C A S E   R E P O R T S

Translational approaches in treatment-resistant depression based on animal model

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Abstract

An intensively researched and yet poorly understood phenomenon, both at clinical and neurobiological level, is the determinism of treatment-resistant depression. Even more controversial are the stages of approaching therapeutically this pathology because there are no evidence-based recommendations stating that a pharmacological agent is superior to another, on medium and long-term. Due to the lack of "golden standard" approaches, physician's experience, therapeutic alliance and a close monitoring stand as the most useful good practices in the treatment of resistant depression. The neurobiology of this pathology is incompletely characterized, and the current paper will present data derived from single-photon emission computed tomography as arguments for a better understanding of the treatment-resistance in major depression. These data have been compared with the existing data in the literature and arguments in favor of using this investigational method have been formulated. All the three cases presented are patients diagnosed with treatment-resistant major depression, each case with its own psychiatric and somatic background, and therefore with its own therapeutic approach. In all these cases, structured interviews and psychometric scales were applied in order to allow a flexible pharmacological regimen, adjusted to the patient's dynamic needs. Measurements for health-related quality of life were considered necessary for treatment-resistant depression monitoring because low values registered in this domain have important prognostic significance. Translational studies on animal models of depression support the existence of cerebral structural dysfunctions or lesions which can be correlated with clinical and neuroimaging data, allowing for the formulation of neurobiological and psychopharmacological models for treatment-resistant depression.

Keywords: translational research, resistant depression, animal model of depression, single-photon emission computed tomography, antidepressants, neurodevelopmental dysfunctions.

⮌ Introduction

Although clinical criteria for treatment-resistant depression have been validated through extensive practice, there is a lack of pathogenic models and well-defined therapeutic strategies. Data resulted from animal models in translational research, integrated with clinical, psycho-pharmacological and neuroimagistic information derived from the case studies presented here, may lead to the formulation of therapeutic recommendations for treatment-resistant depression. These recommendations are intended to have neurobiological and psychopharmacological basis and to represent a reference for further clinical and translational research.

Treatment-resistant depression is a very important clinical and pharmacoeconomic problem, associated with higher probability of hospitalization, either general medical or psychiatric, higher outpatient visits, with individuals using 1.4 to three times more psychotropic medications (including antidepressants), and total medical costs reaching a value of over six times the mean of non-treatment-resistant patients [1]. These cases of resistant depression are also associated with functional impairment, poor quality of life, more frequent self-aggressive and suicidal behavior and ideation, higher relapse rate [2].

It is important to underline that the number of lifetime episodes of major depression was significantly associated with the probability of recurrence, such that this risk was increased with 16% by each new episode [3]. If we add to this observation the negative consequences of residual depressive symptoms, like higher risk of recurrence, myocardial infarction, cerebrovascular accidents and overall worse prognosis of their medical comorbidities [4], it becomes obvious that clinician should have as the main target obtaining of remission [that means a final value of *Hamilton Depression Rating Scale* (HAMD) ≤7, *Montgomery–Asberg Depression Rating Scale* (MADRS) ≤10, or a *Clinical Global Impression – Severity* (CGI-S) score of 1], not only securing a response (defined as HAMD decreases of 50%) [4].

Reported incidence of treatment resistance in major depression is variable, but tends to be in the 10% to 30% interval [2].

Various definitions of treatment-resistant depression exist, but their minimal common background is the lack of an adequate response to at least one antidepressant trial with adequate doses and for a sufficient duration [5]. Another, more restrictive, definition considers treatment resistance as lack of significant improvement in depressive symptoms severity after two adequate trials of two different antidepressants from two different pharmacological classes, adequate in terms of dosage, duration, and compliance [6]. Inclusion of a tricyclic agent between the two

antidepressants administered for sufficient duration is considered necessary by some authors before declaring a depression non-responsive [7]. If clinical scales make part of the treatment-resistant depression definition, then final HAMD 25 items version score should be ≤17% and ≤50% of initial score and/or a *Clinical Global Impression – Improvement* (CGI-I) value ≥4, as suggested by some authors [8, 9]. Still other trials have defined treatment resistance as failure to decrease HAMD 21 items version score with more than 50% of initial value [10].

Even duration of an antidepressant trial is disputed, while the mean duration is estimated to be eight weeks, the clinical practice supports a longer duration of exposure to treatment [11]. At least four consecutive weeks of treatment during which an adequate dose was administered for a minimum of three weeks is another definition of what "adequate length of treatment" should be [2].

Use of structured instruments for diagnosis of treatment-resistant depression like "antidepressant treatment history" could be helpful in order to avoid the "pseudo-resistance" phenomenon, induced by inadequate dose regimen, duration of treatment or lack of adherence [12].

As risk factors for treatment-resistant depression, authors suggest elements like bipolar depression, comorbid substance abuse or anxiety disorders, not enough duration of treatment, skipping doses, low tolerability, pharmaco-genetic peculiarities, drug interactions, failure to correctly diagnose somatic or neurological comorbidities, presence of personality disorders, social or psychological stressors [1, 2].

Treatment strategies proposed for this form of depression include, but are not limited to: combination of antidepressants, switching of antidepressants, augmentation with atypical antipsychotics (as the most extensive documented treatment option), adding psychostimulants like Lisdexamphetamine, adding thyroid hormones, Estrogen, Lithium, Pindolol, Inositol, omega-3-fatty acids, mood-stabilizers, physical exercise, psychotherapy, or even immuno-inflammatory based therapies and metabolic interventions [2, 13, 14]. Also, transcranial magnetic stimulation, deep brain stimulation, electroconvulsive therapy (ECT), vagus nerve stimulation are reported as treatment methods in cases of resistant depression.

However, the largest trial ever conducted on major depressive disorder treatment, *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) trial, that lasted for seven years and included 2876 patients that received various antidepressants and augmentation agents, reflected the lack of superiority of any antidepressant when compared to others [14].

In one of the few meta-analyses focused on efficacy and tolerability of various pharmacological augmentation strategies in resistant depression, Quetiapine, Aripiprazole, thyroid hormone, and Lithium were superior to placebo, with atypical antipsychotics more efficacious than the other two agents, but in terms of tolerability, Quetiapine, Olanzapine, Aripiprazole and Lithium were significantly less accepted [15]. A literature review evidenced that almost 50% of patients with resistant depression responded to lithium augmentation within four weeks [16].

Olanzapine/Fluoxetine combination is superior to either drugs alone in producing improvement in patients with treatment-resistant depression, according to a pooled analysis that included five out-patient trials [17]. A head-to-head comparison of Quetiapine and Lithium in treatment-resistant depression showed a trend for superiority in patients receiving antipsychotic from day 14, that became significant at day 28 [18].

Open-label Risperidone augmentation improved response in treatment-resistant patients, but the longer-term benefits of augmentation were not revealed [19]. Aripiprazole augmentation of selective serotonin reuptake inhibitors (SSRIs) for treatment-resistant patients proved itself a good option [20] and Nortriptyline also showed proves of efficacy [21].

Lamotrigine as augmentation strategy was studied in a double-blind randomized controlled trial (RCT) and showed improvement on CGI scales at endpoint both in major depressive disorder and bipolar II disorder resistant to treatment [22]. A more detailed analysis of Lamotrigine's efficacy based on retrospective charts review showed that patients with shorter periods of depression, failure to fewer previous trials, comorbid anxiety and chronic pain syndromes benefited most from this antiepileptic [23].

Venlafaxine (200–300 mg/day) presented some evidence of superiority to Paroxetine (30–40 mg/day) in patients resistant to two previous antidepressant treatments [24].

Summing up all the above-mentioned data from clinical research, it becomes obvious that no clear recommendations could be formulated and also that the majority of data have a poor quality. Atypical antipsychotics and Olanzapine/Fluoxetine combination seem advantaged by these trials, but the lack of head-to-head comparisons in well-designed RCTs is a very important drawback. Also, antipsychotics are not very well tolerated in depressive patients, but neither is lithium or high dose Venlafaxine. Lamotrigine could be helpful, but it has a slow titration profile and its efficacy seems to be restricted to several specific populations.

Therefore, we formulate a few general rules as the basis for approaching treatment-resistant patients:

(*i*) An initial structured interview should be focused on the treatment length, drugs doses and therapeutic adherence during previous and current episodes, what kind of adjunctive agents or non-pharmacological approaches have been used, if partial or no response was obtained, if there are any somatic or psychiatric comorbidities, if the real diagnosis is that of unipolar or bipolar depression, etc.;

(*ii*) Psychological instruments should be used initially and at every visit, so that a quantification of depression dimensions could be documented;

(*iii*) The objectives of treatment are remission of depressive symptoms, functional recovery and obtaining an optimal quality of life;

(*iv*) Pharmacogenetic factors and pharmacological negative interactions should be evaluated as causes for refractoriness whenever possible;

(*v*) The length of an antidepressant trial in cases of treatment-resistant depression should be no less than 6–8 weeks; one or more augmenting agents could still be introduced, especially if the patient is hospitalized, even if the 6–8 weeks interval criteria is not fulfilled; however, premature switch of antidepressants is discouraged, except

for cases of low tolerability or impossibility to increase the dose to a therapeutic level due to adverse events;

(*vi*) Non-pharmacological approaches should not be avoided in cases where a positive effect is anticipated [*i.e.*, psychotherapy for depression with defined negative stressors or if the patient expresses a preference for this method, ECT, for depression with catatonic features];

(*vii*) The importance of therapeutic alliance in this context cannot not be overemphasized, and all patients' worries related to incurability, hopelessness, negative expectations in general, related to depression but amplified by repeated treatment failures should be discussed; although we do not support the idea of creating false expectations for a complete recovery in these subjects, it is certain that in some cases such negative expectations could act counter-therapeutically.

⬚ Single-photon emission computed tomography results in treatment-resistant depression

A case-series of eight patients diagnosed with treatment-resistant depression reported used Technetium (^{99m}Tc)-hexamethylpropyleneamine oxime (HMPAO) single-photon emission computed tomography (SPECT) to evaluate peculiarities of regional cerebral blood flow in these cases [25]. All patients presented significant increase in hippocampus–amygdala activity, compared to non-treatment-resistant depressed subjects and healthy controls, suggesting functional abnormalities in limbic circuitry may be involved in the onset of treatment resistance [25].

A large, retrospective trial included 127 consecutive treatment-resistant non-psychotic depressed patients and 37 healthy controls who underwent ^{99m}Tc-ethyl-cysteinate dimer (ECD) SPECT, and revealed significant hypo-perfusion within bilateral frontotemporal, insular, and anterior cingulate cortices, as well as within the left caudate nucleus [26]. Also, this study detected functional connectivity between left frontal and left cerebellar regions was higher in patients than in healthy subjects [26].

There are also studies suggesting, based on ^{123}I-5-I-R91150 SPECT, that treatment-resistant depression is associated with down-regulation of 5-hydroxytryptamine (serotonin) 2A (5HT2A) receptors in the dorsal regions of the prefrontal and the anterior cingulate cortex, compared no first episode of depression and healthy controls [27].

HMPAO-SPECT was investigated as a potential instrument for predicting the risk of suicide in a trial who detected hypoperfusion of Brodmann area 25 in treatment-resistant depressed patients who committed suicide, and a cluster of 10 regions hypoperfusion in the suicidal patients, including the bilateral superior frontal lobes, the right precuneus, the Rolandic operculum, postcentral gyrus, left caudate and insular cortex [28].

⬚ A case series of treatment-resistant depression diagnosed patients

Case No. 1

The first patient, M.O., is a female, age 44, diagnosed with recurrent major depressive disorder – severe major episode, without psychotic features [according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, revised (DSM-IV-TR) criteria] [29], with two previous episodes of moderate and severe intensity (both involved hospitalization). Patient is a widow, with two daughters she provides for, but with little help from her relatives. She works in a shop as seller, and she consider this job as exhausting because it involves night shifts. She has no somatic comorbidities and no other psychiatric diagnoses on either axis I or II.

She could not specify exactly what treatments she received on her first hospitalization, but remembered Venlafaxine 150 mg/day (administered six weeks after the first discharge) and Lorazepam 2 mg/day (only during hospitalization). She did not continue the recommended treatment because she said she felt better. The second episode was more severe and necessitated treatment with Sertraline 200 mg/day, but since the response was not satisfactorily, she was switched on Venlafaxine 225 mg/day after six weeks. She had a gradually improvement after eight weeks of treatment, but as she stated "I never succeed in becoming who I was before", due to the persistence of asthenia, difficulties in concentration, and anhedonia. She continued Venlafaxine treatment, but after her husband died (about six months before the current hospitalization), a new depressive episode emerged. She was switched on Fluoxetine, with doses up to 60 mg/day for six weeks, with Lorazepam 3 mg/day and Sodium Valproate 900 mg/day as adjunctive agents, but she did not felt any improvement. Her physician added Venlafaxine 75 mg/day to the previous treatment but after 10 weeks, still no major improvement was observed. She changed her physician and received a new treatment with Olanzapine 10 mg/day and Duloxetine up to 90 mg/day. She discontinued treatment after two months because still no improvement was observed and she also complained of gaining weight.

Initial evaluation of this patient detected as main symptoms mixed insomnia, anhedonia, depressive mood, feelings of uselessness, hopelessness, ideas of incapacity, lack of initiative in daily activities with loss of efficiency in her professional activity ("I feel tired all the day, I can't sleep well and can't focus on my job. I need to work with clients and also to keep the evidence of the money in this shop...").

The initial psychological evaluation data are included in Table 1. Depression had a severe intensity (both MADRS and CGI-S support this conclusion), and anxious symptoms were associated. No psychotic symptoms or active suicidal ideation were detected during initial evaluation. Patient's quality of life was very poor, *Euro Quality of Life Scale* (EQ-5D-5L) profile was synthesized as 13414, with an *Euro QoL Visual Analogic Scale* (EQ-VAS) score of 33%.

A cerebral ^{99m}Tc HMPAO-SPECT was performed during the initial visit and the following data were collected: hypoperfusion in the left temporal cortex, mainly polar and internal areas; hypoperfusion of the right thalamus associated with asymmetric fixation of the radiotracer in the cerebellum (hypoperfusion in the left areas) (Figure 1).

Treatment began with Mirtazapine 30 mg/day, then doses were increased to 45 mg after three days. We also initiated a non-benzodiazepine anxiolytic, Pregabalin 75 mg/day, up to 150 mg after five days. Because MADRS scores decreased minimally after two weeks (from 37

to 34), an augmenting agent was initiated. We started Aripiprazole 10 mg/day and increased Pregabalin to 75 mg three times a day (*ter in die – tid*).

Table 1 – *Initial clinical psychological evaluations*

Instruments for evaluation	Values
MADRS	37 (severe)
GAF	30 (severe impairment)
CGI-S	6 (severely ill)
EQ-5D-5L	Mobility: 1 Self-care: 3 Usual activities: 4 Pain/discomfort: 1 Anxiety/depression: 4 EQ-VAS: 33 General profile: 13414
HAMA	21 (moderate-severe anxiety)
SSI	5 (minimal)

MADRS: Montgomery–Asberg Depression Rating Scale; GAF: Global Assessment of Functioning (Scale); CGI-S: Clinical Global Impressions – Severity; EQ-5D-5L: Euro Quality of Life (QoL) Scale; EQ-VAS: Euro QoL Visual Analogic Scale; HAMA: Hamilton Anxiety Rating Scale; SSI: Scale for Suicidal Ideation [29–34].
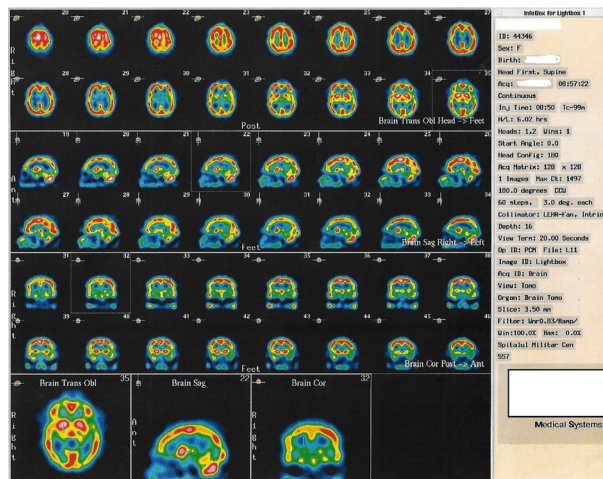

Figure 1 – *Case No. 1: HMPAO-SPECT imaging at initial visit.*

After four weeks of hospitalization, MADRS score decreased to 27 and CGI-S to 4. Symptoms like insomnia and lack of initiative diminished significantly, but cognitive symptoms persist, therefore the patient was referred to a cognitive-behavioral therapist.

After six weeks of combined Mirtazapine 45 mg one a day (*quaque die – qd*), Pregabalin 75 mg *tid*, Aripiprazole 10 mg *qd* and structured psychotherapy the patient obtained a response – MADRS score <50% the initial value, CGI-S decreased to 3, *Hamilton Anxiety Rating Scale* (HAMA) decreased to 8 and *Global Assessment of Functioning Scale* (GAF) increased to 60. Still, the quality of life measures reflected a marked disconfort in the formula 12313, although the EQ-VAS increased to 64%.

An outpatient regimen was initiated, with bi-weekly monitoring visits, and after 14 weeks she succeeded in obtaining remission, according to MADRS (6), CGI-S (2), HAMA (4) scores, with a GAF value of 80, a 11211 formula on EQ-5D-5L and 85% score on EQ-VAS.

Pharmacological treatment was maintained for one year, psychotherapy was discontinued after week 14, as the patient requested. After one year, Pregabalin was decreased and eliminated in a four week-interval, but

Mirtazapine and Aripiprazole were recommended to be continued at full doses for another six months, with possible discontinuation of Aripiprazole after this interval and maintenance of only Mirtazapine as maintenance treatment.

Monitorization of general status and tolerability-related issues are represented in Table 2. Since Mirtazapine has H1 antagonist properties it frequently induces weight gain. Aripiprazole does not have this side effect, but its D2 partial agonist properties could explain mild extrapyramidal symptoms, while Pregabalin could be associated with somnolence and sometimes with weight gain.

Table 2 – *Monitoring of the pharmacological treatment (12-month vs. initial values)*

Variables	Values
Weight	Initially 76.8 kg, after one year 79.2 kg
BMI	24 kg/m^2 (initial) *vs.* 24.7 kg/m^2 (12-month)
Waist	84 cm (initial) *vs.* 26 cm (after 12 months)
Self-reported adverse events	Matutinal somnolence during first week of treatment Fine bilateral hand tremor day 8–16
ECG	66 bpm, QTc 431 ms, no abnormalities
BP sitting *BP standing*	130/70 mmHg, no significant variations 120/70 mmHg, no significant variations
Blood sugar	104 mg/dL
Lipid profile	Cholesterol 210 mg/dL Triglycerides 166 mg/dL

BMI: Body mass index; BP: Blood pressure; ECG: Electrocardiogram; bpm: Beats per minute.

Case No. 2

The second patient, F.M., is a male, age 24, diagnosed with severe major episode, without psychotic features (according to the DSM-IV-TR criteria) [25], at his first admission in a psychiatric unit. Patient is single, works occasionally for his father in a family business and he is also a student at University. He has no somatic comorbidities and no other psychiatric axis I or II diagnoses.

Patient presented his disorder onset with six months before the current evaluation, and received Paroxetine 40 mg/day for two months, with no significant results. After another trial with Doxepin 300 mg/day for two months, the patient discontinued treatment on his own, accusing adverse events like somnolence, weight gain and dry mouth, but he also reported little improvement in general status and impossibility of studying and working as previously.

Initial evaluation in our Department reflected as main symptoms apathy, lack of initiative, diurnal sedation, slowness of motion and cognitive processes, multiple somatic symptoms (nausea, epigastralgia, low back pains), anxiety and depressive mood.

No significant stressors were detected during the first psychiatric interview.

All initial investigations reflected a healthy organic status (Table 3).

A cerebral ^{99m}Tc HMPAO-SPECT was performed during the initial visit and the following data were collected: discrete hypoperfusion in the posterior cortex compared to the anterior cortical areas; hypoperfusion in the right temporal cortex (external, internal, inferior pole) with a difference of 15% comparative to the left areas (Figure 2).

Table 3 – *Initial clinical psychological evaluations*

Instruments for evaluation	Values
MADRS	35 (severe)
GAF	32 (severe impairment)
CGI-S	6 (severely ill)
EQ-5D-5L	Mobility: 1 Self-care: 2 Usual activities: 4 Pain/discomfort: 3 Anxiety/depression: 4 EQ-VAS: 30 General profile: 12434
HAMA	15 (moderate anxiety)
SSI	4 (minimal)

MADRS: Montgomery–Asberg Depression Rating Scale; GAF: Global Assessment of Functioning (Scale); CGI-S: Clinical Global Impressions – Severity; EQ-5D-5L: Euro Quality of Life (QoL) Scale; EQ-VAS: Euro QoL Visual Analogic Scale; HAMA: Hamilton Anxiety Rating Scale; SSI: Scale for Suicidal Ideation [29–34].
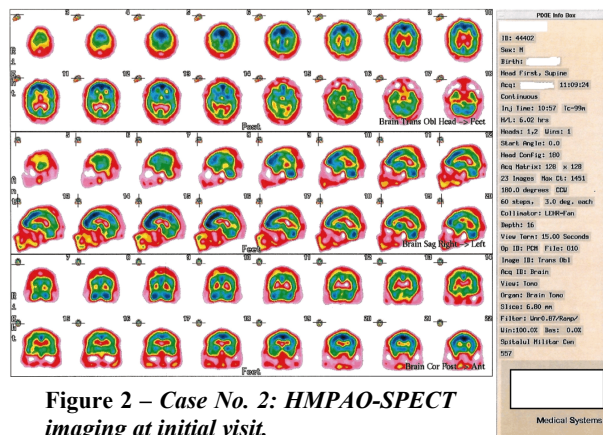
Figure 2 – *Case No. 2: HMPAO-SPECT imaging at initial visit.*

Patient received Duloxetine from 30 mg in day 1, up to 90 mg/day and Alprazolam 1 mg/day. After two weeks, psychological evaluations and psychiatric interview did not detect relevant changes, and patient complained most of the psychomotor inhibition. Bupropion 150 mg/day, up to 300 mg/day, was initiated in addition to the current treatment. Covering all three main neurotransmitter systems with this antidepressant combination was felt as useful. Moreover, noradrenergic and dopaminergic systems are more stimulated than serotoninergic system by this drug combination, because psychomotor inhibition correspond to the dopaminergic pathogenic model of depression.

After three weeks, MADRS score begun to decrease, and CGI-S and GAF paralleled this symptomatic improvement. Quality of life did not improved very much, EQ-5D-5L profile was 12423 and EQ-VAS 37%. Because anxiety symptoms decreased significantly (HAMA 7), Alprazolam was gradually decreased and eliminated in two weeks.

Patient was discharged after 30 days, with a therapeutic regimen consisting of Duloxetine 90 mg *qd* and Bupropion 150 mg two times a day (*bis in die – bid*). After 14 weeks, MADRS reached a value of 6 (remission), CGI-S 2 (borderline mentally ill) and GAF value increased to 77. EQ-5D-5L improved also, to a general profile 11212 with VAS 75%.

Treatment was maintained at the same doses for one year and after this interval, Bupropion was eliminated gradually from the therapeutic combination, while Duloxetine was decreased to 60 mg/day for another six months.

Tolerance of this combination was monitored and variables values are presented in the Table 4.

Table 4 – *Monitoring of the pharmacological treatment (12-month vs. initial values)*

Variables	Values
Weight	Initially 70.5 kg, after one year 68.2 kg
BMI	23.3 kg/m² (initial) *vs.* 22.5 kg/m² (12-month)
Waist	100 cm (initial) *vs.* 99 cm (after 12 months)
Self-reported adverse events	Nausea during first three days of treatment Increased anxiety in the first seven days of treatment
ECG	88 bpm, QTc 420 ms, no abnormalities
BP sitting BP standing	110/60 mmHg, no significant variations 110/70 mmHg, no significant variations
Blood sugar	89 mg/dL
Lipid profile	Cholesterol 180 mg/dL Triglycerides 130 mg/dL

BMI: Body mass index; BP: Blood pressure; ECG: Electrocardiogram; bpm: Beats per minute.

Case No. 3

The third patient, S.I., is a female, age 64, diagnosed with severe major episode, without psychotic features (according to the DSM-IV-TR criteria) [29], at her first admission in a psychiatric unit. Patient is married, retired recently and lives currently with her husband. She has a stage I high blood pressure in treatment with Enalapril 10 mg *bid*. She is also diagnosed with cervical discopathy (no current treatment) and essential tremor (also no recommended treatment).

Patient presented her depression onset with five months before the current evaluation, and received Amitriptyline 150 mg/day for six weeks, but discontinued it due to side effects (somnolence, orthostatic hypotension, dry mouth). She was initiated on Sertraline 150 mg/day and Agomelatine 50 mg/day was added later due to persistence of insomnia, anxiety, residual depressive mood and anhedonia. After another 10 weeks of combined anti-depressant treatment Sodium Valproate 300 mg *tid* was added for anxiety and mood lability. Residual symptoms are still obvious, the patient acutely reports functional impairment and her relationship with her husband has begun to deteriorate ("he accuses me for not being able to get out of this dark period, to be too weak or to have too little interest for changing my way of being…").

Initial evaluation in our department detected as main symptoms depressive mood, recurrent thoughts of death, low drive, initial insomnia, hopelessness, reduced interest for social interactions, hyperesthesia ("I can feel everything, like the sound of the room clock, the cars driving outside during night, almost anything…"), mood lability, irritability.

Recent retirement was detected as a risk factor for depression and a counseling program focused on increasing coping strategies during this stage of life was recommended. All initial investigations found no acute threatens within the somatic status. Current treatment for high blood pressure was preserved. Psychological initial evaluations are highlighted in Table 5.

A cerebral ⁹⁹ᵐTc HMPAO-SPECT was performed during the initial visit and the following data were collected: minimal, scattered hypoperfusion in the frontal, temporal, and parietal cortices, bilaterally, and a lacunary image in the right temporal cortex (Figure 3).

Table 5 – *Initial clinical psychological evaluations*

Instruments for evaluation	Values
MADRS	38 (severe)
GAF	30 (severe impairment)
CGI-S	6 (severely ill)
EQ-5D-5L	Mobility: 2 Self-care: 4 Usual activities: 4 Pain/discomfort: 4 Anxiety/depression: 5 EQ-VAS: 20 General profile: 24445
HAMA	12 (moderate anxiety)
SSI	14 (moderate)

MADRS: Montgomery–Asberg Depression Rating Scale; GAF: Global Assessment of Functioning (Scale); CGI-S: Clinical Global Impressions – Severity; EQ-5D-5L: Euro Quality of Life (QoL) Scale; EQ-VAS: Euro QoL Visual Analogic Scale; HAMA: Hamilton Anxiety Rating Scale; SSI: Scale for Suicidal Ideation [29–34].

Figure 3 – *Case No. 3: HMPAO-SPECT imaging at initial visit.*

This patient received Fluoxetine from 20 mg/day up to 40 mg/day, as the main antidepressant agent, and Carbamazepine 200 mg/day up to 600 mg/day for mood lability and irritability. After two weeks, psychological evaluations and psychiatric interview did not detect any changes, so Quetiapine was added from 150 mg/day up to 300 mg/day. Adding Quetiapine in cases of resistant depression has a strong pharmacodynamic support, because this antipsychotic and its active metabolite block 5HT2A receptors and thus enhancing dopamine release in certain brain regions like prefrontal cortex, have 5HT1A partial agonist actions, and also induce norepinephrine reuptake blockade [35]. However, Quetiapine has histaminergic H1 antagonistic properties and thus could increase weight, so dietary recommendations should be formulated in case of body mass index (BMI) rapid/significant increase.

After four weeks, MADRS score registered an improvement of clinical status, and CGI-S and GAF also reflected this amelioration. Quality of life reached a value of 22233 and an EQ-VAS value of 67%. Mood lability diminished and Carbamazepine dose was reduced to 200 mg *qd*. *Scale for Suicidal Ideation* (SSI) score decreased to 5, and HAMA score to 7.

After discharge, therapeutic regimen consisted of Fluoxetine 40 mg/day, Quetiapine 300 mg/day, and Carbamazepine 200 mg/day. After 20 months, MADRS reached a value of 6 (remission), CGI-S 2 (borderline

mentally ill) and GAF value increased to 77. EQ-5D-5L improved also, to a general profile 11212 with VAS 75%.

Treatment was maintained at the same doses for eight months and after this interval, Carbamazepine was eliminated from the therapy, and Quetiapine dose decreased to 150 mg/day for another four months. Because the patient had at one time an increase of body weight of 5 kg to baseline, and she felt this as a major discomfort, a nutritionist was contacted and dietary recommendations were formulated.

Tolerance of this combination was monitored and changes in variables were presented in the Table 6.

Table 6 – *Monitoring of the pharmacological treatment (12-month vs. initial values)*

Variables	Values
Weight	Initially 58.5 kg, after one year 61.2 kg
BMI	22.6 kg/m^2 (initial) *vs.* 23.6 kg/m^2 (12-month)
Waist	72 cm (initial) *vs.* 74 cm (after 12 months)
Self-reported adverse events	Moderate matutinal somnolence during days 15–30 Orthostatic hypotension during days 15–18 Weight gain during days 30–90
ECG	79 bpm, QTc 441 ms, negative T waves in D2, D3, no other abnormalities
BP sitting BP standing	140/80 mmHg, no significant variations 130/70 mmHg, no significant variations
Blood sugar	99 mg/dL
Lipid profile	Cholesterol 211 mg/dL Triglycerides 150 mg/dL

BMI: Body mass index; BP: Blood pressure; ECG: Electrocardiogram; bpm: Beats per minute.

⌗ Discussions

Therapeutic resistance in depressive disorder is a clinical reality, which is influencing in a negative way the evolution and prognosis of this disorder. Lack of pathogenic, neurobiological-based therapeutic strategies leads to long and difficult clinical evolution in patients diagnosed with major depression, with many relapses, recurrences, and incomplete remissions. All these unfavorable evolutions are associated with cognitive dysfunction and cortical-subcortical disconnection syndrome [36]. Neurobiological-based approaches to the pathogenesis of depression have identified changes in cerebral structures supported by high sensitivity neuroimaging techniques (SPECT).

We identified two neurobiological-based theoretical models of therapeutic resistance in depression:

■ Primary resistance, which correlates with thalamic lesions detected by hypoperfusion on SPECT (Figure 1). These thalamic lesions are considered important markers for neurodevelopmental dysfunctions, and they may be correlated with blood flow abnormalities in posterior cerebral artery, translated in right thalamus hypoperfusion syndrome on SPECT. This disruption in the local blood circulation could be associated with contralateral hypoperfusion in the cerebellum and left temporal lobe. Within this primary resistance, we have identified a global dysfunction in the posterior cortex, compared to anterior cortices (Figure 2). This phenomenon confirms thalamocortical circuits' disconnectivity, assuming thalamic lesions are responsible for the frontal cortex functional alteration (which explains working memory deficits, attentional

deficits, reduced flow of ideas, motor retardation) [37]. Frontal cortex disconnectivity is suggested by diffuse hypoperfusion in frontal areas, but also in temporal and parietal lobes, bilaterally (Figure 3). Frontal and parietal dysfunction may worsen the cognitive deficits observed in treatment-resistant depression. In the third case presented here, regions of isolated ischemia (lacunae) in the right temporal cortex (Figure 3) support the involvement of endothelial dysfunction in treatment-resistant depression, explaining the onset of cerebral small vessel disease in patients diagnosed with this form of depression. Cerebral vascular dysfunction represents an important predictor of the evolution towards cognitive impairment, and it is considered an early neuroimaging marker [38]. Another neuroimaging marker of the primary resistance is suggested by the dysfunctions of the fronto-thalamic circuit, which is considered an indicator for therapeutic non-responsivity in depression [39]. Primary disconnectivity may be detected at the cortico-limbic circuitry, as reflected by the regional hypoperfusion syndrome, a neuroimaging marker associated with high risk for suicidal behavior [28].

■ Secondary resistance is related to the hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, because of the chronic stress induced by incomplete remissions and high number of depressive episodes requiring hospitalization. HPA hyperactivity associates endogenous hyper-cortisolemia, which favors hippocampal and frontal dysfunction. Translational studies on animal models (Wistar rats) conducted by our team support this observation (Figure 6).

The data from our research bring arguments for two conceptual frameworks of therapeutic resistance in major depression:

■ A theoretical framework, focused on neurobiological factors involved in the pathogenesis of this condition (Figure 4). Within this framework, the main risk factors identified for treatment-resistance are:

● Significant personal history for neurodevelopmental abnormalities or birth distress;

● Dysfunctions of the posterior cerebral artery blood flow associated with diffuse hypoperfusion within cerebral cortex or predominant posterior hypoperfusion;

● Thalamic hypoperfusion syndrome and right hemisphere cortical hypoperfusion, left temporal cortex hypoperfusion, or lacunae within left temporal cortex detected on SPECT.
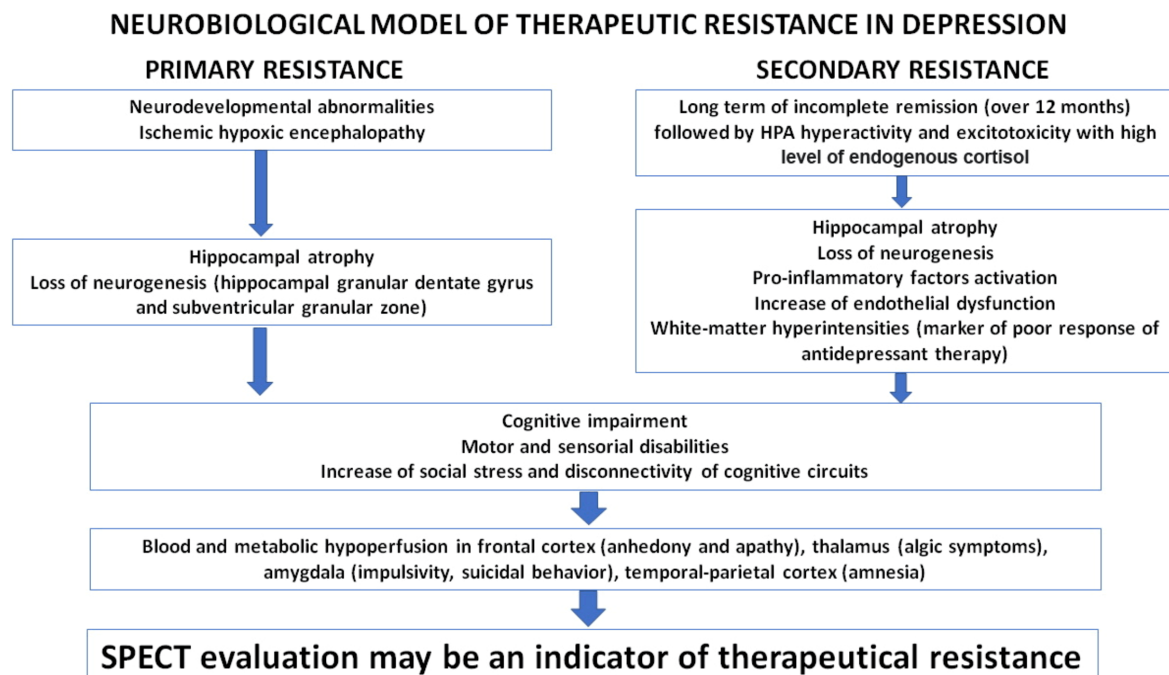

NEUROBIOLOGICAL MODEL OF THERAPEUTIC RESISTANCE IN DEPRESSION

PRIMARY RESISTANCE
Neurodevelopmental abnormalities
Ischemic hypoxic encephalopathy

Hippocampal atrophy
Loss of neurogenesis (hippocampal granular dentate gyrus and subventricular granular zone)

SECONDARY RESISTANCE
Long term of incomplete remission (over 12 months) followed by HPA hyperactivity and excitotoxicity with high level of endogenous cortisol

Hippocampal atrophy
Loss of neurogenesis
Pro-inflammatory factors activation
Increase of endothelial dysfunction
White-matter hyperintensities (marker of poor response of antidepressant therapy)

Cognitive impairment
Motor and sensorial disabilities
Increase of social stress and disconnectivity of cognitive circuits

Blood and metabolic hypoperfusion in frontal cortex (anhedony and apathy), thalamus (algic symptoms), amygdala (impulsivity, suicidal behavior), temporal-parietal cortex (amnesia)

SPECT evaluation may be an indicator of therapeutical resistance

Figure 4 – *Neurobiological framework of the therapeutic resistance in major depression. HPA: Hypothalamic–pituitary–adrenal (axis); SPECT: Single-photon emission computed tomography.*

■ The other framework is focused on the psycho-pharmacological factors involved in therapeutic resistance (Figure 5). Within this framework, the major mechanisms for treatment resistance are:

● Low effectiveness of the pharmacological agents is associated with extrapyramidal symptoms induced by antidepressants or antipsychotics administered during multiple episodes of a treatment-resistant depression;

● Extrapyramidal syndrome, which results from reduced activity of the dopamine D2 receptors localized in neurons arising from substantia nigra (SN), basal ganglia (BG), and ventral tegmental area (VTA). Clinical manifestations associated with these D2 dysfunctions are Parkinsonian extrapyramidal syndrome and akathisia [40]. These manifestations may be determined by other drugs blocking D2 receptors, like Metoclopramide, and may suggest a neurodegenerative evolution if they are observed on long-term, and especially if they are detected in the elderly.

Social chronic stress factors associated with major depression are important risk factors for the phenomenon of therapeutic resistance. HPA hyperactivity may determine dysfunctions of the cortical-subcortical circuitry, especially of the cognitive networks, *i.e.*, the hippocampal–thalamic–cortical circuit. If antidepressants or antipsychotics with anticholinergic properties are administered, they may increase the cholinergic dysfunction within the cognitive networks and may therefore lead to cognitive impairments [41].

The main risk factors of the pharmacological framework are:

● Chronic stress;

● High levels of endogenous cortisol;

● Extrapyramidal symptoms or akathisia;

● Psychiatric symptoms that could be associated with low dopamine levels (*e.g.*, dopamine-based depression, anhedonia); dopamine-based depression does not respond well to the serotonin antidepressants, and these drugs may even worsen the dopaminergic dysfunction and the low responsivity rate.

Translational researches of neurobiological psychiatry on animal model (rat) highlighted the pathogenic connection between high levels of glucocorticoids (Dexamethasone) and lesions of hippocampus and frontal cortex, these being arguments for a theoretical model explaining therapeutic resistance in major depression (Figure 6).

PSYCHOPHARMACOLOGICAL MODEL OF THERAPEUTIC RESISTANCE IN DEPRESSION FOR WOMAN
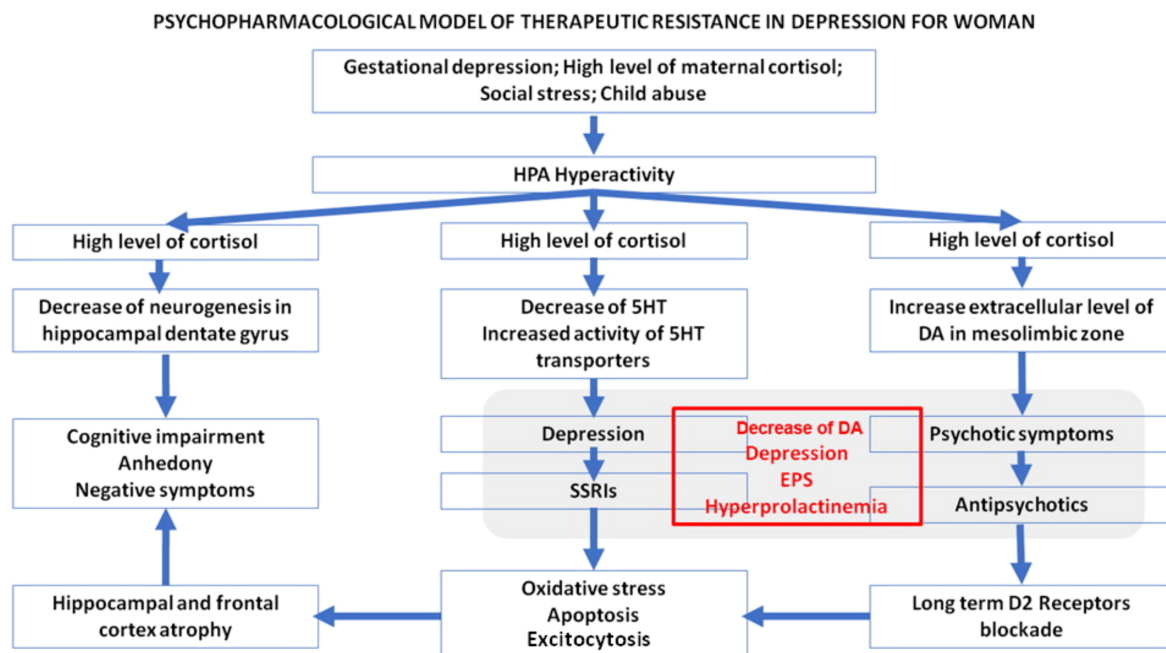
Figure 5 – *Psychopharmacological framework of the therapeutic resistance in major depression. DA: Dopamine; EPS: Extrapyramidal symptoms; HPA: Hypothalamic–pituitary–adrenal (axis); 5HT: 5-Hydroxytryptamine (serotonin); SSRIs: Selective serotonin reuptake inhibitors.*
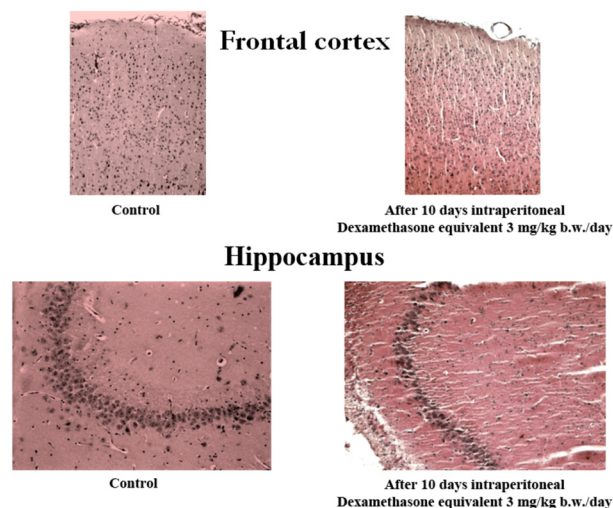
Figure 6 – *Translational research on animal model (Wistar rat) for hyperactivity of the HPA axis with neuronal loss in hippocampus and frontal cortex. HPA: Hypothalamic–pituitary–adrenal; b.w.: Body weight.*

⊟ Conclusions

Various pharmacological therapies are used in treatment-resistant depression, however no clear-cut recommendations for a stratified approach could be found in the literature. SPECT could be a useful investigation for detection of hypoperfusion in cerebral areas involved in emotional and cognitive processing, and existing data in the literature support this recommendation in cases of resistant depression.

In our series of cases, augmentation with an atypical antipsychotic (Quetiapine in one case and Aripiprazole in another), combining two antidepressants from different pharmacodynamic classes (Bupropion and Duloxetine), and/or adding non-benzodiazepine anxiolytics (*i.e.*, Pregabalin), benzodiazepine anxiolytics (Lorazepam, Alprazolam) or mood-stabilizers (*i.e.*, Carbamazepine) helped in obtaining remission of the depressive symptoms. Continuation of the antidepressant treatment at therapeutic doses for at least one year, with close monitoring through psychiatric and structured psychometric evaluations are very important elements for obtaining a good result on long term. ^{99m}Tc HMPAO-SPECT detected various abnormalities, mainly hypoperfusion in temporal cortex (in all the three cases analyzed here), but also in other areas, like right thalamus, left cerebellum, frontal and parietal cortices. Further research, using larger number of patients diagnosed with treatment-resistant depression could help in finding the neurobiological explanations of this clinical and therapeutic phenomenon.

The use of theoretical models, neurobiological and psychopharmacological frameworks support the idea that treatment-resistant depression may be anticipated through the identification of several risk factors or some neuro-

imaging abnormalities. Translational studies on animal models will be able in the future to illustrate new pathogenesis factors that could lead to the formulation of new therapeutic approaches in treatment-resistant depression.

There are certain limits of our research, like the lack of data regarding the statistical significance of psychometric determinations. We consider that major risk factors for the negative evolution of treatment-resistant depression (*e.g.*, multiple somatic comorbidities, progressive cognitive impairment, high suicide risk) and the high costs of this disorder, together with the data derived from the present study regarding patients' health-related quality of life, could grant further research in this field. New treatments focused on severe forms of major depression will lead to lower pharmaco-economic burden over society, higher quality of life and a better overall functionality of these patients.

Conflict of interests

The authors declare potential conflict of interests, as follows: Ileana Marinescu – "I was speaker for Servier, Lundbeck and Janssen-Cilag"; Octavian Vasiliu – "I was speaker for Servier, Eli Lilly and Bristol-Myers Squibb, and participated in clinical trials funded by Janssen-Cilag, Orion Pharma, AstraZeneca, Otsuka Pharmaceutical, Sanofi-Aventis and Sunovion Pharmaceuticals"; Daniel Vasile – "I was speaker for AstraZeneca, Bristol-Myers Squibb, CSC Pharmaceuticals, Eli Lilly, Janssen-Cilag, Lundbeck, Organon, Pfizer, Servier, Sanofi-Aventis, and participated in clinical trials funded by Janssen-Cilag, AstraZeneca, Eli Lilly, Sanofi-Aventis, Schering-Plough, Organon, BioLine Rx, Forenap Pharma, Wyeth, Otsuka Pharmaceutical, Dainippon Sumitomo, Servier, Sunovion Pharmaceuticals".

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