

# Overactive bladder: A review and update

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**Abstract.** Overactive bladder syndrome is a chronic, disabling condition with physical, psychological and social consequences that significantly affects the quality of life of millions of patients worldwide. The economic impact of this disorder is crucial. Overactive bladder syndrome is a little-known condition, with different manifestations from patient to patient, which causes a great deal of frustration to the medical staff involved. The patient requires a clear explanation and the full support of the attending physician. It is extremely important to establish a correct diagnosis and an effective individualized treatment. The collaboration and understanding of these patients are extremely important aspects. Improving the quality of life in these patients is the main purpose in managing this condition. There are several treatment modalities that may be used progressively, with favorable albeit inconsistent results. This condition remains extremely challenging for specialists and, unfortunately, always one of maximum interest.

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## 1. Introduction

Overactive bladder (OAB) syndrome is a chronic condition that affects both men and women, accompanied by a marked impairment of the patients' quality of life (1,2). Although it is more common in the population over the 4th decade, it can affect both children and young individuals (3). A study published in 2011 with a sample size of 10,000 individuals from Europe found that approximately 36% of men and 43% of women over the age of 40 had symptoms of OAB (4). It has been established that the severity of symptoms has a direct correlation with the patient's age: more severe symptoms at an older age (5,6). The National Overactive Bladder Evaluation Program (NOBLE) also showed a prevalence of over 33 million individuals with OAB in the US population (7).

The term OAB was first used in 1988 by The International Continence Society (ICS) Committee on Standardization of Terminology, referring to detrusor hyperactivity shown in urodynamic tests (8). Over the years, the definition of OAB has undergone many changes. The most accurate and accepted worldwide definition at this moment is that of the International Consultation on Incontinence Research Society (ICI-RS) from 2014: 'overactive bladder syndrome is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology' (9).

Thus, the symptoms that characterize OAB are urgency, frequency, nocturia and urgency incontinence. Many patients have combinations of these symptoms, with varying preponderance (1,6). The key element that characterizes OAB is urgency which together with nocturia and urgency urinary incontinence, are considered the most irksome symptoms (1,10-13). It is

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estimated that urgency incontinence is more common in women, and urgency and frequency are more common in men (14).

The symptom has a significant impact on the quality of life of these patients leading to frequent sleep disorders, anxiety and depression, as well as reduction of physical activity and social interactions, reduction of sexual activity and marital satisfaction (15-18). Due to sleep disorders, it has been shown that patients with OAB have a much higher risk of fractures or fall-related injuries (6,13,15).

The economic impact of OAB is crucial. As an example, a study conducted in 2005 in the USA showed total costs of over 12 billion USD per year for patients with OAB. To these are added indirect costs such as temporary loss of work capacity (15,19-21). OAB is a captivating and still unknown subject in many aspects, especially in terms of the possible risk factors, pathological mechanisms involved and effective treatment, causing marked frustration in physicians and conflicting feelings in patients (1,18,22).

For the literature review a database search was performed in MEDLINE and ScienceDirect with the following key words: 'overactive bladder', 'quality of life', 'antimuscarinic drugs', 'β3-agonists', 'intravesical botulinum toxin A'. The time frame that the studies covered was 1988 to 2020. A total of 80 studies were analyzed and cited.

## 2. Risk factors

A well-known risk factor is age (1,14,15). In women, due to the postmenopausal status, by reducing the level of estrogen, the prevalence of symptoms is higher, as demonstrated by numerous studies (15,22,23). Genital prolapse is also associated with an increased risk of OAB (consequently, treatment of prolapse leading to relief of OAB symptoms) (24). However, there are studies that have not clearly demonstrated this (24). Stress urinary incontinence surgery may also cause OAB (15). In men, the data related to possible hormonal factors involved in the occurrence of OAB, are extremely low and contradictory (22). Other possible risk factors involved include, i) BMI >30 kg/m<sup>2</sup>: there are studies that have shown a clear link between OAB and obesity in both sexes, the possible explanations being related to mechanical factors, and to inflammatory syndrome or oxidative stress (15,22,25,26). ii) Affective disorders: OAB can cause many mental disorders such as anxiety or depression; however, there are studies that show that the presence of these disorders itself can increase the risk of OAB; corticotrophin-releasing factor (CRF) being the possible common factor (22,27). iii) Functional gastrointestinal disorders: the most common is irritable bowel syndrome, present in approximately 33.3% of OAB cases (22,28). iv) Autonomic nervous system dysfunction (autonomic balance dysfunction) (22). v) Ethnicity is another potential risk factor, with studies showing a higher prevalence of OAB in African-American and Hispanic patients (29). vi) Sleep apnea, urinary microbiota, smoking, increased coffee consumption, artificial sweeteners, alcohol, spices and sour drinks are other possible involved factors (2,15,26,30).

## 3. Pathophysiology of OAB syndrome

According to the ICS, detrusor overactivity (DO) is defined as: 'a urodynamic observation characterized by involuntary

detrusor contractions during the filling phase which may be spontaneous or provoked' (31). The etiology of OAB is not well known, but all theories are related to the term 'detrusor overactivity', suggesting that the sensory mechanisms of the bladder are affected in these situations, which leads to the creation of an 'urgency' in emptying the bladder at smaller or much smaller quantities than under normal conditions. This is because the detrusor (bladder muscle) is very strongly innervated, and the function of the bladder is ensured by a complex mechanism of interactions between the central and peripheral nervous system (1,32).

The motor component of the bladder is served by the parasympathetic nervous system (S2, S3 and S4) and coordinates the intensity of detrusor contractions. The sympathetic component comes from the hypogastric nerve, acts on beta receptors and is responsible for relaxing the detrusor (33). However, not all patients with OAB also have DO, which is proven in only approximately 50% of cases (6,13,22). Various theories have been posited to identify the factors involved. These theories include, i) the myogenic theory whereby urgency is caused by a problem with the detrusor. The detrusor is much more sensitive to cholinergic stimulation, as demonstrated by Brading (34). Other authors have demonstrated other detrusor dysfunctions that contribute to uninhibited detrusor contractions (22,35). ii) The urotheliogenic theory where urgency is determined by a bladder urothelium/suburothelium problem (1,22,36). iii) The urethrogenic theory where urgency is caused by a problem in the urethra. This hypothesis was based mainly on the observation that many patients have urgency especially when changing position (22,37). iv) The supraspinal theory: urgency has its origin in the brain and brainstem. With age, deterioration in certain segments of the white matter is possible, leading to urinary disorders (38). v) Detrusor underactivity: secondary to urothelial or suburothelial dysfunction or from detrusor muscle dysfunction, accompanied by detrusor underactivity appears urgency, which has been found in many studies [due in particular to recurrent urinary tract infections (UTIs) that occur through chronic urinary retention] (22,39).

## 4. Evaluation of patients with OAB syndrome

A detailed history is extremely important and can clearly highlight possible risk factors for OAB. Aspects related to pre-existing conditions or surgery (especially urinary tract, but also systemic disorders, important for differential diagnosis), eating habits, medication that interferes with urinary function are crucial. History should be focused especially on voiding and storage lower urinary tract symptoms, the severity of symptoms and their impact on quality of life (1,6,13,15,18,22).

A focused clinical examination is imperative, as it can highlight risk factors and pre-existing conditions. It should include abdominal examination, digital rectal examination of the prostate in males and vaginal examination in women (important to highlight hormonal status, presence of prolapse and cough testing for the presence of leakage) (1,6,15,18,22). A residual postvoid should also be performed using ultrasound or a straight catheter, especially in groups at risk of urinary retention (6,18).

Symptom questionnaires should be used especially to highlight the impact of the condition on quality of life and to determine whether or not the patient should undergo treatment.

There are numerous validated questionnaires, useful in highlighting the progression of treatment, but not currently widely used (6,15,18).

The use of voiding diaries is recommended as it shows the patient's daily urination habits. It is a simple tool, easy to apply, which can highlight urinary volume, frequency, pattern of voiding, incontinence episodes and can assess the severity of symptoms (sometimes underestimated by the patient or overestimated by the doctor). It is estimated that three days of a bladder diary provides very important information about the patient. A bladder diary can also be useful to evaluate the response to treatment (1,6,15,18,40).

Urinalysis and urine culture are recommended for all patients in order to rule out other associated pathologies that may cause OAB-type symptoms (especially UTI and hematuria) (1,15,18). Blood tests can provide additional information including levels of creatinine and glycosylated hemoglobin (HbA1C) (1).

In more complicated situations or in patients refractory to treatment, other additional tests may be performed such as cystoscopy (in case of recurrent hematuria or UTI), urodynamic evaluation (especially in situations where there is a history of neurological symptoms or concomitant voiding dysfunction), upper genitourinary tract imaging (in case of hematuria or to exclude other concomitant diseases) (1,6,15,18).

## 5. Treatment

*Non-pharmacological treatment (first-line treatment).* Its main role is to educate the patient in order to understand what OAB is and to assist the patient in identifying symptom management strategies. The patient must understand, from the beginning, that they are to undergo treatment over a lengthy period of time, that they must remain motivated and, especially tolerant (1,6,13-15,18).

First-line treatment is considered to be behavioral therapy, especially since it does not involve risks and its effectiveness is proven in many cases (6,13). The patient is advised to make changes in lifestyle: to lose weight, reduce fluid intake (six to eight glasses of water per day, avoiding fluid intake 2 h before bedtime), to give up coffee, spices, sour drinks and alcohol, smoking cessation, bowel regulation (avoid constipation), to increase the level of physical activity and to improve overall health. All these have been confirmed to have beneficial results (1,6,13-15,18,41,42).

Bladder training is part of the arsenal of non-pharmacological treatment, with promising results (1,6,13,15,43). It consists of urinating at regular intervals, starting with urination at 30 min, then reaching intervals of 3-4 h, once the patient manages to have control over urination. The patient must know that every minute of postponing urination during the urge is an important gain (13,15,44). The use of the micturition calendar can increase patient compliance and motivation through visual feedback and evaluate outcome (14,18).

Optimal results are obtained by combining with emergency control techniques, especially the Kegel contraction or deep breathing (as a relaxation technique), which the patient may use in order to obtain gradual control (6,15,44).

On the other hand, the use of pelvic floor muscle training (PFMT) can be substantially positive, especially in reducing

episodes of urgency and incontinence, by reducing detrusor contractions through inhibitory reflection of the pelvic floor and improving urethral stability (1,6,13-15,18,45). PFMT results appear to be improved when combined with oral drug therapy (1,6). The main types of PFMT used are: Kegel exercises, pelvic-floor electrical stimulation, and pelvic floor exercise with biofeedback or vaginal weight training. There is no single and/or effective PFMT regimen, thus therapy should be individualized and performed under the supervision of a physical therapist or by advanced practice nurses (1,6,13,15). An important problem, however, is that long-term adherence to treatment (PFMT) is poor (13,46).

*Pharmacological treatment (second-line treatment).* The first group of pharmacological drugs are represented by antimuscarinic drugs (anticholinergic), with the help of which some relaxation of the detrusor is obtained. During years of use and clinical trials, they have been shown to be safe, fairly well tolerated and effective, leading to significant improvement in symptoms and consequent quality of life (1,6,14,15). The main problem with these drugs is that muscarinic receptors, on which they act, are found in many organs of the body, which leads to the occurrence of numerous common side effects: dryness of the mucous membranes (dry mouth, dry eyes, dry vagina), constipation, heart palpitations, arrhythmia, tachycardia and cognitive impairment (somnolence, hallucinations, confusion, delirium, blurred vision, memory problems) or urinary retention (1,15,18,47,48).

Anticholinergic medication has been shown to be beneficial in relieving symptoms, as indicated in numerous studies (1,13,15,18,49,50). However, many patients cease taking medication (1,51). Most often patients discontinue medication due to constipation (approximately 50%) (52) or dry mouth (approximately 30%) (13,18).

The most common antimuscarinics used are: oxybutynin, tolterodine, fesoterodine, trospium, propiverine, solifenacin; subsequent studies failed to prove that one is more effective than the other (1,13-15,18). Extended-release (ER) drugs are considered as effective as immediate-release (IR), but with an improved safety profile, with lower side effects (13,14,18). If both types of medication are available, then ER drugs should preferentially be prescribed (6,13). Transdermal oxybutynin or oxybutynin topical gel is another option, as it avoids liver first-pass effect, with lower systemic side effects, and a low dry mouth rate. Even in this case continuing treatment over a long period of time is a problem, due to adverse skin reaction (pruritus and erythema at the site of application) (6,13,14,18).

Although the effectiveness of antimuscarinics has been clearly proven, the discontinuation rate of treatment is very high, especially due to side effects (43-83% in the first 30 days of treatment), but also low level of efficacy or cost (13,53). Thus, it is opportune to commence with small doses, on a plan as flexible as possible, and to evaluate the patient as closely as possible, at 1-3 months, in order to manage the case as correctly as possible and, especially, the patient's ability to cope with the side effects. This is crucial as the rate of side effects increases with increasing doses (1,6,13,14,54). Contraindications to antimuscarinic medication are: patients with narrow-angle glaucoma (unless approved by the ophthalmologist treating), myasthenia gravis, severe ulcerative colitis, toxic megacolon,

urinary retention or intestinal obstruction. Caution should be accorded when prescribed to elderly patients or those who already have cognitive impairment, or if the patient is using other medications with anti-cholinergic properties, although studies are contradictory in this regard. Cognitive side effects are cumulative and increase with length of exposure, so antimuscarinics should be used with caution in elderly patients. In other words, each case must be managed carefully and individually, sometimes in collaboration with other clinicians in other specialties, to weigh the ratio between risks and benefits (1,6,13,15,18).

The second type of drug that is used is  $\beta_3$ -agonists. Of the three  $\beta$  adrenoceptors present in the bladder, findings have shown that  $\beta_3$  is predominant and responsible for detrusor relaxation during the filling phase (55,56). Mirabegron is the only licensed  $\beta_3$ -agonist available since 2013, and studies have shown favorable results on OAB symptoms. Additionally, this agonist is well tolerated. Mirabegron is considered a second-line therapy. The effectiveness is comparable to that of antimuscarinics, but with decreased side effects, especially those related to the incidence of dry mouth (1,6,15,18,57).

The side effect profile is different in  $\beta_3$ -agonists because the mechanism of action is different.  $\beta_3$  adrenoceptors are also present in vascular and cardiac tissue, with studies showing some changes in heart rate and increases in blood pressure, albeit not notable ones. Other possible side effects are nasopharyngitis and UTI, which are less common (13,15,58).

The use of mirabegron as an alternative to antimuscarinic therapy is recommended especially in patients who do not respond to first-line treatment and in those who cannot tolerate side effects (6,13,15,18). There was a much greater adherence to mirabegron treatment when compared to antimuscarinics (13,59). Additionally, in patient refractory to monotherapy, antimuscarinics may be combined with mirabegron, the results being superior to monotherapy (6,13,15,18,60). In elderly patients, existing data have shown that mirabegron is safe (13).

*The management of refractory patients (third-line therapy).* When patients do not respond to anticholinergic medication or to  $\beta_3$ -agonists, they are considered refractory. This category also includes patients who have used at least 2 types of anticholinergics or combination treatment without results, or those who do not tolerate side effects or have contraindications for first-line or second-line therapy. In such cases resorting to third-line therapy is inevitable: temporary chemical denervation of the bladder detrusor muscle, peripheral tibial nerve stimulation (PTNS) or neuromodulation (1,6,14,15).

*Temporary chemical denervation of the bladder detrusor muscle with intravesical botulinum toxin A (OBTA).* OBTA is derived from *Clostridium botulinum* and selectively blocks presynaptic release of acetylcholine from nerve endings. This results in reduced contractility and a degree of muscle atrophy at the injection site (a temporary degree of paralysis). The result is not permanent due to the formation of new functional synapses. Another mode of action appears to be directly in the urothelium by inhibiting the release of neurotransmitters at this level, thus acting on the sensory system (1,15,18,61). OBTA is administered intravesically, by injection into certain

areas of the bladder, using a cystoscope. The injection is made in 20 places at the level of the posterior wall of the bladder, above the trigone, to avoid extreme paralysis and significant urinary retention. The optimal dose is considered to be 100 units (6,13,15,18). Findings have shown that higher doses are more effective, but reported side effects have been much more common (18,62). Higher doses may be used in selected cases, but patients should be informed of the much higher likelihood of urinary retention (15).

Local or systemic side effects are reduced at the standard dose of 100 units, but the main problem is related to increased PVR (residual volume). As a result the patient must be compliant and able to perform clean intermittent self-catheterization. It is reported that urinary difficulties appear in 4-45% of patients (6,13,15,18,55,63). Other side effects of the injection are UTIs (13-44%), hematuria, dysuria, rash, transient flu-like illness or generalized muscle weakness (14,18,64). Favorable results of OBTA treatment, with marked improvement of symptoms, urodynamic parameters and significant improvement of quality of life have been reported. The duration of the favorable effect is estimated to be 6-9 months, after which a new administration of OBTA may be necessary (1,13,15,18,65). The most common causes of withdrawal are ineffective treatment (13%) and problems with secondary urinary disorders (11%) (1). Intravesical OBTA was approved by FDA in 2013 for the treatment of idiopathic OAB.

Posterior tibial nerve stimulation (PTNS) was first described in 1983 and is a minimally invasive procedure with favorable results and low risks. It consists of intermittent stimulation applied to the posterior tibial nerve using a small needle electrode (34-G) inserted just above the medial aspect of the ankle (P-PTNS). The success rate is estimated at 60-80% (1,6,13,14,66-68). The optimal duration is not very clearly defined, but it is estimated as optimal 30 min sessions for 3 months, and the favorable effect can last up to 1 year. Repeated treatments may be required for sustained efficacy. Local discomfort is minimal and no serious side effects have been reported, being especially local and temporary (local inflammation, mild bleeding, pain) (1,13,14,18,67,69). PTNS contraindications are patients with implantable defibrillators, pacemakers, and nerve damage that can affect tibial nerve, bleeding problems, pregnancy or attempts to conceive (15). PTNS was approved by the US Food and Drug Administration (FDA) in 2005. There is also a possibility of a T-PTNS (transcutaneous stimulation) being performed (15).

Sacral neuromodulation (SNM) is recommended in selected severe cases that are refractory to other types of treatment and should be considered before resorting to other more radical ways of treatment (1,6,14,18). SNM consists of S3 nerve root stimulation using a percutaneously implantable device under fluoroscopic control, which generates electrical impulses (continuous low frequency stimulation is used to modulate bladder/pelvic floor function). The major disadvantage surgery is necessary to permanently implant a device, accompanied by related complications (pain, bleeding, infection, movement of the device or its malfunction) sometimes requiring reinterventions to revise the device (approximately 33% of cases). The final surgery occurs only after the patient's qualification for this procedure. A preliminary phase is necessary to determine whether or not the patient has a significant improvement in

symptoms (50% improvement in baseline symptoms). Only such patients may benefit from a full implant (1,13-15,18,70).

The advantages are important: the symptoms are significantly improved in over 50% of patients, with marked improvement in quality of life, the favorable effect being maintained up to 3-5 years (1,13,15,18,71,72). SNM is contraindicated in patients who need frequent MRI, pregnancy or if a patient aims to conceive. The device is not cost-effective, and the patient must be very compliant because lifelong follow-up is needed (14,15,73). Sacral neuromodulation was FDA approved in 1997.

*Augmentation cystoplasty and urinary diversion (fourth-line therapy).* In rare severe cases, refractory to any other type of treatment, surgical treatment can be performed; a form of fourth-line therapy (6,14). It is addressed to only selected cases. Patients must be very well informed about the consequences of interventions and should be very motivated. These forms of treatment are irreversible with a significant morbidity (13,14,18).

Augmentation of the bladder (cystoplasty) is performed by adding to its intraluminal surface area a 10-15 cm loop of small bowel, preferably ileum (detubularized segment of bowel is inserted into the bivalved bladder wall). The complications of the intervention can be redoubtable, with obstructions, disinsertions of anastomoses, abscesses, or fistulas (1,13,74).

Urinary diversion is an intervention that involves implanting the ureters in an ileal segment and creating a skin stoma (13,14,18).

The long-term complications of these types of surgery are electrolyte disturbances, renal failure, urinary tract stones, ischemia of the ileum and ureteric stricture, a need for clean intermittent self-catheterization (for bladder augmentation), change in bowel symptoms, or UTI (13,14,18). Patient satisfaction after such interventions is quite high, especially due to the fact that, having to resort to surgical treatment, they faced severe symptoms, refractory to any other type of treatment (13,14,18).

*Other possible treatments.* Other possible treatments for OAB are currently under investigation:  $\alpha$ -adrenoceptor antagonists, gene therapy, neurokinin receptor antagonists, nerve growth factor inhibitors, stem cell-based therapies, potassium channel opening gates, capsaicin (resiniferatoxin), vaginal estrogen as a monotherapy for OAB as well as in combination with other therapies (including behavioral and pharmaceutical) (1,6,14,75-78).

## 6. Discussion of the treatment algorithm

OAB is a chronic, disabling condition, which requires a correct and sincere understanding of the problems it raises. The patient requires an explanation as clear as possible and the full support of the attending physician. Such a condition can be a considerable challenge for healthcare professionals, with a complete cure of OAB being almost impossible.

Often a multidisciplinary team is needed for a correct and complete approach to the case. In the vast majority of cases no additional investigations are necessary to establish the diagnosis. In most of the cases medical history and simple

investigations are sufficient. Urodynamic tests or other investigations are necessary only in refractory to treatment cases.

It is advisable to utilize the 3-day micturition calendar, which has both the role of additional knowledge of the problem and the basis for subsequent reassessments. The use of quality of life questionnaires bring a great value in terms of scaling the degree of suffering (6,14,15,18,79,80).

The treatment must always be carried out gradually, starting with first-line treatment (behavioral therapy), lifestyle changes and bladder training. These have a low-risk profile (6,14,15,18). If no improvement is found in the patient's re-evaluation, the second-line treatment should be considered (pharmacological treatment)-anticholinergic medication or  $\beta$ 3-agonists. At this stage the age, safety profile and history of the patient should be considered in order to select the optimal medication with maximum benefits and least side effects. The patient should also be informed of possible side effects and adjusting the doses accordingly upon re-evaluation (1-3 months) or at any time during treatment. The association between the two types of medication is allowed and even recommended in certain situations. In the vast majority of cases, the combination of first-line and second-line treatment produces excellent results (1,6,14,15,18,40,78-80).

If there is no improvement in any reassessment of the patient or if side effects are not tolerated (even if anticholinergic medication has been replaced or combination therapy has been used), the patient should be offered third-line therapy: temporary chemical denervation of the bladder detrusor muscle (intravesical botulinum toxin A), peripheral tibial nerve stimulation (PTNS) or neuromodulation. Patients must understand very clearly the favorable effects and the side effects of these types of treatment in order to make an informed decision (1,6,14,15,18).

In exceptionally rare cases, refractory to any type of exposed treatment, with marked impairment of quality of life, counseling is required in order to resort to fourth-line therapy: augmentation cystoplasty or urinary diversion. Patients must be very well informed about the consequences of the interventions, these interventions being irreversible and with significant morbidity (13-15,18).

## 7. Conclusions

OAB is a chronic, very disabling condition with physical, psychological and social consequences that significantly affect the quality of life of millions of patients worldwide. It is a little known condition, with different manifestations from patient to patient, which causes a lot of frustration to the medical staff involved. It is extremely important to establish a correct diagnosis and a treatment as efficient as possible, often individualized. The collaboration and understanding of these patients is an extremely important aspect. There are several treatment modalities that should be used progressively, with favorable but inconsistent results, which have been described in this study. Other types of treatment are being studied, with promising results. In the case of OAB, the patient's involvement must be optimal, so that the treatment options are clearly understood; the advantages and disadvantages of each, to make a correct and informed decision. Improving the quality of life in these patients is the main goal in managing this condition.

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## Authors' contributions

IS, SL, OGB, AT, LSM and CCS, collected, analysed and interpreted the literature data. IS, SL, OGB, AT, LSM, AB, AGL, RMR, AML and CCS made substantial contributions to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. IS, SL, AT, CCS contributed equally to this study and should be regarded as co-first authors. All the authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript to be published, and are responsible for confirming the authenticity of the raw data.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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