

Memantine may acutely improve cognition and have a mood stabilizing effect in treatment-resistant bipolar disorder

Memantina pode melhorar acentuadamente a cognição e possui efeito estabilizador do humor no transtorno bipolar resistente ao tratamento

Dear Editor,

Bipolar patients can often show cognitive deficits, which are sometimes not associated with acute affective episodes.¹ In the most severe cases, cognitive deficits are disabling and may interfere with treatment adherence.

Cholinesterase inhibitors are used in patients with Alzheimer Disease in order to delay cognitive impairment. Donepezil was reported as a useful add-on medication in treatment-resistant bipolar patients in a case series report.² However, there have also been reports of mania, induced by donepezil and galantamine.³⁻⁴

Memantine is an effective drug for the treatment of moderate-to-severe cognitive impairment related to Alzheimer Disease.⁵ We are reporting two cases of treatment-resistant bipolar disorder patients who showed substantial cognitive and mood symptom improvements.

Case 1 (Table 1): a 29-year-old female fashion stylist with bipolar disorder type II and bulimia nervosa, who used to read and had been able to write short stories, was suffering from severe depression over the last 2 years, having spent most of her time in bed. She was unable to read a newspaper or to write a single letter. Lamotrigine and lithium were useful for 2 years, but they lost their efficacy. Other mood stabilizers (divalproex, carbamazepine, oxcarbazepine) were tried with no success. She did not tolerate some atypical antipsychotics, such as aripiprazol, olanzapine, quetiapine, risperidone and ziprasidone, due to severe tachycardia or reported lack of effect of these medications. In August 2005 she received memantine as an add-on treatment up to 20 mg/day. During the first week following treatment with memantine, she could go to the computer and wrote a short story, spending most of the time out of bed. After one month's treatment, she showed a moderate improvement in psychomotricity and depressive mood, along with cognitive gains.

Case 2 (Table 2): a 32-year-old male judge (retired), with bipolar disorder type I, who had recently suffered from treatment-resistant mixed states, mostly with depressive symptoms. He reported mental incapacity, difficulty in concentrating and in performing abstract reasoning. He also reported hypomanic episodes characterized by compulsive shopping, binge eating and lack of insight. Previous unsuccessful treatments had included divalproex, oxcarbazepine, olanzapine, ziprasidone and haloperidol. The introduction of memantine up to 10 mg/day, in November 2005, promoted a rapid improvement in depressive symptoms, concentration and performance of tasks that were hitherto considered impossible, such as reading. Despite the maintenance of impulsivity, his insight into the compulsive shopping behavior and binge eating improved.

Discussion

There are similarities in the mechanism of action of memantine, an anti-glutamatergic drug, and lamotrigine, the latest drug associated with antidepressant and mood stabilizing effects in bipolar depressive patients. This mechanism of action could explain the positive effects of memantine in these treatment-resistant patients.

The patients described in this report used medications that could cause cognitive impairment. Memantine could have antagonized these effects, through unclear mechanisms.

To our knowledge, this is the first report on the usefulness of memantine in the treatment of cognitive impairment in bipolar disorder patients. Randomized double-blind controlled studies are needed to validate these preliminary observations.

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Table 1 - Time schedule of the psychopharmacological treatment of patient 1

Date (Month/year)	Psychopharmacological approach (maximum dosage)	Clinical outcome	GAF*
04/98	Venlafaxine 300 mg + carbamazepine (CBZ) 600 mg	Suicidal behavior + binge eating + mood lability	15
05/98-06/98	Tranilcipromine 40 mg + CBZ 1200 mg + risperidone 2 mg	Suicidal thoughts + bulimic behavior + postural hypotension + staying in bed most of the time	15
06/98-08/98	Moclobemide 750 mg + CBZ 1600 mg + risperidone 4 mg + Diazepam (DZP) 20 mg	Depression + binge eating + improvement of suicidal thoughts + staying in bed most of the time	35
08/98-10/98	Sertraline 250 mg + CBZ 1600 mg + DZP 20 mg	Depression + binge eating + half of the time in bed + insomnia	40
10/98-12/98	Venlafaxine (VLF) 375 mg + CBZ 1600 mg + DZP 10 mg + bromocriptine 12.5 mg	Mild depression + mild binge eating + walking every day	55
12/98-05/99	VLF 225 mg + CBZ 1600 mg + DZP 10 mg	Mild depression + mild binge eating + studying + walking some days	60
05/99-07/99	VLF 300 mg + CBZ 1600 mg + Tianeptine 75 mg + Diazepam 10mg	Moderate depression + moderate binge eating + stopping physical exercises and study	40
07/99-10/99	VLF 225 mg + CBZ 1600 mg + Lithium 1200 mg	Mild depression + mild binge eating + walking and studying	65
10/99-11/99	VLF 225 mg + CBZ 1200 mg + Lithium 900 mg + amineptine 100 mg	Mild depression + over eating + stopping walking	55
11/99-05/01	VLF 300 mg + CBZ 1200 mg + Lithium 900 mg + T4 50 mcg	Euthymia/mild depression + occasional binge eating + subclinical hypothyroidism	70
05/01-07/01	VLF 300 mg + CBZ 800 mg + Lithium 900 mg + T4 50 mcg + Lamotrigine (LTG) 50 mg	Mood lability + occasional binge eating + suicidal thoughts	50
07/01-04/02	VLF 300 mg + Lithium 900 mg + T4 50 mcg + LTG 225 mg	Low self-esteem + no binge eating	70
04/02-11/02	VLF 300 mg + Lithium 900 mg + T4 50 mcg + LTG 300 mg	Brief episodes of severe depression + suicidal thoughts	55
11/02-12/02	Lithium 900 mg + LTG 400 mg	Severe depression and binge eating + anger attacks	40
12/02-03/03	VLF 300 mg + Lithium 900 mg + LTG 400 mg	Mood lability + moderate binge eating	50
03/03-05/03	VLF 300 mg + lithium 900 mg + LTG 400 mg + oxcarbazepine 1200 mg + T4 75 mcg	Severe suicide attempt (lithium + alcohol) + severe depression + aggressive behavior	05
05/03-06/03	VLF 300 mg + lithium 900 mg + LTG 400 mg + T4 75 mcg + Olanzapine 5 mg	Moderate depression + overeating + suicidal thoughts + memory impairment	45
06/03-08/03	lithium 900 mg + LTG 400 mg + T4 75 mcg + Olanzapine 5 mg + topiramate 200mg	Suicide attempt + continuous suicide thoughts + mood lability + overeating + memory impairment	15
08/03-09/03	lithium 900 mg + LTG 400 mg + T4 75 mcg + Olanzapine 2.5 mg + topiramate 300 mg + Aripiprazole 15 mg	Dyspnea + tachycardia + severe anxiety + controlled eating behavior + stopping academic activities due to cognitive impairment	40
09/03-10/03	lithium 900 mg + LTG 400 mg + T4 75 mcg + topiramate 300 mg + ziprasidone 80 mg	Severe depression + most of the time in bed + severe cognitive impairment + intense tremor	25
10/03-11/03	Citalopram 30 mg + lithium 900 mg + LTG 400 mg + T4 75 mcg + topiramate 300 mg	Moderate depression + anergy + suicidal thoughts + most of the time in bed + severe cognitive impairment + intense tremor	30
11/03-12/03	VLF 300 mg + lithium 900 mg + LTG 200 mg + T4 75 mcg + topiramate 300 mg	No changes except improvement of tremors	30
12/03-01/04	VLF 300 mg + lithium 900 mg + LTG 100 mg + T4 75 mcg + topiramate 300 mg + methylphenidate 25 mg	Moderate depression + low energy + severe cognitive impairment (couldn't read a newspaper). Methylphenidate 40mg associated with severe suicidal thoughts	45
01/04-05/04	VLF 300 mg + lithium 900 mg + LTG 100 mg + T4 75 mcg + topiramate 300 mg + methylphenidate 25 mg + bupropion 150 mg	Moderate depression + low energy + severe cognitive impairment + suicidal thoughts	15
05/04-07/04	VLF 300 mg + lithium 900 mg + LTG 50 mg + T4 25 mcg + topiramate 300 mg + methylphenidate 30 mg + quetiapine 25mg	Severe depression + anergy + severe cognitive impairment + suicidal thoughts	15
07/04-08/04	VLF 300 mg + lithium 900 mg + T4 12.5 mcg + topiramate 300 mg + methylphenidate 30 mg	Moderate depression + low energy + cognitive impairment + suicidal thoughts	15
08/04-11/04	VLF 300 mg + lithium 900 mg + T4 12.5 mcg + topiramate 300 mg + methylphenidate 40 mg + divalproate 750 mg	Moderate depression + moderate cognitive impairment + moderate tremors	20
11/04-01/05	VLF 300 mg + lithium 900 mg + T4 12.5 mcg + topiramate 300 mg + methylphenidate 20 mg + divalproate 500mg	Severe depression + severe cognitive impairment + severe suicidal thoughts + severe tremors	15
01/05-02/05	Lithium 450 mg + gabapentin 900 mg + T4 50 mcg	Severe depression + severe cognitive impairment + severe suicidal thoughts + severe binge eating + aggressive behavior	10
02/05-04/05	VLF 150 mg + lithium 600 mg + T4 50 mcg + topiramate 300 mg + gabapentin 1200 mg	Severe depression + severe cognitive impairment + severe suicidal thoughts	15
04/05-07/05	VLF 150 mg + lithium 600 mg + T4 50 mcg + topiramate 300 mg + gabapentin 1200 mg + piracetam 1600 mg	Severe depression + severe cognitive impairment + severe suicidal thoughts	15
07/05-08/05	VLF 150 mg + lithium 600 mg + T4 50 mcg + topiramate 300mg + gabapentin 1200mg + amantadine 200mg + pantoprazole 20mg	Severe depression + severe cognitive impairment + severe suicidal thoughts	15
08/05-11/05	VLF 150 mg + lithium 600 mg + T4 50 mcg + topiramate 250 mg + gabapentin 900 mg + memantine 20 mg + pantoprazole 20 mg	Mild depression + improvement of cognitive impairment	75
11/05-02/06	lithium 600 mg + T4 50 mcg + topiramate 250 mg + gabapentin 900 mg + memantine 20 mg + pantoprazole 20 mg + quetiapine 300 mg	Severe depression + binge eating + suicidal thoughts	30
02/06-	lithium 600 mg + T4 50 mcg + topiramate 400 mg + gabapentin 900 mg + memantine 20 mg + pantoprazole 20 mg	Mild depression	75

* GAF: Global Assessment of Functioning, DSM-IV (APA, 1994)

Table 2 - Time schedule of the psychopharmacological treatment of patient 2

Date (month/year)	Psychopharmacological approach (maximum dosage)	Clinical outcome	GAF*
01/02	milnacipran 200 mg + buspirona 15 mg	Melancholic depression + mood lability, OCD symptoms (unipolar depression?)	45
02/02-03/02	Oxcarbazepine 1200 mg + milnacipran 150 mg (tapering) + citalopram 20 mg	Full DSM-IV Mixed state (Bipolar I), followed by melancholic depression	40
04/98-06/02	Oxcarbazepine 2100 mg + citalopram 20 mg + amineptine 100 mg + ziprasidone 80 mg + gabapentin 600 mg + clonazepam 4 mg	Depression + extreme mood lability + compulsive shopping + irritability	35
07/02-10/02	Oxcarbazepine 2100 mg + lithium 900 mg + citalopram 20 mg + amineptine 100 mg + ziprasidone 80 mg + gabapentin 600 mg + clonazepam 4 mg	More depressive + mood lability + compulsive shopping, less irritability. Stop to work	25
11/02-03/03	Divalproex 1500 mg + lithium 1050 mg + ziprasidone 80 mg + moclobemide 900 mg + clonazepam 4 mg + levotiroxina 175 mcg	Moderate depression + anxiety, lack of energy, daydreaming, alternating with aggressiveness	20
04/03-06/03	Divalproex 1750 mg + lithium 1500 mg + ziprasidone 80 mg + fluoxetine 30 mg + diazepam 10 mg + levotiroxina 200 mcg	Moderate depression + anxiety, lack of energy, daydreaming, less aggressiveness	25
07/03-04/04	Divalproex 1750 mg + lithium 1350 mg + quetiapine 300 mg + fluoxetine 90mg/week + bupropion 225 mg + diazepam 10 mg + levotiroxina 200 mcg	Period of continuous moderate depression and social anxiety, isolation, quit a romantic relationship, stop physical exercises, loss of memory, is dumb*; sleeps only with ziprasidone and/or quetiapine (abuse)	20
05/04-06/04	Divalproex 1250 mg + lithium 900 mg + lamotrigine 100 mg + aripiprazole 15 mg + olanzapina 2.5 mg + fluoxetine 90 mg/week + bupropion 150 mg + diazepam 10 mg + levotiroxina 200 mcg	Less tremor (reduction of lithium and divalproex), Moderate depression + binge eating, gains 20Kg but sleeps well. Tremors. Social anxiety, loss of memory: skull NMR reveals cortical/subcortical mild atrophy	25
07/04-08/04	Divalproex 1000 mg + lithium 900 mg + lamotrigine 100 mg + aripiprazole 15 mg + escitalopram 15 mg + bupropion 150 mg + metilfenidate 20 mg + diazepam 10 mg + levotiroxina 250 mcg	Pervasive depressive background, social phobia, anergy and reduced attention and concentration; sleeps only with ziprasidone (abuse). Tremors better with less divalproex	20
09/04-11/04	Divalproex 1000 mg + lithium 900 mg + lamotrigine 150 mg + aripiprazole 15 mg + ziprasidone 40 mg + escitalopram 5 mg + diazepam 10 mg + levotiroxina 250 mcg. Begins slow titrating of topiramate	Huge weight gain (more 17 Kg), compulsive eating (even without olanzapina), irritable, aggressive; then withdraw bupropion and metilfenidate, reduce escitalopram. Memory, attention and concentration worsening. Tremors remains	15
12/04-04/05	Divalproex 500 mg + lithium 900 mg + topiramate 200 mg + lamotrigine 200 mg + aripiprazole 15 mg + escitalopram 10 mg + diazepam 10 mg + levotiroxina 250 mcg	Can't stand tremors, withdraw divalproex. Memory, attention and concentration still worsening. Hypomanic outbursts with compulsive shopping and binge eating, in a depressive background	15
05/05-11/05	Lithium 1050 mg + topiramate 250 mg + lamotrigine 200 mg + aripiprazole 30 mg + escitalopram 15 mg + diazepam 10 mg + levotiroxina 250 mcg	Tremors much better. Weight loss, but hypomanic outbursts with compulsive shopping persists, low critics. Memory, attention and concentration even worse	20
11/05-today	Lithium 1050 mg + topiramate 250 mg + lamotrigine 200 mg + aripiprazole 30 mg + escitalopram 15 mg + diazepam 10 mg + levotiroxina 250 mcg + MEMANTINE 10 mg	Memory, attention and concentration better. Less hypomanic outbursts with compulsive shopping, but critics much better. Persists depressive background, with less suffering	50

* GAF: Global Assessment of Functioning, DSM-IV (APA, 1994)
OCD: Obsessive-Compulsive Disorder

Problemas de saúde mental em adolescentes: como identificá-los?

Mental health problems in adolescents: How to identify them?

São escassos os estudos epidemiológicos na área de saúde mental da adolescência nos países em desenvolvimento. Os altos custos desses estudos e a falta de ações preventivas em saúde pública desses países implicam em desconhecimento das necessidades das populações jovens com o subsequente prejuízo social. O uso de instrumentos breves e confiáveis que possam viabilizar esses estudos é uma alternativa para o encaminhamento desse impasse.

O Questionário de Habilidades e Dificuldades, *Strengths and Difficulties Questionnaire* (SDQ),¹ é uma boa opção neste sentido e tem sido um instrumento de rastreamento bastante utilizado. O SDQ é um breve questionário para avaliação de problemas de saúde mental na infância/adolescência, que pode ser usado para a avaliação de fatores de risco e de proteção, bem como no estabelecimento de programas de intervenção, pois é sensível às modificações comportamentais/emocionais individuais.²

Nós realizamos estudo transversal para determinar a taxa de prevalência de problemas de saúde mental em adolescentes que frequentam a 6ª série do ensino fundamental de todas as escolas de Barretos-SP (amostra aleatória de 327 estudantes entre 11 e 15 anos de idade; perda amostral: 6,9%).³⁻⁴ Os problemas de saúde mental foram definidos como anormal e/ou limítrofe, com prejuízo funcional na versão brasileira do SDQ, verificando-se uma taxa de prevalência de 12,6%.

Revisão de artigos publicados no MEDLINE e LILACS revela que esta taxa está de acordo com a de outros estudos utilizando o SDQ ao redor do mundo (Tabela 1). Além disso, o SDQ tem se mostrado sensível para revelar diferenças entre classes socioeconômicas. Um estudo comparando crianças/adolescentes da região metropolitana de Campos de Jordão-SP com crianças/adolescentes moradores de favela da periferia daquele município revelou um aumento de praticamente 100% na prevalência de problemas de saúde mental no segundo grupo.⁵ Resultado semelhante foi encontrado em nosso estudo quando identificamos associação entre maior taxa de problemas de saúde mental e pertencer a famílias de classes socioeconômicas mais baixas, segundo a escala ABA/ABIPEME* (p = 0,03). Portanto, a con-

* Associação Brasileira de Anunciantes e Associação Brasileira de Institutos de Pesquisa de Mercado Marplan Brasil: XXXI Estudos Marplan Brasil. Representações e Pesquisas Ltda. São Paulo, 1981.