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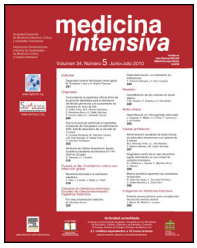

REVIEW

Indications of dexmedetomidine in the current sedoanalgesia trends in the critical patient☆

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Abstract Recently, dexmedetomidine has been marketed in Spain and other European countries. The published experience regarding its use has placed dexmedetomidine on current trends in sedoanalgesic strategies in the adult critically ill patient. Dexmedetomidine has sedative and analgesic properties, without respiratory depressant effects, inducing a degree of depth of sedation in which patients can open their eyes to verbal stimulation, obey simple commands and cooperate in nursing care. It is therefore a very useful drug in patients who can be maintained on mechanical ventilation with these levels of sedation avoiding the deleterious effects of over- or infrasedation. Because of its effects on α2-receptors, it is very useful for the control and prevention of tolerance and withdrawal to other sedatives and psychotropic drugs. The use of dexmedetomidine has been associated with lower incidence of delirium when compared with other sedatives. Moreover, it is a potentially useful drug for sedation of patients on non-invasive ventilation.

PALABRAS CLAVE
Sedación;
Dexmedetomidina;
Alfa2-agonistas;
Ventilación mecánica;
Paciente crítico

Indicaciones de la dexmedetomidina en las tendencias actuales de sedoanalgesia en el paciente crítico

Resumen Recientemente, la dexmedetomidina se ha comercializado en España y en otros países europeos. La experiencia publicada permite dar unas recomendaciones y situar este fármaco en las actuales tendencias de sedoanalgesia del paciente crítico adulto. La dexmedetomidina tiene efectos sedantes y analgésicos, sin causar depresión respiratoria, e induce un nivel de sedación donde el paciente puede abrir los ojos a la estimulación verbal, obedecer órdenes sencillas y cooperar en los cuidados de enfermería. Por tanto, es muy útil en enfermos ventilados que pueden ser mantenidos con estos niveles de sedación, evitando los efectos deletéreos de la sobresedación o la infrasedación. Por su acción sobre los α2-receptores, es eficaz en la

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prevención y en el control de los cuadros de tolerancia y/o abstinencia a otros sedantes y psicotrópicos. Comparada con otros sedantes, la dexmedetomidina se ha asociado con una menor incidencia de delirio. Además, puede ser útil en la sedación durante la ventilación no invasiva.

Introduction

Sedoanalgesia is a key element in the management of many critically ill patients, particularly those requiring mechanical ventilation (MV), and is useful for improving patient well-being, reducing anxiety and facilitating the performance of different procedures.[1] However, inadequate sedative use can cause potentially serious adverse effects.[2,3] On one hand, insufficient sedoanalgesia can give rise to serious agitation with the induction of myocardial ischemia, poor adaptation to the ventilator, or auto-extubation or catheter removal, and is associated with a prolongation of stay in the Department of Intensive Care Medicine, increased costs, greater morbidity and even mortality. On the other hand, excessive sedation prolongs the duration of MV and of patient stay in the DICM, increases the risk of complications such as ventilator-associated pneumonia or neuromuscular alterations, gives rise to a larger number of neurological diagnostic tests with the consequent risks and costs, and leads to a greater incidence of cognitive disorders[4] and even mortality.[5] Moreover, the administration of high sedative doses poses a risk of adverse and toxic effects (hemodynamic, gastrointestinal, infectious, metabolic, withdrawal symptoms, etc.).[3]

The discrepancies found in the literature regarding the recommended optimum sedation range, the variations in the methodology used to evaluate sedation, and the differences in the frequency of evaluation all make it difficult to establish the true incidence of inappropriate sedation. In this context, the published incidence of suboptimal sedation is 1–75%, and oversedation is more common than undersedation, with an estimated frequency of 33–57%.[6] In the DICM, a desirable aim of sedation is to keep the patient calm, comfortable, cooperative and communicative, with easy awakening, the capacity to interact with the healthcare personnel or relatives, and the maintenance of a normal sleep-waking cycle. However, because of their clinical condition, some patients may require deeper sedation (e.g., in situations of intracranial hypertension or acute respiratory distress syndrome).[7,8]

In order to prevent the deleterious effects of undersedation or oversedation, the administration of sedatives and analgesics should be based on an established protocol, with clearly defined sedoanalgesic objectives. Such objectives should be established according to the patient condition at the start of treatment, and must be revised on a regular basis. Collaboration of the nursing personnel is very important in this scenario, since social, personal and professional factors often influence individual interpretation of the patient needs.[9] It must be taken into account that the patient needs vary according to the clinical circumstances, and that the therapeutic objectives can change over time.[10]

Sedatives are to be adjusted to the individual needs of the patient, administering the minimum dose required to achieve the objectives. In attempting to optimize sedoanalgesia, when selecting the appropriate drug it is important to consider the specific characteristics of each agent, including the pharmacokinetics and possible adverse effects. It also must be taken into account that pharmacokinetic and pharmacodynamic alterations occur in the critical patient, secondary to an increased distribution volume, a decrease or increase in drug-binding proteins, possible receptor alterations, organ failure, etc., which modify the effects of sedatives and analgesics.

Theoretically, the ideal drug should offer rapid action, with a predictable pharmacokinetic and pharmacodynamic profile and, once suspended, it should allow fast patient physical and cognitive recovery. At present, the sedatives most commonly used in the DICM are benzodiazepines and propofol.[1] The characteristics of the benzodiazepines, including onset and duration of action, distribution, potency, and the presence or absence of active metabolites, are variable. Caution is advised when administering these drugs in continuous infusion, due to possible accumulation of the drug substance or its metabolites, which can give rise to inadvertent oversedation, the development of tolerance phenomena in a matter of hours or days, and withdrawal symptoms after prolonged use.[3,8] Propofol is the preferred sedative when rapid wakening is desired, or in neurological patients, since it allows the performance of intermittent neurological evaluations. However, its administration for long periods of time or in large doses can produce adverse effects (hypertriglyceridemia, propofol infusion syndrome).[3]

The α2-adrenergic receptor agonists, such as clonidine and dexmedetomidine (DEX), possess sedative and analgesic effects, and in some situations constitute an alternative to the aforementioned sedatives (benzodiazepines and propofol). Different authors have demonstrated the efficacy of DEX in critical patients, affording adequate sedoanalgesia and allowing a reduction of the doses of other sedatives and analgesics, and even a shortening of the duration of MV.[11–14] Since the year 1999, DEX is available in the United States and in other American countries for the sedation of ventilated patients, and is one of the most widely recommended drugs in the clinical guides of these countries.[15,16] However, DEX was only approved by the European Medicines Agency (EMA) in 2011–this representing the first step for its marketing in Spain. The cumulative experience gained with DEX allows us to make a series of suggestions regarding its current place in the sedoanalgesia of critically ill patients.

Pharmacological characteristics of dexmedetomidine

DEX is a selective α2-adrenergic receptor agonist that acts at both peripheral level and in the brain and spinal cord, with a selectivity approximately 7- to 8-fold that of

clonidine, and an $\alpha 2{:}\alpha 1$ affinity of 1600:1.[14,17,18] It exerts sedative and anxiolytic action through presynaptic stimulation of the $\alpha 2$-adrenergic receptors in the *locus coeruleus*, and also has analgesic effects. On the contrary, the action of DEX at other levels such as the imidazoline receptors, has been related to the neuroprotective effects of the drug observed in experimental studies.

Following its intravenous (i.v.) administration, the onset of action of DEX is observed after 15–30 min, and the peak plasma drug concentration is reached approximately one hour after the start of continuous i.v. infusion. DEX is highly lipophilic and is quickly distributed in the tissues, with a distribution half-life of about 6 min and an elimination half-life of 2–3 h. The drug is extensively bound to proteins, with a free fraction of 6%, and the distribution volume is relatively large (1.33–2.1 l/kg). DEX is metabolized in the liver –biotransformation being mediated by the cytochrome P450 enzyme system (mainly isoenzyme CYP 2A6), with posterior glucuronidation. The inactive metabolites are eliminated mainly in urine, while 5–13% are eliminated in stools.[14,17,18]

As regards dosing of the drug, DEX was initially administered in the form of an i.v. at a loading dose of up to 1 μg/kg in about 10 min. During administration of the loading dose, patients may experience hypotension, though transient hypertension can also be observed as a consequence of the initial peripheral vasoconstrictive action of the drug at high doses. This normally resolves without the need for intervention. There have also been reports of clinically significant episodes of bradycardia and sinus node arrest after bolus dosing or rapid infusion. At present, in the sedoanalgesia of critical patients, and to limit possible side effects, loading doses are not advised. In intubated patients we should start with the infusion of approximately 0.7 μg/kg/h i.v., followed by adjustment according to the desired levels of sedoanalgesia and the patient response. After dose adjustment, steady state conditions are not reached again until after one hour. The recommended dosing range is 0.2–1.5 μg/kg/h i.v.[14,17]

The quality of the sedation afforded by DEX differs from that of other sedatives such as benzodiazepines or propofol, which act upon the GABA receptors. The administration of DEX produces a level of sedation in which the patient can open his or her eyes in response to verbal stimulation, obey simple instructions and cooperate with nursing care or certain procedures. However, upon interrupting the stimulus the patient falls asleep again and returns to the previous level of sedation. The sedation induced by DEX is characterized by a respiratory pattern and electrocardiographic (ECG) changes consistent with those seen during natural sleep.

The i.v. administration of DEX is generally well tolerated when used for the sedation of patients subjected to MV,[14,17,19–28] and also during certain diagnostic or therapeutic procedures in non-intubated patients.[17,29,30] Hypotension and bradycardia are the most common adverse effects, though they generally resolve without intervention. In those cases where intervention proves necessary, it is advisable to reduce or suspend DEX infusion, raise the legs of the patient, increase volume support and, if needed, administer vasopressor drugs. The use of anticholinergic agents also should be considered in patients with extreme bradycardia. However, by minimizing the sympathetic response, the cautious use of DEX could afford particular benefit in some patients, e.g., it those admitted with MV and presenting a high risk of postoperative cardiac complications.[20,21,31]

Although DEX can inhibit gastric emptying and gastrointestinal transit,[32] to date there have been no reports of associated complications in critical patients. The effects upon cerebral blood flow vary among different studies.[33] Research in animals has shown a decrease in cerebral blood flow; however, a study in healthy volunteers recorded a dose-dependent decrease in both cerebral blood flow and brain metabolic consumption, with maintained coupling between both phenomena.[34] DEX exerts no effects upon adrenal gland function[35] and does not produce respiratory depression.[22]

Studies in animals have revealed a certain tolerance of the hypnotic effects of DEX after prolonged administration of the drug, though this does not seem to be of clinical relevance.[18] However, as experience with the drug increases, such situations might become more common. At least in theory, a possible problem associated with the prolonged use of DEX could be the development of withdrawal symptoms, with rebound agitation or hypertension. Although there have been isolated reports of withdrawal,[25,36] the incidence is lower than in the case of clonidine, and most studies have not observed this phenomenon despite abrupt suspension of the drug.[18,19,23,28] In any case, gradual dose reduction has been recommended in order to prevent such problems.

Although DEX is more expensive than other sedatives, different pharmacoeconomic analyses in patients with MV receiving sedation during more than 24 hours have shown DEX to be associated with significantly lesser costs than midazolam. This was mainly a consequence of a decrease in costs associated with shorter patient stay, briefer MV, and a decrease in the incidence and duration of delirium.[37,38]

Indications of dexmedetomidine in the critical patient

Based on the existing information, the possible indications of DEX in sedoanalgesia practice would be related to the following.

Brief sedation (<72 h)

In view of its described pharmacokinetic and pharmacodynamic characteristics (shorter half-life than other $\alpha 2$-agonists such as clonidine, no active metabolites or accumulation effects, and anxiolytic, sedative and analgesic action without producing respiratory depression or rebound effects upon suspending administration), DEX may be useful for brief sedation. In this sense it would be an alternative to drugs such as propofol and remifentanil.[7] The studies carried out to date generally describe a similar extubation time, though with a comparatively lesser need for opiates or rescue sedatives.[17,20,21,39] DEX also reduces chills in the postoperative period.

Postoperative patients expected to require mechanical ventilation for only a few hours

These patients include postoperative uncomplicated heart surgery patients and individuals subjected to prolonged

surgery. The sedative and anxiolytic effects of DEX allow us to keep the patient comfortable until the clinical situation has stabilized (hemodynamics, respiratory parameters, absence of postoperative bleeding and of residual effects of the previously administered neuromuscular blockers, adequate level of consciousness) and extubation can be carried out. Although DEX has analgesic effects, some patients require postoperative analgesic reinforcement with opiates or other drugs, depending on the patient-reported intensity of pain.

Postoperative patients expected to require mechanical ventilation for over 12 h

These patients include postoperative complicated surgery patients (e.g., complex maxillofacial surgery, lung transplantation or other complicated operations involving important bleeding, respiratory problems, etc.) requiring a longer observation period until complications can be discarded (e.g., soft tissue edemas, lung edema secondary to reperfusion, lung complications derived from multiple transfusions, etc.). In these situations it is important to distinguish between patients who can be maintained with mild sedation and those who require deep sedation (Richmond Agitation Sedation Score [RASS] under −3). In the former case, DEX (normally associated to an opiate in order to guarantee adequate analgesia) is a good alternative, though not so in the latter. However, in patients requiring deep sedation, once the risk period has passed, DEX could be useful as a sequential sedation strategy in weaning from MV, particularly if the previously administered sedative was a benzodiazepine.

Patients requiring brief mechanical ventilation due to clinical or traumatologic conditions

Dexmedetomidine is able to avoid anxiety, with a RASS sedation score of between 0 and −3, which allows communication with the patient and the adjustment of analgesia according to the reported intensity of pain. As has been commented, many patients–particularly those with polytraumatisms–will also need other analgesics in neuroaxial or continuous i.v. administration, in order to maintain the desired level of comfort.

Prolonged sedation

Patients expected to need more than three days of sedation, but with disease conditions not requiring deep sedoanalgesia (RASS < −3)

A number of studies in critical patients, fundamentally with clinical rather than surgical conditions, have demonstrated the usefulness of DEX as a more prolonged sedoanalgesia strategy. In the MENDS study, the patients received DEX for a median of 5 days, and in comparison with the lorazepam sedation group, they had more days without delirium or coma, a lesser prevalence of coma (RASS −4 or −5), and a longer period of time within the desired sedation range (as assessed by the RASS score) – though no differences were observed in the duration of MV, stay in the DICM, or mortality.[24] A subsequent analysis of this trial showed that in the subgroup of septic patients, DEX afforded greater benefit, presenting more days without delirium or coma, also without MV, and lesser mortality.[40] The SEDCOM study in turn showed that DEX compared with midazolam is associated with a lesser frequency of delirium and a shorter mean time to extubation. There were no differences in mortality after 30 days. The median duration of treatment with DEX was 3.5 days.[25] The pharmacoeconomic analysis likewise proved favorable to DEX.[37] In another randomized, double-blind study comparing DEX with standard sedation (midazolam or propofol plus an opiate), the mean time within the desired sedation range (as assessed by the RASS) and the stay in the DICM were similar in both groups, but the duration of MV was shorter among those sedated with DEX.[26] The MIDEX (Dexmedetomidine versus midazolam for continuous sedation in the intensive care unit) and PRODEX studies (Dexmedetomidine versus propofol for continuous sedation in the intensive care unit) have recently been published. These trials compare the efficacy and safety of DEX versus midazolam and propofol, respectively, for the sedation of patients subjected to MV in the DICM.[28] Both studies present a randomized, double-blind, prospective, multicenter design with a sedation target of RASS between 0 and −3, and a sedation time of ≥24 h (maximum 14 days). Most patients were non-surgical cases in both studies (55–70%). DEX was shown to be non-inferior to the other two sedatives, and the time to desired sedation was similar in all groups. However, DEX shortened the duration of MV compared with midazolam (median 123 versus 164 h; $p = 0.03$) and the median time to extubation compared with both midazolam ($p = 0.01$) and propofol ($p = 0.04$). The mean duration of stay in the DICM from randomization to discharge was shorter among the patients administered DEX, though the difference did not reach statistical significance in either study. In comparison with both midazolam and propofol, the patients sedated with DEX showed easier awakening, increased cooperativeness, and were more able to report whether they experienced pain or not. There were no differences in terms of mortality.

Dexmedetomidine is an alternative to be considered in these individuals, since it can facilitate patient assessment (e.g., evaluation of neurological function) without having to stop the infusion, improve the capacity of the patient to report his or her needs, facilitate patient cooperation in diagnostic procedures or in care maneuvering, and shorten the duration of MV. Furthermore, and although additional studies are needed, the existing data suggest that DEX can reduce the incidence of delirium in comparison with other sedatives (see ''Prevention of delirium in the critical patient'', below).

Sequential sedation

The sedoanalgesia strategy used should not adversely effect weaning from ventilation. In intubated patients, it is useful to switch from sedation with a benzodiazepine (normally midazolam in our setting) to propofol or remifentanil once the patient condition has improved. In this context, DEX may be an alternative to facilitate weaning from MV.

In a German survey, 56% of the DICMs used clonidine in sedation lasting more than 72 h, versus almost 63% during weaning from MV.[12] In prolonged sedation, the sedoanalgesia guides of that country recommend the use of drugs such as clonidine during the withdrawal of sedation.[13] In Spain,

clonidine is available for administration via the oral route, and only some centers have access to formulations for parenteral use. This constitutes an important limitation for the utilization of clonidine in critical patients, since many of them suffer gastrointestinal alterations and therefore have problems in absorption via this route. DEX offers an alternative in this sense. In a sequential sedation strategy, this option would allow us to maintain lighter sedation, avoiding accumulation phenomena, without respiratory depression, and could also avoid possible withdrawal symptoms. In a study involving 20 patients admitted to a DICM, the use of DEX allowed withdrawal or reduction of the dosage of other sedatives and analgesics (midazolam, propofol, morphine, fentanyl), and lowered the incidence of oversedation from 13% to 3%. Sixteen of the 20 patients required either no additional sedation, or only minimal additional sedation.[23]

Patients who develop tolerance to sedatives or sedation failure

Difficult sedation is considered to refer to situations in which the patient subjected to MV requires higher than normal sedative doses in order to achieve the desired level of sedoanalgesia, or when problems arise on lowering the dose of sedatives administered. The concept therefore includes early therapeutic failure, tolerance and withdrawal phenomena.[8] Such situations often require us to increase the usual dose of sedatives and analgesics, or to use combinations of drugs, in an attempt to maintain adequate sedation. On the contrary, such circumstances can give rise to hemodynamic, endocrine and metabolic responses that exert a negative effect upon the patient course, with an increase in morbidity–mortality. The end result is an increased risk of toxicity, greater drug costs, and a rise in costs associated with the prolongation of patient ventilation stay.

As has been commented, the mechanism of action and the physiological effects of the α2-adrenergic agonists differ from those of other traditional sedatives such as the benzodiazepines or propofol. In effect, they do not act upon the GABA receptors but on the α2-adrenergic receptors. The use of α2-adrenergic agonists allows us to reduce the dose of other sedatives and analgesics, optimize the level of sedoanalgesia, and minimize the risk of toxicity.[11,13,41] In this context, DEX has greater affinity for the α2 receptors and a shorter half-life than clonidine, which constitutes an advantage. Although few studies have been carried out to date, DEX may be very useful for the prevention and management of therapeutic failure with common sedatives, and can allow us to lower the dosage of other sedatives and opiates, and facilitate weaning from MV in these individuals.[42–44]

Control of agitation and withdrawal symptoms associated to toxic agents (opiates, alcohol, cocaine)

In view of their analgesic and sedative effects and efficacy in controlling the sympathetic hyperactivity associated with agitation and withdrawal, α2-adrenergic agonists are useful for the management of patients with such problems.[11,41] Although still limited, the literature offers a growing body of evidence supporting the use of DEX for the management and prevention of withdrawal syndromes in the pediatric population and in adults, both in the presence of intubation and in the absence of MV.[45–47] This drug would allow us to control the symptoms related to the sympathetic discharge associated with these syndromes, affording improved sedoanalgesia without increasing the risk of respiratory depression, lowering the doses of benzodiazepines or other sedatives and, in some cases, avoiding the need for intubation. Since bolus dosing of DEX is not advised, an inconvenience of the drug is its limited applicability in patients requiring very fast sedation (e.g., aggressive or agitated subjects who attempt to tear out the tubes). In these situations we need to resort to drugs such as midazolam or propofol to control the acute condition while waiting for DEX to exert its effect.

Delirium

Although the reported incidence of delirium in critical patients varies between 11 and 80%, the real mean incidence is probably between 30 and 70%, which gives us an idea of the magnitude of the problem.[48] In recent years, many studies have shown that delirium increases morbidity, costs and even mortality among such patients. It therefore seems reasonable to develop programs for preventing delirium in the DICM. The most important modifiable risk factors of delirium include sedative and analgesic use. In the study published by Pandharipande et al.,[49] the use of lorazepam was found to be an independent risk factor for increased delirium. Furthermore, the risk was seen to increase with the administered dose. In another study, these same authors obtained similar results with the use of midazolam.[50] Ouimet et al.[51] reported that the administration of sedatives at doses sufficient to induce coma, even during brief periods of time, is associated with an increased risk of delirium.

Although the pathogenesis of delirium is not well known, the GABA receptors appear to play a role in the release of mediators implicated in delirium. The mechanism of action of DEX is independent of the GABA receptor, and the drug could prove useful in the management of these patients.

Prevention of delirium in the critical patient

The existing information suggests that in comparison with other sedatives, DEX used for sedative purposes can reduce the incidence of delirium[25,40,52] or its duration[53] and, in patients subjected to MV, can facilitate extubation. Furthermore, a recent study has shown the duration of delirium to be the factor most closely correlated to mortality.[54]

Based on these data, and although it is still too early to establish firm recommendations, the use of DEX could be considered as a strategy for preventing delirium in patients requiring sedoanalgesia–particularly in individuals with risk factors for delirium, such as for example old age, prior neurological or psychiatric disease, the use of psychoactive drugs, or substance abuse (alcohol, opiates, etc.).

Treatment of delirium in the critical patient

Although the current sedoanalgesia guides published by different medical societies consider neuroleptics to be the most recommended treatment,[13,15,16,55] the supporting scientific evidence is scarce. In recent years there have been some publications, involving a limited number of patients,

that have shown the usefulness of DEX in these circumstances, particularly for the control of agitation and for facilitating weaning from MV.[43,44] However, to date there has been only one small randomized study comparing haloperidol versus DEX, with results favorable to the latter drug, including a shorter time to extubation and stay in the Intensive Care Unit.[56] The recent guides on the management of pain, agitation and delirium suggest the use of DEX for shortening the duration of delirium in critically ill adult patients.[16]

Noninvasive ventilation

Critical patients with respiratory failure subjected to noninvasive ventilation (NIV) often require some degree of sedoanalgesia in order to facilitate adaptation to ventilation. However, in such situations there is a risk of respiratory depression or possible upper airway obstruction, induced by sedatives, and which can contribute to the failure of NIV. As a result of its sedative, respiratory and hemodynamic effects, DEX may be an ideal drug in patients of this kind. Studies in healthy volunteers comparing DEX versus remifentanil–a drug often used to facilitate adaptation to NIV–have demonstrated the advantages of the former in terms of respiratory effects.[57] Although few studies have been published to date, the results are satisfactory, and the patients show adequate sedoanalgesia and correct management of the bronchial secretions, and are moreover able to collaborate in treatment.[58,59]

Contraindications and precautions in the use of dexmedetomidine

Dexmedetomidine is contraindicated in patients with hemodynamic instability, second- or third-degree atrioventricular block, bradycardia (<50 bpm), serious cerebrovascular disease, or hypersensitivity to the drug substance. It should not be used as sole sedating agent in situations where deep sedation (RASS under −3) is intended, and should not be administered to afford sedation during neuromuscular blocker use. During administration of the drug, regular monitoring of the level of analgesia and sedation is required to determine whether the simultaneous dosing of other sedatives and analgesics is needed in order to secure the desired level of sedoanalgesia. Although not an absolute contraindication, it is not advisable to use DEX in patients with serious neurological disorders, particularly in the acute phase, due to the possible lowering of cerebral blood flow. Most clinical trials have excluded patients of this kind, and the existing experience is very limited.[27,33,60] The drug is likewise not indicated for the treatment of intracranial hypertension or in patients with autonomic dysfunction (e.g., secondary to spinal cord damage), since in such situations the hemodynamic effects of DEX may be more intense.

Conflicts of interest

Dr. Carlos Chamorro has received payment as a consultant to Orion-Pharma and for conferences on behalf of GSK. The other authors declare that they have no conflicts of interest.

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