Expert consensus on scientific evidence available on the use of botulinum toxin in overactive bladder

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Abstract

Objectives: Overactive bladder (OAB) is a pathology impairing patients’ quality of life and with a high percentage of patients who are refractory to medication. In this paper, technical opinion of an expert panel is assessed in order to gain the most reliable professional consensus on scientific evidence available on the criteria for the use of Onabotulinumtoxin A (OnabotA) in OAB.

Material and methods: According to DELPHI method, 42 panelists answered a survey of 93 items divided into four strategic areas including clinical criteria and recommendations in order to improve, at different levels, the current approach to patients with OAB. The recent advances in the field, areas of controversy and their real application possibilities in the different areas of our health care system were taken into consideration.

Results: Two rounds of the questionnaire were completed by all experts. In the first round, a criteria consensus was reached for 64 of 93 (68.8%) questions analyzed; in the second round the consensus reached was for 83 items evaluated (89.25%). An agreement among panelists was reached for: (1) definition, classification, detection and differential diagnosis; (2) medical treatment; (3) surgical treatment; and (4) role of OnabotA in the treatment of OAB.

Conclusions: The consensus is broadly in line with the latest scientific evidence on OAB. The panelists believe that it is necessary to propose a change in the current definition of OAB and

Keywords

Overactive bladder; Diagnosis; Treatment; Onabotulinumtoxin A; Delphi method
Consenso experto sobre la evidencia científica disponible acerca del uso de toxina botulinica en vejiga hiperactiva

Resumen
Objetivos: La vejiga hiperactiva (VH) es una enfermedad que afecta negativamente la calidad de vida y con un porcentaje elevado de pacientes refractarios a la medicación. Se pretende explorar la opinión técnica de un panel experto y alcanzar consenso en el criterio profesional en relación con la evidencia científica disponible sobre VH y Onabotulinumtoxin A (Onabota), mediante el debate de un panel de especialistas expertos.

Material y métodos: Encuesta realizada mediante el método Delphi a 42 panelistas con 93 items repartidos en 4 áreas estratégicas, que incluyen criterios y recomendaciones clínicas que pueden ayudar a mejorar en diferentes niveles el abordaje actual del paciente con VH. Se consideraron los avances recientes en la materia, las áreas de controversia y la valoración de sus posibilidades reales de aplicación a los distintos ámbitos asistenciales de nuestro sistema sanitario.

Resultados: Todos los expertos consultados completaron las 2 tandas del cuestionario. En la primera se apreció un consenso de criterio en 64 de 93 (68.8%) cuestiones analizadas, y en la segunda ronda 83 (89,25%) de los items consultados, estableciéndose un acuerdo entre los panelistas respecto a: 1) definición, clasificación, detección y diagnóstico diferencial; 2) tratamiento médico; 3) tratamiento quirúrgico; y 4) papel de Onabota en el tratamiento de la VH.

Conclusiones: El consenso logrado se ajusta ampliamente a la más reciente evidencia científica en VH. Los panelistas consideran que puede plantearse una modificación en la definición actual de VH, y que parece necesario mejorar las herramientas de cribado. El tratamiento médico de la VH debe ser individualizado, escalonado y progresivo. Onabota (Botox®) podría implicar ventajas con respecto a otros tratamientos, y se posiciona como una alternativa segura y eficaz para tratar la VH refractaria a fármacos.

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Background

Overactive bladder (OAB) has been defined since 2002 as the onset of urinary urgency, with or without urge incontinence, which can be accompanied by frequent urination and/or nocturia, provided other concomitant urinary tract diseases such as infection or lithiasis have been ruled out.\(^1\,^2\)

Its etiology is unknown but could be multifactorial and include nervous system (central and peripheral) or bladder muscle abnormalities.\(^3\) OAB has a high prevalence that increases with age. In Spain, OAB affects approximately 21.5% of the population over 40 years of age and approximately 30% of individuals older than 75 years, affecting men and women similarly.\(^4\) European and American epidemiological studies have revealed a similar epidemiology.\(^5\,^6\) Hu et al. estimated the financial cost of OAB in the US at more than 9 billion dollars annually, with more than 1 billion for the treatment of associated urinary infections. This does not take into account the costs due to loss of productivity and unquantifiable losses.\(^7\) The negative impact is also apparent in the patients’ quality of life due to the shame, frustration, anxiety, depression, sexual dysfunction, physical-psychological impairment, insomnia and urinary tract and skin infections resulting from OAB.\(^8\) Fifty-three percent of patients with OAB report that their symptoms are truly bothersome.\(^9\)

Treatment for OAB is usually based on dietary changes, fluid restriction, bladder training, pelvic physical therapy, biofeedback, electrical stimulation and drug therapy (anticholinergic agents as first-line treatment and beta-adrenergic agonists). Anticholinergic drugs often have adverse effects (dry mouth, blurred vision and cognitive changes), which do not occur with beta agonists,\(^10\) and the extended use of anticholinergic drugs decreases their efficacy. Other vanilliod drugs (capsaicin and resiniferatoxin) are under development.\(^11\) Onabotulinum toxin A (Onabota) has proven to be a therapeutic alternative in patients with refractory OAB, due to its ability to reversibly block motor and sensory nerve transmission by inhibiting the release of acetylcholine (effferent) and other neurotransmitters that participate in afferent signaling.\(^12\) This mechanism of action could explain the motor effect in the relaxation of the detrusor muscle and its sensory effect, such as the feeling of urgency.\(^12\)

In fact, the intravesical injection of Onabota is increasingly used as an intervention for refractory OAB.\(^13-19\) The efficacy and safety of Onabota has been demonstrated in 4 phase 3 trials, in the treatment of both neurogenic\(^20-22\)
and idiopathic OAB.\textsuperscript{22,21} The optimal dose in the treatment of neurogenic OAB is 200 U, which reduces the number of incontinence episodes in week 6 of the therapy by 100% in 37% of patients and by 50% in 76% of the patients.\textsuperscript{20-22} The optimal recommended dose in the treatment of idiopathic OAB is 100 U. In this case, the treatment reduced the number of incontinence episodes by 100% in 27.1% and by 50% in 60.5% of the patients included in the studies. The patients tolerated the treatment well; the most common adverse effects were urinary tract infection and urinary retention.\textsuperscript{20-24} Patients also showed significant improvements in quality of life according to standard scales.\textsuperscript{20-24}

A cost-effectiveness study showed that OnabotA\textsuperscript{\textregistered} is more cost-efficient when compared with anticholinergic treatment over a 2-year period.\textsuperscript{25} Due to the cost and loss of efficacy of anticholinergic agents, the use of toxins has been proposed for first or second-line treatment in women with urinary incontinence. The double-blind, randomized ABC trial compared the efficacy of 100 U of toxin versus anticholinergic agents in women treated for 6 months for moderate to serious urinary incontinence. The results of the trial favored OnabotA\textsuperscript{\textregistered}.

Although not accompanied by high levels of recommendation, expert consensus meetings are useful for clarifying new available evidence and facilitating the clinical management of patients in special conditions, as happens with the need for employing botulinum toxin in patients with OAB that is refractory to other treatments. These types of activities favor conceptual homogenization and decision making and attempt to unify the diagnostic and therapeutic criteria used in clinical practice.

Materials and methods

For the implementation of the study, we used the Delphi method modified by Lyn Paul.\textsuperscript{27} Under the direction of a scientific committee, the study was performed in 4 phases. In the first phase, the committee proceeded with a structured review of the most recently published quality literature (in English and Spanish) on OAB in order to select the contents of questionnaires. A national panel of 43 experts was then selected and formed by urologists from various autonomous communities, with special interest and experience in functional bladder disorders and OAB syndrome (Appendix 1).

In the second phase, the items for the survey were developed (professional criteria and clinical recommendations subjected to debate), using a previously employed, in-person, qualitative work procedure by the experts. The final version of the questionnaire included 93 items (see additional material attached), distributed in subject blocks as follows: 24 items on "the definition, classification, detection and differential diagnosis of OAB", 27 items on "the medical treatment of OAB", 20 items on "the surgical treatment of OAB" and 22 items on "the role of OnabotA in OAB". The project’s fieldwork was conducted between September 2012 and October 2012.

The third phase (which was not in person but was performed by an independent technical team) consisted of the application of a modified Delphi method that requested the individual expert’s anonymous opinion on the issue at hand through the completion of a structured written survey (sent by e-mail), in an anonymous and confidential manner. After this phase, there was a second round of surveys on the issues that failed to achieve consensus in the first round, providing the participants with the results obtained by the group in the first questionnaire, as well as the comments explaining their opinions (Fig. 1). A single type of rating scale was proposed for all issues. The scale was a 9-point ordinal Likert scale (1 strongly disagree; 9 strongly agree), based on the format developed by UCLA-Rand Corporation for the assessment method for the appropriate use of health technology.\textsuperscript{38,29} The response categories are described by means of language qualifiers in 3 regions (1-3 = 'disagree'; 4-6 = 'neither agree nor disagree'; 7-9 = 'agree').

The fourth phase corresponds to the collection and analysis of results. We used the median scores of the group and the level of correlation reached by the surveys, according to the following criterion: an item is considered agreed upon
when there is an “agreement” of opinion on the panel, i.e., when the number of experts who score outside the 3-point region that contains the median ([1–3], [4–6], [7–9]) is less than a third of those surveyed. In such cases, the median value determines the group consensus: The majority “disagree” with the item, if the median is \(\leq 3\), or the majority “agree” with the item if the median is \(> 7\). Items for which the median was in the 4–6 region were considered “questionable”. Conversely, a “disagreement” of opinion was determined to exist in the panel when the scores of a third or more of the panelists were in the 1–3 region and another third or more in the 7–9 region. The remaining items on which there was no agreement or disagreement were considered to have an “indeterminate” level of consensus. All items on which the group did not reach a clear consensus in favor or against the issue raised (questionable items, those in which disagreement was observed and those with an indeterminate level of consensus) were proposed for reconsideration by the panel in the second Delphi round. Items with a high distribution of opinions among those surveyed, with an IQR \(\geq 4\) points (scores within the Q1 and Q3 values of the distribution), were also submitted for reevaluation.

The Delphi method provides several advantages including anonymity, which avoids the “effect of authority” related to the evidence generated by the opinion of experts. On the other hand, its potential drawbacks include the difficulties in properly selecting professional experts on the subject and the difficulties in preparing the questionnaire for reaching a consensus. These drawbacks are solved by the selection of representative panelists of recognized prestige and with the proper preparation of an appropriate questionnaire by an objective scientific committee. The bias associated with this type of study is thereby reduced.

Results

The 42 experts completed 2 rounds of evaluation. Sufficient consensus was reached on 83 of the 93 items (89.25%), 78 (94%) agreed upon in terms of agreement with the statement, and the 5 remaining (6%) agreed upon in terms of rejection. In the first round, consensus was established for 64 of the 93 items. For the remaining 29 items proposed for reconsideration by the experts in the second round, consensus was achieved for 19 of the items. Ten of the items, however, did not achieve consensus, representing 10.75% of the opportunities for agreement in the overall series of statements and 34.5% of the opportunities for agreement in the second around.

The supplementary material lists the overall results of the project, indicating for each item the centering statistic (median), the distribution rate for those surveyed who are located outside the region chosen by the majority and the interquartile range. The addendum also identifies whether the item was accepted or rejected by the panel to facilitate the reading of each item in the tables.

Of the agreed-upon items, 9 achieved a median score of 9. Four of these issues corresponded to the definition, classification, detection and diagnosis block (questions 8, 13, 17 and 18). These items refer to the multifactorial etiology of OAB in the elderly, the urologist’s role as responsible specialist for referrals of complex cases or for patients who respond poorly to initial treatment, as well as the role of the urodynamics in patients with neurogenic bladder dysfunction, in OAB that does not respond to treatment and in complex UI. Only one item corresponded to the medical treatment block (question 26), which concerns the 2 well-differentiated treatment levels for OAB: the initial (conservative treatment, antimuscarinic agents) and the specialized (neuromodulation, OnabotA, surgery, stimulation of the posterior tibial nerve). Another 2 items focused on the surgical treatment block (questions 52 and 71), specifying that an assessment of symptom intensity and their impact on quality of life should be conducted before second-line treatment is started and that surgery is clearly justified when OAB is due to an obstructive prolapso. The last 2 items focus on OnabotA (questions 72 and 83), highlighting that this treatment is an effective and safe alternative in OAB refractory to anticholinergic agents and that a urine sediment and culture test should be conducted for all cases before starting this treatment (Fig. 2). The items that, in addition to achieving a median score of 9, had no panelist in disagreement were questions 8, 26, 52 and 72. Three of these focused on second-line treatment and the issues related to the use of OnabotA.

Of all the content agreed upon in the questionnaire, 5 were expressly rejected by group consensus, 4 in the definition and diagnostic chapter and 1 in the medical treatment chapter. These items dealt with considerations such as “OAB has a proper definition for care”’’, ”OAB screening tools are not needed”’’, “the frequency/volume sheet, the urgency diary and/or the urgency scale are dispensable”’’ and “lifestyle change recommendations have low efficacy”’’. None of the statements or items regarding surgical treatment or use of OnabotA were rejected.

Among the 10 proposals not agreed upon, 3 had majority but insufficient support from those surveyed. These were ”detrusor hyperactivity does not determine better or worse response to treatment” (34.1% disagree), ”onabotulinum toxin A can reverse refractoriness to antimuscarinic agents” (30.7% disagree) and ”if the effect of onabotulinum toxin A decreases, its endovascular instillation may be considered” (only 12.5% disagree). The disagreement in expert opinion was also made clear by the fact that more than 35% of the panelists disagreed with the items concerning ”the indication for pelvic floor muscle exercises”, ”the low efficacy of antimuscarinic agents”, ”the inappropriate handling of antimuscarinic agents in consultations”, ”the lack of evidence in peripheral electrical stimulation”, ”the scarcity of reference centers for neuromodulation can result in the undertreatment of refractory OAB”, ”the list of essential and recommended tests before injecting toxins” or ”whether repeated injections of toxin affects postvoid residual urine”. All of these issues reveal the disparity of professional opinion or a lack of criteria for the majority.

Discussion

The Delphi methodology is widely used in biomedicine and helps achieve professional consensus in a group of geographically dispersed experts. Successive rounds with processing and dissemination of interim result help achieve professional consensus, which results in the establishment of important
revisions to improve the quality of content and readability. The table below shows the consensus items on the use of botulinum toxin in overactive bladder.

<table>
<thead>
<tr>
<th>Questionnaire Items</th>
<th>Disagreement</th>
<th>No Consensus</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Is the detrusor injection of botulinum toxin a safe and effective alternative for the treatment of drug-refractory OAB?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Is the detrusor injection of botulinum toxin a safe and effective alternative for the treatment of anticholinergic-refractory OAB?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Is the injection of botulinum toxin into the detrusor safe and effective in 200-U doses?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D. Is the injection of botulinum toxin into the detrusor effective for treating drug-refractory OAB?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. Is treatment with botulinum toxin cost-effective compared to other therapies?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. Is the detrusor injection of botulinum toxin a safe and effective alternative for the treatment of anticholinergic-refractory OAB?</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Figure 2: Issues proposed to the expert panel on the role of botulinum toxin in the overactive bladder and the results from the 2nd round (disagreement, no consensus and agreement). To the right, the degree of consensus reached on the same issues is represented graphically.

recommendations aimed at decreasing variability in standard clinical practice. We have gathered relevant information about the main clinical controversies concerning the management of OAB and the indications and use of OnabotA. Specialists in this disease achieve a high degree of consensus on most issues and help establish the clinical positioning of this drug in the treatment of OAB.

The panelists generally rejected the current definition of OAB due to its ambiguity, multiple origins and to the fact that it precludes potential organic diseases, thereby encouraging diagnoses that are often inaccurate, sometimes wrong and that lead to overtreatment. There is a consensus to include other aspects in the definition of OAB to avoid errors and to consider a third category of OAB secondary to other diseases. There is also consensus in terms of the prevalence, symptoms and epidemiology of OAB, which is consistent with internationally published data. The panelists also considered necessary the use of diagnostic screening tools
and increased training in the disease, especially in primary care.35

In terms of the clinical, diagnostic, therapeutic and prognostic differences associated with detrusor hyperactivity, it has been demonstrated that various treatments for OAB (pharmacological, neuromodulation and OnabotA) have an inhibitory effect not only on detrusor contractility (motor or efferent), but also on the afferent or sensory element (c fibers). Thus, the lack of an increase in the motor phenomenon such as detrusor hyperactivity would not preclude treatment.34

Based on the judgment of most panelists, the medical treatment of OAB must be individualized, phased and progressive due to its multiple etiology (neurogenic, muscle or other), severity and potential pharmacological contraindication. Treatment should start with conservative therapy, which should include pelvic floor muscle training for women. In terms of drug treatment based on antimuscarinic agents, the panelists reported low compliance and disagreement regarding the efficacy and clinical management.35 The associated causes were treatment intolerance, reported adverse events and the loss of efficacy after extended treatment.11,14,36 There are indeed significant variations in antimuscarinic treatment for patients with OAB.37 Additionally, other issues such as the role of beta-adrenergic agonists (mirabegron)38,39 and even its possible combination with antimuscarinic agents,40 the night-time dosage of antimuscarinic agents and the combination with other drugs41 also result in a lack of consensus on the results.

In terms of the surgical treatment of OAB, there was broad consensus on the need to measure symptoms intensity and their repercussion on quality of life before starting second-line treatments. The OABQ-SF scale is probably the best questionnaire for assessment and follow-up.41 For the treatment of refractory OAB, the use of OnabotA and sacral neuromodulation has been endorsed by various publications.42-44 Other techniques such as peripheral electrical stimulation (intravaginal or endoanal) and neuromodulation using TENS or SANS (posterior tibia) are simple and economic procedures.45 Sacral neuromodulation is more complex and has a high financial cost.46

The use of OnabotA in the treatment of OAB refractory to drugs stands as an effective and safe alternative.42,43 The approved dosage for neurogenic and idiopathic OAB is 200U and 100U, respectively.17,19,43 Another characteristic worth highlighting is its simple administration, which represents a significant advantage over sacral neuromodulation.44 OnabotA is also a cost-effective short to medium-term treatment when compared to drug treatment. Long-term OnabotA treatment is similar, and even superior, to sacral neuromodulation.25,26

Conclusion

The consensus achieved by a group of specialists closely matches the most recent scientific evidence on OAB. The panelists considered that a change in the current definition of OAB could be contemplated, due to its ambiguity and to its exclusion of other possible causes. The panelists also emphasized the need for improving screening tools. Finally, it is worth noting that medical treatment of OAB should be individualized, phased and progressive in relation to the various etiologies. Botulinum toxin A (Botox®) could have advantages when compared with other treatments and is a safe and effective alternative for treating OAB refractory to drugs.

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Conflicts of interest

Spanish Urological Association sponsored the present project, in collaboration with Allergan S.A. Allergan S.A. has not participated in the design, data analysis or drafting of the present article. Luzán S performed administrative support necessary for the implementation of this study, including the design, data collection and analysis.

The authors declare that they have no conflicts of interest.

Addendum 1. Expert panel

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acuroe.2014.02.010.

References

Botulinum toxin in overactive bladder


