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Agomelatine in Elderly – Finally a Patient Friendly Antidepressant In Psychogeriatry?

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Background: Geriatric depression is a serious psychiatric conditions with prevalence from 10–40% in community living seniors. Polymorbidity and potential vulnerability of seniors towards medication is a challenge for seeking newer, well tolerated antidepressant with good clinical efficiency and safety. Agomelatine is new promising antidepressant which could fulfill these criteria.

Objective: Evaluation of effectiveness, safety and side effects of agomelatine used for treatment senior patients with major depression hospitalized in inpatient psychogeriatric ward in Mental hospital in Kromeriz (2010-2011).

Methods: Psychiatric scales Montgomery-Asberg Depression Scale (MADRS) and Clinical Global Impression (CGI) were used initially before starting with agomelatine treatment, then after 4 and 8 weeks and finally after 12 weeks of using agomelatine. Potential side effects caused by agomelatine (side effects according AISL databasis– Automatized Information system of Registered Drugs in the Czech republic) were monitored after 12 weeks of treatment with agomelatine.

Results: While treating major depression in seniors with agomelatine, decrease in Montgomery-Asberg Depression Scale (MADRS), Clinical Global Impression scale (CGI) was evident after 4 weeks of treatment and continued constantly after 8 and 12 weeks of treatment. Clinical remission was achieved in all studied patients.

Conclusion: Agomelatine proved excellent efficiency in treating severe major depression in seniors with no serious averse effects.

Key words: Agomelatine, MASSA antidepressant, Major depression, Seniors, Montgomery-Asberg Depression Scale (MADRS), Clinical Global Impression scale (CGI), Side effects

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Agomelatina en el anciano – ¿Un antidepresivo apropiado para el paciente de psicogeríatría?

Introducción. La depresión geriátrica es una condición psiquiátrica grave con una prevalencia de 10–40% en mayores que viven en comunidad. La multiple comorbilidad y la vulnerabilidad potencial de los mayores a la medicación es un desafío para la búsqueda de antidepresivos novedosos bien tolerados con una seguridad y eficacia clínica apropiadas. La agomelatina es un antidepresivo nuevo que podría cumplir estos criterios.

Objetivos. Evaluar la efectividad, seguridad y efectos secundarios de la agomelatina usada en el tratamiento de pacientes ancianos con depresión mayor hospitalizados en una unidad de psicogeriatría en el hospital mental de Kromeriz (2010-2011).

Método. Se usaron las escalas psiquiátricas *Montgomery-Asberg Depression Scale* (MADRS) y *Clinical Global Impression* (CGI) antes de comenzar con el tratamiento de agomelatina, a las 4 semanas, a las 8 y finalmente a las 12 semanas de uso de la agomelatina. Los posibles efectos secundarios causados por la agomelatina (efectos secundarios según la base de datos AISL–*Automatized Information system of Registered Drugs*, sistema de información automatizada de fármacos registrados en la República Checa) se monitorizaron tras 12 semanas de tratamiento con agomelatina.

Resultados. Al tratar con agomelatina la depresión mayor de los ancianos, se evidenció un descenso en la puntuación de las escalas Montgomery-Asberg Depression Scale (MADRS) y Clinical Global Impression (CGI) a las 4 semanas de tratamiento y continuó decendiendo a las 8 y las 12 semanas. La remisión clínica se obtuvo en todos los pacientes del estudio.

Conclusión. La agomelatina ha demostrado una eficiencia excelente en el tratamiento de la depresión mayor grave en ancianos sin efectos adversos graves.

Palabras claves: Agomelatina, Antidepresivos MASSA, Depresión mayor, Ancianos, Montgomery-Asberg Depression Scale (MADRS), Clinical Global Impression scale (CGI), Efectos secundarios

INTRODUCTION

Depression in elderly is not a rarity. On contrary, estimations of prevalence of major depression range from 10 - 40% in seniors living in community[1] to 50-60% of institutionalized seniors[2]. Depression in elderly is often masked by presence of somatic diseases which have usually priority in treatment.[3] Complains about mood, apathy, lacrimosity, suicidal ideations or anhedonia are usually misinterpreted as common part of senescence in routine practice, what is leasing to underdiagnosing or undiagnosing the major depression.[4] However, all the symptoms mentioned above are patognomic for depression and are involved in diagnostic criteria for depression.[4, 5]

Agomelatine is a new antidepressant from melatonin agonist and selective serotonin antagonist group (MASSA antidepressant). It acts as an agonist on melatonine receptors of MT1, MT2 and MT3 type,[6, 7] moreover, agomelatine reveals antagonistic activity on serotonine receptors type 5-HT2C.[8] Agomelatine influences positivelly circadian rhythmicity thanks to its melanotropic action, it improves sleep disturbances in physiological way without damane to sleep architecture.[9, 10] Agomelatine has no afinity to alpha/beta adrenergic, histaminergic, dopaminergic or benzodiazepine receptors. This pharmacological profile makes agomelatine comfortable, patient friendly antidepressant with selective antidepressive and hypnotic effect and with low prevalence of side effects at the same time.[8, 11] Historically, the research of new melanotropic antidepressants started with melatonine, which has been used as a hypnotik in clinical practice.[6] Later, first melatoninergic antidepressants have been synthetized: agomelatine, ramelteon and tasimelteon.[12] Among these compounds, only agomelatine is approved for treating the major depression in the Czech republic nowadays.[11] Compared to conventional antidepressants, agomelatine is relatively safe antidepressant, which is weight neutral, does not affect sexual functionning and does not cause discontinuation syndrome.[7] The contraindication of agomelatine are interactions with concomitantly used fluvoxamine and ciprofloxacine, further liver cirhosis or any other acute liver disease in a patient.[11] Agomelatine is metabolized via CYP1A2 liver enzymes to inactive metabolites which are excreted by urine.[8,11] The dosage of agomelatine should respect individuality of a patient, tolerability by a patient, severity of depression and changes in psychopatology. Initial (and efficient) dosage is 25 mg of agomelatine administered in the late evening, two hours before patients going sleeping.[13] This dosage might be increased to 50 mg daily.[14, 15]

Agomelatine is used for treating major depressions in adult patients, although some authors have observed auxilliary anxiolytic effects of agomelatine.[8, 16] In psychogeriatry, no systematic research on agomelatine in treating senior depression has been done, hence, agomelatine is still seeking its position among antidepressants in psychogeriatry.[9] Worldwide clinical experience in treating senior depression with agomelatine is reduced to case reports or pilot studies,[17-19] hence further research in this field is required.

METHODS

Subjects: 23 patients who have been hospitalized for major depression (first episode) in inpatient psychogeriatric ward in Mental hospital Kroměříž, Czech republic, in years 2010-2011. All the subjects fulfilled diagnostic criteria for major depression according to the DSM-IV, all of them had the first depressive episode. Diagnosis of major was settled by trained psychogeriatrist. All the subjects agreed in participation in the researched. All the subjects were 65 years of age and older. All the subjects were actually treated with agomelatine in for the first time. All the subjects agreed with participation in research. No ethical or financial hazard connected with this research is known to the author of the study.

Design of study: naturalistic observatory study.

Method of study: psychiatric scales Montgomery-Asberg Depression Scale (MADRS) and Clinical Global Impression scale (CGI) were used initially before starting with agomelatine treatment, then after 4 and 8 weeks and finally after 12 weeks of using agomelatine.

Montgomery-Asberg Depression Scale (MADRS) is a psychiatric scale which evaluates severity of depression. This scale has 10 items, each item can be scored from 0 to 6 points according to the severity of depressive symptoms. The maximal score is 60 (showing the most severe depression), the minimal score is 0 (absence of clinical symptoms of depression). Mild depression in MADRS is above 15 points, moderate depression is above 25 points, severe depression is above 31 points and very severe depression is above 44 points.[20] Clinical Global Impression scale (CGI) estimates severity of mental disorder according clinical appearance of a patient. It has 3 items, which may be scored from 1 to 7 points (first and second item), the third item can be scored from 0 to 4 points. The maximal score is 14 (the worst clinical impression, very severe clinical picture of a mental disorder), the minimal score is 2 (the best clinical impression, recovery).

Potential side effects caused by agomelatine (side effects according AISL databasis-Automatized Information system of Registered Drugs in the Czech republic) were monitored after 12 weeks of treatment with agomelatine.

Evaluation of data: Excel program was used for descriptive statistical evaluation of the data.

Table 1 Changes in Psychopathology

	Dosage+	MADRS*	MADRS**	MADRS***	MADRS****	CGI*	CGI**	CGI***	CGI****
Mean	**36.5**	**32.2**	**25.5**	**17.6**	**11.4**	**11.2**	**8.1**	**6.0**	**3.7**
SD	10.4	4.5	5.4	5.6	4.9	3.3	2.5	2.1	1.6

+ daily dosage of agomelatine in miligrams which has been use. SD: standard deviation. * initially; ** after 4 weeks; *** after 8 weeks; *** after 12 weeks. MADRS: Montgomery-Asberg Depression Scale (total score). CGI: Clinical Global Impression (total score)

RESULTS

The research has involved 23 senior patients at the age 65 and older. As for gender representation, 5 patients were men and 18 patients were women. The mean age was 67.8 years (standard deviation 1.4 years). The mean lenght of hospitalization was 94.5 days (standard deviation 9.8 days). The mean daily dosage of agomelatine which has been used for treatment major depression was 36.5 miligrams (standard deviation 10.4 miligrams).

According to initial MADRS score (mean=32.2), all patients had severe depression. Four weeks after the treatment with agomelatine the MADRS score has decreased to moderate depression (mean=25.5), eight weeks after the treatment with agomelatine the MADRS score has further decreased to mild depression (mean=17.6). After twelve weeks of treatment with agomelatine the MADRS score was 11.4 (unsignificant symptomatology). According to initial CGI score (mean=11.2), the depression in patients could be interpreted as severe depression. Four weeks after the treatment with agomelatine the CGI score has decreased (mean=8.1), eight weeks after the treatment with agomelatine the CGI score has further decreased (mean=6.0). After twelve weeks of treatment with agomelatine the CGI score was 3.7 (unsignificant symptomatology).

In general, while treating major depression in seniors with agomelatine, decrease in Montgomery-Asberg Depression Scale (MADRS), Clinical Global Impression scale (CGI) was evident after 4 weeks of treatment and continued constantly after 8 and 12 weeks of treatment. Clinical remission was achieved in all studied patients (table 1).

In accordance with AISL databasis – Automatized Information system of Registered Drugs in the Czech republic – the prevalence of side effects of agomelatine was estimated. All of the potential side effects were bellow 10%, the most often side effect of agomelatine was sedation (2 patients, 8.7%) followed by gastrointestinal dyscomfort (1 patient, 4.3%) and nausea (1 patient, 4.3%). Other side effects were not detected in studied group of patients who have been using agomelatine (table 2).

DISCUSSION

Agomelatine showed good clinical efficiency (expressed by constant decrease in score in psychiatric scales MADRS and CGI) in studied group of seniors with major depression. Initially, all the patients had severe depressive episode of major depression. After 12 weeks of treatment with agomelatine, mean score in MADRS and mean score in CGI showed recovery of treated patients from depressive episode. This result is comparable to other worldwide research in adult patients with depression.[14, 21]

All the 23 patients completed the treatment with agomelatine, no one had to discontinue in agomelatine treatment because of side effects of absence of clinical effect.

Side effects of agomelatine were not frequent and if any, they were mild. This finding is in accordance with other authors.[7, 23]

Sedation, nausea and gastrointestinal dyscomfort were rarely detected, the frequency of these side effects was bellow 10%, this finding is in accordance with literature.[7]

The size of sample is the limit of the study, however, the worldwide research of agomelatine used for treating major depression in psychogeriatric patients is limited to case reports or pilot studies and doesn´t exceed this limitation. Despite this fact agomelatine proved excellent efficiency in treating severe major depression in seniors with no serious averse effects.

CONCLUSION

Agomelatine is a new primising antidepressant with unique pharmacological profile. Agomelatine seems to be potent antidepressant and efficient in treating severe major depression, with little or no serious averse effects. This makes agomelatine interesting for psychogeriatry, where polymorbidity of seniors together with increased sensitivity to side effects is very often.

Table 2 Side effects monitoring

	Nausea	Vertigo	Sedation	Insomnia	Cephalea	GIT	Sweating	Fatigue	Liver
n	1	0	2	0	0	1	0	0	0
%	4.3	0.0	8.7	0.0	0.0	4.3	0.0	0.0	0.0

N: absolutely. %: relatively. GIT: gastrointestinal dyscomfort. Liver: 200% increase in serum levels of liver transaminases (ALT, AST) in comparison with initial values

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