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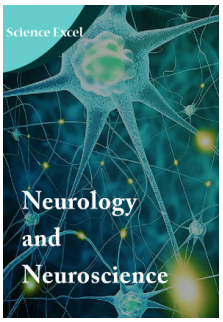

Noradrenergic Modulation and a Treatment Algorithm for Behavioral Symptoms in Patients with Late Life Dementia

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Abstract

Introduction: *Patients affected by neurodegeneration disorders (NDD) often experience difficult to treat disruptive neuropsychiatric symptoms (NPS) i.e. verbal disruption, aggression, psychomotor hyperactivity, sleep difficulties, hallucinations, delusions. The existing treatment algorithms include antipsychotics, gabapentin, trazodone, prazosin, memantine, cholinesterase inhibitors.1,2 Some NPS i.e. anxiety, agitation, aggression, disturbed sleep have been linked to overactivity of the brain noradrenergic system (NAS). The current report suggests a treatment algorithm which includes a method of noradrenergic modulation (NAM).* ***Aims of the study****: A. To evaluate a new treatment algorithm for patients with NPS and late life dementia. B. To evaluate the method of NAM in treatment of NPS.* ***Participants and Methods:*** *Nine elderly community dwelling patients (3 males and 6 females) with probable Alzheimer's dementia and NPS. Age of the patients 71-104 years (86.9, SD 9.4), 4 patients with moderate and 5 patients with severe dementia. Treatment algorithm includes 5 steps and two pathways. Each step is evaluated on the clinical global impression of change (CGI-C) scale. The psychosis pathway (4 patients) begins with an antipsychotic, the alternative pathway (5 patients), with low dose gabapentin (GBP). The psychosis pathway, if ineffective, can switch to the alternative pathway with the add-on of GBP. The alternative pathway proceeds with addition of NAM which includes alpha-1 receptor antagonists (prazosin, doxazosin) and alpha-2 receptor agonists (transdermal clonidine, guanfacine).* ***Results:*** *Treatment was well tolerated. Substantial (7 patients) and moderate (2 patients) improvement in disruptive behaviors such as agitation, aggression, sleep was reflected on the CGI-C scale (score 1.2, SD 0.4), on the Cohen-Mansfeld Agitation Inventory (the score decreased from 52.6, SD 27.0 to 18.6, SD 7.9) and on the de novo introduced VAPS scale (from 8.7, SD 0.4 to 2.7, SD 0.8). The final step of the algorithm, method of NAM was the "game changer" in both psychosis and non-psychosis alternative pathways.* ***Conclusion:*** *The case series provides preliminary evidence supporting the suggested approach to treatment of NPS in patients with late life dementia.*

Introduction

Patients affected by neurodegeneration disorders (NDD) often experience difficult to treat neuropsychiatric symptoms (NPS) i.e. verbal disruption, aggression, psychomotor hyperactivity, sleep difficulties, hallucinations, delusions. Treatment of NPS is difficult because neurodegeneration creates chaos and limits targets for interventions. The existing treatment algorithms include pharmaceuticals of various classes, for instance gabapentin, trazodone, prazosin, memantine, cholinesterase inhibitors [1,2]. Rexulti (brexpiprazole) is the first drug approved by the FDA for the treatment of agitation in patients with Alzheimer's dementia (AD) [3]. Symptoms of psychosis (hallucinations, delusions) are often difficult to elicit and target as triggers of behavioral symptoms. On the other hand, antipsychotics are not always well tolerated, often fail to control behavioral symptoms and carry an FDA black box warning [4]. Hence, the challenge is when to use an antipsychotic and how to proceed if it fails to control behavioral symptoms. The presented report suggests a treatment algorithm in patients with NPS and late life dementia.

Background

A brief review will focus on some aspects of neurobiology, on neurotransmitter networks and some evidence of modulating these systems.

Glutamate (GLU) is the major excitatory neurotransmitter, essential in cognitive functions [5]. However, it is also guilty of excitotoxicity, damage and death of neurons. The excitotoxicity occurs with errors in its metabolism, malfunctions of the glia [6] On the other hand, gamma amino butyric acid

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(GABA) is the major inhibitory and protective neurotransmitter [7] Malfunction of the GABAergic neurons negatively affects cognition [8] and is associated with agitation in patients with dementia [9,10]. Gabapentin (GBP) [11], one of the pharmaceuticals in the existing algorithms [1], was used in multiple case series in patients with various types of dementia and with overall, positive outcomes. The review of this evidence is beyond the scope of this manuscript. The author of this manuscript reported positive results in patients affected by dementia with Lewy bodies [12] (DLB) and treated with low dose of GBP [13]. The authors of the study hypothesized that the behavioral improvement is mediated by the change in GLU/ GABA balance achieved by decrease in GLU and increase in GABA, a known effect of GBP [14,15].

The brain noradrenergic system (NAS) is a vast network of noradrenergic neurons originating in the locus coeruleus (LC) is connected to other types of neurons and glial cells via 9 subtypes of adrenergic receptors: 3 subtypes of alpha -1 adrenoreceptors (A1AR), 3 subtypes of alpha-2-adrenoreceptors (ATAR) and 3 subtypes of beta adrenoreceptors (β1,2,3,) [16]. The NAS modulates attention, learning, various types of memory, promotes plasticity, mediates the adaptive response to stress and adaptation in the long term [17,18]. The A1AR and the Beta -2 receptors on glial cells regulate homeostasis and glutamate metabolism protecting the neural cells from glutamate excitotoxicity, amyloid deposition [19-21].

LC is among the earliest sites affected by formation of neuro-fibrillatory tangles (NFT) in AD and synuclein in DLB [21-23]. The LC neurons, in accordance with the adaptive role and plasticity of the NAS, compensate for the damage with hyperactivity of the surviving neurons and their sprouting in the target areas i.e. prefrontal cortex (PFC) [23-25]. This hyperactivity of the NAS persists through the following progressive course of NDD [26]. At least some of the NPS, agitation, aggression, anxiety, sleep disturbances can be linked to the overactivity of the brain NAS [27-31].

The A1AR are present in the hypothalamus, hippocampus, amygdala, cortex, cerebellum [32] and are important in attention, learning, memory, neuronal plasticity [33-34]. However, overexcitation of the A1AR, for example in stressful conditions, causes cognitive impairment [35-36]. Of note, patients with dementia are always stressed by coping with information and environment. Blockade of the A1AR is a part of the complex pharmacodynamics of antipsychotics [37]. As it would be expected with any receptor, blockade of the A1AR causes its upregulation, increased density and increased affinity to NA which correlates with aggressive behavior [38]. A selective blockade of the A1AR, without interaction with other receptors i.e. dopamine, serotonin receptors, is attractive and can be achieved by using a class of selective.

A1AR antagonists such as prazosin, doxazosin, terazosin [39-40]. Prazosin is a capsule administered every 8-12 hours and doxazosin is a tablet given once daily [40]. Both the form and the half-life favor doxazosin in patients with dementia when medications might need to be crushed and adherence is an issue. Prazosin in an average dose of 6 mg was useful and well tolerated in treatment of agitation and aggression in patients with AD [41]. Prazosin is a part of existing algorithms [1,2], doxazosin has been studied in some psychiatric and neurologic disorders but other than dementia. Pharmaceuticals in the class of A1AR antagonists (terazosin, doxazosin, alfuzosin) seem to improve brain glycolysis and thus increase brain resistance against alpha – synucleinopathies [42].

The pre- and postsynaptic alpha - 2 adrenoreceptors (ATAR) also present a wide strategic network [43]. The presynaptic ATAR, located on the 1st NA neurons, function as self-control auto-receptors measuring the release of NA [44]. It is very difficult to accept the overactivity of the NAS without loss of auto - control by the pre-synaptic ATAR. The postsynaptic ATAR are crucial in attention, memory, brain connectivity, executive functions, complex adaptive responses [45-47]. Therefore, malfunction of the presynaptic ATAR leads to NAS hyperactivity and malfunction of the postsynaptic ATAR, to loss of adrenergic input and cognitive impairment. Stimulation of the ATAR surviving neurodegeneration could help to correct these malfunctions and impairments. This stimulation can be achieved by the use of ATARa, alpha-2 adrenoreceptor agonists such as clonidine, guanfacine, tizanidine [40]. Clonidine is preferably used as the transdermal delivery system (TD CLO), it provides better pharmacokinetics and assures adherence in a patient with dementia [47]. Both clonidine and guanfacine are sedating [40]. Clonidine was useful in the treatment of agitation and cognitive impairment in various disorders [48-52]. Guanfacine, approved for use in attention deficit hyperactivity disorder, was studied in AD however in relatively low daily doses, 0.5 mg [53] an 1.2 mg [54] and had no effect on cognition. It was however useful in treatment of agitation in elderly patients [55] and in treatment of hyperactive delirium [56].

Therefore, there is physiologic grounds and experience of successful interventions directed at GLU, GABA, GLU/ GABA balance, at the NAS. The latter is attempted, for instance, by the introduced in this report plan of noradrenergic modulation (NAM) which includes the blockade of the A1AR and stimulation of the ATAR.

Aims of the study

A. To evaluate an algorithm in the treatment of patients with late life dementia and NPS. **B.** To evaluate several pharmaceuticals (GBP, alpha -2 adrenoceptor agonists, alpha-1 adrenoreceptor antagonists) in the treatment of NPS.

Study design

Case series

Community dwelling elderly patients.

Participants and methods

Nine patients (3 males, 6 females, age 71-104; 86.9, SD 9.4 years) were enrolled in the study. By the time of this report, 3 patients passed away. All patients had co-morbid conditions; systolic blood pressure was at least 110 mm without orthostatic intolerance. Delirium and somatic triggers of disruptive behaviors were ruled out.

All patients (Table 1) had late life dementia, 4 patients moderate and 5 patients, severe based on the Clinical Dementia Rating scale (CDR) [57] scores (1-3; 2.6, SD 0.5). Patients were affected by probable Alzheimer's dementia [58]. The Mini-Mental state exam (MMSE) score [59] (1-7; 3.4, SD 2.2) was not a criterion of dementia severity. Behavioral symptoms before and after treatment were assessed using 2 scales, the Cohen-Mansfeld Agitation inventory (CMAI) [60] and the Verbal disruption, Aggression, Psychomotor hyperactivity and Sleep disturbances (VAPS, acronym of symptoms) scale de novo proposed by the author in the previous case series [13]. The CMAI scores are derived from frequency of each symptom. The VAPS scale scores 4 groups/categories of symptoms separately

Table 1. *Patients' features, treatment regimens and results.*

PATIENT	CO -MORBID CONDITIONS	MEDS /DD	CDR	MMSE	CMAI	VAPS	CGI-C
1.Y. S. M, 90 3 YEARS	OA DYS CKD 4	GBP 600 mg D 4 mg	2	4	24-14	2+2+2+2 1+0+1+1 8-3	2
2. Y. D. M, 98	C H F CKD 4 A OA Pr Ca	GBP 600 mg OXC 300 mg Pr 4 mg	3	2	31-17	2+1+2+3 1+0+1+1 8-3	1
3.Z. Y. F. 80	HTN DM CKD 3 OA	GBP 250 mg TTS 1 D 4 mg	3	1	72-22	2+2+2+3 1+0+1+1 9-3	1
4.M. P. F, 82	HTN OA	GBP 600 mg OXC 300 mg GF 4mg D 4 mg	3	2	108-17	2+2+2+3 1+0+1+1 9-3	1
5.N. M. F, 86	HTN OA Br Ca CHF	GBP 600 mg TTS 1 D 4 mg	3	7	29-7	2+2+2+3 1+0+0+1 9-2	1
6. Y. T. F, 71	HTN OA	TTS 1 Pr 3 mg Qu 150 mg	2	2	70-22	2+2+2+3 1+0+0+1 09-2	1
7.J. D. F, 104	DM HTN OA	Qu 75 mg Tr 75 mg D 4 mg	3	2	38-14	2+1+2+3 0+0+0+1 8-1	1
8. K. G. F, 82	A	R 2 mg Tr 200 mg GBP 600mg TTS 2 D 8 mg	2	4	53-35	2+2+2+3 1+1+1+1 9-4	2
9. D. M. M, 92	HTN CAD CHF CKD OA	O 5 mg GBP 300 mg D 4 mg	2	7	48-20	2+2+2+3 1+0+1+1 9-3	1
Average 86.9, SD 9.4			2.6, 0.5	3.4, 2.2	52.6 27.0 – 18.6 7.9	8.7, 0.4- 2.7, 0.8	1.2 0.4

Abbreviations. A = anemia, AD = Alzheimer's dementia, Br = breast, Ca = cancer, CHF = congestive heart failure, CKD = chronic kidney disease, DLB = dementia with Lewy bodies, D = doxazosin, DD = daily dose, DM = diabetes mellitus, Dys = disequilibrium, GBP= Gabapentin, HTN = hypertension, O = olanzapine, OA = osteoarthritis, OXC = oxcarbazepine P=prazosin, Pr =prostate, Q = quetiapine, R = risperidone, Tr = trazodone.

during the day and during the night. Such scoring better reflects the severity of symptoms since with the disease progression, the pattern of "sundowning "or "the differential nocturnal exacerbation of disruptive behaviors and agitation" [61,62] extends to the daytime. The disruptive score ranges from 0 with no symptoms to 9, when all categories of symptoms are present night- and daytime and sleep less than 2 hours (Table 2). The VAPS scale is simple and easy to use in clinical practice. Both CMAI and VAPS are behavioral rating scales (BRS) focused on the "behavioral phenotype." Results of the treatment were also assessed on the clinical global impression of change scale, CGI-C based on the evaluation of the clinician and input of caregivers [63]. On this scale, a score of 1 means substantial improvement, 2 - moderate improvement, 3 - minimal improvement, 4 -no change and scores 5-7 mean negative outcomes.

In the presented patients, the following treatment algorithm was applied. (Figure 1)

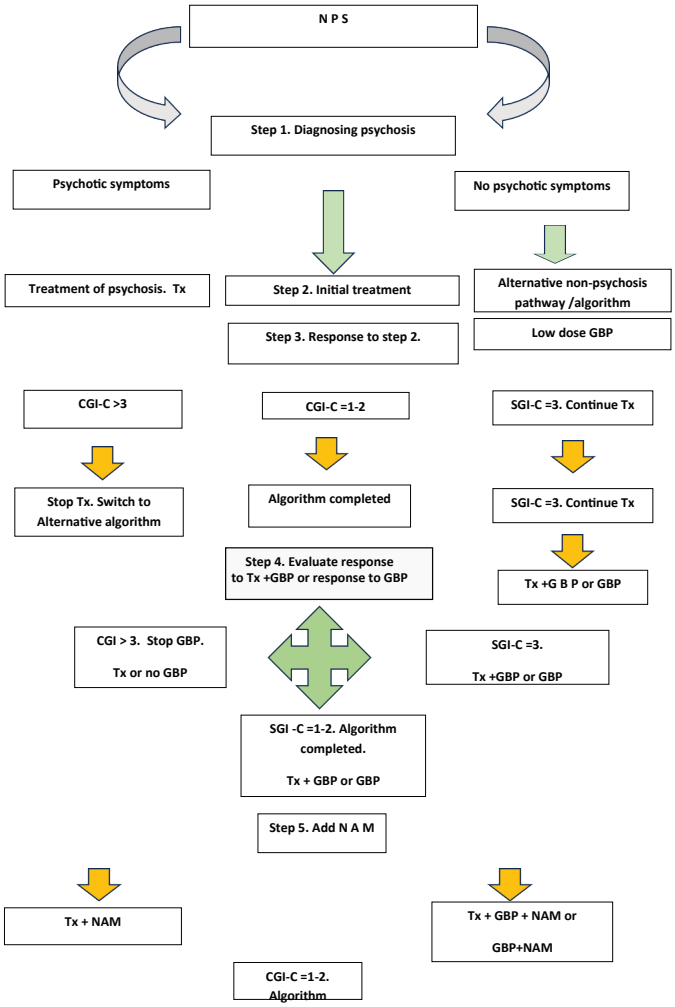

Figure 1. *Treatment algorithm for NPS in late life dementia.*

Step 1. Diagnosing psychosis

As mentioned, in patients with dementia, diagnosing psychosis is often difficult. When it is possible, the algorithm dichotomizes patients into psychosis pathway and alternative non psychosis pathway. In patients 6-9 psychosis was present, in patients 1-5 it was not diagnosed. For convenience, we will separately review the psychosis and alternative non-psychosis pathways.

The psychosis pathway

Step 2. In patients with psychosis (6-9), the initial step was treatment of psychosis (marked as Tx) with an antipsychotic.

Step 3. Evaluation of the step 2 treatment (Tx) based on the CGI-C scale. With no response (CGI-C >3), the antipsychotic would be stopped and treatment switched to the alternative non psychosis pathway (no patients). With full response (CGI-C =1-2) the algorithm would be completed (no patients). With minimal response to Tx (CGI-C = 3) occurring in all 4 patients, the antipsychotic (Tx) was continued and the alternative non-psychosis pathway was added on and started with addition of GBP.

Step 4. Evaluation of the response to Tx + GBP by the CGI-C scale. With satisfactory symptom control (CGI-C =1-2) the algorithm would be completed (no patients). With no response to addition of GBP (CGI-C >3) which occurred in patients 6-7, GBP was discontinued. With minimal response (CGI-C =3) occurring in patients 8-9, Tx + GBP regimen was continued and proceeded via the alternative pathway steps.

Step 5. In patients 6-7 (on Tx, antipsychotic only) and in patients 8-9 (on Tx + GBP), Noradrenergic modulation (NAM) as next step was added on. The regimens became Tx + NAM and Tx + GBP +NAM and led to satisfactory control of behavioral symptoms (CGI -C = 1-2). Algorithm completed.

Table 2*. The VAPS behavior rating scale.*

Symptoms / Points	Daytime	Nighttime
Vocal disruption	1	1
Aggression (verbal, physical)	1	1
Physical Hyperactivity (restlessness, pacing)	1	1
Sleep duration < 2 hours 2-4 hours 5-6 hours		 3 2 1

The alternative non – psychosis pathway.

Step 2. In patients 1-5, started with low daily dose of GBP (600 mg or less) based on principles outlined in the previous report [13].

Steps 3-4. Evaluate the results of step 2 treatment (GBP) on the CGI-C scale. In all five patients, response to GBP was minimal (CGI-C =1). With no response (CGI-C >3), GBP would be discontinued. With full response (CGI-C =1-2), the algorithm would be completed.

Step 5. Continue GBP in all patients (1-5) and add on NAM. The regimen GBP + NAM led to satisfactory control of NPS (CGI -C =1-2). Algorithm completed.

NAM entailed 2 classes of pharmaceuticals: an A1AR antagonist, either prazosin or doxazosin, and an ATAR agonist (ATARa), either transdermal clonidine (TD CLO) or guanfacine. NAM was used in all nine participants. In 4 patients (1,2,7,9) only one agent was used, an alpha-1 receptor antagonist and in the other five patients (3,4,5,6,8), both an A1AR antagonist and an ATARa were used. Two patients (2,4) used Oxcarbazepine and two patients (7,8) took trazodone, both agents were used before entering the algorithm and control of symptoms was achieved only at step 5, addition of NAM to the drug regimen in both pathways. In seven patients (1-5, 8-9), NAM was combined with GBP, in two patients GBP has been stopped due to absence of effect. Details of the drug regimens are shown in Table 1.

Results

All pharmaceuticals, antipsychotics, GBP and NAM agents were well tolerated. Duration of treatment has been 6 months and longer, 3 patients passed away and 6 patients are still undergoing treatment. The behaviors in the participants of this series improved, the average CGI-C score was 1.2, SD 0.4, improvement in 7 patients was rated as substantial (score of 1) and in 2 patients as moderate (score of 2). Changes in the BRS scores also reflect the improvement in symptoms. The CMAI score decreased from 52.6, SD 27.0 to 18.6, SD 7.9, the VAPS score decreased from 8.7, SD 0.4 to 2.7, SD 0.8, the CGI-C score is 1.2, SD 0.4 Table 1). The VAPS scale allows quick assessment in every of the 4 major areas: the V score decreased

from 18 to 8, the A score from 16 to 1, the P score from 19 to 6 and the S score from 26 to 9. Most of the improvement was seen in the aggression (A) and disturbed sleep (S), the areas which cause most of the caregivers' distress. (Table 1).

Discussion

C In this case series, a new algorithm was applied to treat disruptive behavioral symptoms in patients with dementia in the late life. The algorithm is based on several principles.

The first principle is the discreet use of antipsychotics which are not without problems and are recommended to be used short-term [64]. The algorithm in step 1 separates patients into a psychosis and alternative, non -psychosis pathways. The psychosis pathway begins with an antipsychotic, the alternative pathway does not.

The second principle is the combinations of pharmaceuticals. In accordance with this principle, antipsychotics can be combined with the alternative non-psychosis pathway drugs and the drugs in the alternative pathway can be combined with each other. Combinations of drugs allow to target several neurotransmitter systems with a potential synergism of interventions. For instance, GBP tilts the balance between glutamatergic and GABAergic systems, downgrades the former and upgrade the latter. But A1AR blockade may have a synergistic effect because overexcitation of the presynaptic A1AR on glutamatergic neurons increases release of GLU [65] and on gabaergic neurons, decreases release of gaba [66].

The third principle is the evaluation of every step (pharmaceutical) before the next step based on the CGI-C scale. An ineffective pharmaceutical is stopped and not used in the next steps.

The fourth principle is the inclusion of NAM in the algorithm. The NAM itself can be a combo when 2 classes of pharmaceuticals are used. Both classes are likely to have synergism because both the ATARa and A1AR downregulate the NAS.

The suggested algorithm is applicable in non-urgent scenarios. All pharmaceuticals used in this case series have been safely used for a long time in clinical practice. There is experience with use of clonidine, guanfacine and prazosin in patients with dementia, doxazosin is introduced to the field of dementia de novo.

The study is uncontrolled although patients serve as their own historical control and treatment is ongoing for a prolonged time with positive clinical outcomes. This case series provides preliminary and, in author's opinion, interesting evidence in the difficult field of dementia and disruptive behavioral symptoms.

Conclusions

In the presented case series, a new treatment algorithm was applied to treat NPS in patients with late life dementia. Patients treated based on this algorithm have positive results and the six alive patients continue to undergo treatment.

The algorithm is based on certain principles such as discreet use of antipsychotics, combinations of pharmaceuticals targeting multiple neurotransmitter systems with possible synergism, inclusion of pharmaceuticals modulating the function of the noradrenergic system, evaluation of every step with exclusion or addition of pharmaceuticals. The case series provides preliminary evidence supporting the suggested approach to treatment of NPS in patients with late life dementia.

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References

1. Davies S, Burhan A, Kim D et.al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. Journal of psychopharmacology 2018; 32 (5): 509-523
2. Chen A, Copeli F, Metzger E et.al. The Pshycopharmacology Algorithm Project at the Harvard South Shore Program: An Update on management of behavioral and psychological symptoms of dementia. Psychiatry Research 2021; 295: 1136-41
3. Grossberg G, Kohegyi E, Mergel V et al. Efficacy and safety of brexpiprazole for the treatment of agitation in Alzheimer's dementia: two 12-week, randomized, double-blind, placebo-controlled trials. Am J Geriatr Psychiatry 2020; 28 (4):383-400
4. Yan J. FDA Extends Black-Box Warning to All Antipsychotics. Psychiatric News 2008; 43 (14)
5. Niciu MJ, Kelmendi B, Sanacora G. Overview of Glutamatergic Neurotransmission in the Nervous System. Pharmacol Biochem Behav 2012; 100(4): 656-664
6. Mody I, MacDonald JF. NMDA receptor-dependent excitotoxicity: the role of intracellular Ca2+ release. Trends in Pharmacological Sciences 1995; 16: 356–359
7. Neurontin - gabapentin capsule Neurontin- gabapentin tablet, film coated Neurontin- gabapentin solution. Daily Med April 11, 2019.
8. McKeith IG, Boeve BF, Dickson DW et. al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology 2017; 89:88-100.
9. Goldenberg G, Aye N. Low Dose Gabapentin for Behavioral Symptoms in Dementia with Lewy Bodies. Case Series, Brief Review of Pharmacology and a Hypothesis. Neurology and Neurological Sciences: Open Access. Meddocs Publishers. May 2021
10. Banuelos C, Beas B, McQuail J et.al. Prefrontal cortical GABAergic dysfunction contributes to age-related working memory impairment. J Neurosci 2014: 34: 3457–3466
11. Lanctot KL, Herrmann N, Mazzotta P et. al. GABAergic Function in Alzheimer's Disease: Evidence for Dysfunction and Potential as a Therapeutic Target for the Treatment of Behavioral and Psychological Symptoms of Dementia. Clin J Psychiatry 2004; 49: 439-453
12. Lanctot KL, Herrmann N, Rothenburg L et. al. Behavioral correlates of GABAergic disruption in Alzheimer's disease. International Psychogeriatrics 2007; 19 (1): 151-158
13. Coull JT, Frith CD, Dolan RJ, Frackowiak RS, Grasby PM. The neural correlates of the noradrenergic modulation of human attention, arousal and learning. Eur J Neurosci. 1997; 9: 589–598.
14. Coull JT, Büchel C, Friston KJ, Frith CD. Noradrenergically mediated plasticity in a human attentional neuronal network. Neuroimage. 1999; 10:710–715.
15. Goldenberg G. Emerging therapeutic potential of transdermal clonidine: a prospective as an adaptogen. Research and reports in transdermal drug delivery. 2015; 4: 45-54.
16. Hertz L, Lovatt D, Goldman S et.al. Adrenoceptors in brain: cellular gene expression and effects on astrocytic metabolism and [Ca(2+)]i. Neurochem Int 2010; 57 (4): 411–420
17. Verkhratsky A., Parpura V., Vardjan N., Zorec R. Physiology of Astroglia. Adv. Exp. Med. Biol. 2019;1175: 45–91.
18. Braun D, Madrigal J, Feinstein D. Noradrenergic Regulation of Glial Activation: Molecular mechanisms and Therapeutic Implications. Current Neuropharmacology 2014; 12: 342-352
19. Heneka M, Nadrigny F, Regen T et. al. Locus Coeruleus controls Alzheimer's disease pathology by modulating microglial functions through norepinephrine. PNAS 2010; 107 (13): 6058-6063
20. Braak H., Thal D. R., Ghebremedhin E., Del Tredici K. (2011). Stages of the pathologic process in Alzheimer disease: age

categories from 1 to 100 years. J. Neuropathol. Exp. Neurol. 70, 960–969.

21. Kelly S, He B, Perez S et.al. Locus Coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. Acta Neuropathologica Communications 2017; 5: 8
22. Szot P, White S, Greenup L et. al. Compensatory Changes in the Noradrenergic Nervous System in the Locus Coeruleus and Hippocampus of postmortem subjects with Alzheimer's disease and Dementia with Lewy Bodies. Neuroscience 2006; 26 (2): 478-67
23. Hoogendijk W, Feenstra M, Botterblom M et. al. Increased Activity of Surviving Locus Coeruleus Neurons in Alzheimer's disease. Ann Neurol 1999; 45: 82-91
24. Szot P, White S, Greenup L et.al. Changes in Adrenoreceptos in the Prefrontal Cortex of Subjects with Dementia: Evidence of Compensatory Changes. Neuroscience 2007; 146 (1):471-80
25. Erlod E, Peskind L, DsiGlacomo et.al. Effects of Alzheimer's Disease Severity on cerebrospinal Fluid Norepinephrine Concentration Am J Psychiatry 1997; 154: 25-30
26. Ehrenberg A, Suemoto C, Resende E et.al. Neuropathologic Correlates of Psychiatric Symptoms in Alzheimer's Disease. J Alzheimer's Disease 2018; 66(1): 115-126
27. Vermeiren Y, Van Dam D, Aerts T et. Al. Brain region-specific Monoaminergic Correlates of Neuropsychiatric Symptoms in Alzheimer's Disease. Journal of Alzheimer's Disease 2014; 41 :S 19-33
28. Jacobs H, Riphagen J, Ramakers I et. al. Alzheimer's disease pathology: pathways between central norepinephrine activity, memory and neuropsychiatric symptoms Molecular Psychiatry 2021; 26: 897-906
29. Matthews K, Chen C, Esiri M et.al. Noradrenergic Changes, aggressive Behavior, and Cognition in Patients with Dementia. Bio Psychiatry 2002; 51: 407-16
30. Yamamoto K, Shinba T, Yoshi M et. al. Psychiatric symptoms of noradrenergic dysfuntion: a pathophysiologic view. Psychiatry Clin Neurosci 2014; 68 (1): 1-20
31. Domyancic A, Morilak D. Distribution of alpha1A adrenergic receptor mRNA in the rat brain visualized by in situ hybridization. J. Comp. Neurol. 1997; 386: 358–378.
32. Doze V, Papay R, Goldenstein B et.al. Long-term α1A-adrenergic receptor stimulation improves synaptic plasticity, cognitive function, mood, and longevity. Mol. Pharmacol. 2011; 80: 747–758.
33. Gupta M, Papay R, Jurgens C et.al Alpha1-Adrenergic receptors regulate neurogenesis and gliogenesis. Mol. Pharmacol. 2009; 76 (2): 314–326.
34. Arnstein A., Mathew R., Ubriani R. et.al. α-1 Noradenergic receptor stimulation impairs prefrontal cortical cognitive function. Biol Psychiatry 1999; 45: 26-31.
35. Birnbaum S, Gobeske K, Auerbach J et. al. A role for Norepinephrine in Stress-induced Cognitive deficits: α-1-Adrenoreceptor Mediation in the Prefrontal Cortex. Biol Psychiatry 1999; 46: 1266-74
36. Richelson E., Souder T. Binding of antipsychotic drugs to human brain receptors: focus on newer generation compounds. Life Sci 2000; 68:29-39
37. Sharp S, Ballard O, Chen C. et. al. Aggressive Behavior and Neuroleptic Medication Are Associated with Increased number of Alpha-1 Adrenoreceptors in Patients with Alzheimer's Disease. Am J Geriatr Psychiatry 2007; 15: 435-7
38. Menkes D, Baraban J, Aghajanian G Prazosin Selectively Antagonizes Neuronal Responses Mediated by α1-Adrenoreceptors in Brain. Naunyn-Scmiedeberg's Arch Pharmacol 1981; 317: 273-75
39. Tilley D, Houser S, Koch W. Chapter 14. Adrenergic agonists and antagonists. In Goodman and Gilman's The Pharmacological Basis of Therapeutics, 14th Edition. McGraw-Hill Education; 2023
40. Peskind E, Bonner L, Li G et.al. Adrenergic antagonists for disruptive agitation in nursing home residents with Alzheimer's disease. Nerobiol Aging: The 8-th International Conference on Alzheimer's disease and Related Disorders; 2002: p S150
41. Wang L, Shofer J, Rhode K et.al. Prazosin for the treatment of behavioral symptoms in Alzheimer's disease patients with agitation and aggression. Am J Geriatr Psychiatry 2009; 17 (9): 744-751
42. Hart A, Albridge G, Zhang Q et.al. Association of Terazosin, Doxazosin and Alfuzosin Use and Risk of Dementia with Lewy bodies in Men. Neurology 2024; 103 (2)
43. Unnerstall J, Kopajtic T, Kuhar M. Distribution of alpha 2 agonist binding sites in the rat and human central nervous system: analysis of some functional, anatomic correlates of the pharmacologic effects of clonidine and related adrenergic agents. Brain Res Rev. 1984;7: 69–101
44. Starke K, Gotheri M, Kiblinger H. Modulation of neurotransmitter release by presynaptic auto-receptors. Physiol Rev. 1989; 69: 864–889
45. Arnsten A, Steere J, Hunt R. The contribution on a-2 noradrenergic mechanisms to prefrontal cognitive function. Arch Gen Psychiatry. 1996; 53(5):448–455
46. Arnsten A, Li B. Neurobiology of executive functions: cathecholamine influences on prefrontal cortical functions. Biol Psychiatry. 2005; 57: 1377–1384.
47. Mair R, McEntee W. Cognitive enhancement in Korsakoff's psychosis by clonidine: a comparison with L-dopa and ephedrine. Psychopharmacology 1986; 88(3) 374-80
48. Hughes CP, Berg L, Danziger W et.al. Clinical Scale for the Staging of Dementia. British Journal of Psychiatry 1982; 140 (6): 566-572
49. McKhann G, Drachman D, Folstein M et.al. "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease". Neurology 1984; 34 (7): 939–44.
50. Folstein M, Folstein S, McHugh P. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–198
51. Cohen-Mansfield J, Marx M, Rosenthal A. A description of agitation in a nursing home. J of Gerontology 1989; 44(3), M77-M84
52. Cummings J, Mega M, Gray K et.al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44(12):2308–2314.
53. Reisberg B, Borenstein J, Salob S et.al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry. 1987; 48(5, suppl):9–15.
54. Buner J, Atrium S. The Clinical Global Impressions Scale. Psychiatry 2007; 4 (7): 28-37
55. Mouradian R, Sessler F, Waterhouse B et. al. Noradrenergic potentiation of excitatory transmitter action in cerebrocortical slices: evidence for mediation by an alpha 1 receptor-linked second messenger pathway. Brain Re 1991; 546: 83–95.
56. Braga M, Aroniadou - Anderjaska V, Manion S et.al. Stress impairs alpha 1a adrenoceptor-mediated noradrenergic facilitation of GABAergic transmission in the basolateral amygdala. Neuropsychopharmacology 2004; 29: 45–58.