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REVIEW ARTICLE

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The Importance of Appropriate Management and Differential Diagnosis Patient's Vocalizations (Groaning or Moaning) In the Last Days and Hours of Life

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ABSTRACT

In the last days of life, patients often present with disorganized vocalizations, repetitive and incomprehensible sounds, which are often interpreted as a sign of discomfort primarily for the patient, but also for everyone involved in his/her care. In this context, groaning is not only, but often, linked to behavioral disorganization and psycho-motor agitation (pre-terminal delirium), representative of a path of clinical deterioration that can manifest itself in different ways. Therefore, there is an urgent need to identify the aetiology at the base of these vocalizations (moan/groan) in order to properly address it with correct non-pharmacological and pharmacological approaches. This article, in the format of a narrative review aims to gather data with clinical relevance, namely aetiology, approach and impact of this important symptom, in order to change incorrect practices, improve the quality of care and provide practical guidance.

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Framework

Symptomatic control is one of the fundamental pillars of intervention in suffering in situations of end of life namely those receiving palliative care. We are aware of the countless symptoms that can arise in this group of patients and the importance of good symptom control.

The most fragile patients, such as those in the last days/hours of life and who present in confusional states and agitation, frequently present with some type of vocalization, commonly called moaning or groaning. From what we observe in clinical practice, also confirmed by the literature, this groan is often assumed to be exclusively associated with physical pain, without other causes being considered. Hence, it is essential to know how to appropriately evaluate this symptom and understand what the mechanism behind it [1-4]. Even in more complex patients suffering with multiple symptoms when causation for vocalizations is difficult to identify differentiate it is still extremely important to individualize the care since it may not be a representation of pain and therefore, it should deserve a directed and distinct approach [5].

By assuming that a patient who moans has pain, he/she may mistakenly be given opioids leading to an inadequate dose increase or, alternatively, to starting continuous infusions, which not only do not solve the problem, but can cause toxicity and aggravate the groan itself if it´s a result of delirium [2,5].

The evidence points to a low prescription of antipsychotics in these phases and an excessive use of opioids, when we already know that there is an expected increased in the prevalence of delirium in the last days of life, what is frequently called pre-terminal agitation [2,4,5]. The patient may also remain agitated and then be physically restrained, which generally corresponds to bad practice, aggravates suffering, is ethically questionable in this population and also contributes to aggravating agitation in addition to other negative consequences [6,7].

Simultaneously, these situations frequently occur in the emergency department, where there may be less knowledge of the patient's previous clinical status and usually there is suboptimal care for patients with palliative needs [8]. This is another reason to highlight the need to properly assess and address groaning or moaning in the terminally ill.

Inadequate assessment may lead to a spiral of inappropriate measures that will not solve the situation nor alleviate the patient's discomfort. Furthermore, there is also a very negative impact on the health professionals and caregivers who directly

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take care of these patients, with a marked increase in stress, psychological distress and fear of being unable to provide appropriate care [5,7].

These are reasons justify the need to explore groaning/moaning and guide their correct approach, which we will do in this article, using a narrative bibliographic review based on: Pubmed, Cochrane library and Google Scholar.

Assessment and Approach of the Groan in the Last Days of Life

With the progression of various chronic and irreversible diseases, there is an inexorable clinical course of gradual functional decline 5 with different evolutionary patterns depending on the underlying pathology, associated with multidimensional suffering (physical, psychological, spiritual, social). In the most advanced stages of the diseases, two symptoms can often coexist, and if they are incorrectly approached, can be very distressful for patients and caregivers. Those symptoms are: pain and delirium, often manifested in the last days/hours of life in a very similar way, in the form of disorganized and disruptive vocalizations such as groaning, though delirium is much more frequent [9].

Delirium is the most common neuropsychiatric symptom in patients with advanced disease, about 85% experience it in the last weeks / days of life [2,10,11]. In about 70% of the cases it is not diagnosed or is incorrectly diagnosed, assuming moaning as an exclusive manifestation of pain, will cause an inappropriate intervention, particularly in the agonizing patient [2,12].

In the spectrum of signs and symptoms associated with delirium, sound manifestations are an important warning sign. In delirium, vocalizations are disorganized, include moaning, murmuring, shouting, incoherent and fragmented speech [1,13-15].

Cohen et al16 demonstrated that the vocalizations of agitated institutionalized patients (hyperactive delirium) are usually short in duration and high in frequency. They are more exacerbated in patients who are physically restrained (that is why it is usually contraindicated, ethically doubtful and is associated with trauma, fear and loss of dignity), at night or during the provision of care (hygiene, positioning) [9].

As mentioned, disruptive vocalizations are often interpreted primarily and exclusively as a sign of physical discomfort/physical pain (without using differential diagnosis tools), which leads to an immediate response by the informal caregivers, fear and doubts about the possible presence of pain, and on the part of clinicians, a pharmacological approach focused only on analgesia (namely, opioids) that can worsen the cognitive condition due to neurotoxicity [1,13].

Several studies have been developed to identify characteristics of these sounds to support a correct differential diagnosis. A phonetic characterization study of vocalizations during episodes of pain demonstrated that the pitch of the sound increase in these episodes, such can help to differentiate states of pain from states without pain [17]. However, this only occurs in very specific vowels, as in the "u" and "schwa" sounds; in all others, this effect was not verified and studies are still needed to be able to attribute non-verbal vocalizations exclusively to pain.

It is also important to take into account clinical signs that can help the clinician to predict delirium as the cause of the groan. As an example, we mention a few: the possibility of interrupting the moan without recourse to analgesia and through the use of non-pharmacological strategies; pain as the only isolated complaint with concomitant presence of repetitive movements; attempts to get up, to undress, to get out of bed, attempts to externalize intravenous accesses; changes in facial expressions ("grimaces"), changes in sleep patterns, irritability, repetition of a certain name or inconsistent complaints of pain (pain in the whole body, for example) [3,18].

Sequences studied by Samuelson and Hýden showed that these disorganized vocalizations are likely to be interrupted with interaction initiated by third parties (which is not usual in pain) and the fact that they can be interrupted has obvious clinical significance, demonstrating the need for behavioral interventions such as reassuring and effective communication in patients with moaning/groaning and agitation [9].

In advanced stages of disease there is an overlap of symptoms, increased weakness and reduced functionality, which constitutes a challenge in the correct identification of the triggering factor of particular symptoms [5]. Pain is undoubtedly a prevalent symptom (41-76%) in patients in palliative care, but not necessarily in the last days of life [19,21]. Entering this period, by itself, does not determine that pain will arise (however, this hypothesis must be ruled out).

Pain is classified systematically by health professionals based on its etiopathogenic mechanism and its location, irradiation, intensity and frequency. However, this classic approach does not take into account the multidimensional nature of pain (particularly important in palliative care, where contributions of a different source have a direct influence on it´s final expression). Thus, it is vital that pain is addressed as a whole (total pain as described by Cicely Saunders) and based on amodel of "production-perception-expression" of pain (figure 1 - adapted from Bruera et al 5), where the focus is on expression of the patient's suffering, more than the production or perception of the symptom.

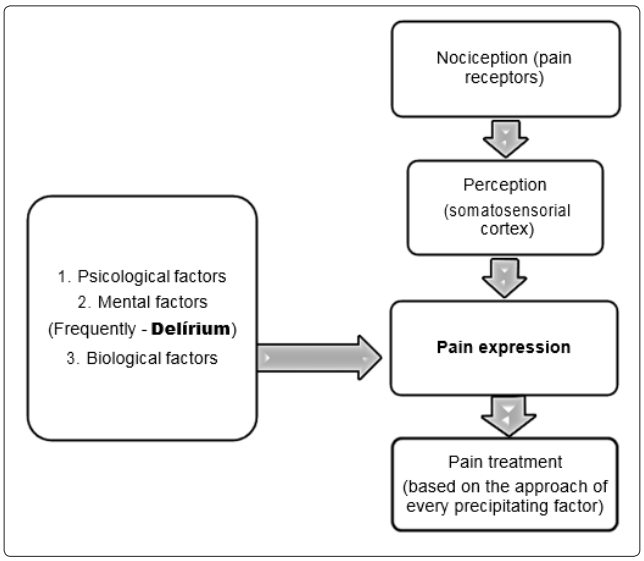

Figure 1: Pain Expression Model - Adapted from Bruera et al

One-dimensional pain scales (numerical, analogue) are unlikely to identify affective dimensions in the expression of pain, as is possible when using, for example, the multidimensional ESAS scale (Edmonton symptom assessment scale). This scale is indicated for the patient able to apply it (communicating patient and with preserved cognitive function). Delirium is a process of global brain dysfunction, which consequently alters the ability to perceive

and report pain in a reliable and consistent manner. Correct pain assessment requires preserved cognitive status, under penalty of incorrect valuation, as demonstrated by Bruera et al, in which doctors and nurses tended to misinterpret agitation (delirium) as an expression of pain in patients with hyperactive delirium, with controlled pain immediately before and after episodes of mental disorganization [22]. In more fragile patients, a detailed objective examination and the use of pain assessment scales applicable to patients without the ability to communicate / express symptoms effectively, such as DOLOPLUS23 (non-communicating patients), validated in Portugal and where posture, facial expression and sleep pattern are considered ,should be used. Also mentioning that in patients unable to communicate, the use of information transmitted by family and caregivers regarding their usual behavior can be useful [5].

In a patient with disruptive vocalizations (groaning), the systematic use of pain scales adjusted to the situation (communicating / non-communicating) allows the clinician, together with other elements of a clinical nature (concomitant presence of non-vocal symptoms of delirium), to obtain a differential diagnosis (of delirium and pain) appropriately. With this, we will be able to correctly direct the pharmacological and non-pharmacological treatment (of extreme importance in these patients) and put an end to bad practices, such as assuming that groan/moan is the exclusive manifestation and expression of states of pain.

Delirium in patients with advanced disease is a clinical sign of poor prognosis, a reliable predictor of mortality and an indicator of approaching death (days / weeks) [24-26]. It is important to note that the early approach to delirium can abort the groan or the pain referred by the patient and, therefore, it is legitimate under these conditions to consider a therapeutic trial with neuroleptics.18 If neurotoxicity is a possible causal agent in a patient with pain taking opioids and is also agitated, dose reduction and / or rotation should be considered as well as route of administration.13 After this trial, and unless the cycle is broken, if an incorrect increase in therapy is maintained in response to the groan, namely opioid, functional decline may be more accelerated and situations of severe and lethal toxicity may arise [18].

Some less experienced clinicians are afraid of using more sedative drugs (necessary and useful in the control of delirium), sue to the risk of possible cause of respiratory depression, hypotension and reduced oral intake. However, several studies, similarly to what happens with opioids, support that the correct use (with appropriate titration) of psychotropics is associated with a prolongation of life and not shortening of life [4,27-29].

Several meta-analyzes have demonstrated the efficacy of neuroleptics in the treatment and prevention of delirium in high-risk patients [13,30,31]. Haloperidol, a potent dopamine blocker, remains the first-line drug in hyperactive delirium, due to its efficacy, fewer active metabolites and a less sedative profile [13,32]. Other options are atypical neuroleptics such as risperidone, quetiapine or olanzapine [13]. In patients with alcohol-related delirium, with Lewy or Parkinson's body dementia, benzodiazepines may be an alternative, as they do not exacerbate extrapyramidal symptoms. Also in the patient with severe agitation, short-acting benzodiazepines such as lorazepam or midazolam can be combined with haloperidol [13,33,34].

The patient's quality of life is clearly improved with the early detection and prompt treatment of delirium [35]. Being aware of this, it is essential that symptoms such as groan/moan be interpreted as a potential manifestation of delirium, leading to a correct prescription of baseline treatment as well as SOS (analgesic versus antipsychotic). Therefore, it is urgent to integrate into daily clinical practice with fragile end-of-life patients that disruptive sounds such as moaning should always have delirium as a differential diagnosis(in addition to pain) [18].

Impact of Groan/Moan and Delirium on Health Professionals and Caregivers

Psycho-behavioral changes, such as delirium, associated or not with moaning, constitute an enormous challenge for those involved in care, health professionals and informal caregivers. The evidence shows that there are intense feelings / emotions associated with caring for people with these clinical conditions such as fear, shame, anger, sadness, guilt, feelings of incapacity and loss of control [36-38].

It is important to highlight that caring for patients with terminal delirium, caregivers are twelve times more likely to develop anxiety, in contrast to caregivers of patients without delirium [2,39]. In some cases the impact is even greater in families than the patient himself (Hosker et al, 2016) [3,40-43]. This is observed not only during life, but also in the grieving process, in the form of duplicate grief, in which the process is experienced in two stages: the first part with the loss of connection to the patient and later, at the moment of the loved one's death [2]. The high level of associated stress can even condition the decision about the place of death (hospital versus home) [44].

The impact on the family/caregiver is multi-dimensional; affective, psychological and physical. It arises with the difficulty in mobilization, management of giving food in fluctuating states of consciousness1, difficulty in communication (consequently, in patient-centered decision making) and, very importantly, in the interpretation of disruptive and disturbing symptoms as non- verbal vocalizations (moan) [9,13,45]. These come to be understood by the caregiver as a sign of suffering or exclusively of pain, often generating anxiety for the end of suffering and, at the same time, ambivalent feelings when sedative therapy is used afterwards, which may imply limited communication [13, 37,45].

When studying the impact of delirium, Namba et al, concluded that there are great variations in the experience of each person in relation to terminal delirium in terms of emotions, perceptions and desires regarding care, thus determining the importance of individualizing them to each patient and family, since the family detects the patient's behavioral changes earlier [36]. It is at this time that health professionals play a vital role interacting with family members, clarifying the nature of delirium, namely the multifactoriality of triggering causes, the possible behaviors to be observed, the strategies to deal with them, the demystification that delirium does not develop due to the administration of opioids or due to mental weakness, and that, after a correct clinical evaluation to exclude it, it may not represent physical pain and / or anxiety in the face of death at all [36]. It is essential to explain to family members that the groan can still represent an attempt at rudimentary communication by a frankly fragile person, without signs of suffering being associated.

It is urgent, when caring for a patient with hyperactive delirium, a synchronized interaction by the health professionals with the family, in order to reduce the possible negative burden that this imposes. At the same time, it is essential that this also happens

between doctors and nurses, where the negative impact of delirium with agitation is well studied and are well known feelings of vulnerability and frustration due to the increase in the volume of work (in particular, in the teams of nursing during the night), the perception of the lack of teaching / training in the diagnosis and managment of delirium [3,47,48].

When it comes to pharmacological intervention, it is essential to highlight the need to reduce the frequent use of opioids as an SOS (to the detriment of anti-psychotics) in patients with groaning in a clinical situation with concomitant presence of other stigmas of delirium, making it the most likely diagnosis. It should also be ensured that there is no undertreatment of other symptoms and, therefore, greater suffering, in patients treated by a team that may fear causing harm, not administering medication. This is extremely counter-productive for the patient, especially in a process of last days or hours of life [49].

Non-pharmacological therapeutic interventions have also been shown to be important in the control of delirium, namely behavioral and educational [13]. The patient's subjective world must be respected, he or she should be addressed as previously. If feasible, it is advisable to explore psychological needs not addressed before, to coordinate care to achieve effective communication according to variations in the state of consciousness throughout the day and to use simple expressions, special care taken to avoid medical jargon. It is important for professionals to adjust the assessment of vital signs, particularly at night, in order to ensure uninterrupted sleep [13,36].

It can also be useful in these situations for the family, allowing someone close to the patient to stay in hospital, providing regular information about the delirium condition, holding family conferences and distributing information leaflets about the nature of the delirium. All of these, are measures that increase the confidence of caregivers and should be done regularly and with increased frequency as the disease progresses [13,37].

In relation to the environment, whenever possible, a quiet and private environment should be offered, allowing the presence of personal objects, eye-glasses and hearing aids, providing frequent guidance (date, time and space) to the patient, explaining in advance all the procedures undertaken. Regarding the support to the team, the rotation of professionals should be avoided, train them with communication skills, encourage the use of diagnostic tools for delirium (eg CAM - confusion assessment method) that help distinguish pain - as previously mentioned, as well as the use of protocols in the management of it which include regular as well as as required medication.

Approaching patients with groaning and moaning at the end-of-life is very challenging. It is necessary to insist on a thorough clinical evaluation in order to distinguish the etiopathogenesis of this symptom, namely pain and delirium. Health professionals have a lot to offer, especially in exceptional occasions such as the COVID pandemic that we are experiencing. They can take advantage of knowledge in palliative care, focusing on the provision of rigorous and compassionate care, to promote the dignity of the sick person, on judicious use of non- pharmacological and pharmacological measures as well as mitigating social isolation imposed at the end of life and alleviating the anxiety of caregivers [50].

Delirium and Groan: Practical Recommendations for a Correct Approach
- In the face of a patient in the last days / hours of life (which must be properly recognized) and with an associated groan, it is essential to make a differential diagnosis between pain and delirium. Do not assume pain as the only causal agent.
- Most cases of groaning in the terminally ill occur in the context of delirium and should, after a correct diagnosis (differential diagnosis of pain), be treated using anti-psychotics and not opioid therapy.
- Over-prescription of opioids has been demonstrated in these clinical situations, namely through continuous infusions, which not only do not resolve the cause when this is delirium, but aggravate it and lead to severe toxicity.
- In case of doubt, it is justified in this context to carry out a therapeutic trial of haloperidol, in an adjusted dose and to the holder, measuring the result.
- Delirium, with or without an associated groan, has a strong impact on patients, but also on family members and health professionals, so the correct diagnosis and treatment, through pharmacological and non-pharmacological measures, are mandatory in this group of patients.

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