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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи.** Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректуре авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Abstract.

Objective: To evaluate the clinical efficacy and safety of a combined rehabilitation program consisting of intradetrusor injection of botulinum toxin type A followed by a course of percutaneous tibial nerve stimulation (PTNS) in women with urgency urinary incontinence associated with diabetes mellitus.

Materials and methods: This prospective, non-randomized comparative clinical study included 135 women with type 2 diabetes mellitus. Of these, 105 women had urgency urinary incontinence persisting despite standard conservative therapy and entered the treatment comparison, and 30 women with diabetes mellitus but without urgency urinary incontinence or overactive bladder symptoms served as a non-incontinent reference (control) group. Assignment of the 105 symptomatic women to treatment was made prospectively on the basis of predefined clinical eligibility for third-line therapy and documented patient preference; no randomization procedure was used. The main group (n=50) received intradetrusor injection of botulinum toxin type A with hemagglutinin complex at a total dose of 300 U followed by 12 weekly PTNS sessions. The comparison group (n=55) received standard conservative therapy. The reference group received no study intervention and was used only for general clinical and nosological characterization; it was not included in any efficacy or safety comparison. The primary endpoint was the change in the number of daily urgency urinary incontinence episodes after 12 weeks.

Results: After 12 weeks, the frequency of urgency urinary incontinence episodes decreased from 5.8 ± 1.4 to 1.4 ± 0.8 episodes per day in the main group and from 5.7 ± 1.3 to 3.9 ± 1.2 episodes per day in the comparison group. The between-group difference in final values was -2.5 episodes per day (95% CI: -2.9 to -2.1; $p < 0.001$). The main group also demonstrated a more pronounced decrease in ICIQ-SF score, OAB-q Symptom Bother score and NGF/Cr level, an increase in effective voided volume, and improvement in pelvic floor ENMG parameters. Transient urinary retention was recorded in 3 patients (6.0%) in the main group and was reversible.

Conclusion: A combined program including intravesical botulinum toxin therapy and PTNS provides a statistically and clinically significant reduction in symptoms of urgency urinary incontinence in women with diabetes mellitus and has an acceptable safety profile. Dynamic monitoring of postvoid residual urine is necessary to reduce the risk of complications after botulinum toxin therapy. Because treatment was not allocated at random, these findings should be regarded as

hypothesis-generating and require confirmation in randomized controlled trials.

Key words. Urgency urinary incontinence, overactive bladder, diabetes mellitus, botulinum toxin, percutaneous tibial nerve stimulation, nerve growth factor.

List of Abbreviations.

BoNT-A - Botulinum Toxin Type A; CI - Confidence Interval; ENMG - Electroneuromyography; ICIQ-SF - International Consultation on Incontinence Questionnaire - Short Form; NGF - Nerve Growth Factor; NGF/Cr - Urinary Nerve Growth Factor-To-Creatinine Ratio; OAB - Overactive Bladder; OAB-q - Overactive Bladder Questionnaire; PTNS - Percutaneous Tibial Nerve Stimulation; PVR - Postvoid Residual Urine; STROBE - Strengthening the Reporting of Observational Studies in Epidemiology; UUI - Urgency Urinary Incontinence.

Introduction.

Urgency urinary incontinence in women with diabetes mellitus represents an important interdisciplinary problem involving urology, endocrinology and medical rehabilitation [1-4]. Unlike isolated idiopathic overactive bladder, storage symptoms in patients with diabetes mellitus often develop against the background of diabetic autonomic neuropathy, impaired sensory regulation of the bladder, altered detrusor contractile activity and secondary dysfunction of the pelvic floor muscles. This combination of factors is associated with a more severe clinical course, reduced quality of life, restriction of social activity and a higher probability of an insufficient response to standard conservative therapy.

Current clinical guidelines consider behavioral therapy, bladder training and pharmacological correction to be important components of overactive bladder management [5-7]. However, in patients with diabetes mellitus, anticholinergic drugs and beta-3 adrenoceptor agonists may have limited efficacy or insufficient tolerability because of comorbidity, polypharmacy and age-related factors [8]. Under these conditions, third-line methods, including intradetrusor injection of botulinum toxin type A and neuromodulation technologies, become particularly important.

Botulinum toxin type A reduces detrusor overactivity through effects on cholinergic transmission and sensory mechanisms of the urothelium [9-12], whereas PTNS modulates sacral reflex pathways through stimulation of the posterior tibial nerve [13-17]. Sequential use of these methods may affect two key pathogenetic components of UUI in patients with diabetes mellitus - motor detrusor overactivity and sensory neurogenic

dysregulation. However, clinical studies of the combined use of botulinum toxin therapy and PTNS specifically in women with UUI associated with diabetes mellitus remain limited.

The use of objective markers of efficacy provides additional scientific value. Along with voiding diaries and validated questionnaires, promising indicators include urinary nerve growth factor, which reflects sensory hyperactivity and neurogenic inflammation, and ENMG parameters of the pelvic floor muscles [18]. Comprehensive assessment of these indicators makes it possible to move from simple symptom registration to a pathogenetically based evaluation of the rehabilitation outcome.

Objective.

To evaluate the clinical efficacy and safety of a combined rehabilitation program including intradetrusor injection of botulinum toxin type A followed by a course of PTNS in women with urgency urinary incontinence associated with type 2 diabetes mellitus.

Materials and Methods.

Study design and participants: This was a prospective, single-centre, open-label, non-randomized comparative clinical study (a controlled quasi-experimental design) conducted at the clinics of Samarkand State Medical University. The report follows the STROBE statement for observational studies [19]. The overall design, group assignment and assessment schedule are summarized in Figure 1.

A total of 135 women with type 2 diabetes mellitus were enrolled. Of these, 105 women had clinically confirmed UUI corresponding to the OAB symptom complex that persisted despite standard conservative therapy, and 30 women had diabetes mellitus without UUI or OAB symptoms and formed the reference (control) group described below.

Group assignment:

No randomization procedure of any kind was used. Patients were not allocated by a random number sequence, by concealed envelopes, or by any other chance mechanism, and no allocation concealment or blinding of participants, treating clinicians or outcome assessors was applied. Instead, the 105 symptomatic women were assigned prospectively at the time of enrolment according to predefined clinical criteria and documented patient choice:

- women who met all inclusion criteria, had no contraindication to intradetrusor botulinum toxin injection or to electrical stimulation, were able to attend 12 consecutive weekly PTNS sessions, and gave separate written consent for third-line invasive treatment after a structured discussion of the expected benefits, risks and alternatives, were assigned to the main group (n=50);
- women in whom the invasive third-line option was contraindicated, who declined it after the same structured discussion, or who were unable to commit to the weekly PTNS schedule, continued optimized standard conservative therapy and formed the comparison group (n=55).

Because assignment followed clinical eligibility and patient preference rather than chance, the two treatment groups were not protected against selection bias by design. To make the residual

risk of confounding explicit, all baseline clinical, functional, biochemical and neurophysiological parameters were compared between the two groups before treatment (Table 1), and the structure of concomitant disease was compared as well (Table 2); the corresponding limitations are stated in the “Strengths and limitations” section.

Reference (control) group:

The 30 women of the reference group were recruited over the same period from the endocrinology service of the same institution. They had type 1 or type 2 diabetes mellitus of comparable clinical status but no urgency, urgency incontinence or other OAB symptoms, and therefore had no indication for any of the interventions studied. This group was defined a priori as a non-incontinent diabetic reference group with a single, explicitly descriptive purpose: to characterize the general clinical and nosological background - in particular the structure of concomitant somatic disease (Table 2) - against which UUI develops in women with diabetes mellitus, and thereby to show that the comorbidity profile of women with diabetic UUI is not simply that of the diabetic population at large.

Members of this group received no study intervention, underwent no repeat assessment at week 12, and contributed no data to any efficacy or safety comparison. Their data are consequently not pooled into the baseline efficacy comparisons of Table 1: they were neither symptomatic nor treated, so they cannot serve as an untreated control arm for a treatment effect and combining them with the symptomatic groups would produce a biased baseline. To make their inclusion informative rather than merely descriptive, the nosological distribution reported in Table 2 is now analysed statistically (see “Statistical analysis” and Table 2).

Inclusion and exclusion criteria:

The inclusion criteria for the two treatment groups were female sex; age 45-70 years; presence of type 2 diabetes mellitus; clinical symptoms of UUI and OAB; urgency, increased urinary frequency and/or nocturia; persistent symptoms despite previously administered standard therapy; ability to maintain a voiding diary and complete questionnaires; and written informed consent. The exclusion criteria were stress urinary incontinence as the predominant type of incontinence, active urinary tract infection, organic bladder pathology, pronounced lower urinary tract obstruction, decompensated somatic disease, pregnancy, lactation, and contraindications to botulinum toxin therapy or electrical stimulation.

A formal sample size calculation was not performed before the study, which was considered a methodological limitation. Nevertheless, the number of included patients made it possible to detect statistically significant differences in the primary endpoint after 12 weeks of follow-up.

Therapeutic interventions:

Patients in the main group underwent endoscopic intradetrusor injection of botulinum toxin type A with hemagglutinin complex at a total dose of 300 U. The study drug was Dysport® (botulinum toxin type A - hemagglutinin complex; Ipsen Biopharm Ltd., United Kingdom; marketing authorization holder: Ipsen Pharma, France; dosage form: lyophilizate for

solution for injection, 300 U per vial). The drug was injected into 15 standard detrusor sites, excluding the trigone of the bladder. This dosage refers to the specific botulinum toxin type A formulation with hemagglutinin complex used in the study protocol; activity units of different botulinum toxin preparations are not interchangeable, which is essential for the correct interpretation of safety.

The choice of a total dose of 300 U was made prospectively and rests on three considerations. First, 300 U of abobotulinumtoxinA is an established therapeutic dose for this indication: it was the dose used in a recent randomized clinical study of intradetrusor abobotulinumtoxinA in women with overactive bladder, which reported significant improvement in incontinence episodes, urinary frequency and quality-of-life scores [20]. Second, units of different botulinum toxin type A preparations are not interchangeable, and the abobotulinumtoxinA-to-

onabotulinumtoxinA conversion ratio most often applied in the lower urinary tract lies between approximately 2.5:1 and 3:1 [21]; a total dose of 300 U therefore corresponds approximately to the 100 U onabotulinumtoxinA dose established for idiopathic OAB, rather than to the higher doses (500-750 U abobotulinumtoxinA) used for refractory or neurogenic detrusor overactivity [22]. Third, and decisively for this population, higher abobotulinumtoxinA doses carry a substantially greater risk of impaired bladder emptying: in a direct comparative series, abobotulinumtoxinA 500 U was followed by symptomatic urinary retention requiring intermittent self-catheterization in 42% of patients, versus 23% after onabotulinumtoxinA 200 U, with no gain in symptomatic efficacy [21]. In women with diabetes mellitus, in whom diabetic cystopathy, impaired detrusor contractility and increased susceptibility to urinary tract infection make incomplete bladder emptying particularly

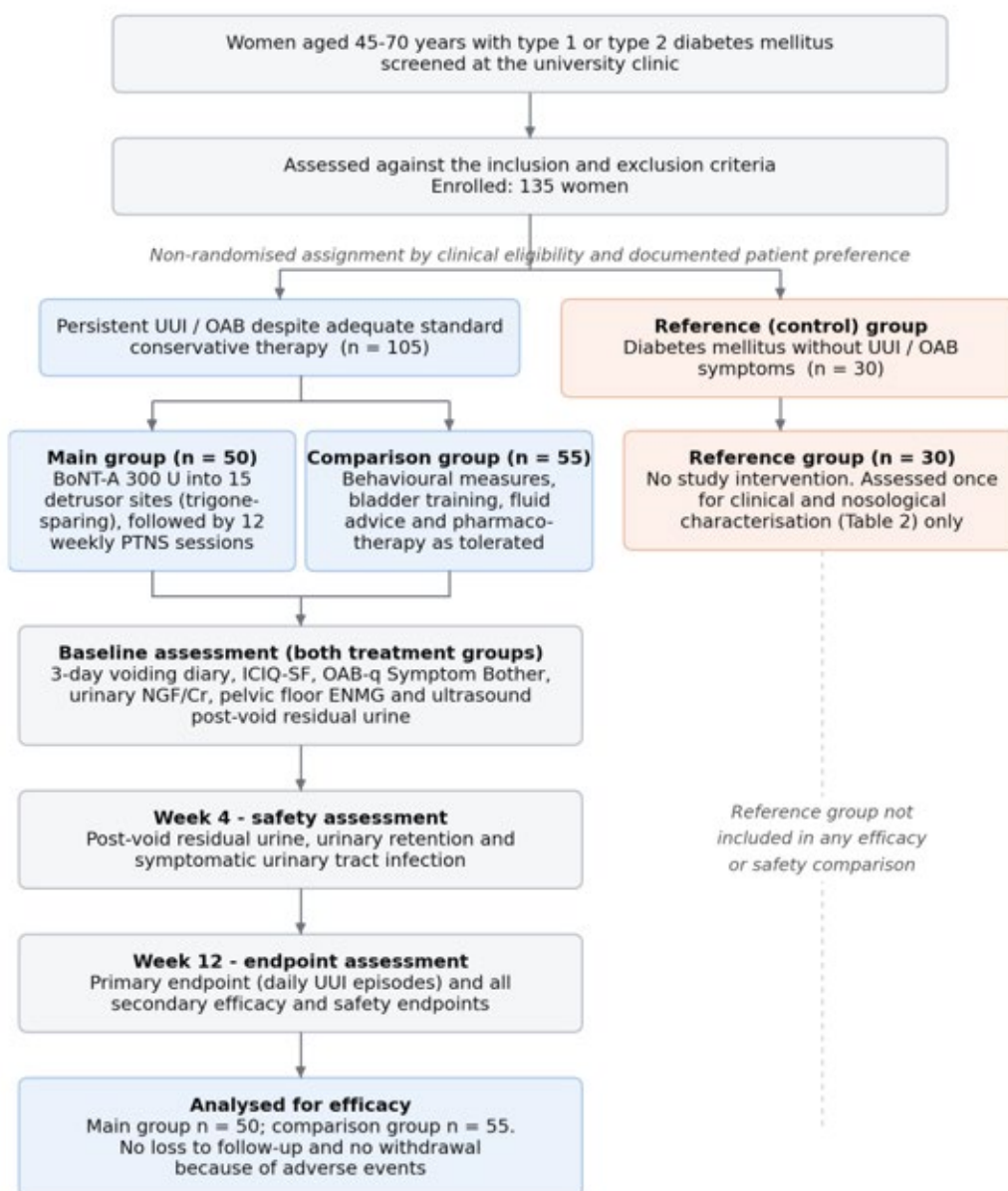


Figure 1. Study design, group assignment and assessment schedule. BoNT-A - botulinum toxin type A; PTNS - percutaneous tibial nerve stimulation; UII - urgency urinary incontinence; OAB - overactive bladder.

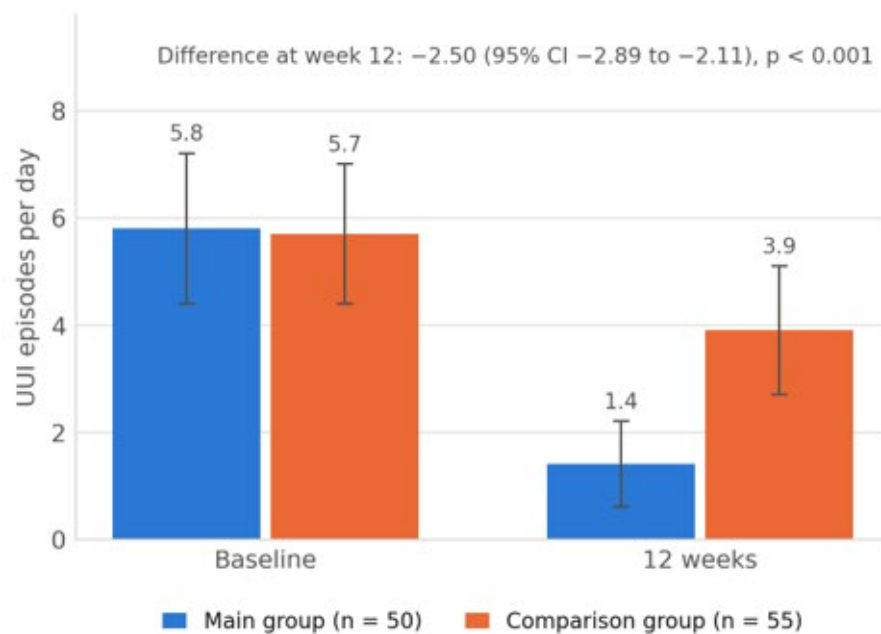


Figure 2. Dynamics of daily urgency urinary incontinence episodes at baseline and after 12 weeks of treatment. Bars show mean values; whiskers show standard deviations.

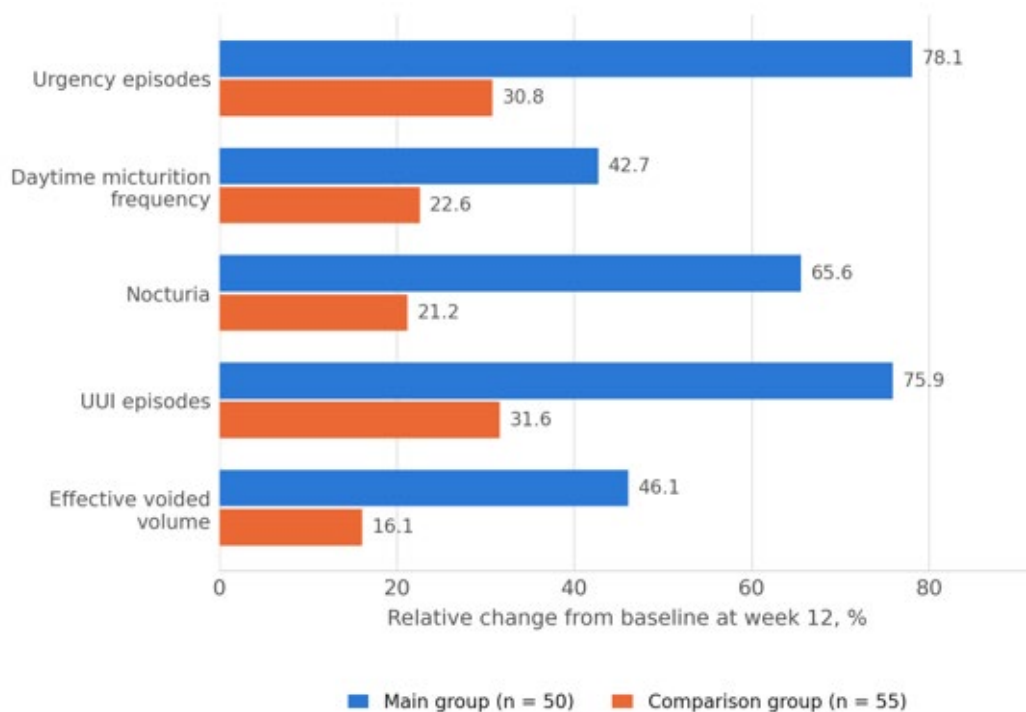


Figure 3. Relative improvement of key clinical parameters after 12 weeks of treatment (%).

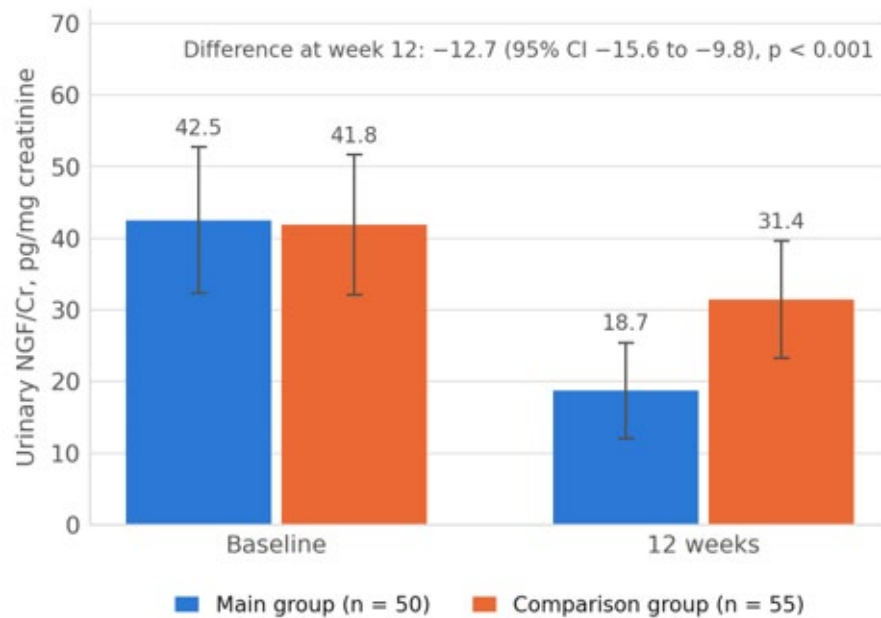


Figure 4. Dynamics of the urinary nerve growth factor-to-creatinine ratio (NGF/Cr) at baseline and after 12 weeks of treatment. Bars show mean values; whiskers show standard deviations.

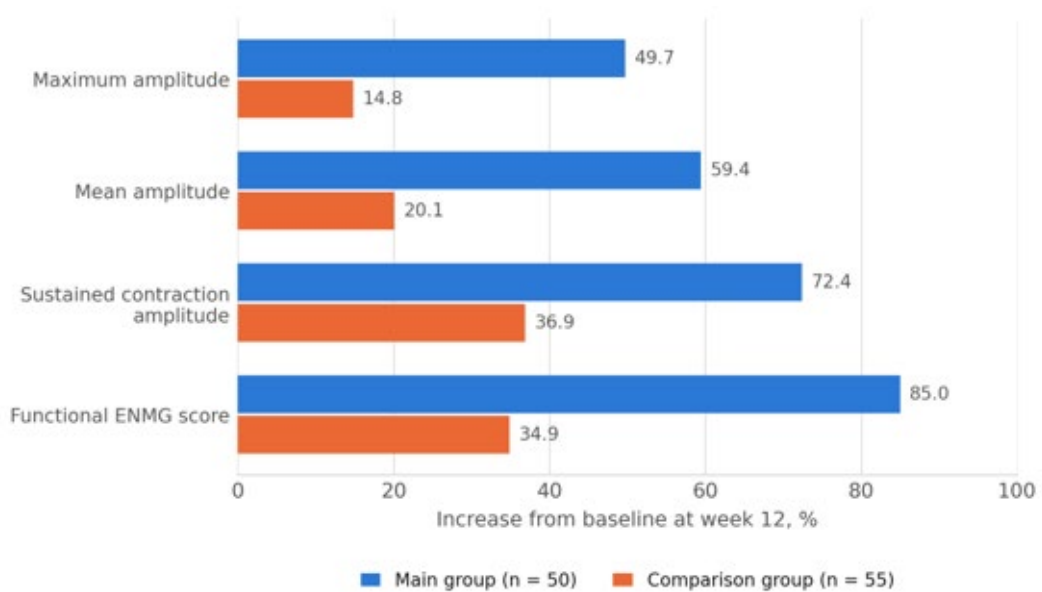


Figure 5. Relative dynamics of key ENMG parameters of the pelvic floor muscles after 12 weeks of treatment (%).

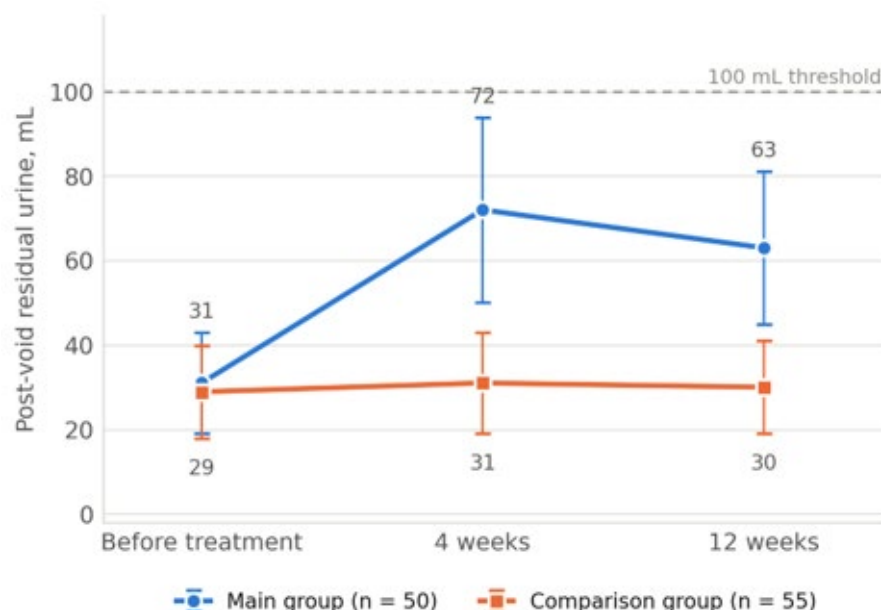


Figure 6. Dynamics of postvoid residual urine volume as a safety indicator of therapy. Symbols show mean values; whiskers show standard deviations. The dashed line marks the 100 mL threshold used clinically to prompt closer monitoring of bladder emptying.

Table 1. Baseline clinical and functional parameters of patients in the treatment groups.

Parameter	Main group (n=50)	Comparison group (n=55)	p
Urgency episodes, per day	9.6±1.9	9.4±1.8	0.582
Daytime micturition frequency, per day	11.7±2.0	11.5±1.9	0.601
Nocturia, episodes per night	2.9±0.8	2.8±0.8	0.524
UUI episodes, per day	5.8±1.4	5.7±1.3	0.706
Effective voided volume, mL	158.1±33.0	161.1±31.0	0.633
ICIQ-SF score	16.4±2.0	16.2±2.1	0.618
OAB-q Symptom Bother, 0-100 score	67.9±7.3	68.1±7.0	0.887
OAB-q Symptom Bother, original 8-48 scale	35.1±3.0	35.2±2.8	0.861
NGF/Cr, pg/mg creatinine	42.5±10.2	41.8±9.8	0.721
Maximum ENMG amplitude, µV	314.0±72.0	318.0±69.0	0.772
Urgency holding time, s	3.9±1.1	4.0±1.0	0.628
Postvoid residual urine, mL	31.0±11.9	28.9±11.0	0.351

Note. Data are presented as $M \pm SD$; Student's *t*-test or a non-parametric analogue was used for between-group comparisons depending on distribution. The reference (control) group is not shown in this table because its members had no UUI or OAB symptoms and received no intervention; including them would not provide a valid untreated comparator for the endpoints listed above.

Table 2. Distribution of patients by concomitant nosological groups excluding diabetes mellitus.

Nosological group	Main group (n=50)	Comparison group (n=55)	Reference group (n=30)	p ¹	p ²
Cardiovascular system	7 (14.0%)	15 (27.3%)	17 (56.7%)	0.149	<0.001
Musculoskeletal system and connective tissue	24 (48.0%)	27 (49.1%)	4 (13.3%)	1.000	<0.001
Bronchopulmonary system	8 (16.0%)	7 (12.7%)	1 (3.3%)	0.782	0.121
Gastrointestinal and hepatobiliary system	2 (4.0%)	4 (7.3%)	8 (26.7%)	0.680	0.003
Nervous system / psychoneurological pathology	4 (8.0%)	1 (1.8%)	0	0.189	0.586
Gynecological system	0 (0.0%)	0 (0.0%)	0	n/a	n/a
No other nosology except diabetes mellitus	5 (10.0%)	1 (1.8%)	0	0.100	0.338

Note. Data are presented as n (%). The reference (control) group comprises women with type 1 or type 2 diabetes mellitus without UUI or OAB symptoms, who received no study intervention. p^1 - Fisher's exact test, main group vs comparison group; p^2 - Fisher's exact test, both treatment groups combined ($n=105$) vs reference group ($n=30$).

Table 3. Dynamics of main clinical and functional parameters after 12 weeks of treatment.

Parameter	Main group: baseline -> 12 weeks	Comparison group: baseline -> 12 weeks	Relative change	Difference at week 12, 95% CI
Urgency episodes, per day	9.6±1.9 -> 2.1±1.0	9.4±1.8 -> 6.5±1.9	-78.1% / -30.8%	-4.40 (-4.98; -3.82)
Daytime micturition frequency, per day	11.7±2.0 -> 6.7±1.4	11.5±1.9 -> 8.9±1.6	-42.7% / -22.6%	-2.20 (-2.78; -1.62)
Nocturia, episodes per night	2.9±0.8 -> 1.0±0.5	2.8±0.8 -> 2.2±0.7	-65.6% / -21.2%	-1.20 (-1.43; -0.97)
UUI episodes, per day	5.8±1.4 -> 1.4±0.8	5.7±1.3 -> 3.9±1.2	-75.9% / -31.6%	-2.50 (-2.89; -2.11)
Effective voided volume, mL	158.1±33.0 -> 231.0±40.0	161.1±31.0 -> 187.0±35.0	+46.1% / +16.1%	44.0 (29.4; 58.6)
ICIQ-SF score	16.4±2.0 -> 5.2±1.6	16.2±2.1 -> 11.7±2.0	-68.5% / -27.5%	-6.50 (-7.20; -5.80)
OAB-q Symptom Bother, 0-100 score	67.9±7.3 -> 27.1±5.9	68.1±7.0 -> 50.0±7.1	-60.1% / -26.6%	-22.9 (-25.4; -20.4)
NGF/Cr, pg/mg creatinine	42.5±10.2 -> 18.7±6.7	41.8±9.8 -> 31.4±8.2	-56.0% / -24.9%	-12.7 (-15.6; -9.8)
Maximum ENMG amplitude, µV	314.0±72.0 -> 470.0±84.0	318.0±69.0 -> 365.1±73.0	+49.7% / +14.8%	104.9 (74.3; 135.5)
Urgency holding time, s	3.9±1.1 -> 6.1±1.4	4.0±1.0 -> 4.6±1.1	+56.3% / +15.2%	1.50 (1.01; 1.99)

Note. CI - confidence interval. *p* reflects between-group comparison of final values at week 12.

Table 4. Extended dynamics of ENMG parameters of the pelvic floor muscles.

Parameter	Main group baseline	Main group 12 weeks	Comparison group baseline	Comparison group 12 weeks	<i>p</i> at week 12
Maximum amplitude, µV	314.00±72.00	470.00±84.00	318.00±69.00	365.10±73.00	<0.001
Mean amplitude, µV	232.80±55.60	371.10±69.50	237.40±51.30	285.10±57.30	<0.001
Sustained contraction amplitude, µV	198.10±45.60	341.50±63.80	197.10±46.70	269.80±58.70	<0.001
Resting tone, µV	5.40±0.80	4.60±0.70	5.30±0.80	4.70±0.90	0.525
Activation latency, s	0.60±0.10	0.50±0.10	0.60±0.10	0.60±0.10	<0.001
Time to peak, s	1.70±0.30	1.40±0.30	1.60±0.30	1.50±0.30	0.091
Contraction holding time, s	3.80±0.60	5.80±0.80	4.00±0.50	4.70±0.60	<0.001
Relaxation time, s	2.60±0.40	2.00±0.40	2.60±0.30	2.30±0.40	<0.001
Fatigue index, %	35.90±4.20	26.10±5.40	35.20±4.60	28.60±4.80	0.014
Variability coefficient, %	22.10±2.80	18.40±2.90	22.50±3.80	20.40±4.30	0.006
Recruitment index	0.74±0.03	0.79±0.03	0.75±0.04	0.78±0.03	0.091
Symmetry index, %	83.00±4.70	88.80±4.30	83.50±3.90	87.20±4.50	0.065
Functional ENMG score, 0-100	35.40±7.40	65.50±10.00	37.30±7.70	50.30±7.10	<0.001

Note. Data are presented as *M*±*SD*. *p* reflects between-group comparison of final values.

Table 5. Treatment safety indicators.

Parameter	Main group (n=50)	Comparison group (n=55)	<i>p</i>
Postvoid residual urine before treatment, mL	31.0±11.9	28.9±11.0	0.351
Postvoid residual urine after 4 weeks, mL	72.0±21.9	31.0±12.0	<0.001
Postvoid residual urine after 12 weeks, mL	63.0±18.1	30.0±11.0	<0.001
Transient urinary retention, n (%)	3 (6.0%)	0 (0.0%)	0.105

Note. Data are presented as *M*±*SD* or *n* (%).

Table 6. Practical algorithm for combined rehabilitation of patients with UUI and diabetes mellitus.

Stage	Content	Clinical purpose
1. Patient selection	Confirmation of UUI/OAB and diabetes mellitus; exclusion of urinary tract infection, organic pathology, pronounced obstruction and contraindications	Prevention of inappropriate invasive therapy
2. Baseline assessment	Voiding diary, ICIQ-SF, OAB-q, NGF/Cr, ENMG and ultrasound assessment of postvoid residual urine	Formation of an objective baseline
3. Botulinum toxin therapy	Intradetrusor injection of botulinum toxin type A with hemagglutinin complex into 15 sites, excluding the bladder trigone	Reduction of detrusor overactivity and urgency
4. PTNS	Twelve weekly 30-minute sessions started 7-10 days after injection	Neuromodulation of sacral reflex pathways
5. Safety monitoring	Ultrasound assessment of postvoid residual urine after 4 and 12 weeks; assessment of urinary retention and infection	Early detection of controllable complications
6. Efficacy assessment	Repeated voiding diary, scales, NGF/Cr and ENMG after 12 weeks	Justification of further rehabilitation tactics

consequential [23-25], a dose at the lower end of the reported abobotulinumtoxinA range was therefore selected deliberately, in order to retain efficacy while minimizing the risk of clinically significant postvoid residual urine. The observed retention rate of 6.0% in the present study is consistent with that intention.

The PTNS course was started 7-10 days after botulinum toxin therapy. It included 12 weekly sessions lasting 30 minutes each. Stimulation was performed according to the standard technique targeting the posterior tibial nerve area. The clinical purpose of PTNS was neuromodulation of sacral reflex pathways involved in the regulation of bladder storage function.

Patients in the comparison group received standard conservative therapy, including behavioral recommendations, bladder training, correction of drinking habits, and pharmacological treatment according to the clinical situation and tolerability. If necessary, conventional physiotherapy methods were used as part of the standard rehabilitation program. The heterogeneity of standard therapy was considered a possible source of clinical variability when interpreting the results.

Endpoints and assessment methods:

The primary endpoint was the change in the mean number of daily UII episodes after 12 weeks according to a three-day voiding diary. Secondary endpoints included changes in urgency frequency, daytime micturition frequency, nocturia, effective voided volume, ICIQ-SF score, OAB-q Symptom Bother score, urinary NGF/Cr level, ENMG parameters of the pelvic floor muscles and postvoid residual urine volume.

Efficacy was assessed before treatment and after 12 weeks. Subjective symptom severity and impact on quality of life were evaluated using the validated ICIQ-SF and OAB-q Symptom Bother questionnaires. The biochemical activity of the sensory neurogenic component was assessed using the urinary NGF/Cr ratio. Functional status of the pelvic floor muscles was determined by ENMG with registration of maximum and mean amplitude, sustained contraction amplitude, resting tone, activation latency, time to peak, contraction holding time, relaxation time, fatigue index, variability coefficient, recruitment index, symmetry index and integrated functional ENMG score.

Safety was assessed by the frequency of adverse events, dynamics of postvoid residual urine volume after 4 and 12 weeks, presence of transient urinary retention and study discontinuation due to complications.

Statistical analysis:

Quantitative variables are presented as mean and standard deviation ($M \pm SD$). Normality of distribution was assessed using the Shapiro-Wilk test. Independent groups were compared using Student's t-test or the Mann-Whitney U test, and paired data were analyzed using the paired t-test or Wilcoxon test. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. For key endpoints, between-group differences in final values are additionally presented with 95% confidence intervals. The effect size for the primary endpoint was assessed as the standardized mean difference. Differences were considered statistically significant at $p < 0.05$.

All efficacy and safety analyses were restricted to the two treatment groups; the reference group entered only the descriptive comparison of nosological structure. In Table 2 the distribution

of concomitant disease was compared in two prespecified ways: between the main and comparison groups (Fisher's exact test), to document baseline comparability of the groups that were actually compared for efficacy, and between the two treatment groups combined ($n=105$) and the non-incontinent reference group ($n=30$), to characterize the comorbidity background of diabetic UII. Because several cells contained small counts, exact tests were used throughout for these comparisons. No adjustment for multiple comparisons was applied, and no multivariable or propensity-score adjustment for baseline confounders was performed; the comorbidity comparisons are therefore descriptive, and the efficacy analyses are unadjusted.

Ethical considerations:

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All patients signed informed voluntary consent to participate in the study and to allow processing of anonymized data. Women in the main group gave an additional, separate written consent for intradetrusor botulinum toxin injection after a structured discussion of benefits, risks, alternatives and the possible need for temporary catheterization. The study was approved by the Local Ethics Committee of Samarkand State Medical University (Protocol No. 7, November 10, 2022). The study was not prospectively registered in a public clinical trials registry, which is acknowledged as a limitation.

Results.

Baseline characteristics of patients:

Baseline clinical and functional parameters in the main group and the comparison group were comparable, which made it possible to correctly evaluate differences in treatment efficacy. No significant between-group differences were found before therapy in urgency frequency, number of UII episodes, questionnaire scores, NGF/Cr level, ENMG parameters or postvoid residual urine volume. Baseline comparability, however, was established by observation rather than secured by randomization, and unmeasured differences between the groups cannot be excluded.

Concomitant disease and the role of the reference group:

Concomitant somatic pathology was important for rehabilitation planning. In the structure of comorbidity among patients in the treatment groups, disorders of the musculoskeletal system and connective tissue predominated, followed by cardiovascular and bronchopulmonary pathology. These data emphasize the need for individualized treatment and monitoring of intervention tolerability in women with diabetes mellitus.

Two findings follow from the statistical analysis of Table 2. First, the main and comparison groups did not differ significantly for any nosological category (all $p \geq 0.10$), which supports their comparability at baseline in a study where comparability could not be secured by randomization. Second, the comorbidity profile of women with diabetic UII differed markedly from that of women with diabetes mellitus but no storage symptoms: musculoskeletal and connective tissue disorders were recorded in 48.6% of the treatment groups combined versus 13.3% of the reference group ($p < 0.001$), whereas cardiovascular disease (21.0% vs 56.7%; $p < 0.001$) and gastrointestinal or hepatobiliary

disease (5.7% vs 26.7%; $p=0.003$) were considerably more frequent in the reference group. The reference group thus documents that diabetic UUI in this cohort was not simply a marker of a generally sicker diabetic population, and it clarifies which comorbidities have to be taken into account when planning invasive rehabilitation. At the same time, precisely because the reference group differed so clearly in comorbidity structure, age-related risk profile and the absence of storage symptoms, it could not serve as a comparator for treatment effect, and it was not used as one.

Dynamics of symptoms according to voiding diaries and questionnaires:

After 12 weeks, the main group showed a more pronounced improvement in all key indicators of bladder storage function. The frequency of urgency episodes decreased from 9.6 ± 1.9 to 2.1 ± 1.0 per day, whereas in the comparison group it decreased from 9.4 ± 1.8 to 6.5 ± 1.9 per day. The number of UUI episodes decreased from 5.8 ± 1.4 to 1.4 ± 0.8 per day in the main group and from 5.7 ± 1.3 to 3.9 ± 1.2 per day in the comparison group. The relative reduction in UUI episodes was 75.9% versus 31.6%, respectively.

Figure 2 demonstrates a pronounced advantage of the combined program. In the main group, the number of UUI episodes decreased from 5.8 ± 1.4 to 1.4 ± 0.8 per day, whereas in the comparison group it decreased from 5.7 ± 1.3 to 3.9 ± 1.2 per day. The between-group difference after 12 weeks was -2.50 episodes per day (95% CI: -2.89 to -2.11; $p<0.001$), confirming the clinical significance of the effect.

At week 12, all key endpoint values differed significantly between the groups in favor of the combined program. For the primary endpoint, the between-group difference in final values was -2.50 UUI episodes per day (95% CI: -2.89 to -2.11; $p<0.001$), and the effect size was large (Cohen's $d=2.43$ in absolute value). This indicates not only statistical significance but also clinical relevance of the obtained result.

The combined rehabilitation program provided a more pronounced improvement in all clinical parameters. In the main group, reductions in urgency episodes, UUI episodes and nocturia were 78.1%, 75.9% and 65.6%, respectively, whereas the corresponding values in the comparison group were substantially lower - 30.8%, 31.6% and 21.2%. This indicates a comprehensive effect of botulinum toxin therapy and PTNS on symptoms of overactive bladder.

Dynamics of NGF/Cr and neuromuscular function of the pelvic floor:

The decrease in urinary NGF/Cr was more pronounced in the main group: from 42.5 ± 10.2 to 18.7 ± 6.7 pg/mg creatinine compared with a decrease from 41.8 ± 9.8 to 31.4 ± 8.2 pg/mg creatinine in the comparison group. The between-group difference in final values was -12.7 pg/mg creatinine (95% CI: -15.6 to -9.8; $p<0.001$), as shown in Figure 4. This makes it possible to consider the combined program not only as a symptomatic treatment, but also as a pathogenetically oriented method that affects sensory bladder hyperactivity.

According to ENMG data, patients in the main group demonstrated an increase in maximum and mean bioelectrical activity amplitude, an increase in sustained contraction

amplitude, a decrease in fatigue index and variability coefficient, and an increase in the integrated functional ENMG score. These changes indicate more stable and coordinated activation of the pelvic floor muscles after combined rehabilitation.

As shown in Figure 5, combined rehabilitation was associated with a more pronounced restoration of neuromuscular control of the pelvic floor. In the main group, the increase in maximum ENMG amplitude was 49.7%, mean amplitude 59.4%, sustained contraction amplitude 72.4%, and functional ENMG score 85.0%. In the comparison group, improvement was less pronounced, confirming the additional rehabilitation effect of PTNS combined with botulinum toxin therapy.

Treatment safety:

After botulinum toxin therapy, an expected transient increase in postvoid residual urine volume was recorded in the main group: from 31.0 ± 11.9 mL to 72.0 ± 21.9 mL after 4 weeks and to 63.0 ± 18.1 mL after 12 weeks. Transient urinary retention occurred in 3 patients (6.0%), was reversible and did not lead to discontinuation of participation in the study. Urinary retention was not recorded in the comparison group. The between-group difference in the frequency of urinary retention did not reach statistical significance according to Fisher's exact test ($p=0.105$); however, clinically it confirms the need for monitoring postvoid residual urine after botulinum toxin therapy.

The safety of the combined program was assessed considering the dynamics of postvoid residual urine volume, because this indicator is one of the key criteria for monitoring the risk of bladder emptying impairment after intradetrusor botulinum toxin therapy, as shown in Figure 6.

In the main group, an expected transient increase in postvoid residual urine was observed from 31.0 ± 11.9 mL to 72.0 ± 21.9 mL after 4 weeks and to 63.0 ± 18.1 mL after 12 weeks. In the comparison group, the indicator remained practically stable. These data confirm the acceptable safety profile of the intervention when mandatory ultrasound monitoring of postvoid residual urine is performed dynamically.

Practical algorithm for combined rehabilitation:

Based on the obtained data, the combined program can be considered a rehabilitation option in patients with UUI on the background of diabetes mellitus when standard therapy is insufficiently effective. To reduce the risk of complications, it is advisable to use a stepwise algorithm for patient selection, treatment and follow-up.

Discussion.

The obtained results show that sequential intradetrusor botulinum toxin therapy and PTNS in women with UUI associated with diabetes mellitus provides more pronounced clinical improvement compared with standard conservative therapy. The most important finding of the study is the significant reduction in the frequency of UUI episodes, which reached 75.9% in the main group versus 31.6% in the comparison group. Improvement was confirmed not only by voiding diaries but also by validated ICIQ-SF and OAB-q scales, the biochemical marker NGF/Cr and ENMG parameters of the pelvic floor muscles.

The clinical interpretation of these data is that the combined program acts at several pathogenetic levels. Botulinum toxin

type A reduces pathological detrusor activity and may decrease the release of mediators involved in sensory hyperactivity [9-12]. PTNS, in turn, has a modulatory effect on afferent and efferent sacral mechanisms controlling urination [15-17]. In diabetic autonomic neuropathy, when both sensory and motor components of bladder regulation are impaired, this multimodal strategy appears pathogenetically justified.

The dynamics of NGF/Cr deserve particular attention. This indicator decreased more than twofold in the main group and was accompanied by a pronounced reduction in urgency episodes and UII episodes. This is consistent with the concept of NGF as a marker of sensory bladder hyperactivity and neurogenic inflammation [18]. Including NGF/Cr in the efficacy assessment strengthens the evidence base of the study because it makes it possible to objectify the biological component of treatment response.

ENMG data also have important practical significance. Increases in maximum and mean amplitude, increased sustained contraction amplitude, decreased fatigue and improved functional ENMG score indicate better neuromuscular control of the pelvic floor. This is especially important in patients with diabetes mellitus because diabetic neuropathy may impair coordination of the pelvic floor muscles and reduce the patient's ability to suppress urgency.

The safety profile of the combined intervention was acceptable. Transient increase in postvoid residual urine after botulinum toxin therapy is an expected effect and requires scheduled monitoring. In the present study, urinary retention was observed in 6.0% of patients in the main group, was reversible and did not lead to withdrawal from the study. This result confirms that, with appropriate patient selection, patient information and monitoring of postvoid residual urine, combined therapy can be used without a significant increase in clinically dangerous complications.

The dose selected in this study deserves separate comment, because 300 U of abobotulinumtoxinA is lower than the 500-750 U most often reported in earlier series of intravesical abobotulinumtoxinA for refractory detrusor overactivity [22]. Two arguments support the more conservative dose in this population. First, efficacy at 300 U is documented: a randomized clinical study of intradetrusor abobotulinumtoxinA in women with OAB used exactly this dose and reported significant improvement in incontinence episodes and quality of life, with urinary retention requiring catheterization in 9.3% of patients [20]. Second, dose is the principal determinant of impaired emptying: abobotulinumtoxinA 500 U was followed by intermittent self-catheterization in 42% of patients, compared with 23% after onabotulinumtoxinA 200 U, without any efficacy advantage [21]. In women with diabetes mellitus, in whom detrusor contractility may already be reduced by diabetic cystopathy and the risk of urinary tract infection is elevated [23-25], that trade-off shifts further in favour of the lower dose. The retention rate of 6.0% observed here, together with a mean postvoid residual urine volume that remained below 100 mL at every time point, suggests that 300 U combined with trigone-sparing injection into 15 sites achieves a clinically useful effect at an acceptable emptying risk in this specific population. This dose should not be extrapolated to other botulinum toxin type A preparations, whose units are not interchangeable.

Comparison with current guidelines and published studies shows that botulinum toxin therapy and tibial neuromodulation are recognized methods for treating refractory OAB symptoms [5,7,11,15,17,26]. However, most studies consider these methods separately or in the general population of women with OAB. Where combinations have been examined, they have usually paired neuromodulation with pharmacotherapy rather than with intradetrusor toxin, and have reported additive benefit in idiopathic OAB [27]. The scientific novelty of the present study lies in its focus on patients with diabetes mellitus, the inclusion of the biochemical marker NGF/Cr and objective ENMG assessment of the pelvic floor, and the analysis of a sequential combined strategy.

The magnitude of the difference observed here should nevertheless be interpreted with the design in mind. Because women were assigned to the combined program partly on the basis of their own preference and of their ability to attend 12 consecutive weekly sessions, the main group may have been more motivated and more adherent than the comparison group, and part of the observed advantage may reflect that difference rather than the interventions themselves. The absence of blinding and of a sham PTNS control means that a placebo component cannot be excluded, although sham-controlled trials have shown that the effect of PTNS on detrusor overactivity incontinence is not attributable to placebo alone [14,15].

The practical value of the study lies in the possibility of using the proposed approach as a staged rehabilitation algorithm in patients with UII and diabetes mellitus when standard therapy is insufficiently effective. For clinical practice, it is important not only to prescribe the intervention, but also to correctly select patients, monitor postvoid residual urine, assess comorbidity and perform repeated objective evaluation of the result after 12 weeks.

Strengths and Limitations of the Study.

The strengths of the study include its prospective comparative design, the use of several independent levels of efficacy assessment, including voiding diaries, validated questionnaires, NGF/Cr and ENMG, and a separate safety analysis. This comprehensive approach reduces the risk of one-sided interpretation of the results and increases the clinical persuasiveness of the conclusions.

The principal limitation is that the study was not randomized. Assignment to the combined program or to standard therapy followed clinical eligibility and documented patient preference, so the groups were formed by a process that could favour the intervention arm: patients who chose an invasive third-line option and committed to 12 weekly sessions may differ systematically in motivation, adherence, symptom severity and general health from those who did not. Although no significant baseline differences were detected in any measured clinical, functional, biochemical or neurophysiological parameter (Table 1) or in the structure of concomitant disease (Table 2), unmeasured confounding cannot be excluded, and no multivariable or propensity-score adjustment was performed. The study was also unblinded at every level - participants, treating clinicians and outcome assessors - which may inflate the between-group difference in the patient-reported endpoints (voiding diary, ICIQ-SF, OAB-q) more than in the objective

ones (NGF/Cr, ENMG, postvoid residual urine). For these reasons the between-group differences reported here describe an association observed under routine clinical conditions and do not by themselves establish a causal treatment effect.

Further limitations concern design and scope. No formal sample size calculation was performed, and the study was not prospectively registered. It was conducted at a single centre, which limits generalizability. The design cannot separate the individual contributions of botulinum toxin therapy and PTNS, because no botulinum-toxin-only arm and no sham-PTNS arm were included; the study therefore quantifies the effect of the sequential program as a whole rather than the incremental benefit of adding PTNS. The comparison arm received heterogeneous standard therapy, which adds clinical variability. Follow-up was limited to 12 weeks, so the durability of the effect, the timing of repeat injection and long-term safety remain unknown. Finally, results were not stratified by duration of diabetes mellitus, HbA1c level, type of diabetes, body mass index, menopausal status or severity of diabetic autonomic neuropathy, all of which may modify the response.

These limitations do not negate the clinical significance of the observed results, but they define the next step: a multicentre randomized controlled trial - ideally with a botulinum-toxin-only comparator and a sham-stimulation arm, prospective registration, blinded outcome assessment and follow-up of at least 12 months - is required before the combined program can be recommended as established practice.

Conclusion.

1. The combined rehabilitation program, including intradetrusor injection of botulinum toxin type A followed by a course of PTNS, was associated with high clinical efficacy in women with UUI associated with type 1 or type 2 diabetes mellitus.
2. Compared with standard conservative therapy, the combined approach provided a more pronounced reduction in urgency frequency, UUI episodes, daytime micturition frequency and nocturia, as well as an increase in effective voided volume.
3. Improvement in clinical symptoms was accompanied by a marked decrease in ICIQ-SF and OAB-q Symptom Bother scores, a decrease in urinary NGF/Cr level and favorable dynamics of ENMG parameters of the pelvic floor muscles.
4. The safety profile of therapy was acceptable. The main controllable risk is a transient increase in postvoid residual urine after botulinum toxin therapy, which requires mandatory dynamic ultrasound monitoring.
5. The proposed approach can be considered as a pathogenetically justified option for comprehensive rehabilitation of patients with UUI and diabetes mellitus when standard treatment is insufficiently effective, pending confirmation in randomized controlled trials.

Practical recommendations.

1. In patients with UUI on the background of diabetes mellitus, a comprehensive assessment should be performed before choosing treatment, including a voiding diary, ICIQ-SF and OAB-q questionnaires, determination of postvoid residual urine, NGF/Cr and pelvic floor ENMG.
2. Combined use of intravesical botulinum toxin therapy and PTNS should be considered in patients with persistent UUI

symptoms after standard conservative therapy.

3. After intradetrusor injection of botulinum toxin, postvoid residual urine volume must be monitored, especially during the first 4-12 weeks after the intervention.
4. The efficacy of combined rehabilitation should be assessed not only by reduction in incontinence episodes, but also by quality-of-life indicators, biochemical markers and neurophysiological markers.

Conflict of interest.

The authors declare that they have no competing interests. No author has received funding, honoraria, consultancy fees or material support from Ipsen or from any manufacturer of botulinum toxin preparations or neuromodulation equipment.

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Author Contributions.

SMM conceived and designed the study, contributed to the methodology, data collection, investigation, and interpretation of the findings, and critically revised the manuscript. IMS contributed to the study methodology, data collection, investigation, and interpretation of the results, and critically reviewed the manuscript. KAY contributed to data collection, investigation, data curation, and interpretation of the findings, and critically revised the manuscript. MZF contributed to the methodology, investigation, data collection, and interpretation of the results, and critically reviewed the manuscript. KFT contributed to the study conception and methodology, supervised the scientific aspects of the study, contributed to interpretation of the findings, and critically revised the manuscript. MI contributed to the study conception and design, methodology, data analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, and overall supervision of the study. All authors contributed to the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

Data availability.

The anonymized datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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