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Advancements in the management of overactive bladder in women using nano-botulinum toxin type A: A narrative review

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Abstract

Intravesical injections of botulinum toxin type A (BTX-A) are effective for treating refractory overactive bladder (OAB) in women. However, the adverse effects linked to the injections, such as hematuria, pain, and infection, and need for repeated injections can lower patient compliance and make the treatment inconvenient. Hence, urologists are actively pursuing less invasive and more convenient methods for the intravesical delivery of BTX-A. Advances in nanotechnology have facilitated noninvasive intravesical drug delivery. Currently, liposomes, hydrogels, nanoparticles, and many other forms of carriers can be used to enhance bladder wall permeability. This facilitates the entry of BTX-A into the bladder wall, allowing it to exert its effects. In this review, the feasibility and efficacy of liposomes, thermosensitive hydrogels, and hyaluronic acid-phosphatidylethanolamine for the treatment of OAB in women are discussed along with recent animal experiments on the use of nanotechnology-delivered BTX-A for the treatment of OAB in female rat models. Although the clinical efficacy of nanocarrier-encapsulated BTX-A for the treatment of OAB in women has not yet matched that of direct urethral muscle injection of BTX-A, improvements in certain symptoms indicate the potential of bladder instillation of nanocarrier-encapsulated BTX-A for future clinical applications. Consequently, further research on nanomaterials is warranted to advance the development of nanocarriers for the noninvasive delivery of BTX-A in the bladder.

Keywords: Botulinum toxin; Drug delivery; Hydrogel; Liposomes; Nanoparticle

1. Introduction

Overactive bladder (OAB) is defined by the International Continence Society as "urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, with no proven infection or other obvious pathology."[1] Urinary urgency is the most striking feature of OAB; it is defined as the sudden onset of an intense urge to urinate that is difficult to postpone. An accurate estimation of the prevalence of OAB poses challenges and tends to increase with age, varying between 7.0% and 30.3% in women aged over 30 years.[2] A recent study reported a gradual increase in the prevalence of OAB among Chinese women.[3] The prevalence rate has increased, from 8% before 2006 to 18% between 2016 and 2021. Overactive bladder not only affects the quality of life of the patient but also contributes to a higher prevalence of other conditions, such as depression, metabolic syndrome, and fractures.[4–6]

Behavioral therapies (e.g., bladder retraining and pelvic floor muscle training) and oral medications (e.g., antimuscarinic medications and beta-3 adrenergic agonists) play an important role in the treatment of OAB as first- and second-line therapies, respectively.[7,8] Failure of first- and second-line therapies for treating OAB occurs due to various reasons, including poor long-term compliance, constipation, dry mouth, dementia, and other side effects caused by anticholinergic medications; this often leads to confusion regarding patient treatment.[9] Botulinum toxin A (BTX-A), delivered using intravesical injection, is recommended in both the European Association of Urology and American Urological Association guidelines as third-line therapy for refractory OAB.[8,10,11]

Botulinum toxin (BTX), which originates from *Clostridium botulinum*, is divided into 7 types using serotyping: BTX (A-G).[12] Botulinum toxin, which is renowned for its potency as a neurotoxin, has been extensively applied in the treatment of diverse ailments owing to its uncommon prevalence in humans and their lack of immunity to the same.[13,14] Botulinum toxin A is the longest acting and most widely utilized subtype in clinical practice, including urologic diseases. Although BTX-A plays an important role in functional urological disorders, its clinical use is still limited by the adverse effects associated with the intravesical injection of BTX-A in a therapeutic manner, such as hematuria, bladder pain, leakage or uneven distribution of the drug, and infection.[15] Injection of BTX-A under local anesthesia is often associated with pain and poor patient tolerance. In addition, as the efficacy of BTX-A decreases over time, repeated injections may be required for patients with recurrent symptoms, and the inconvenience and side effects of intravesical BTX-A injections often lead to decreased adherence in some patients.[16,17]

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Therefore, urologists need to find new methods of intravesical drug delivery (IDD) for BTX-A to alleviate patient pain and the associated side effects of intravesical injections.

Nanomaterials are generally defined as materials with a diameter between 1 and 100 nm. The advantages of nanomaterials over traditional drug delivery materials include a high surface area-to-volume ratio, high bioavailability, precise targeting properties, and a controlled drug release rate.[18] Nanomaterials with different sizes, shapes, chemical compositions, and surface chemical properties can be developed for drug delivery in various ways.[18] Considering their potential for multiple drug delivery benefits, nanomaterials show significant promise as drug delivery vehicles.

This review aimed to discuss the advancements in utilizing nanomaterial-encapsulated BTX-A for the treatment of OAB in women, along with relevant animal experimentation.

2. Bladder structure and barrier mechanisms

The bladder is an organ that stores urine for a short period and plays an important role in preventing toxic substances from attacking the body. There are 4 layers of the bladder wall from the outside to inside: the adventitia covering the outer surface of the bladder, muscularis consisting of detrusor muscles, submucosa and mucosa consisting of the lamina propria, and transitional epithelium.[19] The urothelium is a stratified transitional epithelium that prevents the body from absorbing toxic substances in the urine and pathogens from the external environment.[20,21] The urothelium is composed of 3 types of cells: basal, intermediate, and superficial (also known as umbrella cells).[21] Basal cells are localized along the basement membrane and are the most numerous and smallest cell population among the different species of human urothelium.[22,23] The intermediate layer of the urothelium consists of approximately 5 layers of intermediate cells that are responsible for the rapid production of the urothelium in cases of injury or infection.[24] Umbrella cells are located on the apical surface; they maintain the impermeability of the urothelium and form a high resistance barrier.[21] The 3 types of cells in the urinary epithelium coordinate and work with each other to keep the bladder impermeable to the bladder wall during storage and urination. Therefore, this layer of the urothelium is also known as the bladder permeability barrier (BPB), as shown in Figure 1.[25]

The BPB has profound implications in the construction of carriers for drug delivery. Umbrella cells are the main cells involved in the BPB function. The tight junctions of the umbrella cells reduce the permeability of solutes, ions, and some lipids in urine, and the plaques covering the apical membrane block small molecules such as water and urea.[26] Each plaque contains approximately 1000 subunits composed of 4 major urokinases: UPIa (27 kilodalton [kDa]), UPIb (28 kDa), UPII (15 kDa), and UPIII (47 kDa).[27] In addition, the glycosaminoglycan (GAG) layer on the surface of the urethra has antiadhesion, anti-infection, and histolytic effects on tight junctions.[28] As a result, the BPB of the urinary epithelium limits the permeability and adhesion of the drug in the bladder, leading to a decrease in the effectiveness of the drug and, ultimately, the inability to achieve the desired therapeutic effect.

3. Drug mechanism of BTX-A

Botulinum toxin A is a protein containing a 50 kDa light chain and 100 kDa heavy chain, which are connected by a disulphide bond and noncovalent bonds.[29] The protein consists of 3 structural domains: 2 in the heavy chain and 1 in the light chain.[30] Each structural domain has a specific molecular function. The light chain is a zinc-dependent protease with a catalytic activity. Heavy chains are transport carriers in which the *N*-terminal structural domain (~50 kDa) of the heavy chain is responsible for transporting the light chain to the cell membrane, and the C-terminal domain (~50 kDa) is responsible for recognizing specific cell surface receptors.[31]

When BTX-A comes into contact with the cell membrane surface, the receptor-binding domain at the C-terminal of the heavy chain binds to the polysialogangliosides on the cell surface. Subsequently, the BTX-A is internalized by binding glycosylated Sv2.[32] Internalized BTX-A remains in the synaptic vesicles. Afterward, H+ enters the vesicle through its proton pump, causing the vesicle to

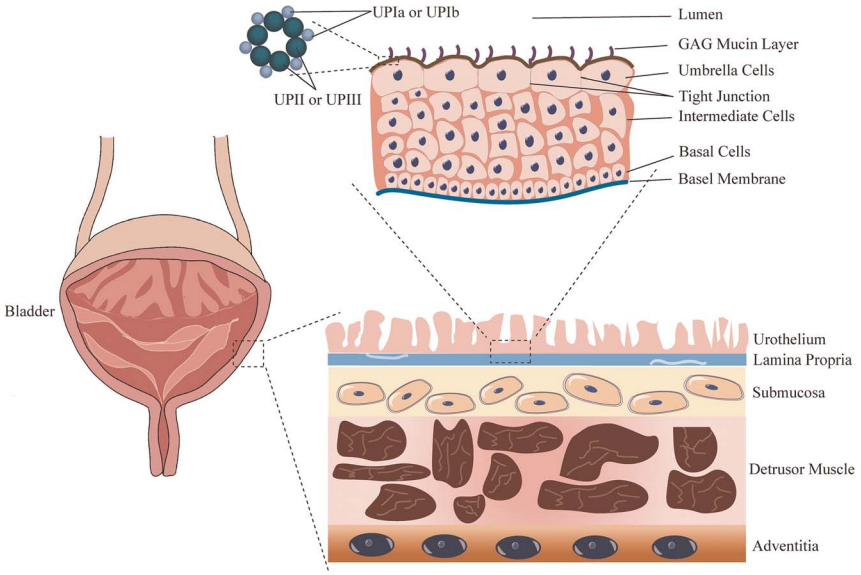

Figure 1. Schematic diagram of the bladder wall and bladder permeability barrier. GAG = glycosaminoglycan; UP = uroplakins.

acidify and activate the Ach transporter protein in the vesicle membrane, allowing Ach to enter and concentrate in the vesicle. If BTX-A is not present at this time, synaptic vesicles will be ready to fuse with the presynaptic membrane and release Ach into the synaptic cleft. However, the presence of BTX-A inhibits this stage of the release.[33,34]

First, the light chain is "translocated" from the vesicle to the cytoplasm through the *N*-terminal domain of the heavy chain and is converted to the active state after translocation and release by cleavage enzymes such as heat shock protein 90 and the thioredoxin reductase–thioredoxin system.[34] The free reactive light chain cleaves synaptosomal-associated protein (25 kDa) (SNAP25), which belongs to the soluble *N*-ethylmaleimide-sensitive factor attachment receptor family of proteins essential for the release of Ach.[35,36] Synaptosomal-associated protein promotes vesicle fusion with the presynaptic membrane and facilitates Ach release. Botulinum toxin A blocks Ach release and causes reversible chemical paralysis in the muscle by inactivating the protein (Fig. 2).[34]

Botulinum toxin A not only acts on cholinergic receptors at the neuromuscular junction but also affects neurotransmission at chemical synapses in the peripheral and central nervous systems. Molecules in small synaptic vesicles (e.g., acetylcholine and glutamate), neuropeptides in large dense core vesicles (e.g., calcitonin gene-related peptide [CGRP], pituitary adenylate cyclase activating peptide 38, and substance P), and proteins (or receptor) in large dense core vesicles (e.g., transient receptor potential cation channel subfamily V member 1 transient receptor potential cation channel subfamily A member 1, and purinergic receptor P2X ligand-gated ion channel 3 are affected by BTX-A.[37]

Reduced transient receptor potential cation channel subfamily V member 1 and purinergic receptor P2X ligand-gated ion channel 3 immunoreactivity following intradetrusor injections of BTX reduced the number of urinary urgency episodes.[38] A previous study showed that in a rat model, BTX-A injection favored the reduction of CGRP release, which was beneficial for improving the interval between bladder contractions.[39] Other studies have shown that intravesical injection of BTX-A effectively inhibits the release of ATP and neurotrophic growth factors.[36,40]

4. Role of nanomaterials in IDD

Intravesical drug delivery involves the instillation of drugs into the bladder via a catheter. Intravesical drug delivery allows the drug to enter directly into the bladder and come in direct contact with the bladder lesion, resulting in an increase in drug concentration at the site of the confined lesion, thereby contributing to enhanced therapeutic efficacy. However, IDD also has the following limitations. First, regular elimination of the urinary bladder shortens the retention time of the drug in the bladder and reduces the concentration of the drug in the bladder. Second, the BPB can interfere with the entry of the drug into the bladder wall, thus reducing its efficacy. Finally, the physiological mechanism by which the kidneys produce urine gradually dilutes the concentration of the drug in the bladder.[25]

Nanomaterials are primarily characterized by their 1- or 2-dimensional structures at the nanometer scale and can be synthesized into various configurations based on different administration methods.[41] Nanomaterials can serve as carriers for IDD, offering a potential solution to their limitations. Nanomaterials can be synthesized using liposomes, synthetic or biopolymers, proteins, and

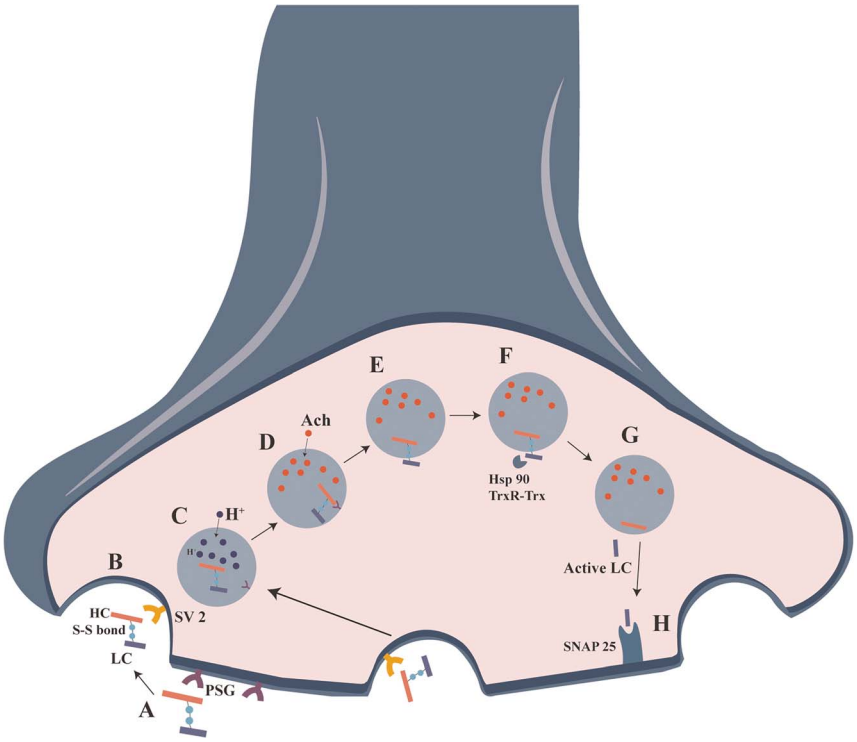

Figure 2. Schematic representation of the mechanisms involved in the action of botulinum toxin A (BTX-A) on synapses. (A) BTX-A comes into contact with the cell membrane surface, first the receptor-binding domain at the C-terminal of the heavy chain binds to the polysialogangliosides on the cell surface; (B) BTX-A is internalized by binding glycosylated Sv2; (C) H+ enters the vesicle via the proton pump of the vesicle and acidifies the vesicle; (D) Activation of Ach transporter proteins in the vesicle membrane allows Ach to enter the vesicle and concentrate in the vesicle; (E) The light chain is "translocated" from the vesicle to the cytoplasm through the *N*-terminal domain of the heavy chain; (F–G) The light chain is converted to the active state after translocation and release by cleavage enzymes such as heat shock protein 90 and the thioredoxin reductase–thioredoxin system; (H) Free reactive light chain cleaves synaptosomal-associated protein 25.

organic or inorganic metals. Although nanoparticles synthesized using inorganic compounds are not biodegradable, those synthesized from biopolymers, liposomes, proteins, and certain synthetic polymers are biodegradable within the human body.[42] Moreover, these biodegradable nanoparticles have the capability to regulate the drug release rate.[42,43]

5. Application of nanotechnology in IDD of BTX

5.1. Hyaluronan-phosphatidylethanolamine

Hyaluronic acid (HA), a GAG present in the extracellular matrix of epithelial cells, can enhance penetration of the bladder wall by mimicking the interaction of GAG with the bladder mucosa. Moreover, the application of HA for drug delivery is restricted to low molecular weight drugs. Researchers have developed drug delivery systems for the macromolecular delivery of HA-based drugs by incorporating HA and phospholipid chains (PE). This system leverages the high viscosity of HA to bind macromolecular drugs, such as BTX. Subsequently, the drugs are co-delivered with HA-PE into the epithelial layer, enabling controlled release of the drugs.[44]

An animal study showed that bladder instillation of BTX-A through a hyaluronan-phosphatidylethanolamine carrier facilitated the entry of BTX-A into the bladder.[45] The study findings indicated that the group receiving BTX-A 5 U + HA-PE 0.2–0.5 g instillation for 60 minutes and the group receiving BTX detrusor injection exhibited comparable changes in intercontraction intervals (ICIs) following acetic acid (AA) instillation. Additionally, a decrease in SNAP25 protein levels confirmed the potential of this novel method of delivery combined with BTX-A to the bladder.[45]

5.2. Liposomes

Liposomes comprise synthetic or natural phospholipids that self-assemble to form a bilayer around an aqueous core. Hydrophilic drugs can be dissolved in the core, and the outer lipid bilayer can be fused with other lipophilic drugs. Liposomes can adsorb both hydrophilic (e.g., BTX) and hydrophobic drugs.[46,47] Chuang et al.[47] were the first to study the effects and molecular changes of liposome-encapsulated BTX-A on AA-induced postictal voiding in rats. It was found that after pretreatment with liposomes and BTX-A, the ICI of the bladder at the time of AA instillation was reduced considerably (by 57.2% and 56%, respectively), the ICI response was significantly reduced, and voiding function was unaffected after pretreatment with liposome-encapsulated BTX-A. In addition, rats pretreated with liposomal BTX-A showed lower levels of SNAP25 and CGRP. Thus, they concluded that liposomes acting as BTX-A carriers facilitated the entry of BTX-A into the bladder wall in the form of bladder instillation. A study of liposome-encapsulated BTX for the treatment of ketamine-induced cystitis in a rat model demonstrated that liposomal BTX instillation through the bladder was beneficial in reducing the frequency of bladder voiding, bladder overactivity, and restoration of uroepithelial tight junctions and adhesion proteins.[48]

A double-blind, randomized, parallel-controlled trial was conducted by Kuo et al.[49] by enrolling 24 patients with OAB who were followed up after bladder instillation of 80 mg liposomes and 200 units of BTX-A. They found that the liposome-encapsulated BTX-A instillation group showed significant improvement in urgency episodes and urinary frequency per 3 days after 1 month of treatment.[49] Molecular biology results showed that SV2A and SNAP25 were expressed in both urothelium and suburethral tissues, demonstrating the function of liposome-encapsulated BTX-A. Another phase II, double-blind, randomized, parallel, placebo-controlled clinical trial reached similar conclusions. They enrolled 62 patients who, after 4 weeks of liposomal BTX-A infusion therapy, found a significant decrease in the number of micturition events per 3 days (4.64 for liposomal BTX-A vs. 0.19 for placebo, $p = 0.0252$) and a significant improvement in urgency severity scores relative to the control group but no significant improvement in urgency events relative to the control group.[50] Although both clinical trials involved male patients with OAB, the majority of individuals with OAB were women. This observation may offer novel therapeutic insights into the use of BTX-A in the management of OAB in women.

5.3. Thermosensitive hydrogel

Thermosensitive polymer hydrogels exhibit a sol-gel state at room temperature, which converts to a gel state at higher temperatures (e.g., body temperature). When formed in the bladder, the hydrogel acts as a matrix for drug delivery, maintaining long-term exposure of the drug to the uroepithelial cells and avoiding the need for repeated catheterization.[51]

Krhut et al.[52] conducted a double-blind, randomized clinical trial in which BTX-A was mixed with a hydrogel called TC-3 (a thermosensitive hydrosol that is a liquid at 5°C and a gel at body temperature) to treat refractory OAB. They enrolled 39 female patients with OAB symptoms and randomized them into saline, BTX-A/TC-3 gel, dimethylsulfoxide + BTX-A/TC-3 gel, and dimethylsulfoxide instillation groups. The results showed that patients who received 50 mL of TC-3 gel bladder instillation with 200 U of BTX-A showed a significant reduction in urgency grade 3 + 4 episodes/72 hours and leakage episodes after 1 month of treatment. However, a recent multicenter, randomized, double-blind clinical trial that enrolled 294 patients (including 268 female patients) compared the efficacy of different doses of hydrogel/BTX-A (100, 300, 400, and 500 U) relative to saline/hydrogel in improving OAB symptoms.[53] Their study showed opposite results to those of previous clinical trials, finding no significant improvement in urgency, nocturia symptoms, or the OAB Questionnaire value in the BTX-A/hydrogel intravesical instillation group at different doses versus the placebo/hydrogel control.[53] The varying outcome measures noted in the clinical trials mentioned above could be linked to potential biases in the selection of study participants[53] and restricted capacity of high molecular weight commercial BTX-A (950 KDA) to overcome the BPB, thereby hindering its ability to penetrate the urothelium.

Although the thermosensitive hydrogel TC-3 demonstrates the ability to provide sustained and consistent drug release, it was limited by its short storage time in the bladder.[54,55] Therefore, it is imperative to explore the development of various types of hydrogel intravesical instillation systems such as mucoadhesive, thermosensitive, floating platform, and liposomal hydrogels. These hydrogel bladder drug delivery systems should be further improved to ensure sustained and stable drug release by incorporating features, such as biodegradability, adhesion, and biocompatibility.[56] This enhancement is crucial for preventing urethral obstruction and mitigating potential toxic effects resulting from degradation.

5.4. Microbubbles

Nanotechnology plays a pivotal role in the development of microbubbles for medical applications.[57] These tiny gas-filled spheres are designed with a structured composition; their core is a gas center made up of different gases, which is encased with a shell material that forms the middle layer. The shell is engineered to safely contain gas. The outermost layer is the liquid layer surrounding the entire microbubble.[58] The integration of microbubbles with

ultrasound technology has led to significant advancements in the field of drug delivery.[59] When these microbubbles are combined with therapeutic agents, they can be used to create innovative drug delivery systems. Utilizing ultrasound, these systems can effectively overcome biological barriers that normally hinder efficient drug delivery. The synergy between microbubbles and ultrasound enhances drug permeation through biological tissues, offering a promising strategy for IDD in urology.

This approach holds particular promise for delivering drugs directly into the bladder, where it can be challenging to achieve adequate drug concentrations due to the protective barriers of the bladder.[26] By exploiting the unique properties of microbubbles and ultrasound, researchers can improve the therapeutic efficacy of intravesical drug administration, potentially transforming the treatment of urological conditions.

Recently, Liu et al.[60] demonstrated the potential of this technology in the context of BTX-A for IDD. They prepared a mixture of BTX-A and microbubbles and applied a specific ultrasound regimen utilizing a frequency of 1 MHz, an intensity of 1.5 W/cm^2, and a pattern of 10 seconds of ultrasound followed by a 10-second pause, repeated for 10 minutes, to the bladder through a PE-50 catheter.[60] This method led to a significant decrease in the bladder reaction to AA, with a 57.31% reduction in the ICI observed after the procedure.

Immunohistological staining showed increased cleavage of protein SNAP25 and elevated expression of the neurotransmitter CGRP, indicating the effectiveness of this treatment in modulating both muscle activity and pain signaling.[60] These findings highlight the potential of ultrasound-assisted drug delivery as a noninvasive and efficient therapeutic approach for OABs, offering new hope for patients seeking alternatives to traditional injections.

The innovative application of nano-BTX-A for IDD, as recently demonstrated, is anticipated to significantly advance the treatment of OAB in women. This approach is expected to offer an effective alternative for managing this condition with the potential for broader clinical adoption in the future.

5.5. Nanoparticle technology

Nanoparticle technology offers a sophisticated approach for drug delivery, particularly for addressing bladder cancer and lower urinary tract dysfunction. These particles possess superior targeting capabilities compared to standard chemotherapies, allowing for increased drug concentrations at tumor sites, reduced dosages, and enhanced tumor suppression. Precise targeting is a significant advancement that offers more effective treatments with fewer side effects.[61]

Despite the variety of nanoparticles available, those selected for treatment with IDD must meet stringent criteria to ensure safety and efficacy. They must be biodegradable, nontoxic, and capable of precisely delivering drugs to the intended target within the body. This precision is crucial for achieving targeted drug delivery, which enhances therapeutic outcomes while minimizing side effects.[62] Nanoscale materials with great potential currently being studied include chitosan, dendritic polymers, and lipid, protein, polymer, magnetic, and inorganic nanoparticles.[28,63] For example, solid lipid nanoparticles, which are colloidal particles with a solid lipid matrix formed from lipids that are compatible and biodegradable, are capable of forming lipid membranes similar to liposomes, with the potential to be used for the treatment of OAB.[28] In addition, due to the good mucosal adhesion and permeability of nanoparticles, they also have the potential to be used as a carrier for BTX-A, and in the future, nanoparticles can play the role of BTX-A carriers in the IDD, to achieve a safer and more effective submucosal delivery.

Limitations

The present review has some limitations. Specifically, certain studies included in this review are confronted with issues such as limited sample sizes and discrepant research outcomes.

6. Conclusions

Intravesical injection of BTX-A is a common therapeutic approach in women with refractory OAB. However, adverse effects associated with injections and the need for repeated treatments often diminish patient compliance. Botulinum toxin A is a large protein molecule with a molecular weight of 150 kDa. Commercial preparations of BTX-A have even larger molecular weights, reaching 950 kDa. Botulinum toxin A cannot effectively penetrate the BPB when administered through direct instillation to achieve therapeutic effects. Nano-based drug delivery via the intravesical route not only facilitates the transport of drugs into the bladder but also mitigates the concentration reduction caused by urine, enabling controlled and precise therapy. Liposomes and hydrogels have been utilized by researchers in clinical settings for the treatment of women with OAB, demonstrating promising therapeutic prospects and good safety profiles; however, they also have limitations. Nanoparticles, which are often used as targeted drug carriers in bladder cancer treatment, show potential when combined with BTX-A for the future management of OAB in women. The integration of nanotechnology with BTX-A holds great promise as a novel and potentially more effective treatment strategy for this condition.

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Statement of ethics

Not applicable.

Conflict of interest statement

The authors declare no conflicts of interest.

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Author contributions

YZ: participated in the writing of the paper;
QL, LL: participated in research design;
HC: provide critical revision of this article.

Data availability

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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