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Selective Serotonine Reuptake Inhibitors prevents emotional lability in healthy subjects

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Abstract. – *Background:* **Many subjects with depression and with brain lesions can poorly control their emotions with fits of weeping and tearfulness; neurological patients present outbursts of laughter as well. This condition is called Emotional Lability (EL). The antidepressant drugs of the family of selective serotonine reuptake inhibitors (SSRI) improve EL within a few days in both depressive and neurological disorders. EL can be present in healthy subjects as well, in whom it is considered as normal, although often embarrassing.**

Methods: **Two healthy subjects with EL, were treated with 20 mgs of Paroxetine or placebo for cycles of 5 days. Moreover the effect was observed of either Paroxetine or Fluoxetine on the emotion control of three patients with mood disorders both when they were depressed and after recovering from the depression.**

Results: **In all subjects, after few days of treatment, EL disappeared, and their emotion control and behaviour were both modified.**

Conclusions: **1. In healthy subjects EL is often embarrassing; the possibility is interesting of preventing it on selected occasions with a brief treatment with no side effects and a cheap cost. 2. SSRI are among the most used drugs in the word and every day they are assumed by millions of people including politicians, business man, soldiers, army commanders, policemen and criminals. The idea is very stimulating and highly worrying that the control of the emotions and behaviour of these million of people can be quickly modified by the assumption of one pill of SSRI for a few days or by its discontinuation.**

Key Words:

Emotional lability, Antidepressant drugs, SSRI, Paroxetine, Fluoxetine

Introduction

In the last two decades a new family of drugs called selective serotonine reuptake inhibitors (SSRI) revealed to have a potent antidepressant effect. SSRI include fluoxetine, fluvoxamine, sertraline, paroxetine and a few other molecules largely and successfully used in psychiatry especially for the treatment of mood, anxiety, and obsessive-compulsive disorders.

Patients affected by depression often present tearfulness and uncontrollable fits of weeping. These phenomena have been called Emotional Lability (EL) or Emotionalism, terms now preferred to the outdated definition of emotional incontinence. Usually during the pharmacological treatment with SSRI, EL improves more rapidly than the mood does. Data from the literature show that the antidepressant effect of SSRI is often associated with a decrease in the emotional responsiveness of the patients to both trivial and important problems they have to face. This decreased responsiveness was called "emotional blunting"[1] and it was reported to involve many emotional responses, including crying, irritation, sadness, creativity and sexual interests. A similar blunting was noticed in an high percentage of the patients with psychiatric disorders treated by the Authors.

EL is also observed in about 10% of patients with multiple sclerosis[2], and in other neurological disorders, both with cognitive impairment, such as acute major stroke[3-7] or pseudobulbar palsy (due to multiple ischemic lesions on both sides of the brain), and with-

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out cognitive impairment, such as amyotrophic lateral sclerosis, a rapidly fatal disease due to the selective degeneration of upper and lower motor neurons. At variance with the mood disorders, in these neurological disorders EL is characterized by outbursts of laughter other than crying, appearing alternatively both without an adequate reason or with no reason at all.

SSRI have revealed to be useful in improving EL in several neurological disorders independently from their pathogenesis[4,6,8-10]. Being the action of all these drugs on EL rapid, it appears to be independent from their effect on the depression.

EL with easy and frequent crying and laughter is instead a constant and normal phenomenon during infancy and childhood. Furthermore, among old people, EL is frequently present although they present a normal cognitive assessment.

Anyway, adult healthy subjects as well can present fits of weeping and sobs in front either of a great sorrow or of an intense and touching joy. This form of EL is commonly and correctly considered as normal, but it often results embarrassing for the subject.

We here present the effect of two types of SSRI, the Paroxetine and the Fluoxetine, on the control of the emotions of five subjects: two healthy subjects and three subjects with previous mood disorders, who had recovered from these diseases.

Materials, Methods and Results

Our evidence consists of five adult subjects, four males and one female who since their adolescence had EL. They all had a completely *normal* neurological examination, *normal* cognitive functions and a good to excellent social, working, and economical functioning. Since the adolescence, when in front of an intense sorrow or a joy, they all presented tearfulness and bursts of weeping and sobs, sometimes causing a greatly embarrassing problem for them.

The first *healthy* subject is a 55-year male who had to commemorate with a public talk a strict relative of him who had died, for three times over a 2-month period. The first and the third time he was treated with paroxetine, 20 mgs/day for the five days preceding his talks, becoming able to speak in public without emotionalism. The second time he was treated with placebo for 5 days and during the talk he was interrupted by several fits of weeping.

The second *healthy* subject is a 50-year male who had to comment his daughter wedding first in a home party, and fifteen days later in the church. The first time he was given a placebo for the 5 days preceding the party and presented several burst of weeping during the talk. The second time he was treated with paroxetine 20 mgs once a day every morning for the 5 days preceding the wedding. On this occasion he was able to speak with high and clear voice, without emotionalism, even though he himself declared that in the church he was feeling much more touched than he had been at home two weeks before.

The third subject is a 44-year male, with a brilliant activity as top manager, who in October 2002, presented a moderate depression, reactive to some problems suddenly occurring in his company. It was diagnosed that he was affected by a Minor depressive Disorder according to the criteria of the DSM-IV edited by American Psychiatric Association, and he was treated with Paroxetine 30 mgs/day. From the first days of treatment he noticed that he was no longer presenting the emotional lability he had experienced since the young adult age. He later recognised that he had obtained exactly the same effect several years before when, during a slimmer diet, he had been treated with Fluoxetine, 30 mgs/day. After a two-months treatment, the depression had improved and it is interesting to reporting a sentence of him when speaking with one of the authors: "Thanks to your treatment I was able to overcome the terrible situation of communicating without crying to lots of my collaborators they were fired. Such a thing would have been impossible in the past." After five months of treatment the subject was feeling well and the treatment was gradually discontinued. A few months later his mood was good but the burst of emotionalism reappeared and were embarrassing for him. Remembering his first experience he assumed (by himself) 20 mgs/day of fluoxetine and after a few days

the emotional lability disappeared. He proudly announced to his doctor his successful initiative.

The fourth subject is a 60-year female, who, since adolescence suffered from EL and presented since 1992 a chronic moderately depressed mood (Dysthymic Disorder of the DSM-IV).

She had several real reasons for feeling unwell: the suicide of her mother when she was 34, the severe mental insufficiency of one of her 4 children, and severe difficulties in the relationship with her husband. From 1992 to 2002 her bursts of cry increased. In 2002 she eventually accepted a psychopharmacological treatment and she was treated with Fluoxetine, 20 mgs/day. After a few days of treatment the EL disappeared and 4 weeks later her mood as well began to improve. After 6 months of therapy, she was feeling well, although obviously not happy given the real difficulties present in her life. The treatment with Fluoxetine was then discontinued. The bursts of emotionalism reappeared and she was embarrassed from crying when she was discussing with her husband or her son. Therefore she began by herself to take a pill/day of 20 mgs of Fluoxetine for cycles of one to two week/s every two or three months. She reports that the effect was almost immediate allowing her to speak with great detachment and calm.

The fifth subject is a 40-year male who presented EL from adolescence. Moreover he had frequent violent reactions sometimes resulting in fights after verbal quarrels for trivial reasons. He had always refused psychotherapy and, at the age of 39, he developed a moderately severe depression. One year later he accepted a consultation. According to the criteria of the DSM-IV, he was diagnosed as affected by a Minor Depressive Disorder in a subject with personality traits that do not reach the threshold for a Borderline Personality Disorder. A treatment with paroxetine, 20 mgs/day, was set on. After few days the patient noticed he no longer had tearfulness. Three months after beginning this treatment, when his mood had already normalised, his closest friend died in a motorcycle accident. The patient reported that during the funeral he felt extremely sorrow but he appeared cold with no tears or other phenomena of emotionalism. Moreover he had noticed a blunting of his emotions and emotional reactions and the absence of further quarrels and fights during the whole period. After 8 months of treatment the mood had become normal but the patients preferred continuing the treatment with paroxetine because it was preventing EL and his violent reactions. The absence of these violent reactions was improving his social life.

Discussion

To our knowledge, this is the first report on the effect of SSRI on the emotional status of *healthy* subjects.

SSRI are largely used and result to be very useful in the treatment of mood, anxiety, and obsessive-compulsive disorders, probably because they enhance the serotoninergic activity in some areas of the brain. The antidepressant action of SSRI is usually explained by the accumulation of serotonin in the synapses, due to the inactivation of the reuptake mechanism designed to clear the synaptic space of the transmitter. The slow buildup of serotonin in brain fluid (over several weeks of SSRI administration) attenuates the depressive condition.

Much less on the contrary is known about the brain areas and the neurotransmitters involved in the control of emotional range and emotional stability.

A PET study[11] on neuroanatomical correlates of pleasant and unpleasant emotions suggested a role of the medial prefrontal cortex, thalamus, hypothalamus, and midbrain for both pleasant and unpleasant emotions whereas other areas seem to be interested either for pleasant or for unpleasant ones.

In a mouse model of increased EL[12], an overexpression of glucocorticoid receptor in forebrain was described, suggesting that natural polymorphism in the expression of glucocorticoid receptor gene can contribute to emotional reactivity and vulnerability in healthy subjects as well as to mood disorders. Further support to the involvement of prefrontal cortex in emotion processing comes from recent data showing that chronic SSRI treatment alters the serotoninergic regulation of GABA transmission in this brain area[13]. However, the brain region most

firmly involved in acquiring, storing and retrieving of emotional memories is the amygdala (see for review 14). Recent data show that amygdala is responsible for the discrimination of emotional faces in a cortically blind subject, unable to identify any other visual cue[15]. The medial temporal lobe likely cooperates with the amygdala in handling emotional recollection[16].

Due to largely demonstrated effect of SSRI on pathological emotional lability, a serotoninergic hypothesis for the emotions and their control has been proposed. Most of psychiatric patients report that during the treatment with SSRI they have an emotional blunting in front of both pleasant and unpleasant emotions. Possibly in them, the therapeutical effect of SSRI in part is helped by this decreased emotional responsiveness which probably works by elevating the "threshold" for feeling intense unpleasant emotions. Moreover a similar emotional blunting is observed in patients with brain lesions independently by the type of the lesion.

In healthy subjects SSRI have been seldom used; in healthy volunteers they demonstrated to have no effect on psychological status[17], but significant action on the personality and the social behavior[18]; these Authors first found that SSRI in normal volunteers reduced negative affective experience and increased affiliative behavior. As well several patients cared by the Authors of this article reported that SSRI improved their familiar and social behavior. Moreover the fifth subject of the present small series, reported that Paroxetine had modified his reactive behaviour which had sometimes led him to verbal and physical fights and decided to continue the treatment even after recovering from the depression.

Our comments can be summarised as follows:

The EL of healthy subjects is more similar to that of psychiatric patients consisting only in tearfulness and fits of weeping, rather than to the problems of patients with neurological illness who present pathological laughter as well.

In all 5 subjects, the EL was not due to mood disorders: two were *healthy* subjects whereas in the others EL had been present for decades before the depressive disorder and the SSRI treatment, when they were healthy subjects, with the only exception of the moderate traits of a personality disorder in the fifth subject.

In the first two (*healthy*) subjects a 5-days treatment with 20 mgs of Paroxetine revealed to be sufficient to preventing emotional lability in both the conditions of intense sorrow or joy. In the same subjects, placebo was of no help.

In the third, fourth, and fifth subject, who had a mood disorder, two types of SRRI (Paroxetine and Fluoxetine) were effective in changing a condition of emotional lability into a condition of emotional stability both during depression and after this period. In them this effect was so evident that the patients themselves self-prescribed the drug.

In all the subjects the effect on EL was greatly appreciated because embarrassing situations were prevented. In all of them the time of action of SSRI on emotional lability consisted in a few days, being therefore too short to be related to the antidepressant action of the SSRI which usually set on after several weeks of treatment.

A possible explanation of this rapid effect of SSRI on EL can be provided by recent investigations: Fluoxetine has also been shown to inhibit neuronal and muscle nicotinic receptors, in particular the receptor subtype made up by $\alpha 7$ subunit[19,20]. This receptor is well represented in the amygdala of primates[21]. Other classes of antidepressants also interact with nicotinic acetylcholine receptors[22], which might contribute to their therapeutic action[23]. The anti-cholinergic action of antidepressant drugs, being due to a direct action of the drugs on nicotinic acetylcholine receptors, might be much faster than the serotoninergic action. Thus, a working hypothesis worth of further investigation is that, the prompt reduction of EL by SSRI could be mainly due to their action on the cholinergic system, later followed by a stronger antidepressive action mediated by serotonin accumulation.

A first eventual speculation is practical: EL often embarrasses the subject. The possibility of preventing it on selected occasions with a treatment of few days with no side effects and a cheap cost, may be interesting. Both fluoxetine and paroxetine proved to be effective in healthy subjects. It is possible that other SSRI work in the same manner as it has been

demonstrated for pathologies such as the stroke, the pseudobulbar palsy, and the traumatic injuries[6,8,9,24].

The second speculation: we know very little about the mechanisms of controlling emotions and therefore of the emotional stability, reactivity and vulnerability in both healthy life and mood disorders. The SSRI revealed to have an extremely rapid and potent effect on the control of emotions by changing a chronic behaviour within a few days of treatment. One of our subjects with a long-term EL became able to fire lots of his co-workers without emotionalism after few days of treatment with Paroxetine. An other one decided to continue the treatment with paroxetine because for the first time in his life he was able to live without verbal and physical fights.

SSRI are among the most used drugs in the word and every day they are assumed by millions of people including a wide variability of workers, politicians, business man, soldiers, army officers and commanders, policemen and criminals.

The idea is very stimulating and highly worrying that the control of the emotions and behaviour of these million of people can be quickly modified by a few days assumption of one pill of SSRI or by its discontinuation.

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