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Review

New perspectives in the treatment of obstructive sleep apnea–hypopnea syndrome☆

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ABSTRACT

Introduction: Obstructive sleep apnea–hypopnea syndrome (OSA) is an increasingly prevalent disorder in the population, which seriously compromises the quality of life of sufferers. Although continuous positive airway pressure remains the most commonly used treatment modality, its poor adhesion and relative failure have provoked several studies seeking to develop more convenient and effective alternatives for treating this condition.
Objective: To review the most effective, recent and innovative strategies that scientific evidence suggests for the treatment of OSA from anatomical and physiological mechanisms involved.
Materials and methods: A literature review was performed from items taken from PubMed, ScienceDirect, Springer, LILACS and PEDro databases, published between 2005 and 2015 in English.
Results: OSA is an intermittent and repetitive obstruction of the upper airway during sleep, caused mainly by an imbalance in respiratory muscle synergy. For treatment, the scientific literature has recently described methods such as oral devices, oral and nasal pressure therapies, Pillar, the Night Shift, bariatric surgery and stimulation of the hypoglossal nerve.
Conclusions: Although a fully effective treatment is not yet available, a combination of strategies from an interdisciplinary perspective can enhance the quality of life of patients. It is expected that in the coming years, the scientific and technological advances will allow for the implementation of a treatment protocol that is able to directly address the etiological processes to reduce their prevalence.

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Nuevas Perspectivas en el Tratamiento del Síndrome de Apnea–Hipopnea Obstructiva del Sueño

Palabras clave:
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Obesidad
Comorbilidad
Terapéutica
Obstrucción de las vías aéreas

RESUMEN

Introducción: El Síndrome de apnea–hipopnea obstructiva del sueño (SAHOS) es un trastorno cada vez más prevalente en la población, que compromete seriamente la calidad de vida de quienes lo padecen. Aunque la presión positiva continua en la vía aérea es la modalidad terapéutica más utilizada, su poca adherencia y relativa insuficiencia han promovido diferentes investigaciones para desarrollar nuevas alternativas de tratamiento.
Objetivo: Revisar las estrategias más recientes e innovadoras que la evidencia científica propone para el tratamiento del SAHOS con base en sus mecanismos anatómicos y fisiológicos.
Materiales y métodos: Se realizó una revisión bibliográfica a partir de artículos en idioma inglés, tomados de las bases de datos PubMed, ScienceDirect, Springer, LILACS y PEDro, publicados entre 2005 y 2015.
Resultados: El SAHOS es la oclusión intermitente y repetitiva de la vía aérea superior durante el sueño, causada principalmente por desbalance en la sinergia muscular respiratoria. Para su tratamiento, recientemente se han descrito modalidades como los dispositivos orales, las terapias de presión, el Pillar, el Night Shift, la cirugía bariátrica y la estimulación del nervio hipogloso.
Conclusiones: Aunque aún no se cuenta con un tratamiento totalmente eficaz, la combinación de estrategias desde una perspectiva interdisciplinar puede mejorar la calidad de vida de estos pacientes. Se espera que durante los próximos años, los avances en ciencia y tecnología permitan implementar el protocolo de tratamiento que logre abordar directamente los procesos etiológicos de la enfermedad para poder reducir su prevalencia.

Introduction

Obstructive Sleep Apnea–Hypopnea Syndrome (OSA) has been a relevant problem since the end of the 20th century in Colombia due to the rapid increase in its prevalence, both in the adult and pediatric populations.[1,2] The clinical manifestations typical of this condition, and the multiple comorbidities that tend to appear in the long term, mean that the quality of life of patients with OSA may be affected considerably and it may even cause death.[3,4]

Diverse therapeutic alternatives have been employed that, while mitigating the symptoms and the multi-systemic alterations deriving from OSA, do not offer definitive solutions for eliminating its causes. Many of these treatments experience low adherence by the patients or lead to adverse effects in the long and/or short term.[5–7] Such limitations have motivated more exhaustive studies about the pathogenesis of OSA in order to develop new treatment options from different intervention standpoints.

Objective

To present the most effective, recent and innovative strategies that scientific evidence proposes for the treatment of OSA based on the anatomical and physiological mechanisms involved.

Materials and methods

To carry out this review, information was collected by way of article searches in the databases PubMed, ScienceDirect, Springer, LILACS and PEDro, using the MeSH terms: sleep apnea, obstructive; airway obstruction; obesity; sleep apnea and death; cardiovascular diseases; cognitive disorders; mental disorders; kidney diseases; endocrine system disease; metabolic syndrome X; comorbidity; therapeutics; continuos positive airway pressure; mandibular advancement; hypoglossal nerve and electric stimulation. Meta-analyses, systematic reviews, clinical trials, cohort studies, and review articles published between 2005 and 2015 in English were taken into consideration. Meta-analyses and review articles with fewer than 10 primary sources; clinical trials and cohort studies with sample sizes under 10; and publications for which full online access was not available online were all excluded.

Results

With the search strategy outlined above, initially 311 articles were found. This number was limited to 276 after language

was taken into account. Later, the number dropped to 128 with the restriction to meta-analyses, systematic reviews, clinical trials, and review articles. Finally, 40 full text online texts remained that complied with the criteria regarding the number of references mentioned above. We present the results below in several sections: definition, physiopathology, neuromuscular and anatomical alterations, obesity, treatment, and conclusions.

Definition

OSA is a disorder caused by the intermittent and repetitive obstruction of the upper airway during sleep, which results in the partial (hypopnea) or complete (apnea) of airflow. As a result, arterial oxygen desaturation and transitory and subconscious micro-arousal that rupture the circadian sleep cycle are produced. This causes the sleep to be not restful and presents as daytime excessive sleepiness, the main symptom in most OSA patients. The clinical picture also includes cyclic snoring of varying intensities and pauses of apnea reported by the patients' spouse or family members.[8]

The American Academy of Sleep Medicine[9] defines "*apnea*" as the reduction of airflow by ≥90% during at least 10 s, and "*hypopnea*" as the reduction of airflow by ≥30% during at least 10 s with arterial desaturation by ≥3%. The severity of OSA is determined by the Apnea–Hypopnea Index (AHI), which indicates the quantity of apneas and hypopneas recorded in the lapse of one hour of sleep.[9,10]

Physiopathology

The pharynx, a single, complex structure surrounded by numerous muscles and soft tissues, permits phonation, speaking, deglutition, and respiration. Although it is supported by osseous and cartilaginous structures at the ends, it lacks rigid support in the transverse portion, which gives it the ability to change the size of the lumen. This characteristic is essential for performing its functions, but it also predisposes it to collapse during sleep.[11,12] It has been reported that the most common sites of obstruction in the upper airway are at the level of the retropalatal region, the base of the tongue, and the hypopharynx.[12–14] The place and size of the collapse depend on the anatomical conformation of each subject.

Neuromuscular alterations

The permeability of the upper airway depends to a large extent on the muscular work coordinated between the Pharyngeal Dilator Muscles (PDM) and the inspiratory muscles which exert negative intraluminal pressure to allow the entry of the airflow.[15] The activity of the PDMs is mediated by vagal stimulation, chemoreceptors, mechanoreceptors, and baroreceptors that detect the type of change within the upper airway.[12,16,17] The most important PDMs are the genioglossus (mainly phasic) and the tensor veli palatini (mainly tonic).[18,19]

The tensor veli palatini is responsible for stabilizing the upper airway during the respiratory cycle, while the genioglossus is the main dilator muscle of the upper airway during inhalation.[17,18] At the beginning of sleep, a fall in the activity of the PDMs is seen due to a reduction in the central respiratory drive. During the N stage (non-rapid eye movement) the phasic activity increases while the tonic activity continues to decrease until R stage is reached (rapid eye movements) in which hypotonia of all skeletal musculature occurs, with the exception of the diaphragm. In patients with OSA, there is greater reduction in the muscular activity of the PDMs at the beginning of sleep (more than physiologically expected), which predisposes the airway for collapse when the R stage is reached.[17–20] During wakefulness, patients with OSA do not tend to present problems with the permeability of the upper airway; on the contrary, it has been demonstrated that the activity of the PDMs is more elevated in subjects with OSA than in health subjects, this being a compensatory neuromuscular mechanism.[17,21]

During the apnea episode, the increase in partial pressure of carbon dioxide (PCO_2) and in the breathing effort result in a stimulation of the Reticular Activating System and micro-arousals are generated to activate the contraction of the PDMs (primordially the genioglossus) to reinitiate the circulation of air through the upper airway.[12,22] However, some studies report that micro-arousals are not in direct relation with the re-opening of the upper airway, since it has been seen that episodes of apnea can end via other mechanisms, such as breathing synchronizations.[23,24] In some cases, the abrupt opening of the upper airway because of a micro-arousal causes hyperventilation with subsequent hypocapnia, leading to a reduction in PDM activity and a greater collapse of the upper airway.[23,25,26]

Anatomical alterations

In healthy subjects, the relation of the mass of the soft tissues is disproportionately high for the space made available by the osseous structures that surround the upper airway.[18] Therefore, any traumatic or pathological condition implying an excess of soft tissue and/or a small bony structure will provoke a reduction in the space of the upper airway and will make it susceptible to collapse during sleep (Table 1).[15,18,27–29]

Table 1 – Frequent anatomical alterations in OSA.

Osseous alterations	Alterations in soft tissues
Caudal displacement of the hyoid bone	Macroglossia Tonsillar hypertrophy Thickening of the lateral pharyngeal walls
Hypoplasia and/or maxillary or mandibular retrodisplacement	Thickening of the velum and uvular hypertrophy Arched palate
Increase in pharynx length	Deviated nasal septum Fat deposits in the neck

Source: Authors.

Obesity

Obesity represents the largest predisposing factor of OSA.[11,30,31] A central distribution of fat (abdomen and neck) is more closely related to the obstruction of the upper airway than a peripheral fat distribution (thighs and hips). In 2014, Wosu et al. observed that subjects with high risk of OSA had a greater probability of general obesity (OR 9.96; CI 95%: 4.42–22.45) than of central obesity (OR 2.78; CI 95%: 1.43–5.40) suggesting a strong positive association of a high risk of OSA with obesity.[32] Normally, men present a central distribution pattern (android obesity) while women present a peripheral distribution pattern (gynoid obesity).[33] This is one of the reasons why obese men have 2–4 times more risk to develop OSA than obese women.[11,34]

Fat deposits in the neck reduce the transverse area of the upper airway.[19,35] Those located in the thorax and the abdomen elevate the diaphragm and reduce the size and lung compliance, especially in supine position.[35,36] These alterations lead to a reduction in the lung volume and capacities, particularly the functional residual capacity (FRC).[19,35,37]

The caliber of the upper airway depends on and varies with the volume of the lungs, increasing during inhalation and diminishing during exhalation.[38,39] In patients with OSA, this relationship seems to increase.[38] The mechanical foundation that explains the influence of lung volume on the size of the upper airway is found in the longitudinal traction of the trachea. The caudal displacement of the carina, which occurs during inhalation, exerts a force of longitudinal traction on the trachea that is transmitted to the pharyngeal walls through their anatomical connections with the upper airway.[39] The decrease in the FRC induces a decrease in the traction of the trachea, which implies that, at the level of the trachea, less $P_{extraluminal}$ is required to reach collapse.[40] In this way, in an obese subject with central fat, the quantity of adipose tissue in the neck may be sufficient to cause collapse.

Treatment

CPAP (Continuous Positive Airway Pressure)

CPAP is the first-line treatment for patients with moderate and severe OSA.[41] It consists of a pneumatic splint that provides airflow with positive pressure (above atmospheric pressure),[41,42] in such a way that when the critical closing pressure increases (understood as the point of pressure in which the upper airway begins to collapse due to the increase in the pressure exerted by the tissue surrounding the oropharyngeal portion), it exceeds the upper pressure (the pressure in the nasal and nasopharyngeal portion), altering the normal relationship $P_{upper} > P_{crit}$, allowing the entry of airflow through the upper airway. This is how the closure occurs[12,19] (Fig. 1). The positive pressure provided by the CPAP reestablishes this relationship, reinitiating the opening of the upper airway.

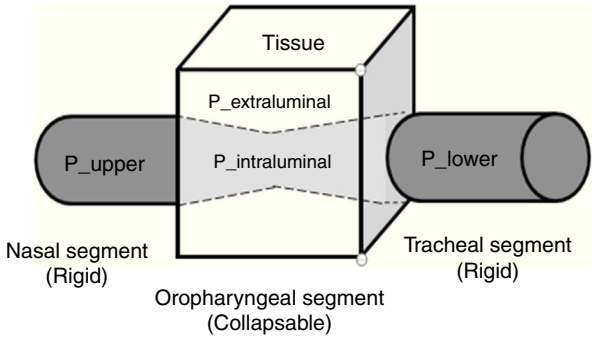

Fig. 1 – Representation of pressures in the upper airway (Starling Resistor Model). Source: Authors.

The efficacy of CPAP as a method for treating OSA has been confirmed, as it reduces the symptoms and risk factors associated with comorbidities.[43–47] Nevertheless, many individuals exhibit low tolerance and adherence to this type of treatment.[48] The efficacy of CPAP results after using it for at least four hours of sleep, five nights per week,[49] but it has been reported that between 23% and 83% of patients use it less than this time,[50] and between 8% and 15% of patients to whom CPAP is prescribed do not begin treatment.[51]

There are many predictors to determine if a subject will or will not adhere to the use of CPAP. Among these, the following stand out: the interface (type of mask), the characteristics of the patient (age, gender, marital status), the severity of the symptoms and comorbidities, the method of initiating CPAP, the secondary effects, and both psychosocial and socioeconomic factors.[48,52] Therefore, diverse strategies have been implemented to increase adherence to CPAP, such as information and education programs, behavioral therapies, and prolonged accompaniment.[53–55]

Regarding secondary effects, studies to evaluate long-term consequences of the use of CPAP in OSA patients have not yet been conducted. Only the immediate effects, mainly related to the CPAP interface and machine have been reported: local cutaneous erosion, dry nose and mouth, conjunctivitis, upper airway irritation, runny nose, temporary deafness, headache, and insomnia.[51,56] Gastric and intestinal distension may also result due to airflow into the digestive tract.[57]

nEPAP (Nasal Expiratory Positive Airway Pressure)

nEPAP is a system adapted to provide low resistance during inhalation and high resistance during exhalation through small mechanical valves placed with adhesives in each nostril.[58] The final expiratory phase has the greatest rate of closure of the upper airway because there is neither positive pressure nor phasic activation of the PDMs that might guarantee the permeability of the airway. The elevated expiratory resistance provided by the nasal valves generates positive pressure that reduces the risk of collapse during late inhalation.[58,59]

Other mechanisms of action by which nEPAP may reduce the collapsibility of the upper airway may include: inducing pulmonary hyperinflation (which increases the FRC and the longitudinal tracheal traction) or hypercapnia from hypoventilation, causing an increase in respiratory activity in the upper airway.[60,61]

Some studies report that nEPAP improves the subjective perception of daytime excessive sleepiness. The AHI descends by 80%, and snoring is reduced after one year of treatment.[58,62] Furthermore, it appears to have greater adherence than CPAP.[58,63,64]

Oral pressure therapy

This method consists of an oral interface connected to a suction pump that applies continuous negative pressure to the oral cavity to pull the soft palate forward, stabilizing the tongue. The use of this device has been associated with reductions in AHI, nighttime desaturation, and daytime excessive sleepiness. At this point, the only secondary effects perceived are irritation and discomfort in the mouth and pharynx.[65–67]

Oral devices

These devices constitute the main alternative for patients with mild to moderate OSA and for those who do not tolerate or adhere to CPAP. They are designed to improve the configuration of the upper airway and prevent collapse through the reposition of the jaw and tongue.[68] The most frequently used are mandibular advancement devices (MAD) that increase the size of the upper airway through the protrusion of the jaw during sleep. This jaw adjustment causes upper displacement of the hyoid bone, lateral displacement of the parapharyngeal fat pads, and anterior movement of the muscles of the base of the tongue. Such modifications are associated with a decrease in the $P_{extraluminal}$ and increase in the neuromuscular activation of the upper airway.[69,70] Through magnetic resonance and cone beam computerized tomography, it has been observed that the sites of greatest widening are the retroglossal and velopharyngeal regions.[69,71]

Although CPAP has been cataloged as the most effective method for the treatment of OSA, the efficacy of the MAD may come to be similar due to its greater adherence.[69,72] It has been demonstrated that it is the best option for patients with the following characteristics: young people, women, patients with small necks, positional OSA, when AHI doubles in supine position,[36] retrognathic jaw, and low body mass index.[73] It may cause alterations such as temporomandibular syndrome, tooth pain and myofascial pain, excessive salivation, dryness of the oral mucous membrane, overbite, and reduction of the protrusion.[73,74]

Recently, a type of MAD has been in development that includes orthodontic micro-implants connected to an extra-orally anchored mask. Although its efficacy is still undetermined, this type of equipment could be used in patients with few teeth, exaggerated gag reflex, or intolerance for classic MADs.[75]

Pillar

Pillar is an implant used for the treatment of snoring, and of mild and moderate OSA. It consists of three pieces of polyethylene, approximately 18 mm each, that are inserted in a parallel fashion in the soft palate with local anesthetic. These pieces cause a chronic inflammatory response that creates a fibrous capsule around them to add structural support, harden the soft palate, and reduce its vibration.[76,77]

Its use has been associated with reductions in AHI, the intensity of snoring, and the perception of daytime excessive sleepiness.[78] However, it is only effective when the patients do not have retropalatal obstructions.[79]

The main advantage of this implant is that it does not require the elimination or destruction of the soft tissue of the upper airway for placement. Thus it reduces the risk of postoperative complications and other morbidities that do present in traditional surgical procedures (such as uvulopalatopharyngoplasty or tonsillectomy).[80,81]

Obstructive Sleep Apnea–Hypopnea Syndrome and bariatric surgery

In patients with morbid obesity, the use of CPAP, oral devices, and upper airway surgeries are ineffective on their own for the treatment of OSA[82] since obesity is the main risk factor for this condition. Bariatric surgery (BS) is presented as the optimal alternative for achieving considerable weight loss in patients with a BMI $\geq$ 40 and with important comorbidities, and for whom other weight-loss options have failed.[83,84]

There are different procedures for bariatric surgery: adjustable gastric band, gastric sleeve, gastric bypass, and biliopancreatic diversion. Evidence has demonstrated, no matter the operation performed, that bariatric surgery is coadjuvant in the treatment of OSA, effectively reducing severity in up to 75% of cases.[83] The remission rate for OSA two years after bariatric surgery in relation to the quantity of weight lost is up to 40%.[84]

Bariatric surgery lessens the circumference of the neck and abdomen, causing an increase in pulmonary volumes and reductions of AHI in the supine position, improving sleep architecture, increasing oxygen saturation, and reducing CPAP requirements.[85–87] At the same time, it has been seen that 40% of patients that undergo bariatric surgery continue to present residual OSA one or two years after intervention, but this occurs mainly because patients tend to suspend, of their own accord, the use of CPAP after the surgery.[84,88]

Night shift

Night shift is a recent device recommended only for patients with positional OSA. It consists of a small electronic monitor attached to the lower part of the neck before falling to sleep. When the user adopts the supine position, 10 s later the night shift begins emitting light vibrations that progressively increase until a change in position is detected.[89]

In studies carried out up to this point, this device has shown greater reduction in AHI and improvement of sleep architecture compared with other types of positional therapy, such as attaching a tennis ball to the neck or sleep hygiene.[90–92] Its use can be combined with CPAP or any other oral device.[90]

Electric stimulating

This is the only "target" therapeutic strategy for the elimination of OSA and its comorbidities. It consists of the electric stimulation of the genioglossus muscle to maintain the permeability of the upper airway during sleep.

The direct electric stimulation of the genioglossus via intraoral, intramuscular, or submental electrodes is able to dilate the upper airway, reduce the P_{Crit} and increase airflow, but it only partially reduced AHI. Furthermore, it induces sense stimulation that causes constant arousals during the night, causing daytime excessive sleepiness to persist and making its long-term use difficult.[93,94] To reduce these limitations and establish a more effective method, a method of electric stimulation of the hypoglossal nerve (cranial nerve responsible for innervating the genioglossus) is being implemented.

The most recent system includes a programmable and implantable pulse generator (IPG), two respiration sensors, and a stimulation electrode. The sensors detect the inhalation effort of the thorax and transmit the signal to the IPG, which sends electric impulses to the hypoglossal nerve through the electrode. A software algorithm regulates the IPG in such a way that it emits stimulation only between the end of the expiratory phase and the beginning of the next expiratory phase of each respiratory cycle. Some commands of the system, like "start", "stop", and "pause" can be controlled with a handheld device.[95,96]

The electrode is generally made of platinum/iridium, has a tripolar design that distributes the current uniformly and

Table 2 – Conclusion chart for the treatment of OSA.

Treatment	Advantages	Disadvantages
CPAP (first-line strategy)	• Effective in the treatment of OSA and its comorbidities	• Low tolerance • Low adherence • Immediate secondary effects may present in skin, eyes, nose, mouth, pharynx, stomach, intestines
nEPAP	• Offers high resistance during expiration only. • Effective in the reduction of AHI, snoring, daytime excessive sleepiness after one year of treatment • Greater adherence than CPAP • Inexpensive	• None reported to date
Oral pressure therapy	• Effective in reducing AHI, nighttime arterial oxygen desaturation, and daytime excessive sleepiness	• Irritation and pain in the mouth and pharynx
Oral devices	• Reduces extraluminal pressure at the oropharyngeal level • Activate the upper airway musculature • Effectiveness similar to the CPAP due to greater adherence	• Dental alterations: pain, overbite, protrusion reduction • Temporomandibular syndrome • Myofascial pain • Excessive salivation • Dryness of oral mucous membrane
Pillar	• Reduces the risk of post-operative complications and morbidities associated with interventions where upper airway soft tissue is eliminated or destroyed	• Discomfort with deglutition • Ineffective with retropalatal obstructions
Bariatric surgery	• Optimal in patients with morbid obesity that have failed in other weight reduction treatments • Resolves positional OSA • Improves sleep architecture • Reduces CPAP requirement	• Residual OSA 1 to 2 years after intervention due to total suspension of CPAP.
Night Shift	• Shown to be the most effective method for positional OSA	• Sleep disruption at the beginning of treatment.
Electric stimulation	• Only treatment that attempts to eliminate OSA • Increases inspiratory airflow	May have secondary effects like: • Respiratory depression • Paralysis of the phrenic nerve • Muscle fatigue • Changes in the type of muscle fiber • Soft tissue abrasions • Hypertrophy of lingual musculature

Source: Authors.

limits contact pressure to avoid possible nerve damage.[95–97] The entire system is implanted subdermally under general anesthesia. Three incisions are made: the first, at the level of the lower edge of the submandibular gland to expose the main trunk of the nerve where the electrode is placed; the second, horizontally in the fourth intercostal region, where a 5 cm tunnel is opened to place the sensors; and the third, 2 cm below the clavicle, where a "pocket" with the pectoralis major muscle is made for the IPG.[95–97]

Different studies have confirmed the efficacy of electric stimulation of the hypoglossus nerve for increasing the flow of inspired air with a resulting reduction in AHI, without sensory stimulation or associated arousals.[95,96] With fluoroscopic images, it has been possible to observe the anterior displacement of the base of the tongue, opening of the retroglossal and retropalatal regions, and anterior displacement of the hyoid bone during stimulation.[98]

Some adverse effects related to the surgical intervention and to prolonged electric stimulation include: respiratory depression, airway obstruction, infection of surgical wounds, hematomas and nerve paralysis, muscle fatigue, abrasions in soft tissue, changes in the type of fibers, and hypertrophy of the lingual musculature. All these alterations have not yet been characterized; more long-term studies are required to corroborate them.[99]

Conclusions

The diverse studies carried out in sleep medicine in recent years have permitted an understanding of the complexity of the physiopathological mechanisms that lead to the appearance of OSA. Thanks to this, new treatment alternatives have been developed that seek to address the heterogeneity of this condition, as observed in Table 2. Although a totally effective treatment is still unavailable, the combination of several therapeutic strategies, the prevent of modifiable risk factors like obesity, and, above all, intervention by an interdisciplinary team can achieve a notable improvement in the quality of life of patients with OSA. It is hoped that advances in science and technology may offer necessary tools for continued work in different fields of knowledge in the search for a treatment protocol that is able to directly address the etiological processes of the disease in order to reduce its prevalence.

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Conflict of interest

The authors have no conflicts of interest to declare.

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