



Canadian Council on Animal Care
Conseil canadien de protection des animaux

**The Characteristics of Analgesia-Withholding in
Animal-Based Scientific Protocols in Canada**

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Summary

The prevention and minimization of pain to animals used in science is acknowledged as a key responsibility for the scientific community, however, in some cases the withholding of analgesia in protocols that cause pain to animals is unavoidable for scientific reasons (supported by literature). In other cases, it is not clear whether the use of analgesia will, or will not, interfere with the experimental objective. This “grey area” has been identified as an area of concern and prompted this survey of animal care committee (ACC) coordinators in order to characterize the prevalence and conditions under which analgesia-withholding occurs.

Survey results suggest that withholding of analgesia is not widespread in Canada: our survey of 91 ACC coordinators (72 replies, response rate =79.1%) found that just 19 (21%) had received protocols requesting approval for withholding analgesia in procedures that cause pain in animal models. In the 12 month survey period these 19 ACCs approved 85 protocols that requested approval to withhold analgesia. Approximately 42,700 animals were used in these 85 protocols, 1.9% of the total animals used in 2008. Survey responses also indicated that not every animal may have experienced unrelieved pain in these protocols, depending on study design. In addition, some participants noted that even in protocols approved to withhold analgesia, analgesia was still occasionally administered.

Our survey found that no animals were subjected to withholding of analgesia for a teaching purpose. The greatest proportion of analgesia-withholding protocols used animal models of pain, inflammation and arthritis and/or occurred in pharmacology, physiology, and immunology research. Results suggest that when investigators prepare protocols that withhold analgesia they do so mainly because analgesia has been *proven* conclusively to interfere with experimental results. The second most prevalent justification is that “Analgesia *may* interfere with experimental results”. The third most reported reason to withhold analgesia was when pain was part of the phenomenon being studied.

Although this survey suggests that analgesia-withholding is not widespread in Canada, it remains a particular problem. To decrease or avoid the need to withhold analgesia and minimize pain and distress to animals used in science, the following strategies are suggested:

- 1) Use of pilot studies to study the effects of using different analgesics in protocols where analgesia would ordinarily be withheld;
- 2) Development of research programs to study use of novel methods of analgesia in fields of research where there is currently more difficulty in alleviating unavoidable pain (i.e. where there is evidence that common analgesics interfere with scientific objectives).
- 3) Development of guidelines specific to pain research and other research that must withhold analgesia to assist those investigators in minimizing pain and distress.

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Introduction

The prevention and minimization of pain to animals used in science is acknowledged as a key responsibility for the scientific community. This is reflected in the Canadian Council on Animal Care (CCAC) policy on the Ethics of Animal Investigation (CCAC 1989) which states:

“If pain or distress is a necessary concomitant to the study, it must be minimized both in intensity and duration. Investigators, animal care committees, grant review committees and referees must be especially cautious in evaluating the proposed use of ... experiments involving withholding pre and post-operative pain-relieving medication”

Therefore, use of animals in science in a way that exposes them to unrelieved pain is subject to additional scrutiny and caution by both investigators and by Animal Care Committees (ACCs) who conduct ethical review of protocols.

Pain is generally described as an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage (IASP 1994). However, there are specific challenges associated with understanding pain in animals. For example, all pain is aversive but level of aversiveness is mediated by intensity, duration and psychological factors. However, the level of aversiveness is hard to assess in animals since it is not possible to obtain verbal feedback (ILAR 2009). In addition, some behavioural and physical responses occur in both conscious and unconscious animals (e.g. anesthetized animals), which highlights the importance of discerning between pain and nociception (ILAR 2009). To deal with these difficulties alternative definitions of pain that apply specifically to animals or particular species have been proposed. ILAR (2009 p3) describes that “Pain may arise in response to a noxious stimulus and in situations likely to cause increased sensitivity to pain (i.e. hyperalgesia), such as injury and inflammation. Psychological factors also likely contribute to pain under these circumstances”. The CCAC subcommittee on fish also debated these issues when developing guidelines on the care and use of fish in science, resulting in a working definition for pain in fish: “a response to a noxious stimulus that results in a change in behavior or physiology and the same noxious stimulus would be painful to humans” (CCAC 2005 p73).

The assessment and management of animal pain presents additional challenges that will not be covered in this report. However, in the majority of cases, analgesic drugs can be administered to manage pain and most animal pain experts support the idea of treating for pain in cases when diagnosis of pain is uncertain. For example, the American College of Veterinary Anesthesiologists (ACVA) states that “it is preferable to empirically administer analgesics pre-emptively if there is any question that a procedure will induce pain in an animal.” Similarly, the CCAC requires the administration of analgesics be based on the premise that the animal should be given the benefit of the doubt and that “the active withholding of [analgesia], where their use is indicated, must be based on scientific fact or experimental data, as documented by pertinent literature, or data from pilot studies” (CCAC 1997, section 9).

The prevalence of analgesia-withholding has been identified as an area of concern in the scientific literature. In their review of trends in the administration of analgesics and anesthetics to rodents, Stokes et al (2009) found that just 20% of published studies report administering systemic analgesics to rodents undergoing surgical procedures. Similarly, in a bibliometric study of original animal research that potentially caused pain and distress, Gomez and Conlee (2007) found that only 39% of the published studies reported administering anesthetic or analgesic drugs.

In some cases the withholding of analgesia in protocols that cause pain to animals is unavoidable for scientific reasons supported by literature. For example, when pain is the phenomenon under study or when analgesic drugs may interfere with other physiological processes under study (e.g. buprenorphine and immune suppression (Carrigan et al 2004)). In other cases, it is not clear whether the use of analgesia will, or will not, interfere with the experimental objective, and this “grey area” has been identified as an

area of concern by CCAC constituents. For example, Charbonneau (2008) wrote that ACCs are faced with requests to withhold analgesia due to *concern* that analgesia will affect the immune system and *potentially* interfere with the experiment (italics added for emphasis). These concerns prompted the CCAC Three Rs Program to undertake this survey of ACC coordinators in order to characterize the prevalence and conditions under which analgesia-withholding occurs.

Methods

In Canada there are approximately 217 ACCs. The number is approximate as it includes both ACCs from institutions that are interested in joining the CCAC program as well as ACCs of some institutions that are no longer part of the program. It does not represent the number of institutions participating in the CCAC Program as large institutions may have multiple ACCs. Rather than attempt to survey the whole population of 217 ACCs, we decided to use ACCs-with-coordinators as our sample population.

ACC coordinators are individuals designated to provide administrative support to ACCs. Typically they ensure that animal use protocols are well managed, that committee minutes and reports are promptly produced and distributed, that all exchanges between the ACC and animal users are well documented and filed in a timely manner, and that animal users and ACC members are provided with all necessary information (CCAC 2006; 2008). We therefore used ACCs-with-coordinators as a reasonably accurate and representative substitution for the population of ACCs.

Presently, there are very few large and medium-sized institutions that do not have one or several people coordinating the ACC's work; generally the only institutions without ACC coordinators are those with small animal care and use programs (with few protocols and few animals). This means that the sample population will be biased towards greater representation of the largest institutions and towards finding information from the institutions that use the most animals. In addition, as ACC members volunteer their time, ACCs without coordinators might not have had the administrative resources to respond to the survey within our time frame.

Our intent was to survey all of the 91 ACCs in Canada with designated coordinators. To accomplish this we attempted to distribute surveys to the 91 ACC coordinators (the participants). To distribute the survey, ACC coordinators were emailed individually with introductory information contained in the body of the email and the survey as an email attachment (see Appendix). The survey was in the form of a Microsoft (MS) Word template. ACC coordinators were given the choice of filling in the template electronically and returning by email; filling in the template, printing and returning by paper mail; or printing and filling out the form by hand and returning by paper mail. The survey was prepared in English and translated to French for distribution to ACC coordinators whose workplace language is French. Data collected in French was translated to English for analysis.

The names of participants and their institutions are confidential. Participants were not asked to identify themselves or their institutions on the survey. To ensure confidentiality was maintained, surveys returned to the CCAC as MS Word files via email were renamed and saved to designated electronic folders. The emails were deleted. Surveys returned to the CCAC as paper printouts via postal mail were removed from their envelopes and stored in a designated file folder in a secured cabinet. Envelopes bearing any identifying names and/or addresses were shredded. Data was entered into an MS Excel spreadsheet maintained on the CCAC's secure data-sharing website (SharePoint).

Similarly, confidentiality was maintained in the analysis and reporting of results. To that end, participant comments and data about fields of research and types of procedures are not linked in this report to avoid the possibility that institutions are inadvertently identified.

As stated, we attempted to send the survey to each of the 91 identified ACC coordinators, however we were only able to successfully distribute the survey to 87 coordinators (two surveys were undeliverable and we were unable to obtain email contact information for two other ACC coordinators). We sent out

follow-up emails one week prior to the survey completion deadline to encourage participation. We received 72 replies, a response rate of 79.1%. This response rate is comparable to the response rates of other email-based surveys and paper-based surveys distributed by mail (e.g. Hayslett and Wildemuth 2004).

The accuracy of the data is limited by the following factors. First for all questions, the participants were asked to provide an approximate answer, therefore some or all of the answers may be estimates. Second, participants were asked to consider the past 12 months when providing their answers resulting in the survey period being August 2008 to August 2009. However, this does not correspond to the calendar year around which ACCs typically collect their animal use statistics, and so there may be some discrepancies in the time period on which participants based their responses on. For example, in one case a participant provided two separate responses based on data from 2008 and 2009 respectively. In this case we chose to include only the data for 2008 as it represented a complete 12 month period.

A third limitation in the data relates to the wording of question 2, which asked “In the past 12 months approximately how many protocols has the ACC reviewed?” Both renewal and new protocols need to be approved, and we did not make a distinction between them in the survey questions. However a few participants specified separate numbers for new protocols and renewed protocols. In these cases we chose to combine the renewed and new protocol numbers to report on total protocols.

Results

Prevalence of Analgesia-Withholding Protocol

In the August 2008-2009 survey period, 19 of 91 (21%) ACC coordinators confirmed that their ACCs had received protocols requesting approval for withholding analgesia in procedures that cause pain in animal models, 53 (58%) reported that they had not, and for the remaining 19 (21%) we have no information (i.e. no response to the survey).

Table 1: Number of ACCs-with-coordinators that have received protocols requesting withholding of analgesia

Request for analgesia withholding	Number of ACCs-with-coordinators	%
No	53	58
Yes	19	21
No information	19	21

Only participants who answered “yes” to Question 1 were asked to continue the survey (i.e. ACCs who had received protocols that withheld analgesia). The 19 ACCs-with-coordinators who had received protocols that withhold analgesia have collectively reviewed a total of 3,021 protocols in the 12 month study period with a range of 21-760 protocols per ACC. Of the 3,021 protocols, 89 protocols requested approval to withhold analgesia, with the number of requests per committee ranging from 1 to 13 (median: 3). Of the 89 protocols requesting analgesia-withholding, 85 (96%) were approved.

Characteristics of Protocols that Withhold Analgesia

A total of 42,711 animals were used in protocols that were approved to withhold analgesia, ranging from 6 to 33,368 animals per protocol (median: 150). Participants were asked to report which species were used in protocols that withheld analgesia at their institutions (Table 2). Thirteen of the 19 ACCs had

approved rats for use in protocols that withhold analgesia in the last 12 months. Eleven had approved withholding analgesia for mice. Withholding of analgesia for guinea pigs, fish, rabbits and cattle had been approved by one ACC each.

Table 2: Species and number of ACCs that approved analgesia-withholding in these species

Species	Number of ACCs that approved analgesia-withholding in species
Rats	13
Mice	11
Guinea pigs	1
Fish	1
Rabbits	1
Cattle	1

Protocols that withheld analgesia occurred in four of the five CCAC Purposes of Animal Use (PAU) Categories (Table 3). The majority were for studies of a fundamental nature and for medical purposes and there were no studies that withheld analgesia for the purposes of education and training.

Table 3: Number of ACCs that approved analgesia-withholding in each Purpose of Animal Use (PAU) category

Purpose of Use	Number of ACCs that approved analgesia-withholding in each PAU category
Studies of a fundamental nature (PAU 1)	10
Studies for medical purposes (PAU 2)	10
Studies for regulatory testing (PAU 3)	2
Studies for the development of products (PAU 4)	5
Education and training (PAU 5)	0

ACC coordinators were also asked to describe the fields of research that originated protocols that withheld analgesia. Pharmacology was cited the most (9 times) followed by physiology and immunology (each cited 5 times) and psychology (cited 3 times) (Table 4). Note that participants were not asked to report on the number of analgesia-withholding protocols per each field of research, therefore the number of times a field of research was cited does not correlate to the total number of protocols approved for withholding analgesia.

Table 4: Number of ACCs that cited fields of research that originated analgesia-withholding protocols

Field of research originating analgesia-withholding protocols	Number of ACCs that cited field of research
Agricultural sciences	1
Behavioural sciences	1
Immunology	5
Infectiology	1

Field of research originating analgesia-withholding protocols	Number of ACCs that cited field of research
Neonatology	1
Neurology	1
Oncology	2
Pathophysiology	2
Pharmacology	9
Physiology	5
Psychology	3
Psychiatry	1
Toxicology	1

ACC coordinators were asked what procedures and/or models were used in protocols that caused pain and withheld analgesia. Pain models were cited the most (10 times), followed by inflammation models (cited 8 times) and then arthritis models (cited 6 times).

Table 5: Number of ACCs that cited procedures and models used without analgesia

Procedures and models used without analgesia	Number of ACCs that cited procedure or model used without analgesia
Pain models	10
Inflammation models	8
Arthritis models	6
Injections of Freund's Complete Adjuvant	4
Survival surgeries	3
Tumor/neoplasia models	3
Neurological procedures	2
Procedures causing severe sensorimotor disruption	2
Aging model (decapitation without analgesia)	1
Colitis models	1
Concussion models	1
Decapitation without sedation	1
Epilepsy model (kainic acid injection)	1
Gastroenterology	1
Hepatic models	1
Post-surgical pain study following surgery	1
stroke ameliorization	1
vaccine development and safety testing	1
Whole body radiations	1

Justifications for Withholding Analgesia

ACC coordinators were also asked to describe the types of justifications for withholding analgesia that investigators provided. The survey provided several possible justifications that participants could select as well as the option to add other justifications. The justifications “analgesia is proven to interfere with experimental results” and “analgesia may interfere with experimental results” were cited by 10 ACCs each (Table 6). The third most reported justification was “pain was part of the phenomenon under study and thus should not be interfered with” (cited by 9 ACCs). We also provided the following justifications in the survey but no ACC coordinator reported these were used: “animals will not experience pain”; “no evidence that analgesia is necessary”; “appropriate analgesic is a controlled substance and difficult to obtain”; and “oral delivery of analgesic is unreliable”.

Table 6: Number of ACCs that cited justifications for withholding analgesia

Justification for withholding analgesia	Number of ACCs that cited justification
<i>Description of justification provided in survey</i>	
Analgesia proven to interfere with experimental results (with citations of literature references demonstrating analgesia-interference conclusively)	10
Analgesia may interfere with experimental results	10
Pain is part of the phenomenon that is under study and should thus not be interfered with	9
Administration of the analgesic would itself be painful (e.g. injection)	1
Animal will be euthanized within 24 hours of the painful procedure	1
<i>Justification description provided by participants</i>	
During monoclonal antibody production in mice, it is difficult to predict at what time, aside from when performing injections of Freund’s Complete Adjuvant, to administer an analgesic.	1
no appropriate analgesics (fish)	1
Contraindicated due to regulatory requirements; Animals will be euthanized immediately if found ill (in cases where death or specified post-challenge incubation times are not necessary endpoints)	1

Pain Assessment Tools

We also asked participants to describe any pain assessment tools, such as clinical signs scoring records that were used by investigators in protocols that withheld analgesia. Over half of participants reported monitoring specific animal behaviours as part of pain assessment (both with and without reference to endpoint monitoring). The specific behaviours reported included: anti-social behavior, excessive licking of wounds, locomotion and exploration, feeding behaviour, immobility, prostration, self-injury, and vocalization. Similarly, over half of the participants also reported monitoring animals for physical/clinical parameters such as body condition scoring, blood and milk parameters, food consumption, shivering, swelling, tremors, piloerection, and weight change.

Six participants specified that some form of endpoint monitoring was used during experiments that were approved to withhold analgesia. Two participants referred generically to monitoring the animals for pain and “evaluat[ion] of the pain threshold”. One respondent listed specific types of tests that were used to

assess pain: hot plate test, tail flick test, formaldehyde test, Von Frey test, Plantar test, and pin prick test². Another respondent explained that their institution requires the veterinarian to attend the first procedure and determine if the pain experienced by the animal is “mild enough to make it a [Category of Invasiveness] D-level of invasiveness or lower”. If the pain was found to be at Category of Invasiveness E, then the protocol would be terminated at that particular institution.

Non-Drug Pain Relief

We also asked participants to describe any non-drug pain relief techniques used by investigators in protocols that withheld analgesia. Ten participants described a variety of non-drug pain relief techniques used by investigators in protocols that withheld analgesia and two participants replied that no non-drug pain-relief techniques were used. The use of euthanasia as a non-drug pain relief method was reported four times, and reducing the dose of products causing pain was cited once. The provision of supportive care measures was cited as a non-drug pain relief technique by half of the participants. These included providing easier access to food and water (e.g. on cage floor, moistened food, highly palatable food), provision of bedding or softer bedding, use of heat and providing “quiet”. Interestingly, one respondent reported use of “increased social contact with conspecifics” as a non-drug pain relief technique while another reported “isolating ill animals” for the same purpose.

Even though the question was about non-drug pain relief in protocols that are approved for withholding of analgesia, two participants described scenarios that end in the use of analgesia. One described the use of highly palatable food treats to induce animals to eat, and animals that still did not eat would then be singled out for extra monitoring. If behavioural cues then indicated the animal was in pain, then the animal may be given opiates and removed from the study. Another described that “In case of serious pain, animals will receive a dose of analgesic” (but gave no details on how the seriousness of the pain was assessed). Similarly, one ACC coordinator reported that an investigator ended up using analgesia in a protocol that had been approved for withholding.

Participants’ General Comments

Participants had the opportunity to provide general comments about protocols that withhold analgesia. Two comments related to the limitations of the information that can be obtained from animal use protocol records. For example, one ACC coordinator described that to determine that a protocol qualified as one that withheld analgesia they simply selected all CI-D protocols that did not specifically mention use of analgesia, noting that in contrast other protocols in CI-D used some sort of pain reliever. Similarly, another participant qualified their data noting that in large regulatory testing protocols that withhold analgesia, not all the animals covered by that protocol will experience pain. This participant suggested that rather than apply a single CI to an entire protocol, that the solution may be to forecast the percentage of animals within a protocol that fit into each CI (while interesting, discussion of how to address use of CIs in protocols that withhold analgesia is beyond the scope of this paper).

Several comments referred to the role of veterinary and veterinary technician oversight in protocols that withhold analgesia. For example these protocols are “very closely followed by technicians” and noting that veterinarians can offer different alternatives to managing pain and can also suggest using drugs that may not interfere with the scientific outcome.

² *Hot plate test*: enclosure on a radiant heated surface; *tail flick test*: focused beam of radiant heat on tail; *formaldehyde test*: intradermal or subcutaneous injection of formaldehyde; *Von Frey test*: body surface stimulation using nylon monofilaments of increasing stiffness; *Plantar test* (aka Hargreaves test): focused beam of radiant heat on hind paw (definitions from Magalhães-Sant’Ana et al 2009); and *pin prick test*: point of a safety pin is pressed slowly against the plantar skin until a dimple is seen (Bennett 2001).

The role of the ACC was touched upon by some participants. They commented that it is very difficult to evaluate these types of protocols and that their ACC looks at all possible options that will not interfere with results. One commented that their ACC puts more “stringent humane endpoints” on animal models that cause pain and withhold analgesia.

Discussion

Overall, survey results suggest that withholding of analgesia is not widespread in Canada. Our survey shows that 19 ACCs approved 85 protocols that requested approval to withhold analgesia in the 12 month study period. Approximately 42,700 animals were used in these 85 protocols. This is 1.9% of the total animals used in Canada over the 12 months of 2008 (2, 272, 815) (CCAC 2009). Survey responses also indicated that not every animal may have experienced unrelieved pain in these protocols, depending on study design. In addition, some participants noted that even in protocols approved to withhold analgesia, analgesia was still occasionally administered.

Our data indicates that 96% of protocols requesting analgesia-withholding are approved. However, we do not know if these were protocols that were approved outright, approved with modifications, or conditionally approved. Data from a previous study of Canadian ACCs found that very few protocols were accepted without modification (9%) and just 14% were rejected outright (Houde et al 2003). Among survey participants, no animals were subjected to withholding of analgesia for a teaching purpose. This is in keeping with the CCAC policy statement that “Painful experiments or multiple invasive procedures on an individual animal, conducted solely for the instruction of students in the classroom, or for the demonstration of established scientific knowledge, cannot be justified” (CCAC 1989).

Survey results still indicate that many animals are used in analgesia-withholding protocols, although they represent a small percentage of the total animals used annually in Canada. The greatest proportions were used as animal models of pain, inflammation and arthritis and/or in pharmacology, physiology, and immunology research. The preceding descriptions of animal models and research fields are very broad and therefore it is not possible to comment in detail. However, several procedures that were reported used without analgesia have been identified as specific examples of Category of Invasiveness D (CI-D): “Experiments which cause moderate to severe distress or discomfort” (CCAC 1991). The painful CI-D procedures reported used without analgesic include injections of Freund's complete adjuvant, procedures causing severe sensorimotor disruption, tumor/neoplasia models and whole body radiations. Similarly, decapitation without sedation was reported used in this study, and it has also been identified as only conditionally acceptable for euthanasia because of prolonged brain activity; anesthetizing the animal first is preferable (CCAC in preparation). Knowing that these procedures in particular are being used without analgesia may assist to focus efforts on either finding alternative procedures or, finding alternative analgesics that would not interfere with the experimental objectives. In these instances pilot studies may be helpful.

This survey found that when investigators prepare protocols that withhold analgesia they do so mainly because analgesia has been *proven* conclusively to interfere with experimental results. The second most provided reason was that “Analgesia *may* interfere with experimental results”. In both instances, it may be possible for pilot research studies to determine other possible sources of analgesia that will not interfere. Investigators should work with a veterinarian to select the most appropriate analgesic drug or technique, as this often requires professional veterinary judgement.

The third most reported reason to withhold analgesia was when pain was part of the phenomenon being studied. When a necessary part of the study, pain in animals may need to be alleviated or managed with greater refinements to the experimental protocol. Magalhães-Sant’Ana et al (2009) have reviewed opportunities for refinement where pain is present and identified several general ways to implement this. One is to use tests in which the animal has the “ability to control exposure to the painful stimulus” instead of the experimenter. They also suggest using pain models that induce just moderate levels of pain without

causing severe body damage. Another is to provide extra levels of support in the animals environment such as more careful handling to animals that may be hypersensitive to pain and facilitation of food and water and provision of soft bedding. Lastly, they suggest additional research is needed to 1) develop techniques to detect specific signs of pain before the general state of the animal is affected (i.e. early endpoints) and 2) determine whether techniques to distract animals can act as non-drug pain relief tools (such as introduction of novel objects) (Magalhães-Sant'Ana et al 2009).

Conclusions

The results of this survey suggest that analgesia-withholding is not widespread in Canada however, it remains a particular problem. Analgesia is withheld for mainly two reasons: because there is a lack of an appropriate analgesic that will not interfere with the experiment, or because the experiment is studying pain. To decrease or avoid the need to withhold analgesia and minimize pain and distress to animals used in science, the following strategies are suggested:

- 1) Use of pilot studies to study the effects of using different analgesics in protocols where analgesia would ordinarily be withheld;
- 2) Development of research programs to study use of novel methods of analgesia in fields of research where there is currently more difficulty in alleviating unavoidable pain (i.e. where there is evidence that common analgesics interfere with scientific objectives).
- 3) Development of guidelines specific to pain research and other research that must withhold analgesia to assist those investigators in minimizing pain and distress.

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Appendix 1

CCAC Survey of Analgesia-Withholding in Protocols That Use Painful Animal Models

Dear ACC Coordinator [*use actual name*],

The CCAC is undertaking a national survey of animal care committee (ACC) coordinators on the topic of analgesia-withholding. Our goal is to understand the scope of analgesia-withholding in protocols that use painful animal models in Canada.

As an ACC coordinator, we invite you to participate in this short, 12-question survey about analgesia-withholding protocols at your institution. (*Even if your ACC has not been asked to approve the withholding of analgesia in painful protocols, we still invite you to answer the first question and return the survey to the CCAC to assist in our efforts to characterize the extent of analgesia-withholding*).

The survey is in the form of an MS Word template. You have the option to fill in the template electronically and return by email OR fill in the template and print and return by paper mail OR print and fill out the form by hand and return by paper mail.

Use of survey results

This survey will provide CCAC with empirical data to determine whether analgesia-withholding is widespread, or not, and under what conditions it occurs. The results of this survey may be used by the CCAC to encourage funding of pilot projects to study the effects of using analgesia in protocols where analgesia would ordinarily be withheld (“top-up funding”). The survey results may also be used by the CCAC in publically accessible documents or presentations. In addition, ACC coordinators may be resurveyed at a future date and results from this, the original survey, would be used for comparative purposes. All ACC coordinators will be informed of the results of survey.

Confidentiality

The returned surveys will be viewed and analyzed by CCAC personnel only. The names of participants and the names of their institutions will be confidential. Participants are not required to identify themselves or their institutions on the survey. Surveys returned to the CCAC as MS files via email will be saved to a designated folder on the CCAC’s secure server. The email will be deleted. Surveys returned to the CCAC as paper printouts via postal mail will be removed from their envelopes and stored in a designated file folder in a secured cabinet. Envelopes bearing any identifying names and/or addresses will be shredded.

If you have any questions please contact me by email or telephone (contact information below). We thank you in advance for your time in completing this survey.

CCAC Survey of Analgesia-Withholding in Protocols That Use Painful Animal Models

Part 1: The questions in this section will assist in determining the extent of analgesia-withholding in Canada.

1. In the past 12 months has the ACC been asked to approve the withholding of analgesia in protocols that cause pain in animal models? Yes No

If yes, please answer the following:

2. In the past 12 months approximately how many protocols has the ACC reviewed? _____.
3. In the past 12 months approximately how many protocols requesting withholding of analgesia in protocols that cause pain in animal models has the ACC reviewed? _____.
4. In the past 12 months approximately how many of the requests to withhold analgesia were approved? _____.
5. In the past 12 months approximately how many animals were used in protocols that were approved to withhold analgesia? _____.

Part 2: The questions in this section will assist in determining the general characteristics of protocols that withhold analgesia.

1. In the past 12 months what types of protocols have withheld analgesia? (please check all that apply)
- Studies of a fundamental nature (PAU 1)
- Studies for medical purposes (PAU 2)
- Studies for regulatory testing (PAU 3)
- Studies for the development of products (PAU 4)
- Education and training (PAU 5)
2. In the past 12 months what types of animals have been used in protocols that withheld analgesia? (please check all that apply)
- | | | | |
|---|--------------------------------------|-----------------------------------|--|
| <input type="checkbox"/> Amphibians | <input type="checkbox"/> Birds | <input type="checkbox"/> Cats | <input type="checkbox"/> Rats |
| <input type="checkbox"/> Cattle | <input type="checkbox"/> Cephalopods | <input type="checkbox"/> Dogs | <input type="checkbox"/> Reptiles |
| <input type="checkbox"/> Ferrets | <input type="checkbox"/> Fish | <input type="checkbox"/> Goats | <input type="checkbox"/> Sheep |
| <input type="checkbox"/> Guinea Pigs | <input type="checkbox"/> Mice | <input type="checkbox"/> Minipigs | <input type="checkbox"/> Other (please list) |
| <input type="checkbox"/> Non-Human Primates | <input type="checkbox"/> Pigs | <input type="checkbox"/> Rabbits | |
3. In the past 12 months what fields of research used protocols that caused pain and withheld analgesia? (please check all that apply)
- | | | |
|--|---|--|
| <input type="checkbox"/> Agricultural sciences | <input type="checkbox"/> Behavioural sciences | <input type="checkbox"/> Immunology |
| <input type="checkbox"/> Infectiology | <input type="checkbox"/> Neonatology | <input type="checkbox"/> Neurology |
| <input type="checkbox"/> Oncology | <input type="checkbox"/> Parasitology | <input type="checkbox"/> Pathophysiology |
| <input type="checkbox"/> Pharmacology | <input type="checkbox"/> Psychology | <input type="checkbox"/> Physiology |
| <input type="checkbox"/> Toxicology | <input type="checkbox"/> Zoology | <input type="checkbox"/> Other (please list) |

4. In the past 12 months what procedures and/or models were used in protocols that caused pain and withheld analgesia? (please check all that apply)
- | | |
|--|--|
| <input type="checkbox"/> arthritis models | <input type="checkbox"/> anti-cancer therapies |
| <input type="checkbox"/> cardiovascular procedures | <input type="checkbox"/> concussion models |
| <input type="checkbox"/> experimental surgeries | <input type="checkbox"/> hepatic models |
| <input type="checkbox"/> inflammation models | <input type="checkbox"/> injections of Freund's Complete Adjuvant |
| <input type="checkbox"/> large volume blood removals | <input type="checkbox"/> metabolic diseases |
| <input type="checkbox"/> multi-organ failures | <input type="checkbox"/> multiple surgeries |
| <input type="checkbox"/> neurological procedures | <input type="checkbox"/> osteoarticular procedures |
| <input type="checkbox"/> pain models | <input type="checkbox"/> procedures causing severe sensorimotor disruption |
| <input type="checkbox"/> survival surgeries | <input type="checkbox"/> tissue healings |
| <input type="checkbox"/> whole-body radiations | <input type="checkbox"/> tumor/neoplasia models |
| <input type="checkbox"/> others (please list) | |
5. What justifications for withholding analgesia were provided? (please check all that apply)
- Analgesia *proven* to interfere with experimental results (with citations of literature references demonstrating analgesia-interference conclusively)
 - Analgesia *may* interfere with experimental results
 - Pain is part of the phenomenon that is under study and should thus not be interfered with
 - Animals will not experience pain
 - No evidence that analgesia is necessary
 - Appropriate analgesic is a controlled substance and difficult to obtain
 - Administration of the analgesic would itself be painful (e.g. injection)
 - Oral delivery of analgesic is unreliable
 - Animal will be euthanized within 24 hours of the painful procedure
 - Other (please list)
6. Please describe any pain assessment tools, such as clinical signs scoring records that were used by investigators in protocols that withheld analgesia.
7. Please describe any non-drug pain relief techniques used by investigators in protocols that withheld analgesia.
8. Please add any further comments about protocols that withhold analgesia.