days for at least six months in respect of a number of

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events or activities (such as work or school performance), has difficulties in controlling the worry, which may be associated with some of the following symptoms:

1. restlessness or feeling tense or with nerves on edge;
2. easy fatigue;
3. difficulty concentrating or mind going blank;
4. irritability;
5. muscle tension;
6. sleep disturbance (difficulty falling asleep or staying asleep, or restless unsatisfying sleep).

There are also frequent somatic symptoms such as sweating, palpitations, nausea, diarrhea, dry mouth, pollakiuria etc.

The anxiety, worry, or physical symptoms cause clinically significant distress or impairment of functioning in social, occupational or other important areas and are not due to direct physiological effects of drugs or medicines or general illnesses such as hyperthyroidism.

It is necessary to distinguish this disorder from others in which the stimulus of the concern is well defined, such as panic attacks or a particular form of phobia as social phobia; as it is also necessary to distinguish the specific psychological conditions that shape adolescent anxiety clear picture of specific disease.

GAD is shown to be the most prevalent anxiety disorder among primary care patients and the prevalence of the GAD according to the latest estimates range from 5% to 10% and the ratio women: men is about 2:1 [2 3].

The majority of patients with GAD receive heterogeneous interventions that include 5 different classes of medication as well as herbal treatments. Given the variety of available interventions, selecting the appropriate therapeutic medication for GAD can be challenging and requires consideration of the drug's efficacy, tolerability and long-term management [4]. Although benzodiazepines and sedatives are frequently prescribed for the treatment of GAD, they may not be an optimal choice due to tolerance, dependence and efficacy concerns [5].

Current consensus recommendations are to use selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) as the first line of treatment for GAD, regardless of whether the GAD occurs as primary or comorbid condition [6 7]. Although SSRIs and SNRIs as a group have each demonstrated efficacy for GAD, the current outcome literature also indicates a continued need treatment development, especially in order to obtain the goal of GAD remission as well as response [5].

Duloxetine (dulo) [8] was chosen as a potent and balanced selective inhibitor of the reuptake of serotonin (5-HT) and norepinephrine (NA). The term "balanced action" indicates that dulo has a similar degree of affinity for transporters of neuronal reuptake of both 5-HT and NA with a relatively similar potency. Dulo has demonstrated effectiveness for the treatment of major depression and peripheral neuropathic pain [9 10]. Preclinical and clinical studies also support the anxiolytic potential of dulo [11].

The aim of the present study was to verify the efficacy of duloxetine 30 mg/die in the GAD and its compatibility and synergy in the integration with non-pharmacological tools.

Materials and methods

This research comes from the observation of a number of clinical cases of GAD treated both with medication and psychological treatment.

From the group of users of ASL Caserta UOSM 13 who received a diagnosis of GAD, we selected a group of patients, differentiated into two cohorts: one treated with dulo 30 mg/die (70 patients), and another is was joined to treatment with dulo 30 mg/die also an educational training group in stress control counseling (60 patients). Patients were required to be medically healthy as determined by physical examination, electrocardiogram and laboratory results (renal, liver and thyroid function tests). Patients were excluded if they met criteria for a recent (past 6 months) diagnosis of major depressive disorder or substance abuse/dependence; a past-year history of panic disorder, post-traumatic stress disorder, or eating disorder; or a lifetime history of psychotic, bipolar, or obsessive-compulsive disorder or psychosis. Patients were required to be free of psychotropic medications at least 2 weeks prior the selection, with the exception of 4 weeks for those patients receiving fluoxetine. Additional exclusion criteria included lack of response of GAD to 2 prior adequate trials of antidepressant or benzodiazepine treatments, any medical illness that would contraindicate the use of dulo, psychotherapy that was initiated within 6 weeks prior to enrollment and the use of any concomitant medications that could interfere with the assessment of efficacy and safety of the study drug. Patients also underwent urine drug screens for benzodiazepine or illicit drug use; antihypertensive medication was allowed if patient has been on a stable dose regimen for 3 months.

Control Stress Counseling

Stress Control Counseling is a technique that aims to facilitate the resumption of the ability to be active and to facilitate the ability to achieve calm and relaxation in those moments when one needs not to be active and engaged. It is based on methodologies experienced such as alphagenic breathing exercises and basic exercises of autogenic method of J.H. Schultz.

Learning is achieved in small groups of 10-15 people in a number of scheduled meetings (one introductory, 8 of learning, one follow-up) and makes use of the ASQ and CDQ Cattel scales as a means of verification for both diseases where anxiety and anxiety symptoms are prevalent, through the single Anxiety Scale Questionnaire (ASQ) [12],

both the diseases in which there are symptoms of anxiety and depression, with the integration of the two scales. The scales are administered at regular intervals at T_0, T_{30}, T_{60} and follow-up to 90 days.

The primary clinical efficacy measure was the total score on the Hamilton Rating Scale for Anxiety (HAM-A) [13], which was administered at each visit. The HAM-A is a 14-item clinician-rated scale exploring anxiety, tension, autonomic and somatic symptoms. Secondary efficacy measures included the HAM-A psychic factor (sum of HAM-A items anxious mood, tension, fears, insomnia, concentration, depressed mood, and behavior at interview), and HAM-A somatic factor (sum of HAM-A items somatic muscular, somatic sensory, cardiovascular, respiratory, gastrointestinal, genitourinary and autonomic symptoms). An additional secondary outcome focused on improvement with the ASQ scale (sum of A + B items; A = unconscious anxiety; B = manifest anxiety).

At each visit throughout the study, tolerability was assessed through collection and monitoring of spontaneously reported adverse events.

All analyses were conducted on an *intent-to-treat* basis; the primary efficacy analysis was the mean change from baseline to endpoint in the HAM-A total score during 12 weeks of treatment. The differences in the two treatment groups were analyzed using an analysis of covariance (ANCOVA) model with treatment and investigator as main effects and the baseline score as the covariate. In addition, a *mixed-effects repeated-measures* (MMRM) analysis was conducted to assess change over time [14]. The MMRM model included the fixed categorical effects of treatment, investigator, visit and treatment-by-visit interaction as well as the continuous fixed covariates of baseline and baseline-by-visit interaction.

Response to treatment was defined as a ≥ 50% reduction from baseline in HAM-A total score at endpoint; remission was defined as a HAM-A total score ≤ 7 at endpoint. Comparisons of two treatment groups for these categorical efficacy measures were analyzed using the Cochran-Mantel-Haenszel test. For the above analyses, the baseline was defined as the first step of evaluation for the recruitment and inclusion of patients in treatment groups (visit 1), while the endpoint was defined as the last post-baseline measurement (12 weeks, last observation carried forward). Efficacy results presented in this paper are from an ANCOVA/ANOVA model unless otherwise specified; statistical comparisons were based on 2-sided, 0.05 significance levels.

The study was conducted in accordance with the principles of the Declaration of Helsinki [15] and country-specific ethical review guidelines. Written informed consent was obtained from each patient.

TABLE I.
Demographic characteristics of patients with generalized anxiety disorder (n = 130); HAM-A and ASQ baseline mean score. *Caratteristiche demografiche dei pazienti con disturbo d'ansia generalizzato (n = 130) e punteggio medio basale delle scale HAM-A e ASQ.*

	Duloxetine 30 mg/die + scc (n = 60)	Duloxetine 30 mg/die (n = 70)
Characteristic		
Sex, N (%) female	40 (66.6)	45 (64.3)
Age, mean	34.1	33.2
Baseline measures, mean score		
HAM-A total	28	28.2
HAM-A psychic anxiety	14.8	15.1
HAM-A somatic anxiety	11.8	11.9
ASQ	40.8	40.6

Results

A total of 130 patients were evaluated for the study and patients were randomly assigned to receive dulo 30 mg/die (n = 70) or dulo 30 mg/die + stress control counseling (scc) (60 patients). There were no statistically significant differences between two groups at baseline in demographics or HAM-A and ASQ baseline scores of patients with GAD (Table I). The majority of the sample was female (65.4%) with a mean age of 33.8 years throughout the sample. The mean baseline HAM-A scores indicated moderately severe GAD.

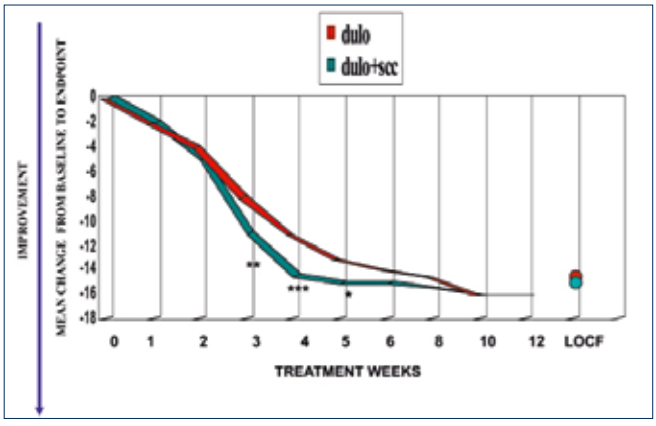

FIGURE 1.
Mean change in HAM-A total score from baseline to endpoint by treatment week (MMRM, Mixed-Effects Repeated-Measures) and at endpoint (week 12, LOCF, Last Observation Carried Forward). *Variazione media del punteggio totale HAM-A dal basale all'endpoint per settimane di trattamento (MMRM, Mixed-effects repeated-measures) e all'endpoint (settimana 12, LOCF, Last Observation Carried Forward).*

$^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$

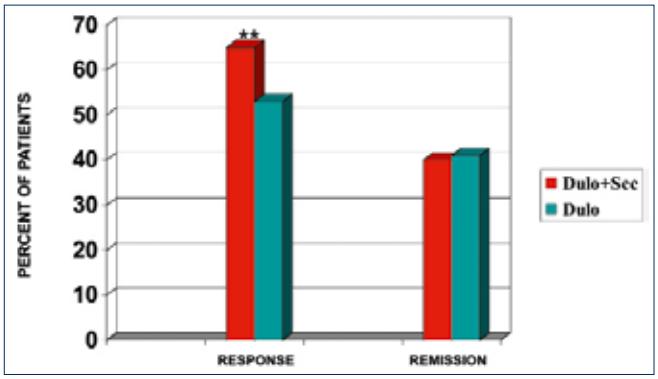

FIGURE 2.
Percent of patients according to the HAM-A criteria have reached the endpoint response and remission. *Percentuale di pazienti che secondo i criteri HAM-A hanno raggiunto la risposta e la remissione all'endpoint.*

** p ≤ 0.01

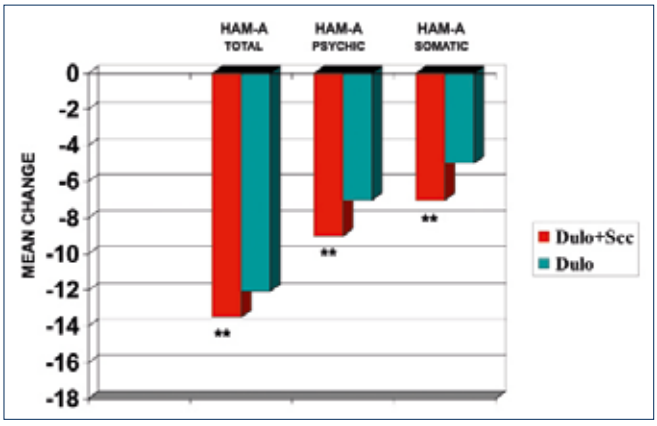

FIGURE 3.
Mean change in HAM-A total score and its factors from baseline to endpoint in the treatment groups. *Variazione media del punteggio totale HAM-A e dei suoi fattori dal basale all'endpoint nei gruppi di trattamento.*

* p ≤ 0.01

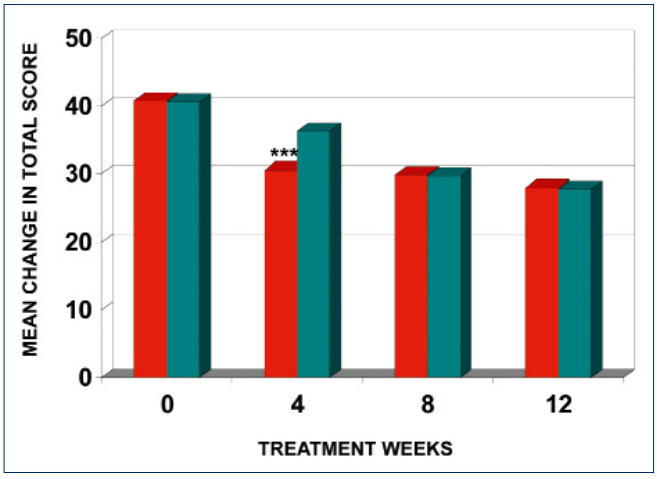

FIGURE 4.
Mean change in total score A + B ASQ scale (A = unconscious anxiety; B = manifest anxiety) from baseline to endpoint by treatment week. *Variazione media del punteggio totale A + B dell'ASQ (A = ansia inconscia; B = ansia manifesta) dal basale all'endpoint per settimane di trattamento.*

*** p ≤ 0.001

Most patients had a significant improvement with a score decrease of rating scales used. However, whereas the HAM-A, we noticed that in the group treated with dulo + scc, the improvement was more rapid than the group treated only with dulo (Fig. 1); after 8 weeks of treatment both clinical evidence and HAM-A scores become overlapping, remaining in time. Further evidence was that in the first 4 weeks, 65% of patients treated with dulo plus scc and 53% of patients treated with dulo alone responded to treatment significantly while, as regards the remission, no statistically significant differences were deduced (Fig. 2). Dulo 30 mg + scc-treated patients also demonstrated significantly greater improvements compared with dulo 30 mg-treated patients on each of the secondary efficacy measures: HAM-A psychic anxiety factor score, HAM-A somatic anxiety factor score, HAM-A anxious mood (item 1), HAM-A tension (item 2) (Fig. 3). Considering the cohort was treated with dulo plus scc, with the ASQ scale, we observed that the sum score of A + B improves statistically significantly in the first month of treatment, gradually stabilizing (Fig. 4). Regarding tolerability, there were no significant differences in the two treatment groups in frequency of side effects. However, nausea was the most frequent adverse event and was judged mostly mild to moderate. Other adverse events most commonly associated with treatment were dry mouth, dizziness, somnolence and constipation; all these events were rated as mild.

Discussion and conclusions

The results of this observational study suggest that duloxetine is effective and well tolerated at a dose of 30 mg/die for the treatment of GAD, as shown in other studies but have used the dose of 60-120 mg/die [16-20]. Patients who received the drug plus the educational training group in stress control counseling have achieved a significant improvement, with reduced severity of anxiety symptoms and improving the overall performance, faster than the group treated only with the medication. These improvements are clinically significant as indicated by the good response from the sustained improvement and remission rates at study endpoint. The clinical evidence that drugs inhibiting serotonin and norepinephrine reuptake

(SNRIs) are particularly effective in treating the short, medium and long-term generalized anxiety disorder has recently found an experimental correlate neurochemical levels. It is well known that exposure of rats to acute stress induces activation of noradrenergic neurons in the locus coeruleus, resulting in increased release of norepinephrine in the cerebral cortex. This effect is antagonized by acute administration of a benzodiazepine and, conversely, increased significantly from that of the SNRI drug. However, chronic treatment with venlafaxine, another SNRI, antagonizes with high efficacy the increase in norepinephrine release in the prefrontal cortex of rats induced by exposure to a weak electric shock to the paws (footshock). This suggests that chronic administration of SNRIs does not change the basal activity of noradrenergic neurons, but reduces the sensitivity to anxiogenic and stressful stimuli, whether environmental or pharmacological; also this evidence shows that these drugs SNRIs, administered for prolonged periods, substantially improve the adaptability and function of the presynaptic component of noradrenergic neurons, an event consistent with the neurochemical anxiolytic effect of chronic treatment. The ability of SNRIs to act simultaneously and more selectively on the serotonergic and noradrenergic transmission is certainly a peculiar property, determinant to allow these drugs to modulate the most efficient synthesis of trophic factors and the process of neurogenesis, the two most important phenomena associated functionally to neuroplasticity; these findings were recently corroborated by *brain imaging* studies, both morphological and functional, demonstrating that a chronic treatment with SNRIs improves cerebral perfusion and restores the reduced volume of specific brain areas such as the hippocampus and the amygdala. The ability of SNRIs to improve cerebral perfusion may play an important role in facilitating neuronal tropism and neurogenesis and, therefore, to give neurons the ability to know how to readjust to environmental needs.

The findings of the present study should be considered with the following limitations. These findings generalize only to short-term treatment, therefore longer trials will be needed to assess efficacy, safety and tolerability of maintenance duloxetine treatment for GAD. The study did not include an active comparator, so direct comparisons cannot be made between duloxetine and other drugs for the treatment of GAD. Furthermore, GAD is often comorbid with depression and other anxiety disorders; as the present study excluded patients with significant comorbidities, the response of the comorbid condition to duloxetine would require additional study.

In summary duloxetine 30 mg + stress control counseling and duloxetine 30 mg alone were efficacious in reducing symptom severity and well tolerated in the treatment of GAD. SSRI and venlafaxine have demonstrated efficacy for the treatment of GAD; the findings of the present study, as those of other studies, support the inclusion of duloxetine 30 mg alone and duloxetine plus integration with non-pharmacological tools as an empirically validated pharmacologic intervention for GAD.

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