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EFFECTIVENESS OF SEROTONERGIC DRUGS IN THE MANAGEMENT OF PROBLEM BEHAVIORS IN PATIENTS WITH NEURODEVELOPMENTAL DISORDERS

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SUMMARY

Neurodevelopmental disorders often result in disabilities associated with auto- and / or hetero-aggressive behaviors, that can be defined as "problem behaviors" (Lacy 2007).

Therapeutic interventions are mainly directed towards the use of neuroleptic drugs or benzodiazepines, to ensure a rapid and significant sedation in most of cases.

These pharmacological devices exposes the patient to clinical risks and/or long-term management difficulties. The main problem of the chronic use of benzodiazepines is the development of tolerance and dependence; furthermore benzodiazepine withdrawal or their abrupt reduction may lead to rebound effect. Regarding the long-term effects of neuroleptics, it is necessary to focus on extrapyramidal effects, motor restlessness and akathisia, anticholinergic effects, as well as endocrine and metabolic alterations.

Several studies have shown that the reduction of serotonergic receptor activity is associated with the appearance of aggressive behavior (Farnam et al. 2017), especially impulsive behaviors (Manchia et al. 2017, Takahashi et al. 2012). The dynamics that subtend these data are still not fully clarified, however there are evidences that the use of selective serotonin reuptake inhibitors (SSRI) is helpful in the treatment of aggressive behavior in mental disabilities (Sterke et al. 2012, Janowsky et al. 2015). In this study we observe the behavioral response to sertraline, for minors, and to vortioxetine, for adults, considering that the literature shows significant evidence of modulation of synaptic neuroplasticity (Waller et al. 2017). To support the observation we used behavioural scales to collect the data, before the administration of the drug, during the course of treatment, at 3 months from the start of the administration. We detected the improve of behavioral disorders with the less use neuroleptic drugs and benzodiazepines.

Key words: *SSRI – problem behaviors – self-aggressivity – neurodevelopment*

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INTRODUCTION

Autism spectrum disorders, such as neurodevelopmental disorders, result in disabilities associated with an auto- and/or hetero-aggressive behavior, repetitive gestures (perseverations, stereotypies), and rituals, up to manifestations related to the clinical sphere of obsessive-compulsive disorder.

It is pleonastic to emphasize how these circumstances require a pharmacological intervention, both for the health of patients and for those around them. Therefore we are directed mainly towards an intervention based on the use of neuroleptic drugs or benzodiazepines, which guarantee, in the majority of cases, a rapid and significant sedation. Benzodiazepines are drugs that act by binding the interface between the γ and α subunits of the GABA-A receptor, causing an increase in the affinity of GABA to its binding site, amplifying the inhibitory action of the neurotransmitter and increasing its sedative, hypnotic and anticonvulsant properties. Neuroleptics, instead, exert their sedative effect by acting as antagonists of the D2, 5HT1A, 5HT1C receptors, as well as the H1 receptor. Often the use of these pharmacological devices, does not guarantee the desired effect and puts the patient to clinical risks and/or long-term management difficulties. The main problem of the chronic use of benzodiazepines is the development of tolerance and dependence. Tolerance is establish in a relatively short time as a drastic reduction of the therapeutic effect of the drug, imposing a gradual titration of the dosage. In addition, benzodiazepine withdrawal especially if it is abrupt may lead to rebound effect or abstinence syndrome: this consists in the return of the symptoms for which the patient was treated, sometimes more marked. Abstinence syndrome appears when benzodiazepines are discontinued and is the main sign of physical dependence. Treatment with neuroleptics usually does not give loss of efficacy over time, but it is necessary to pay attention to the appearance of extrapyramidal effects (tremors, stiffness, involuntary movements), motor restlessness and akathisia, anticholinergic effects (xerostomia, constipation, blurred vision, sedation, as well as endocrine and metabolic alterations (hyperprolactinemia with, galactorrhea, gynecomastia and sexual dysfunction, metabolic syndromes with increased risk of type 2 diabetes and weight gain especially after prolonged treatment). Therefore, considering the necessity of chronic treatments in patients with neurodevelopmental disorders, is critical to evaluate new pharmacological guidelines is evident.

The scientific literature in recent years focuses on the correlation between behavioral disorders and the use of selective serotonin reuptake inhibitors (SSRI), drugs that increase the sinaptic availability of serotonin. Serotonin (5-HT) has long been considered as a key transmitter in the neurocircuitry controlling aggression. Impaired regulation of each subtype of 5-HT receptor, 5-HT transporter, synthetic and metabolic enzymes has been linked particularly to impulsive aggression (Takahashi et al. 2011).

Multiple evidences shown that the reduction of the activity of the serotonin receptors is associated with aggressive behaviors, especially impulsive behaviors (Manchia et al. 2017). At present, the dynamics that correlate these data are still not fully clarified; however there are evidences that the use of SSRI is useful in the treatment of aggressive behavior in mental disabilities (Sterke et al. 2012, Janowsky et al. 2015). Furthermore the fact that this category of drugs is effective in the treatment of obsessive-compulsive disorder (OCD) is consolidated as it can reduce, in a short time, behaviors like ruminations, rituals and the anxiety associated with them. Indeed Sertraline, Paroxetine and Clomipramine have long been the first choice drugs in OCD therapy.

Despite this premise, in clinical practice, the therapies usually chosen in patients that suffering from diseases associated with these disorders, the pharmacological orientation is directed almost exclusively to neuroleptics and benzodiazepines; such use becomes massive (and often not resolutive) when it is necessary to manage acute episodes of psychomotor agitation and aggression.

Therefore we decide to evaluate the clinical response to SSRI, in association or in substitution of the already established therapy, with the aim of managing agitation and aggression, as well as rituals, stereotypies and perseverations.

SUBJECTS AND METHODS

This study will examine the efficacy of the antidepressant drugs Sertraline and Vortioxetine. Sertraline, like all SSRI, acts by inhibiting serotonin transporter (SERT) a transmembrane protein present on the presynaptic neuron, providing to "recycle" the unused serotonin: the blockage of the SERT allows a greater availability of serotonin in the intersinaptic space, a condition that promotes, among others, antidepressive and anxiolytic effects. Vortioxetine is a modulator of serotonin drug because it inhibits serotonin reuptake (such as SSRI) and acts as a SERT inhibitor, a 5HT1A receptors agonist (which could increase antidepressant and anxiolytc efficacy and decrease some side effects especially sexual ones), as an antagonist of 5HT3 receptors (which could help to decrease the side effects of nausea and concurs to the anxiolytic effects since these receptors are involved in the release of GABA) and as an antagonist of 5HT7 (the latter is known to be the site of action of others antidepressant drugs).

In our structure, we assist many patient with mental disabilities and every days we have to manage auto- and/or hetero-aggressive behaviors, in addition to clinical issues related to their clinical conditions.

Few month ago, we started to collect clinical data about them, first of all by clinical observations, then by consulting daily reports that our educators compile about them.

We observed, especcialy, patients with neurodevelopment disorders, mental disabilities and "problem behaviors" like auto- and/or hetero-aggressivity and/or OCD and the response to the treatment with sertraline, for minors, and with vortioxetine, for adults. The drugs were administered orally, in the form of tablets.

To analyze the data, we use these following scales:

- The *Brief Psychiatric Rating Scale* (BPRS) that is a rating scale which clinicians or researchers may use to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behaviour: each of the 24 items is rated 1-7, in increasing order of gravity. The scale is one of the oldest, most widely used scales to measure psychotic symptoms (Overall and Gorham, 1962).
- The *Neuropsychiatric Inventory–Questionnaire* (NPI-Q) that was developed and crossvalidated with the standard NPI to provide a brief assessment of neuropsychiatric symptomatology in routine clinical practice settings The NPI-Q is adapted from the NPI a validated informant-based interview that assesses neuropsychiatric symptoms (Kaufer et al. 2000).
- The *Clinical Global Impression* (CGI) rating scales are measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders. It is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy 1976).

We present preliminary data: we are focused on one patient treated with the Sertraline and a second patient treated with Vortioxetine and we are matching the data collected before the treatment, with data collected after 3 months from the start of the treatment in two patients.

CASE 1

A 17 years old boy affected by moderate-severe intellectual disability, autism spectrum disorder (ASD) from a probable perinatal suffering, with subsequent psycho-motor delay. In addition to the typical motor stereotypes, since the age of 3 impulsive phenomena have appeared, environmental destructiveness tendencies and heterodirect aggressiveness that have constituted, over time, an increasingly important problem, so much so that it was necessary to enter our institute at the age of 16. The boy showed severe heterodirect aggressiveness, sleep disturbances, poor collaboration

with the clinicians and the entire staff. At the time of taking charge his therapy was: haloperidol 9 mg/die, quetiapine 1200 mg/die, levetiracetam 1500 mg/die, fenobarbital 50 mg/die, clonazepam 3 mg/die. Numerous therapeutic modifications have been attempted such as the addition of clotiapine up to 60 gtt/die, the reduction of quetiapine to 600 mg/die, the reduction of the haloperidol to 7.5 mg/die and the addition of risperidone up to 2 mg/die (suspended after about 1 month for sexual disorders). Then was introduced in therapy valproic acid, up to 1500 mg/die, without clinical benefit. The surveys using rating scales showed the following scores: for BPRS 40/126 with greater involvement of the items related to: blunted affected (5/7), tension (6/7), mannerisms and posturing (5/7), unco-operativeness (6/7), emotion withdrawal (5/7), excitement (5/7). We remind that values "5" and "6" concern, respectively: "moderately severe" and "severe" wording. The NPI-Q score was 4/12 for the item elation/euphoria with a distress value of 2/3, was 12/12 for the item agitation/aggression with a distress value of 3/3, was 9/12 for the item irritability/lability with a distress value of 2/3, was 6/12 for the item motor disturbance with a distress value of 2/3. GCI score was 7/7 corresponding to the wording "among the most extremely ill patients". Subsequently additional therapy with sertraline was introduced at the dosage of 25 mg/die.

During the course of treatment, there was a slow but progressive reduction in the frequency and intensity of aggressive and heterodirect behaviors. The patient was more condescending and congruous with the daily life of the structure. Likewise, there was an improvement in the quality of nocturnal sleep. The evaluation by scales carried out after three months from the beginning of the treatment showed a reduction of the BPRS score to 30/126 with an improvement of the items most affected: blunted affected (4/7), tension (4/7), mannerisms and posturing (4/7), unco-operativeness (4/7), emotion withdrawal (4/7), excitement (4/7). We remind that values "4" concern "moderate" wording. The NPI-Q score was 1/12 for the item elation/euphoria with a distress value of 1/3, was 4/12 for the item agitation/aggression with a distress value of 2/3, was 4/12 for the item irritability/lability with a distress value of 2/3, was 4/12 for the item motor disturbance with a distress value of 2/3. GCI score was 6/7 corresponding to the wording "severely ill", with a global improved value corresponding to "much improved" and an efficacy index equal to 6, which means: "decided improvement, partial remission of symptoms" and "do not significantly interfere with patient's functioning". This improvement made it possible to reduce therapy with clotiapine up to 30 gtt/die and to suspend clonazepam. If these changes are confirmed over time, the neuroleptic therapy could be reduced further.

CASE 2

A 46 years old man affected by affected by encephalopathy with a probable genetic genesis characterized by severe intellectual disability, psychotic behavioral disorder, poor language, neuromotor disorders of the march, bilateral congenital cataract and microcornea and flat bilateral foot. The patient has been institutionalized since the first years of life, due to his psychomotor agitation, auto and hetero-direct aggressivity, stereotypies and marked oppositional behaviors. In adulthood, after numerous pharmacological changes, his therapy consisted in quetiapine 400 mg/die, valproic acid 1000 mg/die, clotiapine 15 gtt/die, with a little result on problem behaviors. His behavioral status, evaluated through the scales was as follows: BPRS 31/126 with greater involvement of the items related to: blunted affected (6/7), tension (6/7), mannerisms and posturing (5/7), unco-operativeness (6/7), emotion withdrawal (5/7), excitement (5/7). We remind that values "5" and "6" concern, respectively: "moderately severe" and "severe" wording. The NPI-Q score was 12/12 for the item agitation/aggression with a distress value of 2/3, was 6/12 for the item anxiety with a distress value of 2/3, was 8/12 for the item disinhibition with a distress value of 2/3, was 6/12 for the item irritability/lability with a distress value of 2/3, was 8/12 for the item motor disturbance with a distress value of 2/3, was 6/12 for the item nightmare behaviors with a distress value of 3/3. GCI score was 6/7 corresponding to the wording "severely ill". Subsequently additional therapy with vortioxetine at the dosage of 20 mg/die. In the following 3 months, there was a gradual reduction of psychomotor agitation, with a greater agreement with the educators. The patient often used to oppose to the routine of personal care, while over time he seems to have lost the habit of undressing or selecting the clothes to wear in a small circle of clothes. At the same time, episodes of heterodirected physical aggression are reduced in frequency and intensity. The evaluation by scales carried out after three months from the beginning of the treatment showed a reduction of the BPRS score to 25/126 with an improvement of the items most affected: blunted affected (4/7), tension (4/7), mannerisms and posturing (3/7), unco-operativeness (4/7), emotion withdrawal (3/7), excitement (3/7). We remind that values "4" and "3" concern, respectively, "moderate" and "mild" wording. The NPI-Q score was 2/12 for the item agitation/ aggression with a distress value of 1/3, was 1/12 for the item anxiety with a distress value of 1/3, was 1/12 for the item disinhibition with a distress value of 0/3, was 1/12 for the item irritability/lability with a distress value of 1/3, was 1/12 for the item motor disturbance with a distress value of 1/3, was 1/12 for the item nightmer behaviors with a distress value of 1/3. GCI score was unchanged: 6/7 corresponding to the wording "severely

ill", with a global improved value corresponding to "much improved" and an efficacy index equal to 5, which means: "decided improvement, partial remission of symptoms" in the absence of side effects.

CONCLUSIONS

The cases described show us how it is possible to obtain satisfactory results on the control of behavioral disorders thanks to the use of drugs with serotonergic action. Observation on such a small number of patients obviously requires further confirmation data, but this initial analysis is encouraging. The patients taken into consideration present complex general clinical conditions (in fact the overall score of CGI remains high, despite the treatment), but the single items regarding the behavioral aspects show a significant improvement that deserves further study, as well as a longer follow-up in order to evaluate the durability of the therapeutic effect. We present these preliminary data in order to contribute to the achievement of an adequate and effective management of "problem behaviors", so widespread and so difficult to control.

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Contribution of individual authors:

Moreno Marchiafava: study conception and preparation, interpretation of data, drafting manuscript;

Chiara Bedetti, Antonella Baglioni & Marina Menna: study preparation, interpretation, acquisition of data;

Sandro Elisei & Massimo Piccirilli: revising manuscript.

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