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Résumé de l'article

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Ethics of Amnestics and Analgesics: The Role of Memory in Mediating Pain and Harm

Marina Salis[a], Connor T.A. Brenna[b]

Résumé
L'analgésie et l'amnésie représentent deux piliers complémentaires de l'anesthésie visant, respectivement, à atténuer l'expérience de la douleur et les processus d'encodage de cette expérience dans la mémoire. Ces éléments sont généralement combinés dans les techniques anesthésiques modernes, mais il existe certaines circonstances – comme la sédation consciente – dans lesquelles les conditions de l'amnésie sont remplies alors que l'analgésie joue un rôle auxiliaire et souvent incomplet. Ces activités reflètent une croyance largement répandue mais méconnue dans la pratique clinique selon laquelle, bien que les expériences douloureuses puissent être de courte durée, leur représentation dans la mémoire et ses impacts ultérieurs sur la pensée et l'émotion peuvent avoir des conséquences durables pour les patients. Dans cet article exploratoire, nous définissons des catégories phénoménales et ontologiques abstraites de l'expérience de la douleur, nous affirmons qu'elles sont traitées respectivement par des agents analgésiques et amnésiques et nous décrivons comment chaque catégorie d'expérience est capable de causer des dommages individuels. Partant de la question de savoir comment il peut être permis d'autoriser toute expérience ou tout souvenir de douleur évitable, nous identifions que la douleur phénoménale et abstraite se manifeste sur un spectre de gravité, chacune avec un seuil énigmatique – unique à la circonstance et à l'individu – qui détermine si la douleur se traduira ou non par un préjudice, et quelles permissions entourent donc son traitement. En fin de compte, nous constatons qu'il existe des raisons physiologiques convaincantes pour l'utilisation simultanée d'analgésiques et d'amnésiques lorsque l'expérience de la douleur dépasse ces seuils, tandis que le traitement de l'expérience « sous-seuil » dans l'une ou l'autre catégorie est un impératif purement éthique qui doit être équilibré par des considérations sur les dommages potentiels posés par les traitements eux-mêmes.

Mots-clés
amnésie, analgésie, douleur, préjudice, mémoire, anesthésie, sédation consciente

Abstract
Analgesia and amnesia represent two complimentary pillars of anesthesia directed, respectively, at mitigating the experience of pain and the processes of encoding that experience into memory. These elements are typically combined in modern anesthetic techniques, but some circumstances exist – such as conscious sedation – in which the conditions of amnesia are satisfied while analgesia plays an auxiliary and often incomplete role. These activities reflect a widely held yet underrecognized belief in clinical practice that although pain experiences may be short-lived, their representation in memory and its subsequent effects on thought and emotion can have enduring consequences for patients. In this exploratory article, we delineate phenomenal and abstract ontological categories of pain experience; advance a claim that they are treated by analgesic and amnestic agents, respectively; and describe how each class of experience is uniquely able to bring about individual harm. Beginning with the question of how it can be permissible to allow any preventable experiences or memories of pain, we identify that both phenomenal and abstract pain manifest on a spectrum of severity, each with an enigmatic threshold – unique to circumstance and individual – that determines whether or not pain will translate into harm, and what permissions therefore surround its treatment. Ultimately, we find that there are compelling physiological reasons for the concurrent use of analgesics and amnestics when pain experience exceeds these thresholds, while the treatment of "sub-threshold" experience in either class is a purely ethical imperative to be balanced with considerations of the potential harms posed by the treatments themselves.

Keywords
amnesia, analgesia, pain, harm, memory, anesthesia, conscious sedation

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INTRODUCTION

It is the aim of general anesthesia to afford patients physically and psychologically safe passage through a (usually surgical) experience that is medically indicated but otherwise intolerable, and traditionally this is achieved through several elements working in concert: hypnosis, analgesia, and amnesia, as well as akinesia and hemodynamic support in specific circumstances (1). In this context, hypnosis functions in the central nervous system to render a patient unconscious[1] (2), analgesia in the central and/or peripheral nervous systems to mitigate the perception of pain (3), and akinesia at the neuromuscular junctions to provide muscle relaxation and thereby prevent involuntary movement (4). Amnesia is unique among the components of anesthesia: rather than facilitate an operation per se, it makes it immemorable by interfering with a patient's consolidation of experience into memory (disrupting new memory formation in a process called "anterograde amnesia") (5,6). Although amnestic agents regulate future recollection rather than immediate experience and perception, they

[1] In this context, we refer to unconsciousness as the phenomenological state of being unaware and unrousable.

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are a critical component of anesthesia because of the many demonstrable risks of intraoperative memory formation: even brief moments of unintentional awareness during surgery can facilitate consolidation (7), and the ability to recall surgical experience is associated with long-term psychiatric sequelae such as post-traumatic stress disorder (8).

From an exploratory perspective, the simultaneous use of amnestic and analgesic agents gives rise to interesting practical questions. On its face, the pursuit of amnesia may seem redundant given the antecedent aim of analgesia to preclude aversive experiences. If a patient is completely insensate to pain through the judicious use of analgesics, for example, what is gained by using an amnestic to prevent a negative experience? Two arguments are that: 1) pain may not be the only experience of an (unfamiliar and sterile) operating room that a patient may reasonably elect to forget, and 2) amnestics serve as a safety net in case of inadvertently inadequate hypnosis or analgesia. The inverse scenario is equally intriguing: if a patient is provided with adequate amnesia such that any pain they may experience is not consolidated into memory, why then is it necessary to also supply analgesia?

While the answers to these practical questions may seem a priori commonsensical, they disguise moral arguments which are far more complex. The aim of this paper, while generally exploratory in nature, is to present practical and moral perspectives that engage with these arguments surrounding the use of amnestic and analgesic agents in clinical practice. In addition to the above question, which is the focus of our thesis, we respond to two moral questions arising from this framework. Firstly, what are the relationships between amnesia, analgesia, pain, and harm, and what practical and moral justification do pain and harm give for the use of amnestic and analgesic agents in clinical practice? Secondly, how do these relationships shape a physician's moral duties surrounding the provision of amnesia and/or analgesia (e.g., can medical professionals be justified in forgoing one or the other in clinical practice, and what experiences either warrant or oblige the use of either or both)? To address these questions, we first provide a practical foundation for the use of analgesics and amnestics by outlining their clinical parameters, before exploring the relationships between their effects and the concepts of pain, permissibility, and harm. We demarcate two distinct notions of pain, which we have called "phenomenal" and "abstract" pain, and their unique relationships with analgesia and amnesia. Finally, we explore the moral permissions and limitations arising from these relationships. Drawing on this overall inquiry, we contend that clinical indicators and common sense can inform a reasonable understanding of when and why to pursue amnesia, analgesia, or some combination of both, although an objective threshold to guide this decision is not generally achievable due to the central role of subjectivity in pain experience. Instead, the consideration of amnestic and analgesic agents may be apportioned relative to the expectation of avoidable harms in any given circumstance.

ANALGESICS AND AMNESTICS

The use of analgesic agents such as opioids comes with several risks, ranging from post-operative nausea and constipation to respiratory depression and physical dependence (9). Acknowledging that this is an oversimplification of a broad class of pharmacological agents, amnestic medications such as benzodiazepines tend to offer a relatively large therapeutic index (10) – for example, these agents' most common effect is often sedation, which is sometimes advantageous when they are used in the context of an anesthetic. For this reason, it could be seen as attractive to use only the latter to limit the psychological consequences of pain, rather than subjecting a patient to the potential side effects of both medications. Obfuscating any direct comparison between these two categories of effect, however, is a lack of clearly demarcated amnestics in modern anesthetic practice. Many anesthetic medications provide some amnestic effect, but we do not have access to "pure" or "perfect" amnestics: common agents like midazolam also have analgesic, hypnotic, and anxiolytic effects (11,12), and although they are able to disrupt the genesis of conscious memory[2], they cannot necessarily do the same for implicit memory[3] (13). In addition, there is strong evidence to support the treatment of surgical nociception manifested in its physiological consequences (*not* mediated by psychological experience or memory): unmanaged, the broad effects of acute nociception include an immediate hemodynamic and neuroendocrine response (e.g., heightened blood pressure, cortisol, and blood sugar), and myriad downstream complications such as poor wound healing, infection, respiratory splinting, thromboembolism, and the development of chronic pain (14-16).

Notwithstanding these limitations in clinical amnesia, its conception provides a unique milieu for philosophical dialogue relating to the experience of pain and the ethical reasons to treat it (as opposed to either not treating it or using only enough analgesia to limit its physiologic consequences) when it will not be remembered. Walter Glannon, in 2014, expanded this discourse through a practical example of a patient awakening during anesthesia, and an exploration of moral arguments for and against providing an amnestic which could "erase" consolidated memory in retrograde (if such a drug existed) (17). Responding to this, Andrew Davidson raised two provocative points about Glannon's line of reasoning: that it is not entirely hypothetical, because there are real situations which mirror a "perfect" amnestic (e.g., infants or patients with dementia, who are unable to form long-term memories); and that the practice of conscious sedation constitutes a real example of the broader medical community acting on a notion that the experience of some amount of pain is permissible when an amnestic is used to prevent its consolidation into memory (13).

Davidson's examples of "perfect" amnesia can be extended even further to densely amnesic patients who lack the neurobiological capacity to form memories, such as the well-known patient H.M. who underwent an experimental bilateral

[2] Conscious memory, also called "explicit memory" or "declarative memory", refers to information consolidated in long-term memory which can be actively recalled.
[3] Implicit memory, or "nondeclarative memory", refers to information consolidated in long-term memory which cannot be explicitly recalled but may still unconsciously affect thoughts and behaviours.

medial temporal lobectomy to treat severe epilepsy (18). We propose that his example of conscious sedation falls on a spectrum of medical therapies representing different points of permissibility or reprehensibility in the context of Glannon's questions surrounding the experience and memory of pain (13,17,19). On one end of this spectrum is traditional general anesthesia, wherein a patient is pharmacologically induced into a reversible coma to avoid any adverse experiences (of pain or otherwise) during a procedure. The other end of the spectrum would represent amnesia without any analgesia, which risks the aforementioned physiological consequences of acute pain and is, to the authors' knowledge, not practiced in any setting (and rightly so). Somewhere in the middle of this spectrum are procedures performed with an amnestic but limited analgesia, such as conscious sedation provided for the reduction of a fractured bone (13) or "awake-awake-awake" craniotomies[4] during which patients undergo surgery on the brain while awake in order to limit the risk of iatrogenic damage to critical structures (20), both of which feature in North American practice. In these cases, patients are typically drowsy although often able to wince or vocalize in response to sensations of pain or pressure, but unable to recall the experience even shortly after it ends.

While this paper seeks to explore the motivations behind the extremes of this pain spectrum – procedures only using amnestic and not analgesic, as well as the inverse – cases in the middle of the spectrum also raise several important questions. For example, can an objective standard be drawn in this practical and moral gray area, to identify circumstances in which medical professionals might be justified in using either amnestic or analgesic agents (but not both)? In considering these questions, we seek to understand the ethical motivations and parameters underpinning the use of amnestics, analgesics, or both in concert, as well as how moral arguments may inform the willingness of medical professionals to allow the experience of pain without memory for some procedures (e.g., an endoscopy) but not others (e.g., removing an appendix). We will argue that, while we can recognize the benefits and risks associated with the use of amnestics and analgesics, a concrete objective moral standard for their use cannot be neatly articulated due to the subjective nature of pain – ultimately, though, their use may be better-informed by an examination of the relationships between pain, memory, and harm, which are explored in the following sections.

PAIN, PERMISSIBILITY, AND HARM

A philosophical view of pain mobilizes conceptions of permissibility and when (if ever), in a medical context, a physician is permitted to either induce pain or fail to relieve it when there is access (in the absence of a medical contraindication) to the means of doing so (21). It is our experience that many patients associate receiving an inoculation with pain, but rarely is it recommended to administer anesthesia to mitigate the experience. A priori, one can assume that either the risks of using an analgesic or amnestic agent outweigh the potential benefits (i.e., patient comfort), or that the perceived pain is better dealt with in other ways. This logic does not extend to the pain associated with an extensive Whipple surgery[5], for example, which clinicians recognize would be unbearable for a patient without a general anesthetic. These two examples reflect an intuitive scale of permissibility for the allowance of pain in some clinical circumstances but not others.

We distinguish two philosophical approaches to answering questions about pain: an ontological approach concerned with what pain *is* and where it exists, and an epistemological approach concerned with how we *know* we are experiencing pain. For the purpose of this discussion, we concern ourselves with the former, metaphysical study of what sort of experience pain is (although subsidiary questions surrounding knowledge of the experience are also considered). Philosophers outside the clinical environment have looked for answers to the question of permissibility by developing abstract ontological definitions of pain (23), often delineating it variably as a form of sensory experience such as a physical feature or condition of the body, a form of psychological experience or perception, or a miscellany of both[6] (24-27). These definitions of pain have provided intrinsically compelling and provocative arguments to the philosophical and ethical discourse. With respect to analgesia and amnesia, these ontologies can be operationalized to explore questions of harm – what kind of sensory pain experience, psychological pain experience, or both, it is derived from – and to inform the roles of analgesics and amnestics in medical practice. To do this, we borrow the a priori premises from traditional metaphysics and modern clinical practice, respectively, that: 1) pain is either an experience of physical perception, an experience of non-physical (or psychological) perception, or both, and 2) inducing and/or allowing pain is permissible in some contexts but not others. Given these assumptions, the arguments in support of amnesia with limited analgesia (e.g., in conscious sedation) arise from a moral chasm within the notion of harm as it is applied to physical and psychological pain. In exploring these categories of pain and the relationship each maintains with harm, we seek to provide a richer conception of the profession's prima facie intuition to aggregate the ethical permissions surrounding analgesia and amnesia across various types of medical procedures.

[4] A neurosurgical operation which is performed on an awake patient, to allow for functional cortical mapping during the careful resection of tumours abutting brain regions responsible for generating speech or movement. Traditionally, these procedures might be performed in an "asleep-awake-asleep" fashion where a patient is anesthetized for the beginning and end of the procedure (when the cranial vault is accessed and closed, respectively), and awoken midway to stimulate and map important cortical structures. In the "awake-awake-awake" variation of this procedure, a patient may be awake for the entirety of the operation with pain control (e.g., via nerve blocks of the scalp) but without general anesthetic or sedation (20).

[5] An invasive surgical operation, also known as a pancreaticoduodenectomy, in which the pancreatic head, duodenum, gallbladder, and parts of the stomach and jejunum are excised en bloc (22).

[6] Recent scholarship has argued that pain is necessarily a componential medley of phenomenal experience, on the grounds that that no unitary characterization (such as physical sensation or perceptual representation in consciousness) can independently provide an ontological definition that adequately captures the complexity of pain experience (24).

PHENOMENAL AND ABSTRACT CONCEPTIONS OF PAIN

The delineation of two principal classes of pain experience is a good starting point for exploring the ethics of analgesia and amnesia. The first class refers to a sensory experience defined by concrete spatiotemporal characteristics (25). Philosophers Ned Block and Walter Glannon, among others, have deployed the terminology of "phenomenal pain" to describe this immediate physical experience of pain perceived through nociceptors (17): for example, the acute perception of an uncomfortable sensation in one's toe when a hard external stimulus has impinged on its soft tissue. While the use of the word "phenomenal" in the philosophical tradition often refers to the what-it-is-likeness of experience, here it refers strictly to the (objectively or subjectively) localizable, tangible experience of pain. Phenomenal pain is classically situated in and bounded by specific tissue damage, although this is not definitionally imperative with respect to chronic pain (28). In all cases, it is an immediate sensory or phenomenological experience of pain in physical sensations and properties.

While references to pain classically describe this phenomenology, pain can also be described in terms separate from immediate, physical experience. This latter interpretation of pain, which we term "abstract pain", resists conflating the perception of a physical feature or condition with the physical feature itself (25). Rather, abstract pain represents an often-unlocalizable inner perception of an undesirable experience; put another way, it is all the components of painful experience except for its immediate perception. With this definition, abstract pain follows from the encoding of phenomenal pain experience into memory, from which it can be recalled or re-experienced, and manifests more subtly, such as in behavioural modifications or alterations of thought and emotion reflecting an unpleasant prior experience. Phenomenal pain (e.g., beginning with the sensation of receiving an injection and experienced until local nociceptors cease to signal tissue injury) and abstract pain (e.g., the auxiliary or lasting negative effects of having undergone the phenomenal pain experience, which might lead an individual to avoid future injections) are both necessarily mediated by the nervous system, and together provide a composite definition of pain which can be operationalized to explore the ethics of its management with more granularity.

In practice, phenomenal and abstract pain may be thought to represent unique therapeutic targets. In the context of anesthesia, for example, we argue that local or general analgesic formulations are used to numb physical sensations and ameliorate the experience of phenomenal pain (either at the site of the nociceptive stimulus or through central action on the nervous system). Amnestic agents are similarly provided with the aim of preventing the consolidation of phenomenal pain experiences into memory (therefore sharing in prevention of the undesirable functions of pain). While both analgesics and amnestics are therefore tools for the mitigation of pain experience, their respective uses are grounded in unique and independent conceptions of pain.

BROADLY DEFINING HARM

Motivations to pacify these different notions of pain are grounded in their relationships with each other and with the related concept of harm. We note the important distinction, again, between ontological and epistemic understandings of harm; here, their delineation becomes more ambiguous, as the understanding of what harm *is* as a metaphysical concept is fundamentally informed by the epistemic knowledge of how one might *identify* that they are being harmed. Thus, the determination of what constitutes individual harm requires several further considerations, as we argue that the highly subjective and individual factors that contribute to pain eliminate the possibility of one unambiguous, universal conception of harm. Colloquially, for example, one may recognize the concept of a pain threshold, noting that a person's psychological or genetic disposition may predispose them to different kinds or degrees of experience. An experience like receiving a tattoo may be judged as intolerable for some, but unremarkable – or even pleasurable – to others. The author C.S. Lewis, in *The Problem of Pain* (1940), provides an initial framework with which to examine the experience of pain and its relationship with harm:

> […] the truth is that the word Pain has two senses which must now be distinguished. **A.** A particular kind of sensation, probably conveyed by specialised nerve fibers, and recognisable by the patient as that kind of sensation whether he dislikes it or not (*e.g.,* the faint ache in my limbs would be recognized as an ache even if I didn't object to it). **B.** Any experience, whether physical or mental, which the patient dislikes. It will be noticed that all Pains in sense A become Pains in sense B if they are raised above a certain very low level of intensity, but that Pains in the B sense need not be Pains in the A sense. Pain in the B sense, in fact, is synonymous with 'suffering', 'anguish', 'tribulation', 'adversity', or 'trouble' […]. (29, p.78)

While we may point to some objective factors of experience that are generally recognized as harmful or causally connected to harm, the approach to an ontological definition of harm ought to be inclusive and sensitive to the various subjective factors that contribute to an individual's experience of a "harm threshold", allowing for the breadth of both physical and psychological experiences that can be harmful. This understanding privileges neither outcomes nor means and is therefore consistent with both consequentialist and deontological traditions, accepting that both an individual's actions and their consequences can constitute harm in and of themselves.

Simultaneously, a rational conception of harm must be appropriately specific, because while there is a degree to which an understanding of harm may be influenced by personal opinion, subjectivity, and lived experience, the potential for any experience of pain to be conflated with harm is not tenable in the context of professional obligations to do no harm. Primarily, such a conflation would prohibit any medical intervention associated with even mild discomfort. The duty of clinicians to avoid doing harm is an imperfect, prima facie duty (30), balanced against other competing duties (e.g., to provide beneficent care to

patients); nevertheless, it must be possible for some experiences of pain not to constitute harm, or this duty is an indictment of essentially all medical interventions. In practice, the ethical obligations of clinicians are to offer interventions that balance the assumed risks and benefits, and to avoid subjecting patients to unreasonable degrees of harm without consent. This may also mean balancing the risks of analgesic and amnestic therapies, along with practical considerations in their use such as cost or resource stewardship, against risks associated with patients' experiences if not mediated by these therapies.

We therefore conservatively refer to harm as the lasting phenomenon of an individual's wellbeing falling below that threshold which a rational individual experiencing it could consider reasonably acceptable. In this regard, we loosely borrow conceptions of wellbeing and harm from Powers and Faden (31) and agree with them that, though the exact threshold is never articulated, harm arises when an individual is deprived of or significantly deficient in a core dimension of wellbeing such as health. This would suggest that reasonable action be taken to afford individuals a sufficient state of wellbeing and a minimization of avoidable harm, while also recognizing the intersectional and subjective nature of the phenomena. The definition also allows for the possibility that a single experience of pain may affect two individuals differently, both with respect to its subjective experience and its capacity to cause harm, while remaining consistent with the motivations of clinicians to do no harm despite their constant engagement in practices that sometimes do induce pain (e.g., giving a vaccination without prior topicalization using a local anesthetic). However, our proposed notion of two distinct types of pain experience challenges providers to identify the appropriate permissions surrounding each, and therefore to engage meaningfully with the unique relationship – explored in subsequent sections – that each type bears with harm.

TREATING PHENOMENAL AND ABSTRACT PAIN

Earlier, we presented the idea that the pain experience can be philosophically disaggregated into a dichotomy of phenomenal and abstract pain. The concept of phenomenal pain informs the use of analgesics as a practice seeking to ameliorate the acute physical experience of pain, by forestalling nociceptive signal transduction or transmission through the nervous system. In the absence or failure of an analgesic, a subject undergoing an acute physical experience of severe pain can sustain harm, for example by way of a physiological stress response (e.g., a profound increase in blood pressure) that precipitates a stroke. Abstract pain, in contrast, informs the use of amnestics as a practice seeking to mitigate the consolidation of negative experience into memory. In the absence or failure of an amnestic, the harm done to an individual by way of undesirable mental/emotional states and behavioural modification can manifest immediately, but is also capable of extending beyond the immediate present to encompass a broad class of enduring psychological harms.

Two moral questions arise from this framework, which we will outline and explore further. First, if it is the case that allowing (or even causing) either phenomenal pain or abstract pain can be harmful, then how can medical professionals ever be justified in allowing one or the other – or some uneven combination of both – in clinical practice? For example, why is it that some brief procedures like an endoscopy often predominately use amnestics with limited analgesic effect, whereas traditional general anesthesia is a requirement for more complex and invasive procedures like a cardiac surgery? What are the morally relevant aspects of the dichotomous pain experience that inform this practice? Secondly, at what point within each category does the experience of pain become constitutive of a harm? Though one can attribute both phenomenal and abstract pain to a specific experience, does their existence (or representation in consciousness) necessitate the occurrence of harm?

RELATIONSHIPS BETWEEN PAIN AND HARM

Both phenomenal pain and abstract pain have the potential to be harmful, but the means by which they act as causative agents of harm (and the means by which physicians can prevent this process) are unique. With respect to phenomenal pain, the practice of avoiding or ameliorating harm arising from sensory experience seems prima facie intuitive: by preventing nociception with analgesics or similar modes of therapy, an inherently undesirable experience of pain can be avoided, and therefore precluded from causing harm to an individual. Complicating this framework, the translation of phenomenal pain into harm relies on several mediating physiological factors: for example, nociception changes sympathetic drive, which in turn leads to hemodynamic stress and the potential for end-organ damage. Rather than eliminating the pain experience with analgesics, it is conceivable that providers could instead treat the various mediating responses – high blood pressure with beta-blockers, high blood sugar with insulin, and so on to the extreme of yet-unknown molecular stress responses to pain and yet-unknown means of terminating them[7]. The possibility therefore arises for a perception of phenomenal pain that may *not* be directly causative of harm, though still potentially harmful via its encoding into memory and re-experiencing as abstract pain.

The relationship between abstract pain and harm is more complex, given that this pain cannot be ascribed to a spatial location in the same way as a physical injury. This notion of abstract pain refers to many components of a pain experience beyond its immediate sensation. For example, in the way that one responds to an unpleasant stimulus by encoding knowledge and memory of its experience into the nervous systems, one may form an aversion to that stimulus (just as one might form a predilection for a pleasant one). The harm associated with abstract pain may not necessarily be immediately impairing, but it informs one's beliefs, behaviours, attitudes, practices, and judgements. For example, consolidating the memory of a

[7] Another important mediating phenomenon is "central sensitization", the process by which peripheral nociception modifies central nervous system responsiveness to produce a hypersensitive state that is primed to experience further pain. On the basis of central sensitization, scholars such as Clifford Woolf have drawn compelling arguments that surgical nociception should be forestalled using analgesia (rather than treated reactively after a surgery facilitated by hypnosis alone) to limit long-term consequences (32). Like we argue in this section for other physiological mediators of phenomenal pain, targeting the intrinsic mechanisms of sensitization is a theoretical alternative to preventing transduction of the nociceptive stimulus itself.

traumatizing surgical experience may lead to symptoms of post-traumatic stress disorder (e.g., hypervigilance and recurrent memories about that experience), and a patient who has experienced trauma resulting from awareness under anesthesia may later elect not to undergo another surgical procedure even in dire circumstances. The consequences associated with abstract pain therefore have the capacity to extend beyond the bounds of an original stimulus, encompassing a broad class of enduring and undesirable harms, thus warranting the use of amnestic therapy when feasible. Similar to the caveat provided with respect to the prevention of harm via phenomenal pain, it is worth noting that the harms of abstract pain are also mediated by an individual's ability to – consciously or subconsciously – call them forth from memory, theoretically presenting another therapeutic target for pharmacologic agents that do not yet exist (retrograde amnestics or memory recall inhibitors), but which would intuitively warrant similar (and other) ethical considerations.

In the case of both phenomenal and abstract pain, not all instances of pain are constitutive of harm. For example, the experience of being pinched by a needle and that of sustaining injuries in a car accident both involve experiential pain but describing the former as harmful in any meaningful sense depreciates the term. In the latter, the pain experience has the unique possibility of rendering long-lasting decreases in physical wellbeing (e.g., the loss of a limb) and mental wellbeing (e.g., phantom pain or an adjustment disorder). Although the threshold beyond which an experience becomes harmful evades precise definition (in part due to its inherent subjectivity), two conclusions seem plausible: 1) there are general, objective instances that can be recognized as *potentially* harmful and which can inform the motivation to administer analgesics and amnestics, and 2) these objective considerations can supplement the subjective experience and understanding of harm, and inform the balance of expected benefits and risks associated with the mitigation of pain experience. While we accept that the range of available interventions and subjective perspectives (of both patients and providers) stymies the dictation of a clear line between experiences that will and will not be harmful, in the following section we draw from these conclusions several ethical and practical considerations which may inform clinical practice.

IMPLICATIONS FOR THE USE OF AMNESTICS AND ANALGESICS

The nature of the relationships between phenomenal pain, abstract pain, and harm reflects the existence of an ethical threshold unique to each type of pain, and which can divide experiences as harmful (to varying degrees) or harmless. While we cannot claim to offer a clear and practical injunction for the permissions surrounding pain and harm, we offer several conclusions that can elucidate how a threshold may theoretically be determined. Primarily, clinical permissions are dictated by whether a particular course of action surpasses a given limit with respect to the possibility of harm proportional to the action in question. Factors that link pain experiences to harmful outcomes appear likely to include both objective features (e.g., stimulus intensity or timescale) and subjective patient features (e.g., individual tolerance) of the experience, which may serve as a starting point for attempts to delineate the separation between permissible/harmless and unacceptable/harmful pain experiences.

In light of this proposal, we consider a pragmatic approach to the mitigation of pain and harm in which the standard of practice would be to treat, prevent, or otherwise mitigate all avoidable and probable harms that a reasonable person in similar circumstances would expect to be avoided. However, the extent to which subjective factors ought to be incorporated must also be considered because, as we have observed, the possibility that any experience of pain could be conflated with harm is incompatible with the professional duty to do no harm (and therefore would prohibit all interventions that a patient might reasonably experience as painful, no matter how minimally). A few practical criteria can be drawn from the broader literature focused on reasonableness in the context of offered treatments and informed decision-making (although the precise definition and parameters of each could be subject to their own moral debates). For example, Robert Schwartz (33) has explored the notion that patient autonomy is rarely, if ever, understood as a right to choose from a completely unrestricted range of treatment options. Instead, it is typically accepted that patients have a right to choose from within a reasonable subset of options, which are informed by the intersection of a physician's clinical expertise and a patient's individual preferences. What is determined to be "reasonable" remains open to debate, but we can highlight several factors relevant to this consideration. For example: whether a treatment is, in fact, medical in nature; whether there is any opportunity for further benefit (i.e., whether a treatment is futile); whether it is possible to deliver a treatment; or whether a treatment would displace another patient who may be in greater need (33,34). In parallel to criteria like these, a treating physician might consider whether there are other, more appropriate and less invasive means by which harm can be avoided or mitigated. This approach honours the subjective aspects of pain experience and harm, but also begins the necessary function of delimiting what potential harms could be considered and which might be seen as reasonable. Thus, it also provides a starting point for a provider to determine whether the administration of an analgesic or amnestic agent (and the risks associated with these) are reasonable in view of the potential harms of the experience that a patient might have either with or without them.

We can be confident that, because harm thresholds are modified by patient-specific variables, professionals may never be able to predict every individual's tolerance for pain before it broaches harm. In the absence of objective frameworks for the measurement of pain, the medical system relies on incomplete evidence to anticipate which procedures require complete analgesia and/or complete amnesia, and which can afford to forego the potential negative effects of either of these interventions. Permissions to allow pain therefore appear to be primarily guided by a judgement relating to what an average individual[8] can reasonably be expected to tolerate (e.g., a reasonable person can be expected to tolerate the discomfort of

[8] It is important to note that what is considered average has been the subject of deserved controversy, given the term's attachment to historical inequities surrounding race, sex, and ability. For example, clinical trials evaluating new pharmaceuticals have historically often been performed in samples comprised largely of adult Caucasian male subjects, to the exclusion of other groups, and the applicability of their findings to all patients has been called into question (35-37). Thus, it is critical to consider these disparities when evaluating clinical studies and making any consideration on the basis of what is thought to be "average".

colonoscopy mitigated by the use of an amnestic with only slight analgesic properties, whereas these permissions cannot be extended to an open thoracic surgery). Medical professionals may also consider the gravity of reasonably anticipated effects: permissions may take into consideration what negative effects are likely or logically expected to occur in the absence of interference from an amnestic and/or analgesic and, when it can be anticipated that a patient would experience severe pain, then as professionals we are ethically obligated to mitigate it with the means available. When phenomenal pain can be controlled to the extent that physiologic harms are avoided, the further reduction of pain (e.g., providing local anesthetic through a small-bore needle before establishing intravenous access with a larger-bore one) is a purely ethical imperative.

Recognizing the possibility that harm can be caused through the administration of analgesic or amnestic medications themselves, it may be reasonable to suppose that the overall risk of harm posed to a patient undergoing a brief but stimulating procedure can be best reduced by titrating analgesic agents to the point where phenomenal pain experience is maintained just below the threshold of physiological harm, and supplementing this regimen with amnestic agents to preclude the possibility that any unchecked phenomenal pain may gain access to memory and result in abstract pain or subsequent harms. We propose this theory as a feasible, but unnoticed, ethical justification underpinning the modern practice of conscious sedation. Future directions of this work will include more precise delineations of the relationships between various qualities and degrees of pain and harm, as well as exploration of the limitations that these relationships place on what clinical interventions ought to be considered as reasonable in view of anticipated harms. Practically, these efforts will inform the clinical application of analgesic and amnestic therapies, either separately or in combination, for patients undergoing otherwise painful interventions. To this end, the work of elucidating where the thresholds between pain and harm exist, precisely, remains an ongoing project of medical ethics.

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