

# Association of Primate Veterinarians' Guidelines for Assessment of Acute Pain in Nonhuman Primates

## Purpose

Appropriate management of nonhuman primates (NHPs) in biomedical research studies involving surgery or other invasive techniques requires suitable pharmacologic and non-pharmacologic strategies to mitigate pain. To ensure good animal welfare, it is essential that individuals working with NHPs are adequately trained to recognize and assess pain and are proficient in drug selection, dosing, and administration. The following guidelines provide information for veterinarians, veterinary technicians, animal caregivers, researchers, and institutional animal care and use committees (IACUCs) on assessment of acute pain in NHPs following surgery, other painful procedure, or injury. These guidelines are not intended to address assessment of chronic pain in NHPs.

## Background

Timely recognition and effective treatment of pain is a fundamental task of veterinarians, with the goal of improving animal comfort and overall well-being, and ensuring that pain is not a confounding experimental variable in models of human disease. Unless the contrary is known or established, procedures that are considered painful in humans should be considered painful in animals and managed accordingly.

Despite the importance of treating pain, it can be difficult to recognize and monitor effectiveness of pain-relieving treatments in NHPs. Conversely, efforts to provide adequate pain relief can overestimate analgesic requirements, leading to potential overdose and/or adverse drug effects. To adequately manage pain in NHPs, pain assessment recommendations that are simple to apply and that accurately predict the level of pain are needed to guide clinical decision-making. An important aspect of managing pain associated with scheduled painful events is the administration of preemptive analgesia to avoid sensitization of the nervous system and amplification of pain in the post-procedural period. Continued provision of analgesia and assessment of analgesic efficacy is indicated after the painful stimulus has occurred to ensure the comfort of the animal.

## Guidelines

**Pain Assessment.** It is essential to first recognize signs of pain in an animal to assess the level of pain and provide effective relief. Animal pain is typically assessed through an evaluation of clinical presentation and behavior. With NHPs, because of safety concerns, cage side observation may be the only available assessment tool. Limited interaction, such as offering a food treat may be useful. Grooming the animal through the cage bars may be informative if the nonhuman primate is familiar with the observer, and it can be performed safely. In many cases, it is unsafe to attempt palpation of the painful site in a conscious nonhuman primate unless the animal is trained to cooperate with such an examination.

Pain assessment includes observing for general signs of well-being as well as procedure- or injury-related clinical signs, as appropriate. An important caveat is that many clinical signs are not specific to pain and instead could indicate a health issue that may or may not include pain as a component. It is crucial that the observer is familiar with the typical behavioral repertoire of the species as well as the individual animal to make an accurate assessment of pain. A baseline understanding of an individual animal's normal behavior and its interaction with conspecifics and human care staff when not experiencing pain or distress is critical when conducting subsequent pain assessments. General signs observed across species include changes in food and water consumption, urination and defecation, and posture and appearance, such as an unkempt hair coat, piloerection, hunching, or arching of the back. Painful animals may be reluctant to move, may appear restless with difficulty achieving a comfortable position, or may assume an abnormal location within their enclosure. There may be guarding, increased attention (e.g., licking, rubbing, scratching, biting), or withdrawal of the painful part of the body or body area. Socially housed animals may fail to interact with or may maintain an abnormal distance from cage mates. Alternatively, painful primates may behave more aggressively toward conspecifics or handlers. Vocalization and teeth grinding may be observed in some animals. Specific clinical signs are often associated with particular surgical procedures across species. For example, following laparotomy or laparoscopy, a painful animal may tuck the abdomen and take shallow and rapid breaths. Animals with inadequate pain relief post-craniotomy may display head pressing or rubbing at the cranial incision site(s). An animal with a limb injury may present with lameness or disuse, or may bite or excessively groom the affected limb.

Elevations in heart rate, blood pressure, and respiratory rate have been suggested as evidence of pain, but these physiologic parameters must be interpreted with care as other sources of stress may cause similar alterations. In addition, unless animals are instrumented for telemetry recording, collecting physiologic parameters (with the exception of respiratory rate) requires handling, and often sedation, which can affect physiologic values.

Because of these difficulties in assessing pain in a non-domesticated, nonverbal species, veterinary clinicians have commonly used a more empirical approach for assessing the presence of pain by looking for a beneficial change in behavior after an analgesic has been administered.

**Evaluation Techniques.** The primary evaluation approaches for nonhuman primates are direct cage side observations and indirect video monitoring that can be either live feed or recorded. Either approach can be used to evaluate the signs of pain described above.

Direct cage side observations are easy to perform and inexpensive because the animal is in clear view and can respond

directly to the observer. However, the evaluation outcome may be skewed by the animal masking signs of pain to a human observer or through incorrect assessment of submissive postures as pain. An extended observation period is often required to allow the animal to habituate to the observer and allow accurate assessment. The best observation outcomes are achieved by an observer who is not only knowledgeable about signs of pain in NHPs, but also very familiar with the specific animal being assessed.

Indirect video monitoring has the advantage of not disturbing the animal's natural behavior, but it can be technically challenging and labor intensive to perform. Because the animal remains undisturbed, masking of pain is less likely to occur, making pain easier to recognize. Optimally, the camera is set up such that the animal can be visualized regardless of its location in the cage or its activity. The observer may need to watch extended periods of live feed or video recordings to identify pain in the animal(s) of interest, especially if the animal is not presenting to the camera in a way that facilitates assessment. If video recording is used, the observer needs to watch the video in a timely manner to allow for changes to the analgesic regimen in a relevant and beneficial time frame. Whether a live or recorded feed is used, security of these materials is imperative.

Facial action units (e.g., ear position, squinting of eyes, tightening of perioral facial muscles) of animals experiencing acute pain versus comfortable animals of the same species have been used to produce facial grimace scales in research settings. For several species, these facial grimace scales have been further validated for use in clinical scoring of acute pain. While there has been much interest in developing facial grimace scales for pain scoring in primates, no validated scales have been developed to date. Additionally, primates have an extensive repertoire of facial expressions and body postures that are species-specific, so any pain scales developed would need to be species-specific. There can be significant differences in the meaning of behavioral signs across primate species, which creates challenges in assigning an interpretation of pain to a specific behavior. Care needs to be taken so that the degree of pain is not misinterpreted and inadequate or inappropriate analgesia provided.

**Frequency of Monitoring.** The frequency of pain assessment to ensure adequate pain management is highly variable and relies on multiple factors, such as patient stoicism, the severity or invasiveness of the surgery or injury, the type of assessment (e.g., cage side vs. indirect), and variables related to the analgesic(s) administered. With regard to the analgesic(s), considerations for the frequency of assessments should include the specific type and method of analgesia (i.e., single drug vs. multimodal), pharmacokinetics of analgesic agents used with attention to the expected duration of effectiveness, recent changes to the analgesic plan, and previous clinician experience with the analgesic plan. Veterinarians should use their professional judgement to determine the frequency of monitoring and be prepared to change the plan based on clinical signs. Particular attention should be placed on performing assessments prior to changing the pain management plan. A reassessment after a change should be performed within an appropriate timeline to ensure the new pain management plan is providing adequate analgesia to alleviate pain. When evaluating research protocols for adequacy of analgesia, the IACUC should consider whether

the frequency of observations is adequate. Researchers and IACUCs should consult with the veterinarian to reconcile any possible doubt regarding whether the proposed plan ensures adequate monitoring.

## Record Keeping

Proper record keeping facilitates communication between clinicians, staff, researchers, and the IACUC. Animal health records should include all analgesic agents, doses, frequency, administration routes, and dates. Objective and subjective clinical parameters should be recorded as necessary to track recovery and to determine if the analgesic plan, or a recent change, provides adequate pain relief. Further, appropriate record keeping is a regulatory mandate, and should be in accordance with the Animal Welfare Act and federal funding agency requirements.

## References

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