AGOMELATINE AS A NOVEL THERAPEUTIC OPTION IN THE TREATMENT OF APATHY

I. Callegari[1], C. Mattei[2], F. Benassi[3], F. Krueger[4], C. Serrati[5], L. Emberti Gialloreti[6], M. Pardini[7]

1C. Mondino National Institute of Neurology Foundation, IRCCS, University of Pavia (Pavia); 2Dept. Psychiatry, National Health Service (Ancona); 3Neurorehabilitation Centre, CNAPP (Roma); 4Dept. Neuroscience, George Mason University (Fairfax-USA); 5Dept. Neurology, IRCCS S. Martino (Genova); 6Dept. of Biomedicine and Prevention, University of Rome Tor Vergata (Roma); 7Department of Neuroscience, Rehabilitation, Ophtalmology, Genetics and Maternal/Child Sciences, University of Genoa (Genova)

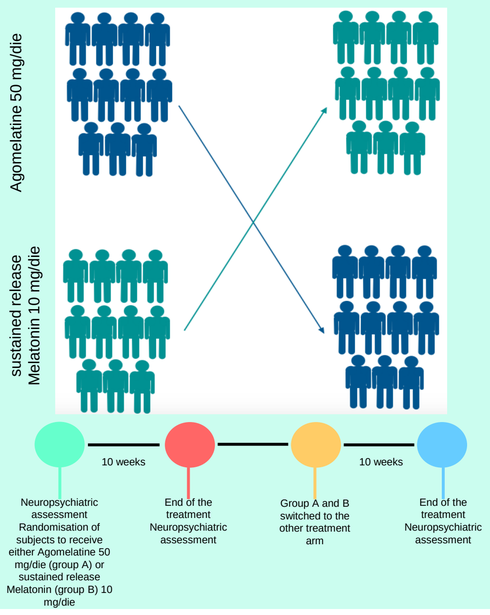
Introduction

Apathy is a disorder of motivation characterized by decline of goal-directed behaviour and flattened affect that lead to decreased interest in social, recreational, occupational and creative pursuit. Apathy is the most common initial symptom of frontotemporal dementia and is present in the majority of patients as the disease progresses. The emergence of apathy has been related to frontal-subcortical dopaminergic system dysfunction. In particular, in FTD apathy has been linked to orbitofrontal abnormalities, extending from Brodmann area 10 to the right anterior cingulate cortex with involvement of right caudate head/ventral striatum. No pharmacological therapy is approved for the treatment of apathy, but based on its physio-pathological basis, increasing prefrontal dopaminergic innervation could improve apathy symptomatology.

Aims of the study

Here we verified the effectiveness of Agomelatine, an antidepressant with MT1 and MT2 receptor agonism and 5HT2C receptor antagonism actions, the latter leading to an increase in prefrontal dopaminergic and noradrenergic tone, in the treatment of apathy in a group of FTD subjects.

Methods



Inclusion Criteria

- number of subjects: 22
- age between 50 and 65
- less than one year of disease duration
- no other relevant medical, neurological or psychiatric co-morbidities
- negative history for depression
- normal liver function
- in therapy with Memantine but with no other psychoactive compound
- with at least 10 years of formal education
- currently living with their primary caregiver
- a neuropsychiatric inventory, depression subscore less than 4
- a Apathy Evaluation Scale, Clinician (AES-C) version score of at least 42

Neuropsychiatric scales

- Frontal Assessment Battery (FAB)
- Neuropsychiatric Inventory (NPI)
- Apathy Evaluation Scale Clinician version (AES-C)
- Frequency Intensity and Burden of Side Effects Ratings (FIBSER)

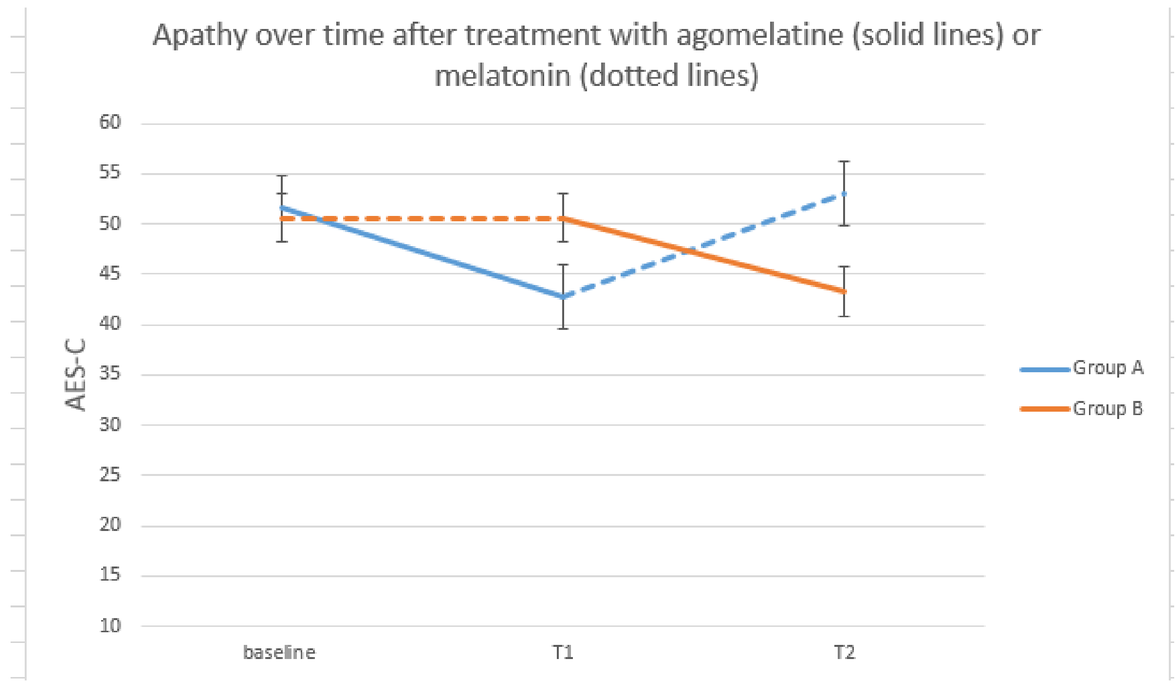
Results

Agomelatine was well tolerated and all patients were able to complete the study, with no drop out for intolerance or appearance of adverse reactions.

There was a significant interaction of treatment arm with AES-C scores ($F=10.7$, $p<0.001$). Treatment with Agomelatine was associated with a significant decrease in AES-C scores ($p<0.005$).

Treatment with Melatonin from baseline was not associated with a significant change in AES scores ($p=0.451$), while the switch from melatonin to Agomelatine was associated with a significant increase in AES-C scores (group B: 44.9 7.4 vs. 49.4 4.4, $p=0.009$)

Results were not materially different when corrected for NPI-D scores.



Longitudinal changes in Apathy Evaluation Scale, Clinician (AES-C). Solid line represents therapy with Agomelatine; dotted line represents placebo. Circles represent data point for group A; squares represent data points for group B.

Discussion

We assessed the effectiveness of Agomelatine in the treatment of apathy in bvFTD. Treatment with Agomelatine was associated with a significative improvement of apathy, as demonstrated by the decrease of AES-C in the treatment arm. Patients receiving Melatonine did not exhibit any significative change in their neuropsychiatric symptoms, thus demonstrating that Agomelatine effectiveness relies on its 5HT2C receptor antagonism, leading to increased dopamine and norepinephrine release in prefrontal cortex.

Take home messages

- Agomelatine reduces apathy in FTD patients
- Treatment with Agomelatine is well tolerated

References

1. R. Levy, B. Dubois, Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cerebral Cortex (2006);16:916:928
2. P. J. Eslinger, P. Moore, S. Antani, C. Anderson, M Grossman, Apathy in frontotemporal dementia: Behavioral and neuroimaging correlates. Behavioral Neurology (2012);25(2): 127-136
3. M. Pompili, G. Serafini, M. Innamorati, P. Venturini, P. Fusar-Poli, L. Sher, M. Amore Agomelatine, a novel intriguing antidepressant option enhancing neuroplasticity: a critical review. The World Journal of Biological Psychiatry (2013);14:412-431