Acta Neuropsychiatrica 2013

DOI: 10.1017/neu.2013.14

ACTA NEUROPSYCHIATRICA

Memantine may affect pseudobulbar affect in patients with Alzheimer's disease

Prokšelj T, Jerin A, Kogoj A. Memantine may affect pseudobulbar affect in patients with Alzheimer's disease.

Objective: Behavioural symptoms are common in moderate to severe Alzheimer's disease (AD) and are improved by memantine with the most pronounced effect on agitation/aggression. Dextromethorphan in combination with quinidine is the only drug approved by US Food and Drug Administration for the treatment of pseudobulbar affect (PBA) on the basis of efficacy in patients with multiple sclerosis or amyotrophic lateral sclerosis. The aim of our study was to evaluate the efficacy of memantine on PBA in patients with AD.
Methods: In a prospective, double-blind, case-control study to assess PBA with pathological laughter and crying scale patients were administered memantine (final dose of 20 mg daily) or citalopram (20 mg once daily), each for 10 weeks. The number of episodes of involuntary emotional expression, Neuropsychiatric Inventory (NPI) and Overt Aggression Scale-Modified (OAS-M) total scores were also recorded. Furthermore, the platelet serotonin (5-HT) concentration was measured.
Results: Although memantine had beneficial effects on PBA, it also had a crucial impact on behavioural symptoms, especially aggression and agitation (to an average of 3.5 times higher end-point scores on OAS-M and increase of NPI total scores for an average of 114% of initial value). Therefore, the study was prematurely stopped. In addition, we had evidenced a drop of platelet 5-HT concentration (to an average of 73% of initial value).
Conclusion: Surprisingly, our research showed the opposite action of memantine on neuropsychiatric symptoms as expected. In a limited number of AD patients with PBA, memantine had a beneficial effect on involuntary emotional expression, but it potentiated agitation/aggression, irritability and caused a crucial drop of the platelet 5-HT concentration.

Tatjana Prokšelj[1], Aleš Jerin[2], Aleš Kogoj[3]

[1]General Hospital Novo mesto, Neuropsychiatric Department, Novo mesto, Slovenia; [2]Institute of Clinical Chemistry and Biochemistry, University Medical Center Ljubljana, Slovenia; and [3]University Psychiatric Hospital Ljubljana, Gerontopsychiatric Department, Ljubljana, Slovenia

Keywords: affective symptoms, aggression, emotional disturbances, memantine, serotonin

Aleš Kogoj, University Psychiatric Hospital Ljubljana, Gerontopsychiatric Department, Studenec 48, 1260 Ljubljana, Slovenia.
Tel: +386 1 5872 506; +386 1 5872 487;
Fax: +386 1 5872 590;
E-mail: ales.kogoj@psih-klinika.si

Accepted for publication December 14, 2012

First published online 24 April, 2013

Significant outcomes

- Memantine may decrease platelet 5-HT levels in Alzheimer's disease (AD) patients with pseudobulbar affect (PBA) and may worsen neuropsychiatric symptoms, especially aggression/agitation and irritability in those patients.
- The clinical importance of memantine sigma ligand properties could be revealed through these outcome findings.

Limitations

- The study had to be prematurely stopped.
- The results are therefore presented as case controls and the findings are based on a limited number of patients.

Introduction

AD is a progressive neurodegenerative disorder manifested by progressive decline in cognition and function, and the emergence of a variety of behavioural disturbances (1). Neuropsychiatric symptoms associated with AD include agitation and aggression; psychosis; mood abnormalities,

including depression, irritability and lability, anxiety; apathy; and other behavioural alterations, including disinhibition, wandering, pacing, rummaging and alterations in sleep and appetite (2).

PBA, also called involuntary emotional expression disorder (IEED), is a syndrome characterised by involuntary episodes of crying or laughing that typically occur suddenly and appear to be independent or in excess of any eliciting stimulus or the prevailing mood (3), and is seen in a significant number of patients with AD with reported prevalence rates from 10% (4), 18% (5) and up to 39% (6).

There are anatomic and functional changes in neurotransmitter systems associated with decline in cognition and development of neuropsychiatric symptoms. Cholinergic pathways are best known, but also other neurotransmitter systems including serotoninergic and glutamatergic are important (7).

The role of 5-HT in AD was investigated in post-mortem brain studies, positron emission tomography studies, neuroendocrine and pharmacotherapy studies, and also in clinical studies looking at putative peripheral markers of serotonin activity (8). Blood platelets have been proposed as an easy obtainable limited peripheral model for some processes in the central serotonergic neurons (9). The studies on platelet 5-HT concentration in AD yielded inconsistent results. The increased (10), decreased (11) or unaltered (12) platelet 5-HT concentrations were observed in AD, and furthermore no relation between platelet 5-HT concentrations and the presence of psychotic features in AD patients were found (13).

The use of citalopram was associated with greatly reduced irritability without sedation in a group of behaviourally disturbed AD patients (14), and it has also been described that citalopram was effective in treating IEED in post-stroke patients (15).

Memantine, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, with moderate affinity and rapid voltage-dependent kinetics, which regulates elevated concentrations of glutamate (16), is approved by the US Food and Drug Administration (US FDA) and by the European Medicines Agency for the treatment of moderate to severe AD. The efficacy and tolerability of memantine have been described in a number of placebo-controlled studies, with significant benefits in global, cognitive, functional and behavioural domains, particularly aggression/agitation, irritability/lability, delusions and hallucinations, compared with placebo (17,18).

Dextromethorphan (DM) is another uncompetitive NMDA ionotropic glutamate receptor antagonist. On the basis of studies that support effectiveness in patients with underlying amyotrophic lateral sclerosis (19) or multiple sclerosis (20), DM in combination with quinidine (DM/Q) recently became the only drug (Nuedexta) approved by the US FDA for treating PBA characterised by sudden outbursts of involuntary emotional displays. DM is also a sigma-1 receptor agonist; however, the mechanism of its action on improving PBA remains uncertain and it has never been studied in patients with AD (21,22).

As memantine possesses similar NMDA glutamate receptor activity as DM, we hypothesised that memantine also improves PBA owing to stabilisation of glutamatergic neurotransmission. To exclude the action on improving PBA via serotoninergic neurotransmission, platelet serotonin concentrations were measured.

Aims of the study

Although memantine possesses similar NMDA glutamate receptor activity compared with DM, the effectiveness on PBA has not been studied yet. In the present study, we intended to evaluate the efficacy of memantine on PBA in patients with AD.

Materials and methods

Patients were enrolled and treated between October 2008 and December 2011 at University Psychiatric Hospital Ljubljana in a prospective, double-blind, case-control study.

The study protocol and consent forms were approved by the institutional review boards and The National Medical Ethics Committee of the Republic of Slovenia. Informed consent of the patients and their caregivers was obtained following the principles outlined in the Declaration of Helsinki.

The entry criteria for study included clinical diagnosis of AD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) (23) and clinical diagnosis of probable or possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke/AD and related disorders association (NINCDS–ADRDA) criteria (24). Patients were included if they met recently proposed diagnostic criteria for IEED (3) and scored 2 or 3 on item 2 (assessing the frequency of crying episodes), item 13 (assessing loss of voluntary control of emotions during episode) and item 18 (assessing distress and embarrassment associated with the episodes) of the pathological laughter and crying scale (PLACS) (25) with a total score $\geqslant$13.

PLACS is an interviewer-rated instrument that measures the severity of IEED symptoms (higher scores indicating greater severity), and has been validated in stroke patients. The scale begins with two screening questions asking whether the respondent has experienced laughing or crying episodes,

https://doi.org/10.1017/neu.2013.14 Published online by Cambridge University Press

following by 16 items (eight assessing pathological laughter and eight pathological crying), which are scored from 0 to 3 points (25).

In addition, we were observing other behavioural changes assessed with Neuropsychiatric Inventory (NPI) (26) and the Overt Aggression Scale-Modified (OAS-M) (27). Furthermore, we were measuring the platelet serotonin (5-hydroxytryptamine, 5-HT) concentrations. Global cognitive abilities were assessed with Slovenian version of mini mental state exam (MMSE) (28).

Patients with prior or current history of major psychiatric disturbances, coexistent systemic disease or abnormal hematological, hepatic and renal function tests that would interfere with interpretation of the results of the study were excluded. Patients were not allowed to take antidepressants, and the treatment with other drugs must have been established at least 1 month before enrolment and had to be maintained at a constant dose throughout the study.

Patients were to be excluded from the study if disruptive side effects or worsening of psychiatric or other medical condition were noticed.

Effects of memantine were compared with efficiency of citalopram.

Memantine or citalopram was administered randomly, each for 10 weeks (including titration) with a 6-week washout period. Dosing of memantine initiated at 5 mg daily and titrated up in weekly steps of 5 mg daily to a final dose of 20 mg daily. Citalopram final dose was also 20 mg. Memantine and citalopram tablets are of the same colour and size and were administered crushed. The person administering drugs to the patients also took blood samples for measuring platelet 5-HT levels before and after taking memantine. He was excluded from the evaluating process. The assessors and the patients were blind to the study drug.

Blood samples for measuring platelet 5-HT levels were taken in the morning and the heparinised plasma samples were assayed at Institute of Clinical Chemistry and Biochemistry, University Medical Center Ljubljana.

Blood samples were collected in the tubes containing EDTA. Platelet-rich plasma was obtained after centrifugation at 1000 g, and the concentration of platelets in plasma samples was measured using Coulter Hmx hematology analyser (Beckman Coulter Inc., Brea, CA, USA). Platelets were separated from plasma by centrifugation and stored at −20°C until analysis.

After thawing, the material was dispensed in saline and centrifuged. The concentration of serotonin was measured in supernatant using ELISA (GenWay Biotech Inc., San Diego, CA, USA). The results were expressed as the amount (pmol) of serotonin in 10^9 platelets.

The primary efficacy variables were based on the change in the PLACS score and number of episodes of involuntary crying or laughing per week. Second efficacy variable was change in platelet 5-HT concentrations after taking memantine and the additional efficacy variables were changed on the NPI and OAS-M. The assessments were obtained before and after the study drug was administered.

The comparison between the groups was made by paired *t*-test. The level of significance was set at $p < 0.05$.

Results

Four patients (two women and two men) from 75 to 81 years of age (average 78 ± 2.9) were included before premature stop of study. All but one already had severe cognitive decline with MMSE 4 to 20 (average 10 ± 6.8).

All four included patients were diagnosed having PBA with PLACS total score ranging from 14 to 30 (average 20.8 ± 7.6), with predominated crying episodes (only one woman having both crying and some laughing episodes). Two patients (one woman and one man) expressed verbal and physically aggressive behaviour assessed with OAS-M total score 9 and 52, respectively (average 30.5 ± 30.4). Neuropsychiatric disturbances were observed in three patients ranging from 6 to 15 total score on NPI (average 11 ± 4.6), one including irritability/lability and the other two also expressing agitation/aggression and aberrant motor behaviour (wandering and rummaging).

Both memantine and citalopram decreased the number of episodes of involuntary emotional expression per week as well as PLACS total scores ($p < 0.05$; Table 1). No deterioration of behavioural symptoms and aggressiveness was noticed in patients receiving citalopram. Crucial behavioural changes occurred in three out of four patients taking memantine. Three patients became more aggressive, assessing with a significant increase on OAS-M total scores to an average of 3.5 times higher scores compared with the initial value. One of them was without previous aggressive behaviour. NPI total scores were significantly increased for 114% of the initial value on average ($p < 0.05$). In those three patients, irritability and aberrant motor behaviour (wandering and rummaging) became more expressed, and furthermore lability of quickly alternating mood changes, disinhibition and alterations in appetite occurred (two patients expressed binge eating and overeating and one patient disregarding to eat). In the woman with coexisting involuntary episodes of crying and laughing episodes, behavioural chances did not occur (Table 1).

Therefore, by all ethical means, we were forced to stop our study because of deterioration of behavioural

https://doi.org/10.1017/neu.2013.14 Published online by Cambridge University Press

Table 1. Summary of efficacy results

	Memantine					Citalopram			
ID	d_NPI*	d_OAS-M**	d_eIEE/w*	d_PLACS*	d_5HT*	d_NPI**	d_OAS-M**	d_eIEE/w**	d_PLACS*
1	12	35	0	−4	−45	3	−6	−14	0
2	0	0	−14	−11	−224	0	0	−8	−11
3	24	250	−28	−14	−1089	−4	−3	−32	−21
4	22	98	12	16	146	/	/	/	/

ID = patients' identification number.

d_NPI = change (difference) of scores on Neuropsychiatric Inventory Scale after taking the study drug.

d_OAS-M = change (difference) of scores on Overt Aggression Scale-Modified after taking the study drug.

d_PLACS = change (difference) of scores on Pathological Laughter and Crying Scale after taking the study drug.

d_eIEE/w = change (difference) in number of episodes of involuntary emotional expression (crying or laughing) per week after taking the study drug.

d_5HT = change (difference) of platelet serotonin concentration after taking memantine.

*$p < 0.05$ (paired t-test); **not significant ($p > 0.05$).

symptoms and our results were presented as a case controls

Memantine crucially decreased platelet 5-HT concentration in three out of four patients to an average 73% of initial value [from an average 617 ± 538 to an average 165 ± 20 pmol/(10^9 platelets); $p < 0.05$].

Discussion

Memantine alleviated involuntary emotional expression in our study; however, severe deterioration of other behavioural symptoms in AD patients with PBA was noticed, although memantine is known to generally improve behavioural disturbances in patients with AD, particularly aggression/agitation and irritability/lability (17,18).

Three patients became more aggressive, of those one without previous aggressive behaviour. In all three patients, irritability and aberrant motor behaviour (wandering and rummaging) became more expressed, and furthermore lability of quickly alternating mood changes, disinhibition and alterations in appetite occurred (two patients expressed binge eating and overeating and one patient disregarding to eat) without any mentioned preexisting disturbances.

In two out of three described patients, changes of mood and alternations in appetite coincided with a significant drop of platelet 5-HT concentration, which is known to have an important role in mood disturbances and aggressive behaviour (8). In the woman with coexisting involuntary episodes of crying and laughing, behavioural changes did not occur, although the platelet 5-HT drop was reported.

Besides its action on glutamatergic neurotransmitter system, memantine acts also as a non-competitive antagonist at the 5-HT3 receptor (29), as well as inhibit the reuptake of both 5-HT and dopamine in mouse forebrain (30). It was also described that memantine was as effective as escitalopram in reducing the baseline level of depression and anxiety in major depressive disorder in patients with comorbid alcohol dependence (31). To determine the overall effect of memantine on serotoninergic neurotransmitter system, platelet 5-HT concentration was measured. The vast extent of decrease of 5-HT concentration in our patients may explain the deterioration of behavioural symptoms.

The significant platelet 5-HT concentration drop and behavioural disturbances could be explained by sigma receptor ligands modulating 5-HT neurotransmission. In an *in vivo* study on animal models, Bermack and Debonnel found that the sigma ligands induce a significant effect on the firing activity of 5-HT neurons of the dorsal raphe nucleus (DRN), which was increased by more than 50%. The sigma ligands demonstrated the fast onset of action, producing increased serotoninergic activity in the DRN after only 2 days of treatment. Throughout their findings they were suggesting that sigma agonists have the potential to produce a fast onset of antidepressant effect, which could be mediated locally in the DRN, or indirectly via feedback loops (32).

The behavioural changes in our patients occurred quickly in less than 1 week after taking low doses (5–10 mg/day) of memantine, which is similar to the rapid onset of action seen in the studies by Bermack and Debonnel. This furthermore supports the suggestion that behavioural changes in our patients could be due to the mechanism of action via sigma receptors sites that modulates serotoninergic transmission. As memantine's sigma properties have not been clearly revealed yet, our research findings support Stahl's description of memantine having sigma-antagonism properties (33), according to the modulation of serotoninergic transmission.

Sigma ligands can also modulate NMDA-mediated glutamatergic neurotransmission via sigma-1 receptors (in a bell-shaped dose-response curve manner) (32). By recent data based on the DM mechanism of action, the main role for improving IEED is stabilising

https://doi.org/10.1017/neu.2013.14 Published online by Cambridge University Press

glutamatergic activity via NMDA receptors antagonism and sigma-1 receptors agonism (19,20).

In our study, memantine decreased platelet 5-HT concentration and had a crucial effect on behavioural changes, but it had a beneficial effect on PBA. That finding excludes regular pathways via serotoninergic neurotransmitter system in PBA and supports the importance of glutamatergic neurotransmitter system and sigma receptors. Citalopram's potency for the subtypes of sigma receptors has been proved in research on rat brain (34), giving possible explanation of its effect on improving PBA, regardless of its action on serotoninergic pathways. Reports on citalopram's efficiency on improving PBA, with relatively low doses, within few days after the initiation of treatment (15,35,36), much sooner than it would be expected for an antidepressant effect, already suggested that this improvement must be because of some other pathways than those via 5-HT receptors, and supports the possibility of the mechanism of action via sigma receptor agonism. On the other hand, the improvement of neurobehavioural changes in AD patients in <12 weeks after treatment with memantine given in maximum therapeutic doses has not been observed; however, there were no studies on AD patients with PBA (16–18). As in our study memantine has shown the alleviation of PBA, improving of PBA could be explained by the mechanism of action similar to DM, which is stabilising glutamatergic neurotransmission by NMDA receptors antagonism and sigma-1 receptors agonism.

Memantine's benefit on improving PBA supports the data that indicate that the main mechanism of pathophysiology PBA refers to glutamatergic neurotransmission, possible via sigma agonism (19,20). Although memantine is effective in many patients with AD, our finding suggests that there may be some subgroups of AD patients with specific behavioural symptoms and specific underlying neuroanatomical disruption in which memantine lacks favourable outcome.

Our study was planned as a double-blind, cross-over study. Owing to a premature ending, findings are based only on a limited number of case-controlled patients. More investigations should be made to reveal the cause of our findings and strengthen our suggestions of memantine's action.

Acknowledgements

The authors thank Prof. Milan Skitek, Eur. Clin. Chem. for approving the implementation of the biochemical analysis carried out on Institute of Clinical Chemistry and Biochemistry, University Medical Center Ljubljana which provided the material and needed equipment.

Authors' contributions

Tatjana Prokšelj's contribution as the first author includes the conception and design of the study, analysis and interpretation of all data, drafting the article and the final approval for the version to be published.

Aleš Jerin's contribution refers to laboratory measurements of platelet 5-HT concentration regarding the design of the methodology, revealing the data and drafting this part of the article.

Aleš Kogoj's contribution refers to the mentorship of the great value helping in making conception and study design, critically revising the data interpretations and overall revising the article for the final approval of the version to be published with important intellectual content.

Potential conflicts of interest

All authors have no potential conflicts of interest to declare.

References

1. Cummings JL, Cole G. Alzheimer disease. JAMA 2002;**287**: 2335–2338.
2. Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;**46**:130–135.
3. Cummings JL, Arciniegas DB, Brooks BR et al. Defining and diagnosing involuntary emotional expression disorder. CNS Spectr 2006;**11**:1–7.
4. Lieberman A, Benson F. Control of emotional expression in pseudobulbar palsy. Arch Neurol 1977;**34**:717–719.
5. Tanaka M, Sumitsuji N. Electromyographic study of facial expression during pathological laughing and crying. Electromyogr Clin Neurophysiol 1991;**31**:399–406.
6. Starkstein SE, Migliorelli R, Tesón A et al. Prevalence and clinical correlates of pathological affective display in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1995; **59**:55–60.
7. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron 1991;**6**:487–498.
8. Lanctôt KL, Herrmann N, Mazzotta P. Role of serotonin in the behavioral and psychological symptoms of dementia. J Neuropsychiatry Clin Neurosci 2001;**13**:5–21.
9. Camacho A, Dimsdale JE. Platelets and psychiatry: lessons learned from old and new studies. Psychosom Med 2000;**62**:326–336.
10. Meszaros Z, Borsiczky D, Mate M et al. Platelet MAO-B activity and serotonin content in patients with dementia: effect of age, medication and disease. Neurochem Res 1998; **23**:863–868.
11. Kumar AM, Sevush S, Kumar M, Ruiz J, Eisdorfer C. Peripheral serotonin in Alzheimer's disease. Neuropsychobiology 1995;**32**:9–12.
12. Mimica N, Muck-Seler D, Pivac N, Mustapic M, Folnegovic-Smalc V. Platelet serotonin and monoamine oxidase activity in patients with early-onset and late-onset of Alzheimer's disease. Period Biol 2005;**107**: 211–215.

https://doi.org/10.1017/neu.2013.14 Published online by Cambridge University Press

13. Mimica N, Muck-Šeler D, Pivac N et al. Platelet serotonin and monoamine oxidase in Alzheimer's disease with psychotic features. Coll Antropol 2008;**32**:119–122.
14. Siddique H, Hynan LS, Weiner MF. Effect of a serotonin reuptake inhibitor on irritability, apathy and psychotic symptoms in patients with Alzheimer's disease. J Clin Psychiatry 2009;**70**:915–918.
15. Andersen G, Vestergaard K, Riis JO. Citalopram for post-stroke pathological crying. Lancet 1993;**342**:837–839.
16. Parsons CG, Danysz W, Quack G. Memantine is clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist – a review of preclinical data. Neuropharmacology 1999;**38**:735–767.
17. Van Dyke CH, Tariot PN, Meyers B, Malca Resnick E. A 24-week randomized controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord 2007;**21**:136–143.
18. Gauthier S, Loft H, Cummings J. Improvement in behavioral symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. Int J Geriatr Psychiatry 2008;**23**:537–545.
19. Brooks BR, Thirsted RA, Appel SH et al. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. Neurology 2004;**63**:1364–1370.
20. Panitch HS, Thisted RA, Smith RA et al. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. Ann Neurol 2006;**59**:780–787.
21. Torella FC, Pellicano M, Bowery NG. Dextromethorphan and neuromodulation: old drug coughs up new activities. Trends Pharmacol Sci 1989;**10**:501–507.
22. Rogawski MA. Low affinity channel blocking (uncompetitive) NMDA receptor antagonists as therapeutic agents toward an understanding of their favorable tolerability. Amino Acids 2000;**19**:133–149.
23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC: American Psychiatric Association, 2000.
24. Mckhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health & Human Services Task Force on Alzheimer's disease. Neurology 1984;**34**: 939–944.
25. Robinson RG, Parikh RM, Lipsley JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. Am J Psychiatry 1993;**150**:286–293.
26. Cummings JL, Mega M, Gray K, Rosenberg-Tompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;**44**:2308–2314.
27. Coccaro EF, Harvey PD, Kupsaw-Lawrence E, Herbert JL, Bernstein DP. Development of Neuropharmacologically based behavioral assessments of impulsive aggressive behaviour. J Neuropsych Clin Neurosci 1991;**3**:S44–S51.
28. Rakusa M, Granda G, Kogoj A, Mlakar J, Vodusek DB. Mini-mental state examination: standardization and validation for the elderly Slovenian population. Eur J Neurol 2006;**13**:141–145.
29. Rammes G, Rupprecht R, Ferrari U, Zieglgänsberger W, Parsons CG. The N-methyl-D-aspartate receptor channel blockers memantine, MRZ 2/579 and other amino-alkyl-cyclohexanes antagonize 5-HT(3) receptor currents in cultured HEK-293 and N1E-115 cell systems in a non-competitive manner. Neurosci Lett 2001;**306**:81–84.
30. Onogi H, Ishigaki S, Nakagawasai O et al. Influence of memantine on brain monoaminergic neurotransmission parameters in mice: neurochemical and behavioral study. Biol Pharm Bull 2009;**32**:850–855.
31. Muhonen LH, Lönnqvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. J Clin Psychiatry 2008;**69**:392–399.
32. Bermack JE, Debonnel G. The role of sigma receptors in depression. J Pharmacol Sci 2005;**97**:317–336.
33. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. New York: Cambridge University Press, 2008.
34. Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol 1996;**307**:117–119.
35. Van Watum PJ. Rapid response to low dose citalopram in pathological crying. Gen Hosp Psychiatry 2001;**23**:166–170.
36. King RR, Reiss JP. Treatment of pseudobulbar affect with citalopram in a patient with progressive multifocal leukoencephalopathy. J Clin Neurosci 2012;**19**:185–186.

https://doi.org/10.1017/neu.2013.14 Published online by Cambridge University Press