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CASE REPORT/CASO CLÍNICO

Esketamine in Treatment Resistant Depression: The Way to Remission
Escetamina na Depressão Resistente ao Tratamento: O Caminho para a Remissão

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Abstract

Major depressive disorder affects an estimate of 5% of the population with nearly 1-third of patients failing to achieve remission with conventional pharmacological treatment. Esketamine, a novel rapid-acting antidepressant, with a noncompetitive antagonism on N-methyl-D-Aspartate receptor, have been recently approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment-resistant depression.

Here, we report a clinical case of a 42-year-old Caucasian woman who endured many years with severe depressive symptoms and high functional impairment. Previous treatments included cognitive behavioral therapy, numerous pharmacological trials with antidepressants and augmentation agents, and neurostimulation approaches. Upon treatment with esketamine, the patient presented remarkable clinical recovery. Psychometric assessments determined an acute reduction on the MADRS score after 1 week and progressive recovery of the depressive symptoms on the following weeks. Likewise, PHQ-9 scale assessments, evaluating the relative frequency of depressive symptoms. and the Sheehan scale, assessing functional recovery, also determined a pronounced symptomatic relief.

Keywords: Antidepressive Agents; Depressive Disorder, Major/drug therapy; Depressive Disorder, Treatment-Resistant/drug therapy; Esketamine/administration & dosage

Resumo

A perturbação depressiva *major* afeta cerca de 5% da população e quase 1-terço dos doentes não consegue atingir remissão com o tratamento farmacológico convencional. Escetamina, um novo antidepressivo de ação rápida, com antagonismo não competitivo do receptor N-metil-D-aspartato, foi recentemente aprovado pela Food and Drug Administration (FDA) e European Medicines Agency (EMA) para o tratamento de depressão resistente ao tratamento.

Aqui, relatamos o caso clínico de uma mulher caucasiana de 42 anos que padeceu durante muitos anos de sintomas depressivos graves e de grande compromisso funcional. Os tratamentos anteriores incluíram terapia cognitivo-comportamental, vários ciclos de tratamento farmacológico com antidepressivos e agentes de aumento e técnicas de neuroestimulação. Após tratamento com escetamina, a doente apresentou uma notável recuperação clínica. Avaliações psicométricas determinaram uma redução considerável na pontuação MADRS após uma semana e recuperação progressiva dos sintomas depressivos nas semanas seguintes. Da mesma forma, as avaliações com a escala de PHQ-9, que avalia a frequência relativa de sintomas depressivos, e a escala de Sheehan, que avalia a recuperação funcional, também determinaram alívio sintomático muito pronunciado.

Palavras-chave: Antidepressivos; Escetamina; Perturbação Depressiva Major/tratamento farmacológico; Perturbação Depressiva Resistente a Tratamento/tratamento farmacológico

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INTRODUCTION

Major depressive disorder is a highly debilitating disease associated with a massive socioeconomic burden.[1,2] Although treatment with regular antidepressants and psychotherapy is effective, one-third of patients fail to achieve remission.[3,4] Patients who have not responded to at least 2 different antidepressant treatment approaches in the current depressive episode are diagnosed with treatment-resistant depression (TRD).[5] Even considering the patients who attain partial response with initial antidepressant trials, many endure several weeks with severe depressive symptoms which increases the risk of suicidal behaviour.[6] For these patients with TRD and prolonged response to conventional treatments, the most common clinical recommendation includes neurostimulation approaches. Although, electroconvulsive therapy (ECT) can improve depressive symptoms, a considerable percentage remain symptomatic or develop cognitive side effects.[7] Another therapeutic possibility is repetitive transcranial magnetic stimulation (rTMS). However, the requirement of highly sophisticated equipment and technical skills have greatly limited the treatment of large numbers of patients.

Esketamine, a novel rapid-acting antidepressant with a noncompetitive antagonism of the N-methyl-D-Aspartate receptor, have been recently approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for TRD.[8] Here, we report a case study of a patient with TRD that was successfully treated with esketamine. This clinical case provides further evidence of clinically meaningful efficacy of this approach particularly when combined with conventional antidepressants.

CASE REPORT

A 42-year-old Caucasian woman, married, with two children and working as a full-time professor in a public university developed depressed mood, apathy, anhedonia, fatigue, psychic anxiety, and loss of self-esteem in the Autumn of 2013. Antidepressive treatment was initiated with doses being progressively adjusted to 60 mg of fluoxetine and 10 mg of diazepam (tid). Clinical recovery was very limited, and the patient was unable to continue her job. A second trial of antidepressants was tried using clomipramine (75 mg, tid) and quetiapine (200 mg) but the patient maintained a progressive clinical decline with further complains of adynamia, clinophilia, psychomotor retardation, and impaired memory and concentration. Medical treatment was then further augmented using venlafaxine (300 mg), bupropion (300 mg), mirtazapine (30 mg) and quetiapine (200 mg). The patient was also referred to cognitive behavioral therapy which she followed for 2 years. Nevertheless, this third attempt was also unable to promote symptomatic relief and the disease further evolved to suicidal ideation. Specifically, the patient was found to be carrying a kitchen knife in her handbag and driving around a cliff region. Both plans were hold with resolute suicidal intent demanding treatment in an inpatient setting. Despite remission of the suicidal ideation, the patient was still unable to work and was finally proposed to retire at 46-years-old.

rTMS was also attempted with 20 sessions stimulating the left dorsolateral pre-frontal cortex.[9] Clinical recovery was not observed and therefore the patient maintained depressed mood, adynamia, physic anxiety and sense of hopelessness that severely conditioned her competence to fulfil household duties and taking care of her children.

Recently, upon the approval of esketamine by the Portuguese Authority for Medication (Infarmed), a new therapeutic approach could be considered for patients with TRD. Esketamine was supplied before marketing authorization through an early access program.[10] Taking advantage of the early access program, patient was enrolled in the first esketamine TRD protocol implemented in Portugal. Briefly, patient comfortably resting in a hospital room, with low sound and visual stimulation, self-administrated esketamine according to the manufacturer instructions. Specifically, the current clinical case was treated twice weekly with 56 mg of esketamine during weeks 1 to 3 and twice weekly with 84 mg of esketamine during week 4 (induction phase). Maintenance phase included once weekly with 84 mg of esketamine during weeks 9 to 14 (Fig. 1).

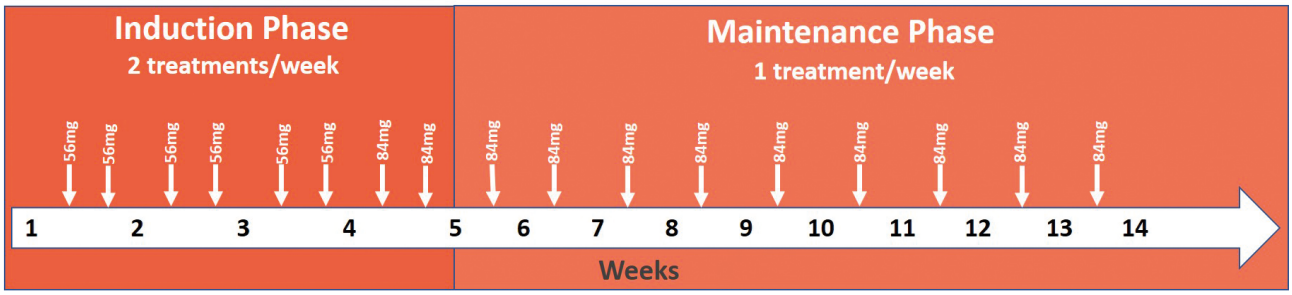

Figure 1. Schematic representation of the induction and maintenance phases of esketamine treatment.

Psychometric assessments during the first week determined a remarkable clinical recovery with considerable reduction of the MADRS[11] score. During week 2 and 3, the clinical recovery was also found to be modest (Fig. 2) and therefore it was decided to titrate the esketamine dose to 84 mg. Patient continue to recover with a gradual and progressive reductions of MADRS score on the following weeks (Fig. 2). PDH-9[12] assessment, focusing on the relative frequency of depressive symptoms, and SDS[13] assessments, evaluating functional recovery, also determined progressive score

reduction up weeks 4 and 5, respectively. In addition, maintenance phase (weeks 5 to 14), consisting of weekly treatments with 84 mg of esketamine, successfully preserved the patient at an asymptomatic state (Fig. 2).

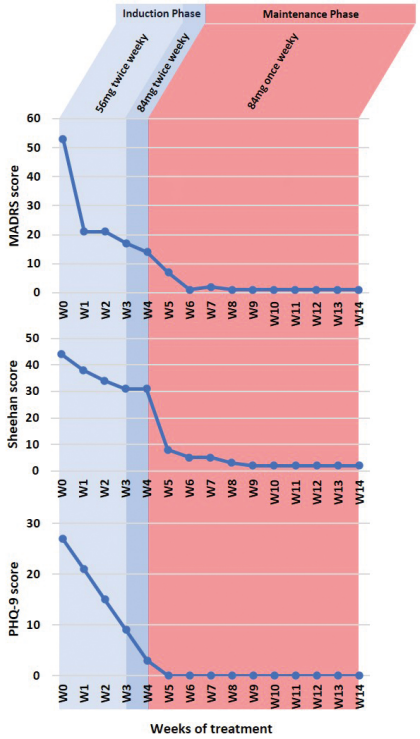

Figure 2. Psychometric assessment during induction phase (weeks 1 to 4) and maintenance Phase (weeks 5 to 14) of esketamine treatment.

Clinical assessment using MADRS, PHQ-9 and SDS were conducted once weekly. Induction phase consisting of 56 mg of esketamine twice weekly during weeks 1 to 3 and 84 mg of esketamine twice weekly during week 4 resulted in remarkable reduction of the MADRS score during the first week and progressive recovery on the following weeks. PHQ-9, evaluating the relative frequency of depressive symptoms, and SDS, evaluating the functional recovery, also determined progressive score reduction. Maintenance phase consisting of weekly treatment using 84 mg of esketamine weekly (weeks 5 to 14) resulted in successfully preservation of the patient asymptomatic state.

Regarding side effects, the patient experienced mild somnolence and dizziness, prolix speech, and auditory hyperesthesia. These side effects lasted only for about 50 minutes and were clearly more pronounced in the first few treatment sessions.

DISCUSSION

The newly available esketamine is expected to address an unmet medical need for the patients enduring TRD and for patients requiring rapid antidepressant action. Indeed, previous studies have demonstrated prompt onset and persistent efficacy compared with placebo in TRD and suicidal patients.[14,15] Higher antidepressant efficacy and long-term maintenance was also demonstrated for esketamine plus oral antidepressant group in comparison to placebo plus oral antidepressant with meaningful reduction of MADRS score at earlier time points and a significantly greater reduction being observed at day 28.[16,17] Besides the medical evaluation, the clinical benefits are also greatly appreciated by the patients enrolling the esketamine plus antidepressant group.[8] Also supporting this data, the clinical case presented here has shown a pronounced clinical recovery and sustained reductions in MADRS, Sheehan and PHQ--9 scores. Importantly, the acute clinical improvement during the first week of treatment further emphasizes the hypothesis that esketamine might be beneficial for suicidal patients and even evocative of a novel concept of treatment whereas the maintenance of the remarkable relief confirms the role of esketamine for TRD patients (Fig. 2). Of note, the described patient continues to be treated with the oral antidepressants and esketamine, up to this date, maintaining a euthymic mood status and being grateful of their functional improvement. Taken together the current manuscript reinforces the safety, feasibility, and clinical relevance of esketamine as an adjunctive approach to the conventional treatment of TRD patients and as a potential alternative to neurostimulation techniques.

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