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**DIAGNOSIS OF OVERACTIVE BLADDER IN WOMEN AND  
THE IMPACT OF THE AUTONOMIC NERVOUS SYSTEM**

**321.22 – UROLOGY AND ANDROLOGY**

**Summary of Ph.D. Thesis in Medical Sciences**

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## THE CONCEPTUAL CHARACTERISTICS OF THE RESEARCH

**The actuality of the subject.** Overactive bladder (OAB) is characterised by the presence of lower urinary tract symptoms such as urgency, nocturia, daytime urinary frequency, with or without urge urinary incontinence [1,2].

OAB is among the 10 most widespread diseases globally. The prevalence of overactive bladder in the general population ranges from 8% to 16.9%. The prevalence of OAB is higher in women than in men (33.7% women vs. 14.6% men) [1,3].

The diagnosis of OAB is based on clinical questionnaires and urodynamic investigations proposed by the *European Association of Urology* and the *American Urological Association / The Society of Urodynamics and FEMA Urology* [2]. Patients with OAB have a vegetative and psychovegetative imbalance. Currently, the concept of PUD (*psychogenic urinary dysfunction*) is being studied – urological disorders accompanied by psychovegetative manifestations caused by dysfunction of various vegetative brain centers. Almost half (48%) of patients with overactive bladder have anxious psychovegetative disorders [4].

A particular importance of psychovegetative disorders is observed in female patients, as they are more vulnerable to the action of psycho-traumatic factors [1,5]. The interrelation between overactive bladder and psycho-emotional state is complex and insufficiently studied: psycho-emotional factors can contribute to the onset/aggravation of overactive bladder, and the presence of this condition may be associated with the onset or intensification of psycho-emotional disorders [1,6].

An unresolved issue is the interrelation of suprasegmental vegetative regulation processes and psychovegetative disorders with detrusor overactivity (DO), the incidence of which is estimated from 22% to 58.4% in women with OAB [1,7].

In women with overactive bladder, urological disorders significantly affect the quality of life, and the association with psychovegetative disorders exacerbates these manifestations. In this regard, it is not known to what extent the quality of life is influenced by the urological component versus psychovegetative disorders [8].

Currently, research is being conducted on the possibility of developing objective diagnostic criteria for overactive bladder based on the pathogenesis of this condition. In the etiopathogenesis of overactive bladder, along with other mechanisms, vegetative regulation processes occupy a central place. Blanc et al. were the first authors to suggest that subclinical dysfunction of the autonomic nervous system may be a causal factor of idiopathic overactive bladder [9]. A new diagnostic variant of vegetative functions presents vegetative evoked potentials, which offer the possibility to quantitatively and qualitatively determine the suprasegmental vegetative functions involved in the pathogenesis of overactive bladder. The first publications in this field elucidated the diagnostic importance of these potentials in patients with overactive bladder [10].

In patients with OAB, there is a close interaction between urological disorders and psychovegetative activity with the functioning of micturition centers located at different levels of the nervous system [11]. Currently, the first investigations are being conducted regarding the reflex activity of the brainstem, where the micturition centers (*pontine micturition center* - PMC) are projected. An objective method for studying the reflex activity of the brainstem is the analysis of the blink reflex [12]. The hypothesis regarding the role of the reticular formation of the brainstem in regulating urinary bladder-sphincteric functions is being postulated [13].

The diagnosis of overactive bladder remains a current and insufficiently studied issue. The analysis of modern specialised bibliographic sources reflects *the need to develop new diagnostic*

*criteria for overactive bladder, which would facilitate the identification of clinical polymorphism and the severity of disorders* by including clinical/urodynamic urological indices, psychovegetative indices, and the reflex activity of the brainstem [1,13]. Clinical validation in this direction could optimise the diagnosis and therapeutic management of overactive bladder.

**Working hypothesis.** The traditional diagnosis of overactive bladder based on clinical/paraclinical urological criteria needs to be supplemented with psychovegetative indices and brainstem activity, which would allow for the optimization of a personalised diagnosis of overactive bladder (urological-cerebral hypothesis).

**The aim of the study:** to analyze the clinical and urodynamic manifestations of overactive bladder in women and to complement with indices of suprasegmental autonomic nervous system activity, brainstem reflex activity, with the development of a complex diagnostic algorithm.

**Research objectives.**

1. To analyze the clinical and paraclinical urological features in women with overactive bladder.

2. To highlight the frequency of manifestation of suprasegmental autonomic dysfunction variants in patients with overactive bladder.

3. To study the interrelation of clinical and urodynamic urological indices, psychovegetative indices, brainstem activity, and quality of life with suprasegmental autonomic activity in patients with overactive bladder.

4. Studying the association variants of overactive bladder manifestations with levels of suprasegmental sympathetic/parasympathetic activity.

5. Developing urological-neurophysiological criteria and a complex algorithm for optimizing the personalised diagnosis of overactive bladder.

**Scientific research methodology.** The research methodology focused on contemporary concepts:

1. The concept of the complex etiopathogenesis of overactive bladder: the impact of psycho-emotional and stress factors; the activity of the urinary bladder-sphincteric complex; modification of peripheral autonomic and somatic nerves; segmental and suprasegmental neurogenic regulation of urinary bladder-sphincteric functions.

2. The concept of clinical polymorphism of overactive bladder: the manifestations of urological disorders depend on several factors (age, sex, etc.); overactive bladder is associated with disorders in various body systems (psycho-emotional, systemic vegetative, etc.).

3. Quality of life in patients with overactive bladder, influenced by several factors (severity and duration of urological, psychovegetative disorders, etc.).

**Scientific novelty and originality:**

1. For the first time, an integrative diagnostic hypothesis for overactive bladder is proposed, based on clinical/urodynamic urological manifestations, systemic vegetative clinical disorders, suprasegmental vegetative regulation processes, brainstem reflex activity, and quality of life indices (*psychovegetative-brainstem reflex urological hypothesis*).

2. The research established that suprasegmental sympathetic vegetative activity has a more significant influence on clinical/paraclinical urological manifestations.

3. For the first time, it has been demonstrated that the clinical/paraclinical polymorphism of the overactive bladder depends on the differentiated involvement of the suprasegmental sympathetic/parasympathetic system and the reflex activity of the brainstem.

4. For the first time, it has been established that in patients with overactive bladder, the quality of life is affected by the severity of urological and systemic psychovegetative disorders in

association with the dysfunction of suprasegmental vegetative regulation processes.

5. The diagnosis of overactive bladder based on the psychovegetative-brainstem reflex urological hypothesis offers new possibilities in the etiopathogenic treatment of the condition (targeted influence on the centers of the cerebral autonomic network, micturition centers, etc.).

**Practical importance:**

1. The personalised diagnosis of patients with overactive bladder can be achieved by associating urological manifestations with psychovegetative dysfunctions, reflex activity of the brainstem, and life activity indices.

2. For the first time, diagnostic examination technology for patients with overactive bladder has been implemented, which includes three levels: 1) urological-visceral; 2) suprasegmental/psychovegetative; 3) brainstem reflex.

3. The structure of clinical manifestations and the expression of urodynamic indices in patients with overactive bladder depend on the quantitative (degree of expression) and qualitative (sympathetic/parasympathetic) functional changes of the suprasegmental vegetative system.

4. In patients with overactive bladder, urological disorders in association with suprasegmental autonomic dysfunctions have a significant impact on quality-of-life indices, predominantly affecting the domains of *Disturbance* and *Concern*.

5. Highlighting the particularities of suprasegmental autonomic system activity and the reflex activity of the brainstem opens new possibilities in the etiopathogenic treatment of overactive bladder (central autonomic network, micturition centers).

**Implementation of scientific results.** The results of scientific research have been implemented in the research process, methodological and clinical activities in the Urology Department with the endourological office of the „Timofei Moşneaga” Republican Clinical Hospital, and in the teaching process at the Department of Urology and Surgical Nephrology of „Nicolae Testemiţanu” USMF (Implementation Act no. 2 from 24.01.2024, Implementation Act no. 3 from 24.01.2024).

**Approval of scientific results.** The results were presented through 13 active participations in national and international scientific forums, including: The annual scientific conference „Research in Biomedicine and Health: Quality, Excellence, and Performance”. The Days of the „Nicolae Testemiţanu” State University of Medicine and Pharmacy (2020, Chişinău, Republic of Moldova; 2021, Chişinău, Republic of Moldova; 2022, Chişinău, Republic of Moldova; 2023, Chişinău, Republic of Moldova); The International Medical Congress MedEspera (2020, Chişinău, Republic of Moldova; 2022, Chişinău, Republic of Moldova); The XXXVIII National Congress of Urology, ROMURO (2022, Bucharest, Romania); The 37th Balkan Medical Week Congress. The perspectives of Balkan Medicine in the post-COVID-19 era (2023, Chişinău, Republic of Moldova); The 8th Congress on Urology, Dialysis, and Kidney Transplant from the Republic of Moldova with International Participation „New Horizons in Urology” (2023, Chişinău, Republic of Moldova); The 6th International Conference on Nanotechnologies and Biomedical Engineering. Proceedings of ICNBME-2023 (2023, Chişinău, Republic of Moldova); The 49th Geneva International Exhibition of Inventions 17-21 April 2024 (2024, Geneva, Switzerland – Gold Medal).

The approval of the thesis topic took place during the meeting of the Scientific Council of „Nicolae Testemiţanu” USMF from the Republic of Moldova (minutes no. 3/5.11 from 06.06.2021). The positive opinion of the Research Ethics Committee for conducting the study was given during the meeting on 23.04.2021. The results were approved at the meeting of the Department of Urology and Surgical Nephrology of „Nicolae Testemiţanu” USMF from the

Republic of Moldova (minutes no. 7 from 16.04.2024) and at the meeting of the Scientific Profile Seminar 321.22 - Urology and Andrology (minutes no. 6 from 22.05.2024).

**Publications on the topic of the thesis.** The main materials of the thesis have been published in 36 scientific works, including 13 presentations/posters at various national and international scientific events (conferences, congresses, symposia), 4 articles in peer-reviewed national profile journals (category B), 3 articles in peer-reviewed international profile journals, 6 summary communications published in the materials of international congresses and conferences, 4 theses of national scientific communications, 1 publication without co-authors, 2 invention patents, 4 copyright certificates.

**The volume and structure of the thesis.** The text of the thesis is presented on 140 pages of the main text, processed on a computer, consisting of: a list of abbreviations, an introduction, 6 chapters, general conclusions, practical recommendations, a bibliography of 278 sources, and 12 annexes. The illustrative material includes 3 tables, 31 figures, and 1 formula.

**Keywords:** *overactive bladder, diagnosis, urodynamics, vegetative evoked potentials, psychovegetative disorders blink reflex.*

## CONTENT OF THE THESIS

### 1. OVERACTIVE BLADDER: THEORETICAL, CLINICAL AND DIAGNOSTIC ASPECTS

The respective chapter provides a review of the specialised literature addressing various aspects of the aetiology and pathogenesis of overactive bladder, risk factors, and the multimodal diagnosis of this condition. Thus, based on the literature analysis, the following particularities were highlighted:

- The theoretical hypotheses of bladder and sphincter control in the genesis of OAB are currently well-argued. Still, specific methods for objectifying these processes (urodynamic, neurophysiological, immune, etc.) are not sufficiently developed and implemented. The essential problem is the development of informative diagnostic methods for OAB at different stages of the disease, *as early as possible*.
- Risk factors for OAB can be both genetic and acquired; the pathogenic action of risk factors can manifest at different levels: urinary bladder-urethral, peripheral nervous system, spinal, and cerebral.
- The central component includes both the regulatory centers of the bladder and sphincter, as well as the psychovegetative centers that create conditions for facilitation/inhibition of urinary bladder-sphincter functions. There is a bidirectional influence between psychovegetative disorders and OAB with common biological mechanisms (neurogenic, hormonal, metabolic, etc.).
- Experimental research demonstrates that severe and subclinical dysfunction of the autonomic nervous system is a causal factor of idiopathic OAB, creating the need to develop effective diagnostic methods for detecting subclinical autonomic dysfunctions. The activity of the autonomic nervous system can influence the function of the urinary tract with the appearance of OAB symptoms even in the absence of organic urogenital signs of impairment.
- The data from the literature reflect the insufficiency of information regarding the correlation of urodynamic investigation indices with the psycho-emotional state of the patient and the processes of vegetative regulation of the urinary tract, which hinders a comprehensive and personalised approach to patients with OAB in the diagnostic process.
- Modern research on the pathogenesis of OAB reflects the involvement of various brain structures (brainstem, cerebellum, central autonomic network, etc.), but diagnostic methods for urological clinical practice that would highlight the level and severity of impairment of cerebral regulation processes of the urinary tract have not been developed. The presence in the brain of multiple zones and centers for regulating the lower urinary tract, whose dysfunction can cause OAB symptoms, suggests the existence of several OAB phenotypes, which require different diagnosis and treatment.
- The quality of life in patients with OAB is considerably influenced by urological disorders and, to varying degrees, by associated disorders. Early diagnosis of OAB and appropriate treatment can significantly limit the negative impact of associated urological and psychovegetative disorders on patients' quality of life indices.
- The diagnosis of OAB and the indication of appropriate treatment are based on clinical and paraclinical investigations according to modern theories of the pathogenesis of this condition (myogenic, neurogenic, urothelial, urethro-genic).



## 2. MATERIAL AND RESEARCH METHODS

### 2.1. General characteristics, study design, inclusion and exclusion criteria

The research project was carried out during the years 2019-2024, within the Department of Urology and Surgical Nephrology at the „Nicolae Testemițanu” State University of Medicine and Pharmacy, head of the department Dr. hab. med. sci., Univ. Prof., Adrian Tanase.

To achieve the objectives, a cross-sectional study was planned based on clinical and paraclinical examination materials of patients who addressed the specialised consultative office of the IMSP Republican Clinical Hospital „Timofei Moșneaga” Polyclinic in the Republic of Moldova, on the paraclinical urodynamic investigations carried out within the Youth Health Center „Neovita” and on the clinical and neurophysiological investigations carried out at the University Clinic „Neuronova” (Chisinau). The investigations and the process of multidimensional analysis of the information were guided by the Department of Urology and Surgical Nephrology at the „Nicolae Testemițanu” State University of Medicine and Pharmacy.

The diagnosis of overactive bladder was established according to: recommendations International Continence Society (ICS); international guidelines European Association of Urology (EAU) „Non-neurogenic lower urinary tract symptoms in women” (2021); American Urological Association (AUA) / The Society of Urodynamics and Female Urology (SUFU) „Diagnosis and treatment of non-neurogenic overactive bladder in adults” (2019), which include: 1) history taking; 2) application of validated clinical questionnaires; 3) urological clinical examination; 4) laboratory investigations (general urine analysis, urine culture); 5) urodynamic paraclinical examination.

The required number of patients for research (cross-sectional study) was determined using the following formula, recommended in the specialised literature:

$$n = (Z_{\alpha} + Z_{\beta})^2 \times 2 \times \frac{P(1 - P)}{D^2} \quad (2.1)$$

$Z_{\alpha}$  – at a statistical significance of 95.0%,  $\alpha$  has a value of 0.05, and the coefficient  $Z_{\alpha} = 1.96$

$Z_{\beta}$  – at the conventional setting of statistical power at 95%,  $Z_{\beta} = 1.645$

$D$  – the difference to detect (size effect) – the difference between groups should be 25% (0.25)

$P(1-P)$  – estimated variance; according to literature data, the prevalence of OAB in women is 24%, so the estimated variance is  $0.24 \times 0.76 = 0.1824$

By inputting the data into the formula, we obtained:  $n = (1.96 + 1.645)^2 \times 2 \times 0.1824 / (0.25)^2 = 75.85$  people

Thus, in the study, 76 healthy women and 76 women with OAB were enrolled.

**Inclusion criteria for research on patients with overactive bladder:** female patients; patients aged between 18-68 years; consent through signing the informed consent form; clinically confirmed urological diagnosis of overactive bladder according to the international diagnostic criteria established by the International Continence Society, European Association of Urology, and American Urological Association / The Society of Urodynamics and Female Urology; patients without depression or with mild depression, evaluated based on the depression questionnaire (PHQ-9) – women with an index  $< 9$  were included; patients with normal menstrual cycle duration variability (calculated according to the follicular phase duration index); patients without severe menopause symptoms, evaluated according to the Menopause Rating Scale (MRS) – women with an index  $< 16$  were included; cooperative patients.

**Exclusion criteria for research on patients with overactive bladder:** stress urinary incontinence as the predominant symptom at screening; infravesical obstruction ( $Q_{max} < 12$  mL/sec); patients with post-void residual urine  $> 100$  ml determined by ultrasonography; an

average total daily urine volume >3000 mL (recorded over a 3-day period from the voiding diary), patients with moderate/severe urgency urinary incontinence (ICIQ-UI <5); interventions on the urinary tract, oncological and inflammatory diseases of the pelvic organs and urinary tract; neurogenic bladder dysfunction (cerebral conditions, degenerative and demyelinating pathologies of the CNS, organic spinal cord conditions, etc.), patients with mental illnesses; gynaecological conditions in the acute phase; endocrine disorders in the acute phase; pregnant women.

**Inclusion criteria for the research group of healthy individuals:** consent through signing the informed consent; female individuals; individuals aged between 18 – 65 years; individuals without acute phase conditions; absence of pregnancy; cooperative individuals.

The average age of women without OAB was 40.43±10.38, while in the study group, it was 43.67±12.82, with the differences between groups not being statistically significant according to the medians ( $W = 2515.500$ ,  $p = 0.1702$ ). The living place of healthy women was 39 (51.31%) in rural areas and 37 (48.68%) in urban areas, while in the study group, it was 34 (44.73% – rural) and 42 (55.26% – urban), with the differences in these frequencies being statistically insignificant ( $\chi^2 = 0.6546$ ,  $p = 0.4185$ ,  $p_{\text{Fisher}} = 0.5162$ ). Based on the individual characteristics of the enrolled individuals, no lack of homogeneity was observed by age and living place.

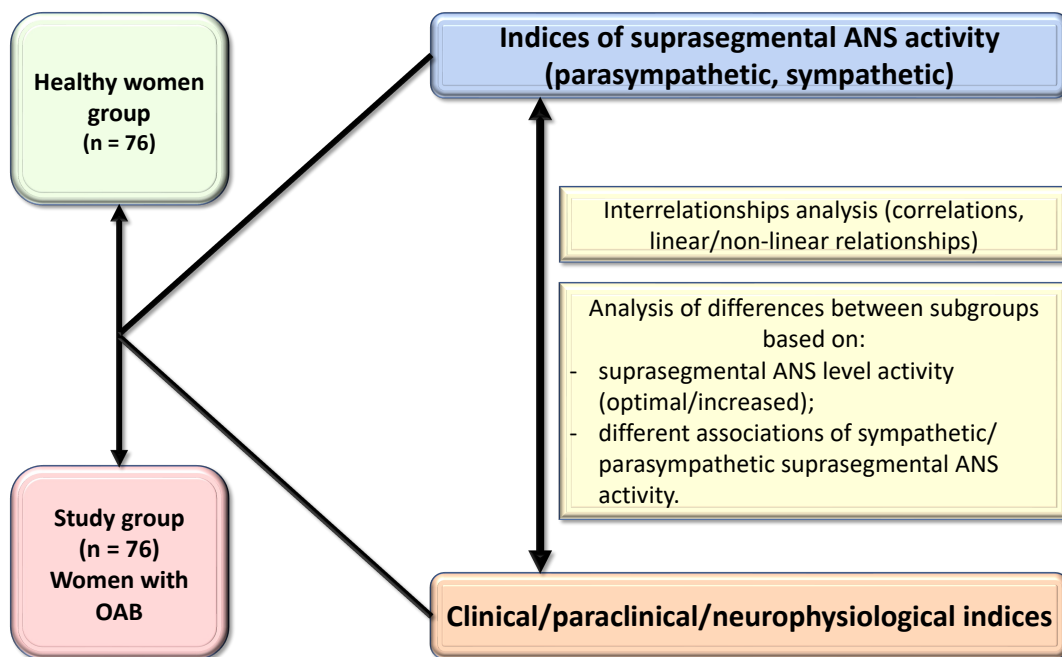


Figure 2.1. Study design of the research

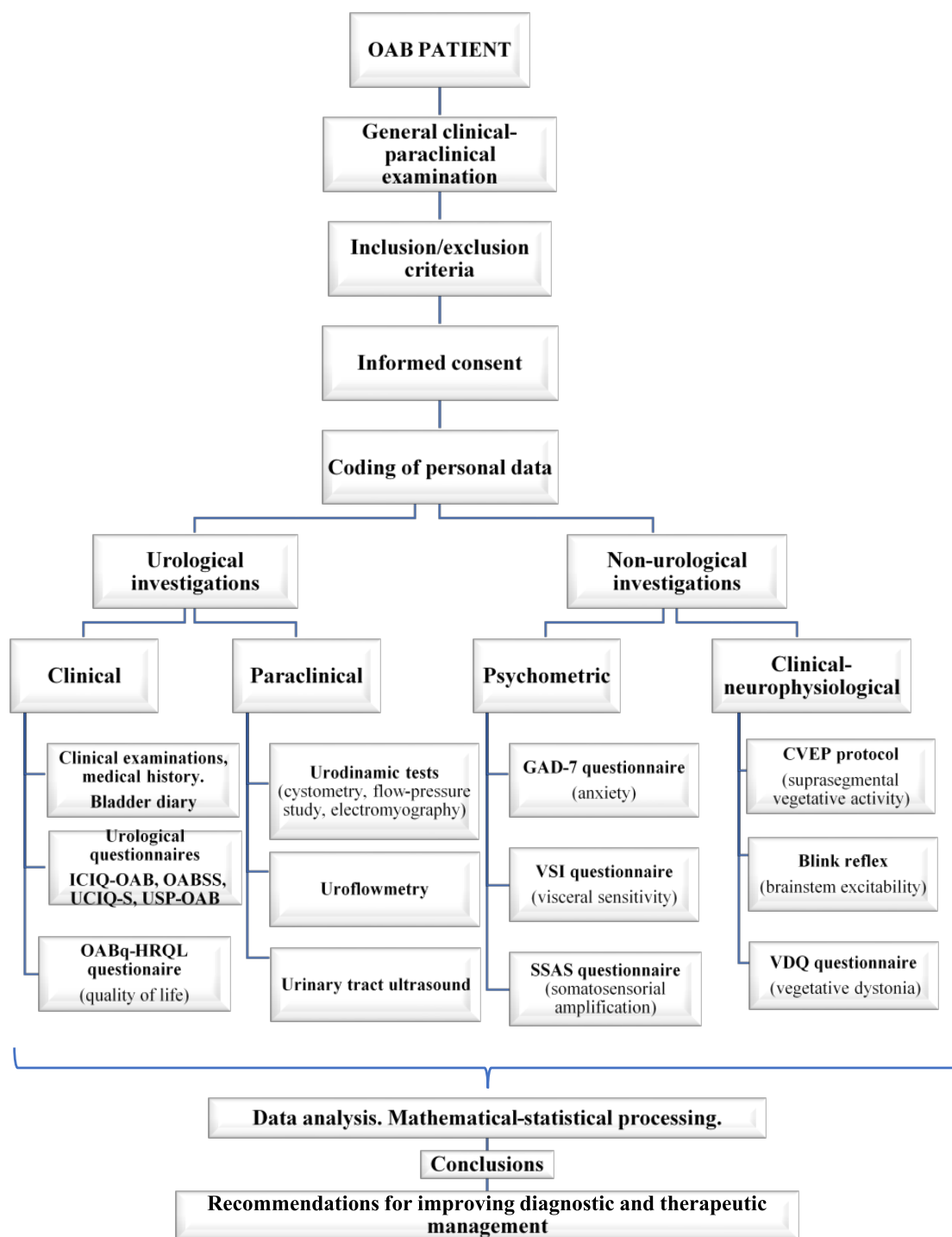


Figure 2.2. **Algorithm of investigations applied to patients with overactive bladder**

The study design and investigation algorithm were created according to the proposed goals and objectives (figure 2.1., 2.2.).

## 2.2. Clinical and paraclinical urological examination

For the diagnosis of OAB, the patient's medical history was initially evaluated in detail, obtaining information about the onset, evolution, and duration of symptoms. The predominant symptoms of lower urinary tract symptoms were elucidated: urinary urgency, urinary frequency, nocturia, and urgency urinary incontinence.

The objective clinical evaluation included an abdominal examination to identify the presence/absence of a palpable bladder or masses. Additionally, a gynaecological examination was performed to evaluate atrophic vaginitis and pelvic organ prolapse.

At the initial visit, the study participants were thoroughly explained the voiding diary by the study coordinators. Indicators evaluated from the voiding diary included: daytime and nighttime urination frequency, the volume of fluid intake in 24h (VLA24), total voided volume (VTU24) in 24h, volume per urination, average voided volume in 24-hour period, nighttime voided volume (VTUN), presence of urinary incontinence episodes, index of nocturia (IN), functional urinary bladder capacity (CFV) over a 24-hour period, index of nocturnal polyuria (IPN), index of nocturnal bladder capacity (ICNV), the average score of the patient's perception of the intensity of the urgency scale (PPIUS), sensation-related bladder diary degree (SR-BD<sub>Duration</sub>), and the total urgency and frequency scale (TUFS).

The clinically validated questionnaires applied in the study were: the International Consultation on Incontinence Questionnaire - Overactive Bladder Symptom Score (ICIQ-OAB), the Overactive Bladder Symptom Score (OABSS), the Urgency Severity and Impact Questionnaire (USIQ-S), the Urinary Symptom Profile (USP-OAB), the Patient's Perception of Bladder Condition (PPBC), and the Health-Related Quality of Life questionnaire for OAB (HRQoL - OABq).

Patients were investigated using ultrasound to exclude bladder emptying problems, and measurements were taken of the residual urine volume remaining after voiding.

Urodynamic studies included uroflowmetry tests, filling cystometry, pressure-flow studies during voiding, and non-invasive electromyography.

Uroflowmetric indices evaluated were maximum urinary flow rate (Q<sub>max</sub>), average urinary flow rate (Q<sub>ave</sub>), voided volume (VV), voiding time, time to reach Q<sub>max</sub>, and the Voiding Index (VI). Cystometric indices included the measurement of volumes at the first sensation to void (ml), normal sensation to void (ml), strong desire to void (ml), urgency, pain, maximum cystometric capacity of the bladder (ml), bladder compliance (ml/cm H<sub>2</sub>O), and provocation tests (sound of running water). Detrusor overactivity was considered present if spontaneous or provoked phasic involuntary detrusor contractions were observed during filling cystometry (Q<sub>max</sub> of >20 ml/s, P<sub>det</sub>Q<sub>max</sub> of >30 cmH<sub>2</sub>O). Detrusor contractility was evaluated using the Projected Isovolumetric Pressure (PIP1) in women, calculated by summing the maximum urinary flow rate (Q<sub>max</sub>) and the detrusor pressure at Q<sub>max</sub> (P<sub>det</sub>Q<sub>max</sub>).

### **2.3. Evaluation of psychovegetative and neurophysiological indices**

Validated questionnaires were applied to all patients in the study to assess the psycho-emotional state.

Generalized anxiety was determined by applying the GAD-7 (Generalized Anxiety Disorder-7) questionnaire. For the evaluation of specific anxiety in patients, the Visceral Sensitivity Index (VSI) questionnaire was used, which is a validated multidimensional tool that assesses somatic sensations specific to panic attacks („I become anxious when I go to a new restaurant”), cognitive discomfort (inability to concentrate), and fear of publicly observable dysfunction. The Somatosensory Amplification Scale (SSAS) was used to evaluate perceived sensitivity to various unpleasant bodily sensations, most of which are not related to OAB. The severity of clinical vegetative dysfunctions was assessed using the Vegetative Dystonia Questionnaire (VDQ).

To achieve the proposed objectives, we used the method of determining the cutaneous vegetative evoked potentials of the brain, which is an objective method, that allows quantitative (amplitude of the sympathetic and parasympathetic wave) and qualitative (presence and ratio of sympathetic/parasympathetic activity) assessment.

The determination of the reflective activity of the brainstem was performed by applying the blink reflex, which integrally represents the functional state of the reticular formation and,

respectively, integrally represents the reflex state of the micturition centers.

#### **2.4. Mathematical-statistical processing**

In the study, data collected from subjects were entered into tabular files in \*.xlsx format (Microsoft Excel, USA) and \*.sav (IBM SPSS v. 27, USA). Statistical processing of the data was performed using specialised statistical analysis programs IBM SPSS v.27 (USA), R Studio (R Project, USA), and MedCalc (MedCalc, Belgium), applying methods: testing the normality of data distribution (Shapiro-Wilk). Differences between frequencies per group (Chi2, Fisher tests) with odds ratio evaluation when necessary. Differences between groups (Mann Whitney, Kruskal-Wallis, post-hoc Conover – Iman test) with size effect calculation based on  $\varepsilon^2$  (epsilon-squared). Calculation of variation coefficients (CV) and significance evaluation according to Forkman. The relationships between variables were evaluated through non-parametric correlations of the Spearman rho type and generalised additive models (GAM – generalized additive model) with reporting of parameters probability, confidence interval CI95%, size effect, EDF, model fit degree (R2adj). Graphical illustration – distribution plots, heat map, boxplot, bar plots. Data were considered valid for p-value < 0.05.

### **3. INTERRELATIONS OF UROLOGICAL AND NEUROPHYSIOLOGICAL CLINICAL INDICES IN PATIENTS WITH OVERACTIVE BLADDER**

Currently, most studies refer to the analysis of the segmental autonomic system activity in patients with OAB. The results of these investigations demonstrate the essential role of the autonomic nervous system in the genesis of symptoms in patients with OAB and the effectiveness of the applied treatment. On the other hand, patients with OAB are characterised by polymorphic psycho-emotional and psychovegetative disorders, which highlight a significant dysregulation of the suprasegmental mechanisms regulating vegetative processes. Modern concepts regard multiple affective disorders, especially anxiety, as suprasegmental vegetative disorders. These data demonstrate that suprasegmental vegetative disorders require in-depth study to deepen the knowledge regarding the etiopathogenesis of the disease.

Indices of suprasegmental vegetative activity (A1 – parasympathetic, A2 – sympathetic) show different values in women with OAB (n = 76) compared to women without OAB (n = 76): suprasegmental parasympathetic vegetative activity (A1) was statistically significantly higher (W = 885.500, p < 0.001) in women with OAB compared to those without OAB (mean/SD 0.7039 ± 0.552, median – 0.7000; OAB – 1.2371±0.5942, median – 0.9300); suprasegmental sympathetic vegetative activity (A2) was statistically significantly higher (W = 909.500, p < 0.001) in women with OAB compared to those without OAB (mean/SD 3.4058 ± 0.0665, median – 3.4000; OAB – 4.4417±1.2574, median – 4.0100); in women with OAB, the coefficients of variation were much higher than in healthy women for the A1 index (0.4803 vs. 0.0785) with statistical significance (F = 0.03260, p < 0.001), as well as for the A2 index (0.2831 vs. 0.0195) with statistical significance (F = 0.00512, p < 0.001).

As seen in Table 3.1, the comparison of clinical index values between patients with overactive bladder – OAB (study group, OAB, n = 76) and healthy women (n = 76) shows that in women with OAB, the medians are statistically significantly different, indicating that in the analyzed dimensions (index groups), the health condition is more aggravated in women with OAB.

**Table 3.1. Comparison of clinical/paraclinical index expression of overactive bladder in patients with overactive bladder versus healthy women**

Indices type	Indices	Group	Mean	Median	DS	ESM	CFV	Statistical test Median (Mann Whitney)	CFV difference test (Forkman)
Total scores of the symptom questionnaires	ICIQ-OAB	LC (n = 76)	0.5526	1.0000	0.6407	0.0735	1.1594	W = 0.0000, p < 0.001	F = 0.04488, p < 0.001
		OAB (n = 76)	9.6316	9.5000	2.3655	0.2713	<b>0.2456</b>		
	OABSS	LC (n = 76)	1.1711	1.0000	1.2690	0.1456	1.0836	W = 45.5000, p < 0.001	F = 0.11329, p < 0.001
		OAB (n = 76)	7.6579	8.0000	2.7931	0.3204	<b>0.3647</b>		
	USP-OAB	LC (n = 76)	1.2632	1.0000	1.3699	0.1571	1.0845	W = 2.0000, p < 0.001	F = 0.04259, p < 0.001
		OAB (n = 76)	9.5263	10,0000	2.1321	0.2446	<b>0.2238</b>		
	UCIQ-S	LC (n = 76)	14.8026	15,0000	13.1514	1.5086	0.8885	W = 97.0000, p < 0.001	F = 0.11455, p < 0.001
		OAB (n = 76)	61.7105	67.5000	18.5572	2.1287	<b>0.3007</b>		
Indices of the psycho-vegetative state	GAD-7	LC (n = 76)	7.7368	7,0000	4.7113	0.5404	<b>0.6089</b>	W = 2155.5000, p = 0.0068	F = 0.33325, p < 0.001
		OAB (n = 76)	9.6316	9.0000	3.3856	0.3884	0.3515		
	SASS	LC (n = 76)	20.4605	21.0000	3.8968	0.4470	0.1905	W = 892.5000, p < 0.001	F = 1.18301, p = 0.46852
		OAB (n = 76)	28.0263	26,0000	5.8080	0.6662	<b>0.2072</b>		
	VDQ	LC (n = 76)	22.3553	23.0000	8.5895	0.9853	<b>0.3842</b>	W = 940.5000, p < 0.001	F = 0.49314, p = 0.00253
		OAB (n = 76)	33.8026	31.0000	9.1200	1.0461	0.2698		
	VSI	LC (n = 76)	18,0000	18,0000	7.8740	0.9032	<b>0.4374</b>	W = 38.5000, p < 0.001	F = 0.30687, p < 0.001
		OAB (n = 76)	42.7895	37,0000	10.3696	1.1895	0.2423		
Urodynamic indices	IU <sub>UFM</sub>	LC (n = 76)	<b>0.6345</b>	<b>0.6450</b>	0.0955	0.0110	0.1505	W = 5556.5000, p < 0.001	F = 15.51943, p < 0.001
		OAB (n = 76)	0.2725	0.2750	0.1616	0.0185	<b>0.5929</b>		
	FSV	LC (n = 76)	<b>268.5132</b>	<b>270.5000</b>	30.3181	3.4777	0.1129	W = 5776.0000, p < 0.001	F = 6.10686, p < 0.001
		OAB (n = 76)	63.5658	63.0000	17.7338	2.0342	<b>0.2790</b>		
	FSV <sub>WT</sub>	LC (n = 76)	<b>253.3158</b>	<b>261.0000</b>	37.2366	4.2713	0.1470	W = 5776.0000, p < 0.001	F = 4.55979, p < 0.001
		OAB (n = 76)	46.6184	44.5000	14.6314	1.6783	<b>0.3139</b>		
	FDV	LC (n = 76)	<b>290.0789</b>	<b>296.0000</b>	28.3670	3.2539	0.0978	W = 5776.0000, p < 0.001	F = 4.28294, p < 0.001
		OAB (n = 76)	90.1053	93.0000	18.2352	2.0917	<b>0.2024</b>		
	SDV	LC (n = 76)	<b>313.3026</b>	<b>321.0000</b>	32.2031	3.6940	0.1028	W = 5776.0000, p < 0.001	F = 3.03871, p < 0.001
		WOW (n = 76)	111.5263	114.0000	19.9876	2.2927	<b>0.1792</b>		
MCC	LC (n = 76)	<b>333.6053</b>	<b>340.0000</b>	34.0408	3.9047	0.1020	W = 5770.0000, p < 0.001	F = 4.38531, p < 0.001	
	OAB (n = 76)	149.6053	147.0000	31.9500	3.6649	<b>0.2136</b>			
PIP <sub>1</sub>	LC (n = 76)	54.6671	53.3000	7.3782	0.8463	0.1350	W = 1070.5000, p < 0.001	F = 1.45069, p = 0.10937	
	OAB (n = 76)	<b>66.2711</b>	<b>64.9500</b>	10.7788	1.2364	<b>0.1626</b>			
Reflex excitability of brainstem (REBS)	LC (n = 76)	1.0037	1.0000	0.1727	0.0198	0.1721	W = 91.0000, p < 0.001	F = 2.50341, p = 0.00010	
	OAB (n = 76)	2.1000	1.9950	0.5718	0.0656	<b>0.2723</b>			

Additionally, most of the analyzed indices demonstrated statistically significant differences regarding the variability of the indices (CFV coefficients), as follows: in the case of the total scores of symptomatic questionnaires (ICIQ-OAB, OABSS, USP-OAB, UCIQ-S), a statistically significantly higher variability is observed in healthy women, whereas in patients with OAB, there is a concentration of values towards more severe values (also demonstrated by the proximity of mean and median values); a similar trend was observed for most indices of psychovegetative state (general anxiety – GAD-7, vegetative dystonia – VDQ, anxiety-associated visceral sensitivity – VSI), indicating that in women with OAB, there is a concentration of values towards the

aggravation pole, compared to the variation observed in the group of healthy individuals; in the case of the urodynamic index group (IU<sub>UFM</sub>, FSV, FSV<sub>WT</sub>, FDV, SDV, MCC), for most of these, a statistically significantly higher variability of indices is observed, indicating the variation of paraclinical urological changes in women with OAB; the reflex excitability of the brainstem (REBS) presents statistically significantly higher median values, as well as a significantly higher variability in patients with OAB compared to healthy women, indicating that there might be an association between REBS changes and the presence of OAB.

Based on the study of the interrelationships of suprasegmental vegetative activity indices and clinical indices of OAB, multiple associations of various magnitudes, directions, and linearities were revealed. We analysed the results (Table 3.2.) to delineate the different impacts of sympathetic/parasympathetic activity on these clinical indices.

**Table 3.2. Summary of statistically significant interrelationships (correlations, GAM models) as well as the average associative/explanatory power between predictors A1/A2 and clinical indices of overactive bladder**

Indices group		No. correlations significantly statistical		Average strength of correlations significantly statistical		No. of GAMs significantly statistical		Average explanatory power (%)	
		A1	A2	A1	A2	A1	A2	A1	A2
Bladder diary	<i>A. Functional capacity</i>	<b>2</b>	0	<b>0.300</b>	-	<b>4</b>	1	<b>11.02</b>	3.71
	<i>B. Nocturia</i>	<b>4 (3)*</b>	2	0.254	<b>0.432</b>	3	<b>4</b>	<b>9.44</b>	7.02
	<i>C. Voiding frequency</i>	0	<b>3</b>	-	<b>0.338</b>	0	<b>3</b>	-	<b>15.12</b>
	<i>D. Bladder sensitivity</i>	1	<b>3</b>	0.276	<b>0.302</b>	2	2	10.96	<b>18.05</b>
	<b>TOTAL</b>	7	<b>8</b>	0.276	<b>0.357</b>	9	<b>10</b>	8.35	<b>10.97</b>
<i>Symptomatic questionnaires</i>		0	<b>4</b>	-	<b>0.355</b>	1	<b>4</b>	7.66	<b>13.97</b>
<i>Urodynamic indices</i>		1	<b>5</b>	0.268	<b>0.312</b>	1	<b>4</b>	<b>21.2</b>	21.15
<i>Life quality</i>		1	<b>5</b>	<b>0.435</b>	0.325	1	<b>4</b>	<b>47.1</b>	14.16
<i>Reflex excitability of brainstem</i>		0	<b>1</b>	-	<b>0.425</b>	0	<b>1</b>	-	<b>20.1</b>
<i>Psycho-emotional state</i>		0	<b>4</b>	-	<b>0.438</b>	0	<b>4</b>	-	<b>34.17</b>
<b>TOTAL</b>		16 (15)*	<b>35</b>	0.301	<b>0.364</b>	21	<b>37</b>	14.71	<b>15.84</b>

Note: \* – based on the analysis of *bootstrapped* confidence intervals, in the case of the IPN index (group of nocturia indices from the voiding diary), it is observed that the value 0 is part of the confidence interval (near the upper limit of the interval), which reveals that the result is an unreliable estimate.

As seen in Table 3.2, the impact of suprasegmental vegetative activity indices (A1/A2) on the clinical indices of OAB is varied as follows: overall, suprasegmental sympathetic vegetative activity (A2) shows more statistically significant correlations, a higher average correlation strength, more statistically significant GAM models, and a higher explained deviance than suprasegmental parasympathetic vegetative activity (A1). In some groups of indices, exclusively statistically significant associations (Spearman correlations) are observed only for suprasegmental

sympathetic vegetative activity (A2) with the frequency indices from the voiding diary; psycho-emotional state indices, brainstem reflex excitability, as well as the severity indices of OAB (total scores of symptomatic questionnaires). The functional capacity indices of the bladder (voiding diary) show statistically significant associations (correlations) exclusively with suprasegmental parasympathetic vegetative activity (A1). Nocturia indices demonstrate statistically significant associations (correlations) predominantly with suprasegmental parasympathetic vegetative activity (A1) compared to sympathetic activity (A2). Urodynamic indices and those of impact on quality of life demonstrate statistically significant associations (correlations) predominantly with suprasegmental sympathetic vegetative activity (A2) compared to parasympathetic activity (A1).

The calculated Spearman correlations largely represented reliable estimates (based on *bootstrapped* confidence intervals), and the determined correlation strength corresponded with the size effect estimated through  $Z_{\text{Fisher}}$ .

At the level of Spearman correlations, the following association characteristics were observed: indices with common associations with both suprasegmental parasympathetic vegetative activity (A1) and sympathetic activity (A2): ICNV; PIP<sub>1</sub> and HRQoL-SOC; indices with distinct associations only with suprasegmental parasympathetic vegetative activity (A1): VMU24, CFV, IN, IPN, NPMN, PPIUS; indices with distinct associations only with suprasegmental sympathetic vegetative activity (A2): NAMN, NM24, NMD, NMN, TUFS, SRBD<sub>Duration</sub>, PPBC, ICIQ-OAB, OABSS, USP-OAB, UCIQ-S, FSV, FSV<sub>WT</sub>, FDV, SDV, HRQoL-SD, HRQoL-COP, HRQoL-WR, HRQoL<sub>ST</sub>, REBS, GAD-7, SSAS, VDQ, VSI.

Between suprasegmental parasympathetic vegetative activity (A1) as a predictor and clinical indices of OAB, 21 statistically significant GAM models were revealed, predominantly showing linear relationships (n = 17). Between suprasegmental sympathetic vegetative activity (A2) as a predictor and clinical indices of OAB, 37 statistically significant GAM models were revealed, predominantly showing non-linear relationships (n = 21).

Some particularities of the impact of A1/A2 predictors of suprasegmental vegetative activity were observed.

A2 (suprasegmental sympathetic vegetative activity) compared to A1 (suprasegmental parasympathetic vegetative activity) has an exclusive predictor effect on psychovegetative indices, frequency indices of micturition (micturition calendar), and brainstem reflex excitability, and predominates in the number of associations in groups of indices (symptomatic questionnaires, quality of life, and urodynamic indices).

A1 (parasympathetic suprasegmental vegetative activity) compared to A2 (sympathetic suprasegmental vegetative activity) has a predominant predictor effect based on the number of associations in the group of indices – functional capacity of the bladder (voiding diary).

At the level of GAM models, the following association particularities were observed: indices with a common impact on both the predictor influence of parasympathetic suprasegmental vegetative activity (A1) and sympathetic suprasegmental vegetative activity (A2): IN, NPMN, ICNV, TUFS, ICIQ-OAB, PIP<sub>1</sub>, HRQoL-SOC; indices with impact only on the predictor influence of parasympathetic suprasegmental vegetative activity (A1): VLA24, VTU24, VMU24, CFV, PPIUS; indices with impact only on the predictor influence of sympathetic suprasegmental vegetative activity (A2): VTUN, NAMN, NM24, NMD, NMN, PPBC, OABSS, USP-OAB, UCIQ-S, FSV, FDV, SDV, HRQoL-COP, HRQoL-WR, HRQoL<sub>ST</sub>, REBS, GAD-7, SSAS, VDQ, VSI.

In general, it is observed that A2 (suprasegmental sympathetic vegetative activity) has a



more varied role as a predictor, impacting a larger number of diagnostic indices associated with OAB, with a predominance of non-linear connections, as well as tendencies for higher values of explained deviation from clinical indices.

#### **4. UROLOGICAL INDICES IN WOMEN WITH OVERACTIVE BLADDER DEPENDING ON SUPRASEGMENTAL AUTONOMIC NERVOUS SYSTEM ACTIVITY**

Based on the previously observed results, given that the overall impact of suprasegmental autonomic activity indices (A1 – parasympathetic, A2 – sympathetic) is multi-faceted and with different magnitudes of association with clinical indices of OAB, it is appropriate to investigate the impact of different levels of suprasegmental parasympathetic (trophotropic) and sympathetic (ergotropic) vegetative activity on clinical indices.

Regarding the level of trophotropic activity, in the healthy group (LC, n = 76), all women had an optimal level (TO, 100%, n = 76). In the patient group, 26 individuals presented an optimal level of trophotropic activity (TO, 34.21%) and 50 individuals had increased trophotropic activity (TS, 65.79%). The differences between groups are statistically significant –  $\chi^2 = 74.5592$ ,  $df = 1$ ,  $p_\chi < 0.001$ ,  $p_{\text{Fisher}} < 0.001$ . The odds ratio (OR – *odds ratio*) reveals that a person with OAB is 291.56 times more likely to have increased trophotropic activity,  $CI_{95\%} = (17.3727, 4893.3418)$ ,  $p = 0.0001$ .

Regarding the level of ergotropic activity, in the healthy group, 75 people had an optimal level (EO, 98.68%) and 1 person had increased ergotropic activity (ES, 1.32%). In the patient group, 24 people had an optimal level (EO, 31.58%) and 52 people had increased ergotropic activity (ES, 68.42%). The differences between the groups are statistically significant –  $\chi^2 = 72.4223$ ,  $df = 1$ ,  $p_\chi < 0.001$ ,  $p_{\text{Fisher}} < 0.001$ . The odds ratio (OR – *odds ratio*) reveals that a person with OAB is 162.500 times more likely to have an increased level of ergotropic activity,  $CI_{95\%} = (21.3112, -1239.0770)$ ,  $p < 0.0001$ .

Based on the study of clinical index manifestations in women with overactive bladder depending on the activity of the suprasegmental autonomic nervous system, we observed multiple associations with different levels of trophotropic/ergotropic ANS activity. We conducted a summary analysis of the obtained results, initially identifying only the clinical variables that demonstrated associations with the levels of ANS activity (trophotropic/ergotropic) (Figure 4.1).

The statistical analysis regarding the presence of the association (Kruskall Wallis), the direction of the association (post-hoc Conover-Iman test), and the strength of the association (size effect) revealed that the level of increased suprasegmental sympathetic vegetative activity presents strong associations: strong for systemic vegetative disorders (Wein test), moderate for micturition calendar indices (NM24, TUFs, and PPBC), clinical questionnaires (ICIQ-OAB, OABSS, USP-OAB, UCIQ-S), urodynamic indices (SDV), anxiety indices (generalized, somatic, visceral), and quality of life domains (*Disturbance, Worry*).

The statistical analysis regarding the presence of association (Kruskall Wallis), the direction of the association (post-hoc Conover-Iman test), and the strength of the association (size effect) revealed a much narrower spectrum of impact of parasympathetic suprasegmental vegetative activity, with weak associations with voiding diary indices (nocturnal polyuria, number of voids per 24 hours) and the *Social* domain of quality of life.

As seen in Figure 4.1, the results reveal the following:

- different levels of ergotropic vegetative activity have a more pronounced impact on the clinical variables of OAB (21 associations *versus* 3 in the case of trophotropic ANS activity);

- the activity of the trophotropic ANS shows an exclusive association with the *Social* subscale of HRQoL (HRQoL-SOC), the nocturnal polyuria index (IPN);
- both the activity of the trophotropic ANS and the ergotropic ANS influence the number of voids per 24 hours (NM24);
- the level of ergotropic ANS activity influences a series of index groups (brainstem reflex activity, psycho-emotional state indices, OAB severity based on symptomatic questionnaires, etc.).

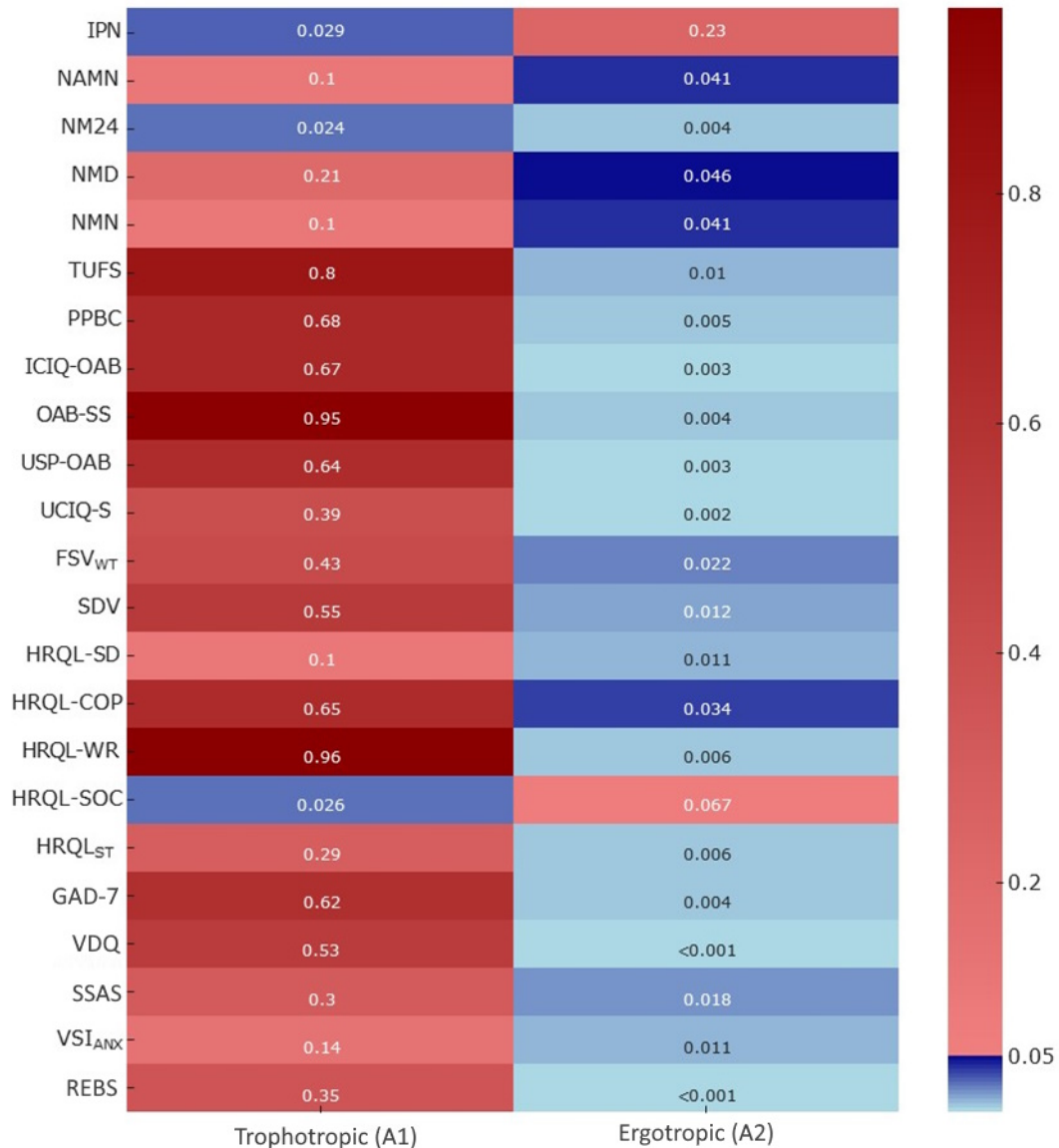


Figure 4.1. **Heat map of p-values (probability) for clinical variables associated with levels of suprasegmental autonomic activity (trophotropic/ergotropic)**

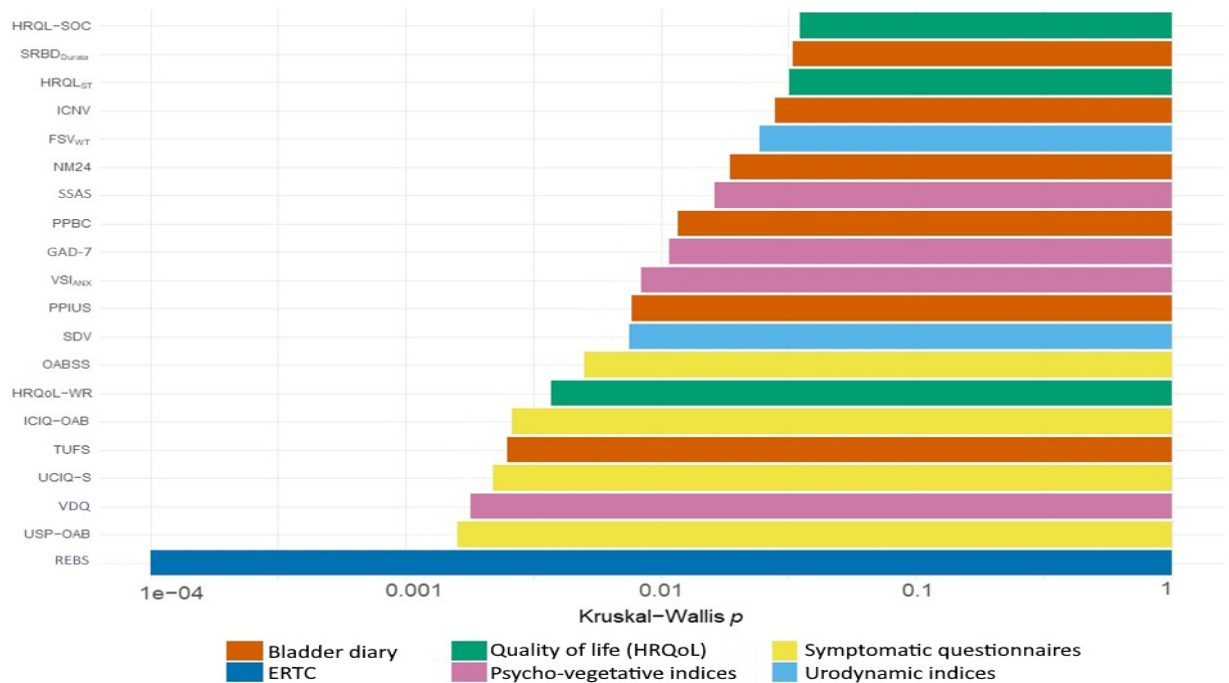
- post-hoc analysis revealed that in cases of increased trophotropic ANS activity, there are more severe values regarding the increase in the number of voids per 24 hours and the impact on the person's social activity (according to the *Social* scale in HRQoL), with a small size effect;
- post-hoc analysis revealed that in cases of increased ergotropic ANS activity, there are more severe values in multiple indices from different domains, indicating the worsening of OAB with increased sympathetic activity, with a predominantly medium-size effect.

## 5. ASSOCIATION OF UROLOGY AND NEUROPHYSIOLOGY INDICES WITH VARIATIONS OF SUPRASEGMENTAL SYMPATHETIC/PARASYMPATHETIC ACTIVITY IN WOMEN WITH OVERACTIVE BLADDER

Because the impact of different levels of suprasegmental vegetative activity (optimal/increased) depending on polarity (trophotropic/ergotropic) with clinical indices of OAB in patients with overactive bladder revealed complex and varying magnitude associations, it is appropriate to investigate the impact of different combinations (different association variants) of levels of suprasegmental vegetative activity (sympathetic/parasympathetic suprasegmental activity) in patients with OAB.

Comparing the frequency of different associations of sympathetic/parasympathetic suprasegmental activity between healthy women and patients with OAB, the following frequencies were observed for the 4 combinations: TO EO – *trophotropic optimal - ergotropic optimal*: healthy – 75 individuals (98.68%) versus 15 individuals (19.74%) in women with OAB; TO ES – *trophotropic optimal - ergotropic increased*: healthy – 1 individual (1.32%) versus 11 individuals (14.47%) in women with OAB; TS EO – *trophotropic increased - ergotropic optimal*: healthy – 0 individuals (0%) versus 9 individuals (11.84%) in women with OAB; TS ES – *trophotropic increased - ergotropic increased*: healthy – 0 individuals (0%) versus 41 individuals (53.95%) in women with OAB. The observed differences are statistically significant –  $\chi^2 = 98.3333$ ,  $df = 3$ ,  $p_\chi < 0.001$ .

We conducted a summary analysis of the results obtained based on the study of clinical indices manifestation in women with overactive bladder and the association with suprasegmental sympathetic/parasympathetic activity (subgroups with different variants of suprasegmental sympathetic/parasympathetic activity association), arranged by p-value (probability) based on the Kruskal-Wallis statistical test (Figure 5.1).



**Figure 5.1. Urological, psychovegetative indices, brainstem activity, and quality of life in patients with overactive bladder arranged by p p-value (probability, Kruskal-Wallis test) regarding the association with suprasegmental vegetative activity**

As seen in Figure 5.1, 20 variables among the tested clinical indices demonstrated associations of varying magnitude with parasympathetic/sympathetic suprasedgmental vegetative activity. Overall, by their nature, the closest associations are observed with the indices of brainstem reflex activity (REBS), the total scores of symptomatic urological questionnaires, and less with the indices of the voiding diary, urodynamics quality of life (HRQoL) indices. Largely, based on the size effect, a moderate to large effect of these associations is observed. In the post-hoc analysis (Conover Iman), it was observed that subgroups with an increased ergotropic component (ES) differ from the other groups by median values, especially the TO ES subgroup (optimal trophotropic – increased ergotropic), followed by the TS ES subgroup (increased trophotropic – increased ergotropic), indicating that with the presence of an increased ergotropic component in combined parasympathetic/sympathetic vegetative activity, the clinical indices of OAB show more severe values, indicating a more aggravated clinical picture of the disease.

## 6. SYNTHESIS OF OBTAINED RESULTS

The study was conducted based on the proposed hypothesis, according to which the traditional diagnosis of overactive bladder based on urological clinical/paraclinical criteria needs to be supplemented with psychovegetative indices and brainstem activity, which would allow the optimization of the personalised diagnosis of overactive bladder (urological-cerebral hypothesis).

Within the proposed hypothesis, before conducting clinical and paraclinical investigations, we performed a detailed analysis of the anamnesis and concomitant pathologies to determine the presence/absence of risk factors in patients with OAB (figure 6.1).

Based on the proposed objectives, we applied clinical urological investigation methods (objective examination, validated clinical questionnaires, self-reported 24-hour voiding diary), paraclinical urological methods (uroflowmetry, filling cystometry, pressure-flow study, ultrasonography), clinical psycho-vegetative methods (validated questionnaires, clinical scales), paraclinical neurophysiological methods (vegetative evoked potentials, brainstem reflex activity), and quality of life indices (HRQL-OABq questionnaire, subscales in urological questionnaires ICIQ-OAB, OABSS, USP-OAB, UCIQ-S).

In our study, we relied not only on clinical and paraclinical urological manifestations but also on the etiopathogenic links of OAB.

The proposed complex diagnosis includes the evaluation of generalized anxiety indices and/or visceral anxiety, indices of general sensory sensitivity and/or the urinary bladder-urethral complex, indices of vegetative dystonia, cutaneous vegetative evoked potentials, and the blink reflex, which will provide the possibility to develop a fundamentally new diagnostic algorithm (figure 6.2). This algorithm is based on the proposed cerebral urological hypothesis, which allows for personalised diagnosis by highlighting the etiopathogenic variants of OAB: visceral-urological variant, urological-anxious, urological-sensitive, urological-vegetative, urological-trunk reflex, as well as the association of these variants. Based on the deepening of the proposed hypothesis, new possibilities for diagnosis, monitoring, and personalised treatment of patients with OAB arise, depending on the etiopathogenic variants.

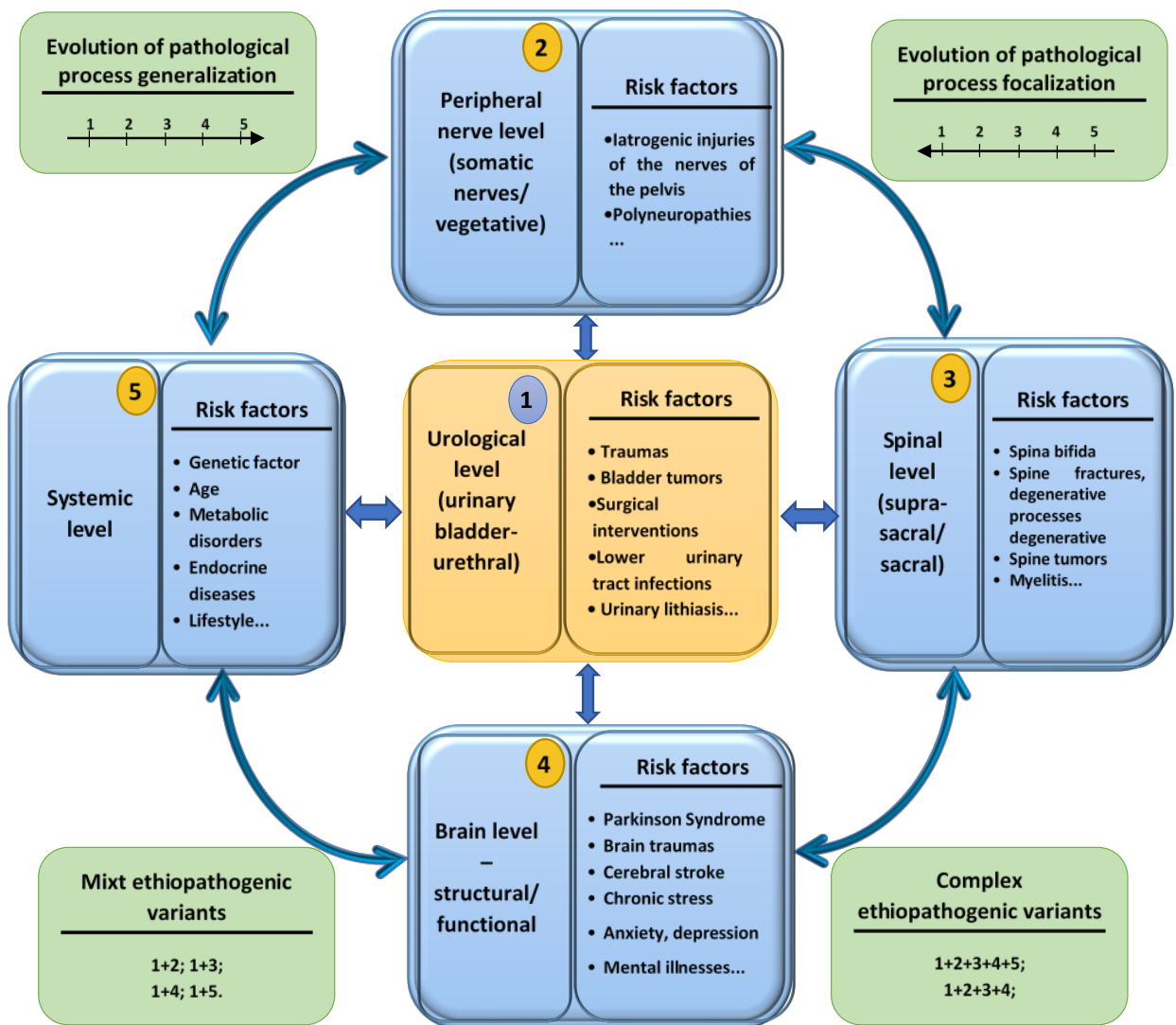


Figure 6.1. **Diagram of the diagnostic evaluation process of conditions and disorders at different levels of the organism as risk factors in patients with overactive bladder**

The diagnosis of the urologic-visceral variant is based on the absence of generalised anxiety ( $GAD-7 < 14$  points) and/or visceral anxiety ( $VSI < 34$  points), general sensory sensitivity ( $SSAS < 29$  points) and/or the urinary bladder-urethral complex ( $PPIUS < 2$ ,  $SR-BD_{Duration} < gr. 2$ ,  $PPBC < 4$ ), absence of vegetative dystonia ( $VDQ < 35$  points), sympathetic activity ( $A2 < 3.34$  mA) and parasympathetic activity ( $A1 < 0.66$  mA), and the reflex excitability of the brainstem ( $REBS < 0.7$ ).

The urologic-anxious variant is highlighted based on the confirmed diagnosis of OAB and in the presence of generalised anxiety ( $GAD-7 \geq 15$  points) and/or visceral anxiety ( $VSI \geq 35$  points).

The diagnosis of the urologic-sensitive variant is based on the presence of confirmed OAB according to international guidelines and in the presence of general sensory sensitivity ( $SASS \geq 30$  points) and/or the urinary bladder-urethral complex ( $PPIUS \geq 3$ ,  $SR-BD_{Duration} \geq gr. 3-4$ ,  $PPBC \geq 5$ ).

The diagnosis of the urologic-vegetative variant is based on the assessment of quantitative indices (amplitude of A1 and A2 waves) and qualitative indices (sympathetic/ergotropic, parasympathetic/trophotropic) of suprasegmental vegetative regulation processes, along with systemic clinical vegetative manifestations. The diagnosis was established based on the presence of OAB, vegetative dystonia ( $VDQ \geq 36$  points), and sympathetic ( $A2 \geq 3.5$  mA) and

parasympathetic ( $A1 \geq 0.81$  mA) activity.

The urologic-brainstem reflex variant is highlighted based on the confirmed OAB diagnosis and brainstem reflex excitability ( $REBS \geq 1.29$ ).

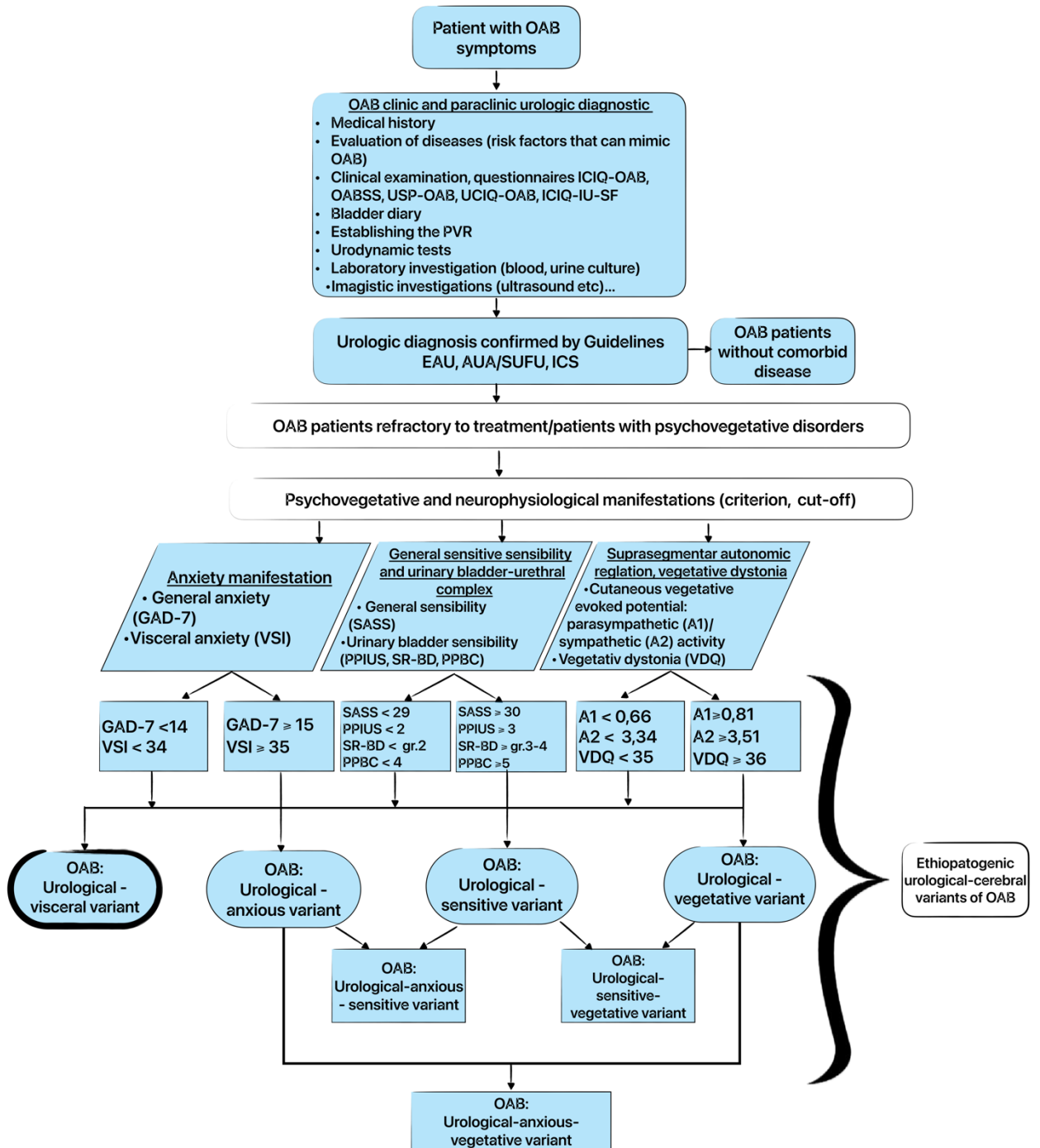


Figure 6.2. **Diagnostic algorithm for overactive bladder based on the structure of urologic manifestations and associated disorders**

Based on the identified etiopathogenic variants of OAB, it is possible to recommend personalised treatment for this condition. To illustrate these therapeutic possibilities, we analysed the corrective effect on disorders in a patient with overactive bladder, with increased brainstem reflex activity versus moderately low activity in another patient.

## GENERAL CONCLUSIONS

1. Based on the study, a new hypothesis is proposed for the diagnosis of overactive bladder, integrating clinical/urodynamic urological manifestations with suprasegmental vegetative regulation processes (cutaneous vegetative evoked potentials), systemic vegetative and psychovegetative dysfunctions in correlation with the functional state of the brainstem (blink reflex), where the micturition reflex centers are projected.
2. Diagnostic indices of the micturition calendar (nocturia - IN, NPMN, ICNV; bladder sensitivity - TUFS), the total score of the ICIQ-OAB symptom questionnaire, the urodynamic index PIP1, and the HRQoL-SOC subscale of quality of life can be influenced by both sympathetic and parasympathetic suprasegmental vegetative activity, serving as predictors in overactive bladder.
3. The indices of the micturition calendar (functional volume - VTUN; nocturia - NAMN; micturition frequency - NM24, NMD, NMN; bladder sensitivity - PPBC), symptomatic questionnaires (OABSS, USP-OAB, UCIQ-S), urodynamic indices (FSV, FDV, SDV); indices of the impact of overactive bladder on quality of life (HRQoL-COP, HRQoL-WR, HRQoLST), indices of psycho-emotional state (GAD-7, SSAS, VDQ, VSI) and the reflex activity of the brainstem (REBS) can be predominantly influenced by suprasegmental sympathetic vegetative activity in patients with overactive bladder.
4. In women with statistically significant overactive bladder, cases with increased values are more frequently encountered compared to healthy women, both for the level of suprasegmental vegetative trophotropic activity (65.79% vs 0%) and ergotropic activity (68.42% vs 1.32%). The evaluation of the impact of different levels (optimal/increased) of suprasegmental vegetative activity on the investigated indices revealed that ergotropic activity has a more pronounced impact on clinical variables compared to trophotropic activity; it is associated with more severe disorders in various domains, with the size effect being predominantly medium.
5. The statistical analysis regarding the presence of association (Kruskall Wallis), the direction of the association (post-hoc Conover-Iman test), and the strength of the association (size effect) revealed a moderate association of the indices of the voiding diary (NM24, TUFS, and PPBC), clinical questionnaires (ICIQ-OAB, OABSS, USP-OAB, UCIQ-S), urodynamic indices (SDV), anxiety (generalized, somatic, visceral), and quality of life domains (*Disturbance, Worry*) with the level of increased suprasegmental sympathetic vegetative activity. Quality of life is influenced not only by urological disorders but also by concomitant factors.
6. Based on the proposed urologic-cerebral hypothesis, the main etiopathogenic variants of overactive bladder (visceral-urologic, anxious, sensitive, vegetative, brainstem reflex) are highlighted, which allow for a personalised diagnosis of the condition and the development of innovative non-pharmacological treatment (e.g., transcranial direct current stimulation).

## PRACTICAL RECOMMENDATIONS

1. It is recommended for patients with overactive bladder and pronounced psychovegetative dysfunctions to analyze the anamnesis and current manifestations of diseases that can mimic overactive bladder or present risk factors (these diseases have a significant impact on the vegetative nervous system and, consequently, on the activity of the urinary bladder-urethral complex):
  - urinary bladder-urethral level (lower urinary tract infections, infravesical obstructions ...);
  - peripheral nervous level (polyneuropathies...);
  - sacral-suprasacral spinal level (spina bifida, myelitis...);
  - structural/functional cerebral level (stroke, Parkinson's syndrome ...);
  - systemic level (lifestyle, metabolic diseases ...).
2. The ICIQ-OAB questionnaire is recommended for assessing the severity of OAB as it is more informative compared to the OABSS, UCIQ-S, USO-OAB questionnaires for assessing the severity of OAB.
3. The personalised diagnosis of patients with OAB can be improved based on standardised clinical urological and urodynamic investigations in conjunction with psychovegetative indices and the reflex activity of the brainstem, which reflect the severity of the disease and the dynamics of the process towards focalization (improvement) or generalization (worsening).
4. Diagnosis of confirmed etiopathogenic variants of overactive bladder, based on the presence/absence of the following criteria:
  - urologic-visceral variant:  $GAD-7 < 14$ ,  $VSI < 34$ ,  $SASS < 2$ ,  $PPIUS < 2$ ,  $SR-BD_{Duration} < gr. 2$ ,  $PPBC < 4$ ,  $VDQ < 35$ ,  $A2 < 3.34 \text{ mA}$ ,  $A1 < 0.66 \text{ mA}$ ,  $REBS < 0.7$ ;
  - urologic-anxious variant:  $GAD-7 \geq 15$ ,  $VSI \geq 35$ ;
  - urologic-sensitive variant:  $SASS \geq 30$ ,  $PPIUS \geq 3$ ,  $SR-BD_{Duration} \geq gr. 3-4$ ,  $PPBC \geq 5$ ;
  - urologic-vegetative variant:  $VDQ \geq 36$ ,  $A2 \geq 3.5 \text{ mA}$ ,  $A1 \geq 0.81 \text{ mA}$ ;
  - urologic-brainstem reflex variant:  $REBS \geq 1.29$ .
5. It is recommended to develop the national protocol and include it in the investigation program for patients with overactive bladder:
  - application of psychovegetative questionnaires (GAD-7, VSI, SASS, VDQ);
  - paraclinical analysis of the activity of the suprasedgmental autonomic nervous system through the application of cutaneous vegetative evoked potentials;
  - analysis of the reflex activity of the brainstem through the analysis of blink reflex indices (activity of the reticular formation, where the micturition reflex centers are projected).



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## LIST OF SCIENTIFIC PUBLICATIONS AND EVENTS

where the research results were presented  
of the doctoral thesis in medical sciences,  
with the topic „**Diagnosis of overactive bladder in women and the impact of the autonomic nervous system**”, carried out within the Department of Urology and Surgical Nephrology,  
„Nicolae Testemițanu” State University of Medicine and Pharmacy, Republic of Moldova by  
**Mrs. IVANOV Mihaela**

- **Articles in accredited foreign journals**

- ✓ **articles in ISI, SCOPUS and other international databases\***

1. **Ivanov M.**, Colasurdo J., Galescu A., Lacusta V., Ceban E. Overactive bladder: correlation between urodynamic values and psycho-emotional indices in women. In: *Archives of the Balkan Medical Union*, 2023; 58(4): 358-367. **(IF:0.125)**

DOI: <https://doi.org/10.31688/ABM U.2023.58.4.07>

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- **Articles in accredited national scientific journals**

- ✓ **articles in category B journals**

3. **Ivanov M.**, Ceban E. Importanța diagnosticului preoperator urodinamic în tratamentul injectabil cu toxina botulinică la pacienți cu detrusor hiperactiv idiopatic. In: *Revista de Știință, Inovare, Cultură și Artă „Akademos”*, 2022;1:50-57. DOI: <https://doi.org/10.52673/18570461.22.1-64.07>
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- **Summaries/abstracts/theses in the works of national and international scientific conferences**
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9. **Ivanov M.**, Lacusta V. Non-invasive evaluation of autonomic nervous system dysfunction in idiopathic overactive bladder in woman. In: *Abstract book. MedEspera 2020: The 8th International Medical Congress for Students and Young Doctors*. Chişinău, 2020. pp. 86-87. ISBN 978-9975-151-11-5.
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- **Invention patents, innovation certificates, and materials at the invention salons**

- ✓ **Authors’s rights**

19. **Ivanov M.**, Ceban E., Lacusta V. *Indicii clinici urologici și urodinamici în subgrupe de paciente cu vezica urinară hiperactivă cu diferite variante de asociere ale activității simpatice/parasimpatice suprasegmentare*. AGEPI Nr. de intrare: 2580 din 23.01.2024.
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23. **Ivanov M.**, Ceban E., Lacusta V. *Evaluarea indicilor urologici și psiho-vegetativi la paciente în perioada reproductivă și climacterică cu vezica urinară hiperactivă*. Nr. 6161 din 02.01.2024
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- ✓ **Materials for invention salons**

- **Participation with communications at scientific forums:**

- ✓ **national with international participation:**

25. Lacusta V., Fala V., Bordeniuc G., **Ivanov M.** Interdisciplinary approach to the pain syndrome in masticatory muscle dysfunction. *International Black Sea Coastline Countries Scientific Research*

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✓ **national**

30. **Ivanov M.**, Galescu A., Ghicavii V., Ceban E. Rolul toxinei botulinice tip A în tratamentul vezicii urinare hiperactive (caz clinic). *Conferința științifică anuală „Cercetarea în biomedicină și sănătate: Calitate, excelență și performanță”* (Online), 20-22 Octombrie 2021. Chișinău, Republica Moldova.
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32. **Ivanov M.** Vezica urinară hiperactivă la femei: o analiză a corelației dintre parametrii urodinamici și aspectele psihoemoționale. *Conferința științifică anuală „Cercetarea în biomedicină și sănătate: Calitate, excelență și performanță”*, 18-20 Octombrie 2023. Chișinău, Republica Moldova.

● **Participation with posters at scientific forums:**

✓ **international**

33. **Ivanov M.**, Arian I., Ceban E. Botulinum toxin efficiency on overactive bladder and detrusor overactivity treatment in women. *Al XXXVIII-lea Congres National de Urologie, ROMURO 2022*, 25-28 mai 2022, București, România.
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✓ **national with international participation**

35. **Ivanov M.**, Galescu A., Ghicavii V., Arian I., Croitor O., Ceban E. Rolul parametrilor urodinamici și clinici la femeile cu vezica urinară hiperactivă. *The 37th Balkan Medical Week. The perspectives of*

*Balkan Medicine in the post COVID-19 era. 2023, 7-9 June, Chişinău, Republica Moldova.*

✓ **national**

36. Lacusta V., Fala V., **Ivanov M.**, Bordeniuc G., Grău C., Litovcenco A. Valoarea diagnostică a potențialului simpatic cutanat evaluat la angrenarea forțată a maxilarelor la pacienții cu dereglări autonome. *Congresul consacrat aniversării a 75 ani de la fondarea USMF „Nicolae Testemițanu”* 21-23 octombrie 2020, Chişinău, Republica Moldova.

## ANNOTATION

Ivanov Mihaela

### „Diagnosis of overactive bladder in women and the impact of the autonomic nervous system”

Doctoral thesis in medical sciences, Chişinău, 2024

**Thesis structure.** The thesis text is presented on 140 pages of main text, processed on a computer, consisting of: list of abbreviations, introduction, 6 chapters, general conclusions, practical recommendations, bibliography from 178 sources and 12 annexes. The illustrative material includes 3 tables, 31 figures, and 1 formula.

**Keywords:** overactive bladder, diagnosis, urodynamics, psychoemotional disorders, suprasegmental vegetative indices, brainstem.

**Field of study:** 321.22 – Urology and andrology.

**The aim of the work:** to analyze the clinical and urodynamic manifestations of overactive bladder in women and to complement with indices of suprasegmental autonomic nervous system activity, brainstem reflex activity, with the development of a complex diagnostic algorithm.

**Research objectives:** to analyze the clinical and paraclinical urological features in women with overactive bladder. To highlight the frequency of manifestation of suprasegmental vegetative dysfunction variants in patients with overactive bladder. To study the interrelation of clinical and urodynamic urological indices, psychovegetative indices, brainstem activity, and quality of life with suprasegmental vegetative activity in patients with overactive bladder. To study the variants of association of overactive bladder manifestations with levels of suprasegmental sympathetic/parasympathetic activity. To develop urological-neurophysiological criteria and a complex algorithm for optimizing the personalised diagnosis of overactive bladder.

**Scientific novelty and originality.** For the first time, personalised diagnosis of overactive bladder has been achieved based on the integration of clinical/urodynamic urological manifestations with clinical vegetative dysfunctions, suprasegmental sympathetic/parasympathetic vegetative regulation processes, and the reflex activity of the brainstem. The study has concluded that more severe urological disorders are predominantly associated with increased reflex activity of the brainstem and ergotropic regulation processes. For the first time, it has been demonstrated that the clinical/paraclinical polymorphism of overactive bladder depends on the differentiated involvement of the suprasegmental sympathetic/parasympathetic system and the reflex activity of the brainstem.

**Practical importance.** Personalised diagnosis of patients with overactive bladder can be achieved by associating urological manifestations with psychovegetative dysfunctions, brainstem reflex activity, and quality of life indices. For the first time, a diagnostic examination technology for patients with overactive bladder has been proposed, which includes three levels: 1) urological-visceral; 2) suprasegmental vegetative/psychovegetative; 3) brainstem reflex. The concept of involving the suprasegmental vegetative system and the reflex activity of the brainstem allows for an innovative therapeutic approach.

**Implementation of scientific results.** The scientific research results have been implemented in the research process, methodological and clinical activities at the Urology Department with the endourological office of the „Timofei Moşneaga” Republican Clinical Hospital, and in the teaching process at the Department of Urology and Surgical Nephrology of „Nicolae Testemiţanu” USMF.

## ADNOTARE

Ivanov Mihaela

### „Diagnosticul vezicii urinare hiperactive la femei și impactul sistemului nervos vegetativ”, Teză de doctor în științe medicale, Chișinău 2024

**Structura tezei.** Textul tezei este expus pe 140 pagini text de bază, procesate la calculator, fiind constituită din: lista abrevierilor, introducere, 6 capitole, concluzii generale, recomandări practice, bibliografia din 278 surse și 12 anexe. Materialul ilustrativ include 3 tabele, 31 figuri și 1 formulă.

**Cuvinte-cheie:** vezica urinară hiperactivă, diagnostic, urodinamica, dereglări psihoemoționale, indici vegetativi suprasedgmentari, trunchi cerebral.

**Domeniul de studiu:** 321.22 – Urologie și andrologie.

**Scopul lucrării:** analiza manifestărilor clinice și urodinamice a vezicii urinare hiperactive la femei și completarea cu indicii activității sistemului nervos vegetativ suprasedgmentar, activității reflectorii a trunchiului cerebral, cu elaborarea algoritmului complex de diagnostic.

**Obiectivele cercetării:** analiza particularităților urologice clinice și paraclinice la femei cu vezica urinară hiperactivă. Evidențierea frecvenței de manifestare a variantelor de disfuncție vegetativă suprasedgmentară la pacienți cu vezica urinară hiperactivă. Studiarea interrelației indicilor urologici clinici și urodinamici, psihovegetativi, activității trunchiului cerebral și calității vieții cu activitatea vegetativă suprasedgmentară la pacienți cu vezica urinară hiperactivă. Studiarea variantelor de asociere a manifestărilor vezicii urinare hiperactive cu nivelele de activitate simpatică/parasimpatică suprasedgmentară. Elaborarea criteriilor urologic-neurofiziologice și algoritmului complex pentru optimizarea diagnosticului personalizat al vezicii urinare hiperactive.

**Noutatea și originalitatea științifică.** În premieră diagnosticul personalizat al vezicii urinare hiperactive, s-a realizat în baza integrării manifestărilor urologice clinice/urodinamice cu disfuncțiile clinice vegetative, procesele de reglare vegetativă suprasedgmentară simpatică/parasimpatică și activitatea reflectorie a trunchiului cerebral. S-a stabilit că dereglările urologice mai severe sunt asociate preponderent cu sporirea activității reflectorie a trunchiului cerebral și proceselor de reglare ergotropă. Pentru prima dată a fost demonstrat că polimorfismul clinic/paraclinic al vezicii urinare hiperactive este în funcție de implicarea diferențiată a sistemului simpatic/parasimpatic suprasedgmentar și activitatea reflectorie a trunchiului cerebral.

**Importanța practică.** Diagnosticul personalizat al pacienților cu vezica urinară hiperactivă se poate realiza prin asocierea manifestărilor urologice cu disfuncțiile psihovegetative, activității reflectorii a trunchiului cerebral și indicii calității vieții. În premieră a fost propusă tehnologie de examinare diagnostică a pacienților cu vezica urinară hiperactivă, care include trei nivele: 1) urologic-visceral; 2) vegetativ suprasedgmentar/psihovegetativ; 3) trunchiular reflector. Conceptul implicării sistemului vegetativ suprasedgmentar și activității reflectorii a trunchiului cerebral permite o abordare terapeutică inovativă.

**Implementarea rezultatelor științifice.** Rezultatele cercetărilor științifice au fost implementate în procesul de cercetare, activitate metodologică și clinică în Clinica de urologie cu cabinet endourologic al Spitalului Clinic Republican „Timofei Moșneaga”, în procesul didactic de instruire la Catedra de urologie și nefrologie chirurgicală a USMF „Nicolae Testemițanu”.



## АННОТАЦИЯ

Иванов Михаела

„Диагностика гиперактивного мочевого пузыря у женщин и влияние вегетативной нервной системы”

Докторская диссертация в области медицинских наук, Кишинев, 2024

**Структура диссертации.** Основной текст, обработанный на компьютере, составляет 140 страниц и включает: список сокращений, введение, 6 глав, общие выводы, практические рекомендации, список из 278 библиографических источников и 12 приложений. Иллюстративный материал включает 3 таблицы, 31 рисунок и 1 формулу.

**Ключевые слова:** гиперактивный мочевой пузырь, диагностика, уродинамика, психоэмоциональные нарушения, надсегментарные вегетативные показатели, ствол головного мозга. **Область изучения:** 323.01 – Урология и андрология.

**Цель работы:** анализ клинических и уродинамических проявлений гиперактивного мочевого пузыря у женщин и дополнение данными о показателях активности надсегментарной вегетативной системы, рефлекторной активности ствола головного мозга, с разработкой комплексного алгоритма диагностики.

**Научно-исследовательские цели:** анализ особенностей клинической и параклинической урологической патологии у женщин с гиперактивным мочевым пузырем. Определение частоты проявления вариантов надсегментарной вегетативной дисфункции у пациенток с гиперактивным мочевым пузырем. Изучение взаимосвязи клинических и уродинамических урологических показателей, психовегетативных показателей, активности ствола головного мозга и качества жизни у пациенток с гиперактивным мочевым пузырем. Исследование вариантов ассоциации проявлений гиперактивного мочевого пузыря с уровнями надсегментарной симпатической/парасимпатической активности. Разработка уро-нейрофизиологических критериев и комплексного алгоритма для оптимизации персонализированной диагностики гиперактивного мочевого пузыря.

**Научная новизна и оригинальность.** Впервые была предложена персонализированная диагностика гиперактивного мочевого пузыря на основе интеграции клинических/уродинамических проявлений с клиническими вегетативными дисфункциями, процессами надсегментарной симпатической/парасимпатической регуляции и рефлекторной активности ствола головного мозга. Было установлено, что более тяжелые урологические нарушения в основном ассоциируются с увеличением рефлекторной активности ствола головного мозга и процессами эрготропной регуляции. Впервые было показано, что клинический и параклинический полиморфизм гиперактивного мочевого пузыря зависит от дифференцированной вовлеченности надсегментарной симпатической/парасимпатической системы и рефлекторной активности ствола головного мозга.

**Практическая важность:** Персонализированная диагностика пациентов с гиперактивным мочевым пузырем может быть осуществлена путем ассоциации урологических проявлений с психовегетативными расстройствами, рефлекторной активностью ствола головного мозга и показателями качества жизни. Впервые была предложена технология диагностического обследования пациентов с гиперактивным мочевым пузырем, включающая три уровня: 1) урологический-висцеральный; 2) надсегментарный /психовегетативный; 3) рефлекторный стволочной. Концепция вовлечения надсегментарной вегетативной системы и рефлекторной активности ствола головного мозга позволяет инновационный терапевтический подход.

**Внедрение научных результатов.** Результаты научных исследований были внедрены в исследовательский процесс, методологическую и клиническую деятельность в Клинике урологии с эндоурологическим кабинетом Республиканской клинической больницы им. Тимофея Мошнеага, в дидактическом учебном процессе на кафедре урологии и хирургической нефрологии ГУМФ «Николае Тестемицану» в Республике Молдова.

## LIST OF ABBREVIATIONS

<b>ANS</b>	Autonomic nervous system
<b>A1</b>	Intensity of the trophotropic (parasympathetic) response
<b>A2</b>	Intensity of the ergotropic (sympathetic) response
<b>CFV</b>	Functional capacity of the urinary bladder volume
<b>CVEP</b>	Cutaneous vegetative evoked potential
<b>DO</b>	Detrusor overactivity
<b>FDV</b>	First desire to void
<b>FSV</b>	First sensation of voiding
<b>FSV<sub>WT</sub></b>	First sensation of voiding – water test
<b>GAD-7</b>	General anxiety disorder – 7 questionnaire
<b>GAM</b>	Generalized Additive Model
<b>HRQoL-OABq</b>	Health-related quality of life scale in patients with OAB
<b>ICIQ-OAB</b>	International Consultation on Incontinence Questionnaire – OAB
<b>ICNV</b>	Index of Nocturnal Bladder Capacity
<b>IN</b>	Index of nocturia
<b>IPN</b>	Index of Nocturnal Polyuria
<b>IU<sub>UFM</sub></b>	Urination index (uroflowmetry)
<b>MCC</b>	Maximum cystometric bladder capacity
<b>NAMN</b>	Actual number of nocturnal voids
<b>NM24</b>	Number of voids/24 hours
<b>NMD</b>	Number of daily voids
<b>NMN</b>	Number of nocturnal voids
<b>NPMN</b>	Estimated number of nocturnal voids
<b>OAB</b>	Overactive bladder
<b>OABSS</b>	Overactive Bladder Symptoms Score
<b>PAU-BSR</b>	Psycho-autonomic urology brainstem reflective hypothesis
<b>PIP1</b>	Projected isovolumetric pressure
<b>PPBC</b>	The Patient's Perception of Bladder Condition
<b>PPIUS</b>	Patient Perception of Intensity of Urgency Scale
<b>PVR</b>	Post void residual volume
<b>REBS</b>	Reflex excitability of brainstem
<b>SDV</b>	Strong desire to void
<b>SR- BD<sub>Duration</sub></b>	Sensation-related bladder diary
<b>SSAS</b>	Somatosensory amplification scale
<b>TUFS</b>	Total urgency and frequency scale
<b>UCIQ-S</b>	Urgency Severity and Impact Questionnaire
<b>UDS</b>	Urodynamic tests
<b>UI</b>	Urinary incontinence
<b>USP-OAB</b>	Urinary Questionnaire Symptom Profiles – OAB
<b>VDQ</b>	Vegetative dystonia questionnaire
<b>VLA24</b>	Volume of fluid intake/24h
<b>VSI</b>	Anxiety-Related Visceral Sensitivity Index
<b>VTUN</b>	Total voided nocturnal volume
<b>VTU24</b>	Total voided volume/24h

**IVANOV, MIHAELA**

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**321.22 – UROLOGY AND ANDROLOGY**

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