NARRATIVE REVIEW/REVISÃO NARRATIVA

Dexmedetomidine as an Emerging Treatment of Agitation in Psychiatric Patients: A Narrative Review
Dexmedetomidina como um Tratamento Emergente de Agitação em Doentes Psiquiátricos: Uma Revisão Narrativa

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RESUMO
A agitação psicomotora aguda ocorre numa variedade de condições médicas e psiquiátricas sendo a forma de apresentação clínica numa percentagem significativa de episódios psiquiátricos urgentes, requerendo intervenção rápida e eficaz. Tradicionalmente, a agitação psicomotora era gerida nas enfermarias psiquiátricas com recurso à contenção física. Com o aparecimento dos neurolépticos tranquilizantes, tais como a clorpromazina, o manejo farmacológico destes estados passou a ser possível. A agitação psicomotora embora seja um resultado potencial da maioria das perturbações psiquiátricas, está frequentemente associada a quadros psicóticos, perturbações do humor e perturbações neurodegenerativas. No presente artigo, os autores propõem explorar a dexmedetomidina como opção terapêutica em estados de agitação psicomotora aguda em quadros psiquiátricos nos quais os fármacos tradicionais não surtiram efeito. Para o efeito, foi realizada uma revisão não sistemática da literatura. As palavras-chave utilizadas incluíram: dexmedetomidine, acute agitation, rapid tranquilisation, restraint, sedation, psychiatric population, psychiatric disorders. Recentemente, um passo significativo nos métodos de tratamento da agitação psicomotora aguda foi alcançado através da utilização da dexmedetomidina em quadros psiquiátricos. A dexmedetomidina trata-se de um agonista seletivo do receptor-α2 tendo aprovação para sedação a curto prazo com o benefício de não provocar sedação excessiva, permitindo desta forma uma abordagem psicoterapêutica concomitante. Este fármaco demonstra ser uma opção de tratamento promissora para doentes em estado de agitação psicomotora aguda. A quantidade de estudos disponíveis sobre a sua utilidade na doença mental são, contudo, escassas. As recomendações acerca da intervenção nos quadros de agitação no doente psiquiátrico presentes na literatura foram desenvolvidas com base em dados de investigação, considerações teóricas e experiência clínica, no entanto são necessários estudos que fornecem dados e recomendações definitivas. É imperativo que a investigação dos episódios de agitação psicomotora aguda e a sua contenção evolua, de forma proteger estes doentes das consequências do comportamento e, eventualmente, do tratamento. A exploração do potencial da dexmedetomidina como ferramenta disponível no arsenal terapêutico para o tratamento dos quadros de agitação em contexto de doença mental, ganha particular sentido face à ausência de alternativas que tranquilizem o doente muito agitado sem provocarem sedação excessiva.

ABSTRACT
Acute agitation occurs in a variety of medical and psychiatric conditions and is the clinical presentation in a significant percentage of urgent psychiatric episodes, requiring prompt and effective intervention. Traditionally, agitation was managed in psychiatric wards using physical restraint. With the advent of tranquilizing neuroleptics, such as chlorpromazine, the pharmacological management of these conditions became possible. Acute agitation, although a potential result of most psychiatric disorders, is often associated with psychotic conditions, mood disorders and neurodegenerative disorders. The authors propose to explore dexmedetomidine as a therapeutic option in states of acute agitation in psychiatric patients in which traditional drugs are not effective. The authors based the work on a non-
Restraint is a common reality in patient safety whilst permitting the treatment of the under restraint is seen primarily as a last effort tool to ensure the highly agitated patient without excessive sedation.

Palavras-chave: Agitação Psicomotora/tratamento farmacológico; Dexmedetomidina/uso terapêutico

Keywords: Dexmedetomidine/therapeutic use; Psychomotor Agitation/drug therapy

INTRODUCTION
Historically, psychiatry has utilized some admittedly creative solutions, albeit at times lacking in empathy and ethically questionable, to restrain the agitated patient. Restraint and Psychiatry have shared a close relationship, having progressed in parallel in the sense that, as Psychiatry has evolved by leaps and bounds throughout the years, so too have the methods of restraint. From the era of the alienists seated at the asylums to the use of shock therapies and lobotomies to the advent of the modern era of psychopharmacology, the final objective has always remained the same: restraint of the agitated patient so as to avoid harm to themselves or others.

Restraint is viewed as a temporary measure that is employed until the agitated condition of the patient, whether due to illicit drug intoxication, alcohol intoxication, organic or psychiatric conditions, are resolved.1 In medicine, restraint is seen primarily as a last-effort tool to ensure patient safety whilst permitting the treatment of the underlying medical condition. Restraint is a common reality in psychiatry;2 mainly because psychiatrists are confronted with conditions such as psychosis, delusions, delirium and substance abuse that predispose patients to potentially violent or dangerous behaviour.

METHODS
A narrative literature review was carried out using PubMed, Medscape and UpToDate search engines. The search terms dexmedetomidine, acute agitation, rapid tranquillisation, restraint, sedation, psychiatric population and psychiatric disorders were searched in isolation or in combination. The last survey was carried out on June 07, 2023, with the majority of the literature having been published posteriorly to 2021, emphasizing the current pertinence of the theme. The primary phase of article selection was based on perusal of abstracts, with a subsequent phase of careful reading and examination of publications selected in the first phase. Those containing subject matter most relevant to the above mentioned topic and related themes were selected. Publications mentioned in the reference lists of initially identified articles were used when justified by their original and/or relevant content. All articles not corresponding to the explored theme or those that did not provide sufficient information on the utilization of dexmedetomidine in the psychiatric setting, were excluded.

RESTRAINT AND THE AGITATED PATIENT
Psychomotor agitation can occur in many environments, being a more common phenomenon in emergency departments and psychiatric wards.3 Agitation is characterized by a range of motor, emotional and behavioural symptoms and may be associated with neurological, psychiatric and/or general medical conditions.4 It encompasses symptoms of restlessness, irritability, anxiety and eventually movements without a specific purpose that can evolve into aggressive or violent behaviour.5,6 In many cases, agitation arises when patients feel anxious, angry or threatened, or when their ability to resolve their distress is compromised, as may occur in the context of an unfamiliar environment or during a state of intoxication, deprivation or altered mental status.7

When agitation and/or violent behaviour is unable to be thwarted by means of verbal intervention or voluntary medication use, recourse to various emergency forms of restraint including pharmacological (forced administration of medication via oral route or intramuscular injection), mechanical (recourse to the 5 point restraints for example) or seclusion (placing and keeping the patient in a bare room) methods might be a necessity.5,6 Traditionally, agitation was managed in psychiatric wards using an array of physical or mechanical restraint techniques and devices. With the advent of neuroleptic tranquilizers (ex. phenothiazides), such as chlorpromazine in the 1950s and later the butyrophenones, the pharmacological or chemical management of these conditions became a possibility.10 In the following decades, the pharmaceutical
industry developed second-generation antipsychotics and benzodiazepines, which added to the professional’s toolbox for managing the agitated or violent patient. Currently, the standards for the acute treatment of agitation recommend patient-centered approaches, in which verbal and non-verbal de-escalation techniques are used, giving preference to less invasive treatments when possible. When these methods are not effective, the use of psychotropic drugs such as antipsychotics (typical or atypical) and/or benzodiazepines is a frequent option utilized. These pharmacological options are available in a variety of forms, including oral tablets, orodispersible tablets, liquid drops and intramuscular injections, which permit some degree choice depending on the context, history and cooperation of the patient. Although these agents are effective in reducing the agitated patient, they are not a panacea, with each having its own limitations, including adverse effects, such as acute dystonia in the case of antipsychotics and risk of respiratory failure in the case of benzodiazepines, for example. Another serious limitation is that they tend to induce a sedative state, which is desirable when taking into consideration the risk that agitation and violent behaviour poses, however, it annuls the possibility of verbal and behavioural intervention thus consequently interfering in the capacity for adequate clinical and mental evaluation as well as conditioning the ability of providing psychological intervention.

EFFECTS OF RESTRAINT ON THE PATIENT
Approaching the agitated patient through restraint must guarantee safety, as well as maintain the patient’s individual dignity, since the use of this technique and intervention can generate harmful physical and psychological effects. Although restraint is employed as a mean to protect the patient and others from the agitated states, restrained patients may present physical injuries resulting from the restraining process, as well as present an increased risk of unfavorable clinical outcomes related to the procedure. These conditions can include dehydration, asphyxia, aspiration, respiratory depression, thrombosis, arterial hypertension, arrhythmias, incontinence, rhabdomyolysis, increased risk of aggression by other patients and death. The deleterious psychological effects are less reported in the literature but are associated with the potentially traumatic event of going through physical and chemical restraint. Emotional reactions, such as fear, anger and anxiety, in addition to intrusive thoughts, recurrent nightmares, avoidance behaviours, increased startle responses and distrust, were observed years after the procedure was performed. Restriction can also temporarily aggravate the agitation and violent behaviour as a response to a breach on autonomy. All of these adverse effects of restraint become relevant because restraint can generate a conditioning for life, where the negative effects can exert long term repercussions years after the restraint, with one study reporting maintenance of intrusive thoughts, recurrent nightmares, avoidance behaviours, startle responses, and mistrust five years after the episode. Considering that these medications are frequently given against patient wishes, paired with the potential secondary effects inherent to those utilized in restraint, such as acute dystonia, these negative associations come as little surprise. Therefore, if the patient’s first contact with Psychiatry is marked by involuntary taking of pharmacological and physical restraint, it might forever condition the patient’s impression of Psychiatry and its interventions. In this manner, it is known that innovation in Psychiatry tends to be a slow-moving process with developments in treatment modalities remaining somewhat stagnant throughout recent years. Methods of restraint, whether physical or chemical are equally stable in terms of available options, however, recent literature explores the potential application of a drug not previously used in the psychiatric context in the restraint of agitated patients.

CHARACTERIZATION OF DEXMEDETOMIDINE
In this context, the importance of expanding the pharmacological options for patient restraint is highlighted, especially considering the high prevalence of psychomotor agitation and potential progression to violence in psychiatric emergency settings and for this reason, a promising next step might involve the repurposing of dexmedetomidine. Dexmedetomidine is considered a promising drug used for sedation in the most varied areas of healthcare, and has been proposed recently as a potential intervention in the restraint of acutely agitated psychiatric patients. A central α-2 adrenergic agonist, it was introduced into clinical practice in the United States of America in 1999 and approved for adults in intravenous form for short-term procedural sedation and agitation control of intubated and mechanically ventilated patients in the intensive care setting as well as for those non-intubated undergoing surgical and other procedures. Mainly utilized through intravenous route, it is a drug that necessitates monitoring of vital signs. The mechanism of action is a predominant action on the locus coeruleus, through which it acts by attenuating central nervous system excitation by decreasing the pre-synaptic release of norepinephrine and exerting sedative and – to a lesser extent – analgesic and anxiolytic effects with minimal ventilatory repercussion while offering no anticholinergic activity (which is of special benefit in the elderly population, in which sedative neuroleptics are contraindicated due to their anticholinergic effects). This action on the locus coeruleus also contributes to the production of a sedative effect that resembles physiological sleep, approximating non-rapid eye movement sleep, by promoting endogenous sleep pathways. This enables conscious sedation, with ease of awakening at lower doses, which makes it a favourable tool for restraint in the psychiatric setting. Patients under the effects of dexmedetomidine were described as being very easy to wake up and with the ability to comply with commands and cooperate, thus allowing a concomitant psychotherapeutic approach.
The literature also suggests that dexmedetomidine may have protective properties on various organs and systems, including the heart, brain, kidney, liver and lung with neuroprotective properties posing as a potential benefit for a portion of psychiatric patients who are especially vulnerable to cognitive decline.27
As mentioned previously, dexmedetomidine is a relatively selective α-2 adrenoceptor agonist that possesses sedative, anxiolytic, analgesic and hemodynamic stabilising effects. Through its activation of central pre- and postsynaptic α2-receptors in the locus coeruleus, it provides a relatively fast onset of sedative properties similar to natural sleep, with minimal respiratory depression. Selectivity is reduced at higher doses and with rapid administration.24
It is potent and highly selective for α2-receptors with an α2:α1 ratio of 1620:1.28 Due to this adrenergic actions, side effects are mainly hemodynamic and include hypertension, hypotension, and bradycardia as a result of vasoconstriction, sympatholysis, and baroreflex-mediated parasympathetic activation.29 In terms of absorption, intravenous administration is predictably associated with high peak plasma levels which could be avoided through alternative routes of administration. After oral administration, an extensive first-pass effect is observed, with a bioavailability of 16%.30 Dexmedetomidine is well absorbed through the intranasal and buccal mucosa, the feature that has garnered interest various populations, including the agitated patient.31 Dexmedetomidine is a highly protein-bound drug with over 90% of dexmedetomidine binding to albumin and α1-glycoprotein in the plasma. It is rapidly and widely distributed throughout the body, readily crossing the blood-brain and placenta barriers.32 A high inter-individual variability in dexmedetomidine pharmacokinetics has been described, where factors such as body size and hepatic impairment, having demonstrated a significant impact on pharmacokinetics, others factors such as plasma albumin levels, cardiac output, and age are less impactful.33 Dexmedetomidine mainly undergoes hepatic metabolism by glucuronidation and hydroxylation (mediated by cytochrome P450 enzymes, namely CYP2A6) with no active metabolites.34 Less than 1% is excreted unaltered with metabolites being excreted renally (95%) and fecally (4%).34 It has an elimination half-life of 2-3 hours.34
The most common adverse effects of dexmedetomidine are, due to its mechanism of action, hypotension and bradycardia, as well as dry mouth and nausea.2 Taking these effects into account, although no definite contraindications exist in regards to dexmedetomidine, relative contraindications to the use of dexmedetomidine have been suggested and include a known sinus node or atrioventricular node dysfunction, and those with limited sympathetic reserve with caution employed in those with comorbid heart disease or when taken with medications with a negative chronotropic effect.2 Given its hepatic metabolism, it should be adjusted in patients with hepatic insufficiency.23
In spite of these adverse effects, the literature demonstrates that it appears to provide a more benign hemodynamic profile based on cardiopulmonary status with minimal effects on QT interval prolongation.2,35 It is considered safer when compared to benzodiazepines because of its limited potential to cause apnea or respiratory depression, as well as demonstrating better clinical outcomes in comparison to the aforementioned pharmacological group.7,36
Dexmedetomidine has been described to have various drug interactions related to its hepatic metabolism with major action by the CYP2A6 enzyme.31 Interactions with antidepressant use (no class has been specifically identified), has been described, leading to an enhanced sedative effect.37 A relationship between the alpha2-adrenergic receptor and antipsychotic and antidepressant efficacy, as well as between alpha2-adrenergic receptor polymorphisms and neuropsychological responsiveness in patients with major depressive disorders have been described in the literature, which could be significant when administering dexmedetomidine.38-39 One study reported that patients with ambulatory antidepressant treatment were more likely to achieve successful sedation with dexmedetomidine when compared to those without antidepressant treatment.37 Sedative and hypotensive effects have been demonstrated when used with other sedative and analgesic agents such as midazolam and other benzodiazepines.40 Associated use with valproic acid may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating.41 Care should be taken when administering dexmedetomidine with other agents that cause bradycardia (i.e. beta-blockers). Potassium or medications that increase potassium – may potentiate possible hyperkalaemia associated with dexmedetomidine use.40

**INTRAVENOUS DEXMEDETOMIDINE**

In Portugal, the currently available formulation is the water-soluble hydrochloride salt, administered intravenously. In Europe, it is approved for adults (intubated or non-intubated) in the Intensive Care Unit (ICU) via continuous intravenous infusion without a restriction on duration of administration.24 In the ICU, where this drug is more commonly used, sedation is typically reached with a typical loading dose of 0.5 to 1.0 mcg/kg over 10 to 20 minutes, usually followed by a continuous infusion the dosage range of 0.2 to 0.7 mcg/kg per hour.42 This can increase to 1.5 mcg/kg per hour in order to reach desired sedation level, with doses higher than this not appearing to provide any additional therapeutic benefit at a cost of increased side effects.42 When used in anesthesia, the typical dosing is a loading dose of 0.5 to 1.0 mcg/kg, usually followed by a continuous infusion of 0.2 to 0.7 mcg/kg per hour titrated to desired sedation goals. For procedural sedation, a loading dose of 1 mcg/kg in 10 min followed by a maintenance infusion of 0.6 mcg/kg/h, titrated to the desired clinical effect with doses ranging from 0.2 to 1 mcg/kg/h, is recommended.42 The sedative effect of dexmedetomidine is concentration dependent, with plasma concentrations between 0.2 and 0.3 ng/mL resulting in significant and rouseable sedation.39 Dosage adjustments for renal or hepatic impairment are typically not required but should be considered in those with hepatic impairment. Due to its mechanism of action, level of sedation, heart rate/rhythm,
blood pressure, and pulse oximetry requires monitoring. According to the 2013 Society of Critical Care Medicine’s Pain, Agitation, Delirium guideline, non-benzodiazepine sedatives, including dexmedetomidine, should be utilized as first line agents to provide effective sedation for mechanically ventilated, ICU patients. A protocol on the intravenous administration of dexmedetomidine in the agitated psychiatric patient, at the time of publication, has not yet been described in the literature.

SPECIAL POPULATIONS

The advantage of dexmedetomidine is that it can be used in special populations, albeit with caution and adequate monitoring. Although, there are no absolute contraindications to the use of dexmedetomidine, precaution should be taken in cases of hypovolemia, advanced heart block, heart failure, bradycardia or severe ventricular dysfunction due to risk of myocardial dysfunction, hypotension and bradycardia. Young patients with increased vagal tone may be more susceptible to bradycardia and sinus arrest. In those with renal impairment, no difference in either volume of distribution or elimination clearance was found, although sedative effects lasted longer than in healthy controls, with no adjustment being necessary. In hepatic impairment, due to its metabolism, has an impact on pharmacokinetics of dexmedetomidine with a decreased clearance and a higher unbound fraction having been described. Therefore, reductions in initial dosage and careful titration are recommended. Although no adequate and well-controlled studies in humans have been conducted, animal studies have not revealed teratogenicity or fertility effects. Placental transfer of dexmedetomidine have occurred. It is a Category C drug according to the US Food and Drug Administration (FDA), where potential benefits may warrant use of the drug when the benefit outweighs the risk. Dexmedetomidine is excreted in animal milk. Limited data indicate that very small amounts of dexmedetomidine are excreted into breastmilk for 6 hours after the end of an infusion and would not be expected to cause adverse effects in breastfed infants or neonates. In regards to the elderly patient, as previously mentioned, age does not appear to influence pharmacokinetic profile of dexmedetomidine. Sedative effects appear to be more pronounced in this populations, with lower doses needed to provide adequate sedation in those aged 65 – 78 years. Increased risk of hypotension and bradycardia in this population have also been described. Age-adjusted dosing is not typically recommended, although caution is warranted as hemodynamic and sedative effects might be more pronounced this population which often present with multiple co-morbidities.

APPLICATION IN THE PSYCHIATRIC SETTING

Dexmedetomidine has been previously utilized in the psychiatric setting, namely in the context of post-electroconvulsive therapy (ECT) agitation, alcohol withdrawal syndrome, catatonia and hyperactive delirium. Due to its previously described “delirium-sparing” characteristics allied with its capacity for promoting a more natural sleep architecture, dexmedetomidine has been proposed as a drug in the management of delirium in the ICU and in post-ECT agitation. Maldonado et al, report that it is It is associated with a lower incidence of postoperative delirium (3%) compared with propofol (50%) and midazolam (50%).

The adjunctive use of dexmedetomidine in alcohol withdrawal syndrome (which does not exclude the use of conventional treatment), as well as in potentially deadly cases of delirium tremens has been shown to reduce hypertension and tachycardia and decrease the necessary benzodiazepine doses. Almeida et al, describe a case series in which dexmedetomidine was utilized with positive results in those presenting with catatonia, thus adding another potential psychiatric repurposing of this pharmacological substance.

The reporting of these positive outcomes throughout the recent literature has led to the consideration of dexmedetomidine as an adjunctive tool for the management of acute agitation in other psychiatric states, namely patients with schizophrenia and bipolar disorder.

The original study that launched the interest for the application of dexmedetomidine in the psychiatric population was spearheaded by Citrome et al. In their study, they explored the application of sublingual dexmedetomidine in the treatment of acute agitation in those with schizophrenia or schizoaffective disorder. They found that, agitation was significantly reduced after sublingual dexmedetomidine administration (compared to placebo) which will be explored subsequently.

SUBLINGUAL DEXMEDETOMIDINE

Dexmedetomidine was reformulated as a soluble sublingual film, which permits sublingual or oral administration. This method of administration allows for a wider use of this agent, previously restrained to the ICU, with a novel application in the psychiatric setting for the management of acute agitation whilst potentially adhering the use of intramuscular injectable administration of antipsychotics and/or benzodiazepines. In 2022, the FDA approved a sublingual formula of dexmedetomidine, representing the first new rapid, noninvasive treatment in nearly a decade aimed at management of acute agitation in those with schizophrenia or schizoaffective disorder. Sublingual dexmedetomidine is a mint-flavoured rectangular film containing 2 microdeposits of dexmedetomidine hydrochloride. The particular formulation is absorbed orally thus bypassing first-pass metabolism, and achieving higher bioavailability than ingested formulations with an onset of effect beginning within 20 to 30 minutes. This formulation has a dose-dependent exposure and due to this it is commercially distributed in doses of 120 mcg, recommended for mild or moderate agitation and 180 mcg.
for severe agitation. The recommended dose depends on the severity of agitation and the presence of liver failure. Dosage is to be adjusted in patients with hepatic impairment of varying degrees and in elderly patients. If agitation persists after the initial dose, up to 2 additional doses halving the initially administered dose can be given with a minimum of a 2 hour interval.

Sublingual dexmedetomidine is an effective and well-tolerated pharmacologic option for the management of acute agitation associated with schizophrenia and bipolar disorder. Regarding dexmedetomidine, it is important to note that it lacks dopamine receptor activity, avoiding extrapyramidal side effects including dystonia, akathisia, and tremor which makes it an attractive choice when compared to the antipsychotics frequently utilized in cases of agitation. The most commonly reported adverse reactions of sublingual dexmedetomidine include somnolence, paresthesia, oral hypoesthesia, dizziness, hypotension, orthostatic hypotension, and dry mouth. In regards to the decrease in mean arterial pressure associated with sublingual dexmedetomidine might prove to be a concerning issue especially in those with medical comorbidities and under polypharmacy, thus limiting its application to settings in which vital status monitoring and professional supervision can be guaranteed.

SUMMARY OF FINDINGS FOR THE USE OF DEXMEDETOMIDINE IN THE PSYCHIATRIC SETTING

• Although the intravenous formulation of dexmedetomidine was first approved by the FDA for sedation and analgesia in the ICU, it has since been used in other settings such as in the management of agitation in delirium, alcohol withdrawal, anticholinergic toxicity and catatonia.

• Administration of sublingual dexmedetomidine has been recently approved by the FDA for the treatment of acute agitation in adults with schizophrenia, schizoaffective or bipolar I and II disorder.

• Reports from the literature have shown that dexmedetomidine could be a significant pharmacological option to treat delirious patients due to its favourable sedative profile, easy titration, fewer side effects than neuroleptics and rare interactions with other drugs. One study demonstrated that a short nighttime dose of dexmedetomidine decreased the incidence of delirium on postoperative day one. A case series described dexmedetomidine as a promising option to treat psychomotor agitation in the context of excited catatonia.

• Alcohol withdrawal syndrome is characterized by agitation, psychosis, and manifestations of autonomic hyperactivity. Since dexmedetomidine reduces symptoms of autonomic hyperactivity as well as reducing benzodiazepine requirements it has been presented as a potential treatment of agitation in the context of alcohol withdrawal.

• Case reports have described using dexmedetomidine for the adjunct treatment of anticholinergic toxidrome so to relieve symptoms of agitation, psychosis, tachycardia, and hypertension.

CONCLUSION

Today, psychiatry continues to evolve and move into a more empathetic and humane era of restraint, where non-invasive formulations such as sublingual dexmedetomidine provide an opportunity to rethink restraint of the agitated patient while exploring new frontiers. This reformulation, together with an enviable safety profile, makes dexmedetomidine a promising drug with the potential to improve the overall patient experience, thereby improving the therapeutic relationship between patient and healthcare professional, since the level of sedation permits communication and concomitant therapeutic interventions. The absence of potentially “traumatizing” effects, such as acute dystonia, diminish the probability that the patient develops a negative preconception regarding Psychiatry and its interventions. This progression in the way agitation is managed holds much promise, but remains one that merits further exploration and structured study so as verify widespread efficacy and safety profile as well as determine the ideal patient profile which might most benefit through this innovative development.

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SJ: Conceção e desenho do estudo; Colheita e análise de dados; Escrita, edição e revisão do manuscrito.
JA: Conceção e revisão do manuscrito
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SJ: Conceptualization; Methodology; Data collection; Writing, editing and review of the manuscript.
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