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ETHICAL MATTERS

Withdrawal of Life-Sustaining Treatments in Perceived Devastating Brain Injury: The Key Role of Uncertainty

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Abstract

Background: Withdrawal of life-sustaining treatment (WOLST) is the leading proximate cause of death in patients with *perceived devastating brain injury* (PDBI). There are reasons to believe that a potentially significant proportion of WOLST decisions, in this setting, are premature and guided by a number of assumptions that falsely confer a sense of certainty.

Method: This manuscript proposes that these assumptions face serious challenges, and that we should replace unwarranted certainty with an appreciation for the great degree of multi-dimensional uncertainty involved. The article proceeds by offering a taxonomy of uncertainty in PDBI and explores the key role that uncertainty as a cognitive state, may play into how WOLST decisions are reached.

Conclusion: In order to properly share decision-making with families and surrogates of patients with PDBI, we will have to acknowledge, understand, and be able to communicate the great degree of uncertainty involved.

Keywords: Brain injury, Decision-making, Disability, Chronic conditions and rehabilitation, End-of-life issues

Withdrawal of life-sustaining treatment (WOLST) is the leading proximate cause of death in patients with *perceived devastating brain injury* (PDBI); this applies to both traumatic, and nontraumatic etiologies [1–7]. The definition of PDBI employed here has as follows: brain injury that is assessed (by clinicians or surrogates) at the time of hospital admission, or early during intensive care, as an immediate threat to life, or incompatible with acceptable functional recovery, or where limitation or withdrawal of therapy is being considered specifically as a response to predictions of poor neurologic function or unacceptable quality of survival.[1] There are reasons to believe that a nontrivial proportion of WOLST decisions, in this setting, are premature and guided by a number of assumptions that falsely confer a sense of certainty. This article aims to show that these assumptions face serious challenges, and that we should replace unwarranted certainty with an appreciation for the great degree of multi-dimensional uncertainty involved. The plan of the article is as follows: the first section provides a taxonomy of uncertainty in PDBI and discusses challenges against some widely shared assumptions. The second section

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[1] This definition of PDBI is inspired by, yet differs from, recent definitions provided by the Neurocritical Care Society [8], and by the Joint Professional Standards Committee of Faculty of Intensive Care Medicine in the UK [9]. The differences with these definitions are that they (a) do not explicitly include surrogates in the perceiving end, (b) make no direct reference to quality of survival as a consideration for WOLST, and (c) the UK definition focuses on decision making at hospital admission and not during intensive care. As an aside, and with an eye on what follows, note the time windows these guidelines suggest for aggressive care before consideration of WOLST; NCS recommends 72 h and the UK guideline 24–48 h. These time windows could be criticized for their lack of patient-specificity, and for arguably being, overall, on the shorter side. Nevertheless, they are likely motivated by a sense of urgency to limit supra-early WOLST.

Table 1 Uncertainty in PDBI: Summary of types with defining features, accompanying considerations, and management suggestions

Type	Defining question	Considerations	Manage
Diagnostic	What is the diagnosis?	First versus second order	Behavioral exam can be unreliable; re-classify (aspects and modes of consciousness)
Prognostic	What outcome and QOL to expect?	We need to understand QOL from the perspective of patients and caregivers	Need empirical data (bias of SFP); be mindful of "thick" language in diagnosis/prognosis
Experiential	What is the nature of the patient's experience?	Minimizing pain; richness of content; ability to communicate	Prioritize pain relief but enhance opportunities for richness; social interaction
Moral	What ought to be done?	Continue or WOLST? how does consciousness matter?	Reconsider WOP; allow options at a later point; recognize biases
Value	How to evaluate different outcomes?	Death versus "stuck with life"; consciousness and theories of well-being	SDM instead of unilateral value-laden judgments; well-being plurality; capabilities approach
Ethical	Which theory, principles or rules should apply?	Principlism versus consequentialism versus rights	Recognize potentially misguided applications and conflicts

QOL quality of life, *SDM* shared decision-making, *SFP* self-fulfilling prophecy, *WOLST* withdrawal of life-sustaining treatments, *WOP* window of opportunity

explores the key role that uncertainty, as a cognitive state, may play into how WOLST decisions are reached. The overarching aim is to sensitize clinicians to the idea that in order to properly care for patients with PDBI, and to optimally share decision-making with their surrogates, we will have to abandon false certainties. Instead, we should acknowledge, understand, and be able to communicate amidst far greater degrees of uncertainty.

Taxonomy of Uncertainty in PDBI

Patients who survive the initial insult may transition from coma into either a vegetative state/unresponsive wakeful syndrome (VS/UWS) or a minimally conscious state (MCS). Decisions about WOLST are often taken during the time patients are still comatose or during emergence to the above disorders of consciousness (DOC). In what follows, will be building on a framework identifying types of uncertainty, as discussed by Dominic Wilkinson in his 2013 book "Death or disability: The Carmentis machine and decision-making for critically ill children" [10]. Specifically, the types of uncertainty discussed are: diagnostic, prognostic, experiential, moral, value, practical, and ethical (Table 1 offers a summary of types with defining features, accompanying considerations, and management suggestions).

Diagnostic Uncertainty (First Order)

First-order diagnostic uncertainty refers to the ability of identifying levels or states of consciousness by bedside clinical examination and behavioral responses, or neuroimaging or neurophysiology. It also applies in terms of diagnosing patients according to the currently endorsed DOC syndromic classification [11]. Second-order diagnostic uncertainty arises from validity challenges to this classification scheme. The unreliability of behavioral responsiveness in properly classifying patients has been demonstrated in reports showing that approximately 30–40% of patients clinically diagnosed in VS retain various degrees of conscious awareness [12]. This has been highlighted by functional neuroimaging [13, 14], and neurophysiology studies [15] demonstrating command following when the bedside examination is consistent with coma, UWS, or MCS with limited nonreflexive behaviors. A recent meta-analysis suggested that approximately 15% of study participants who satisfied the behavioral diagnosis of VS possessed some capacity to respond to commands [16]. This syndrome has been recently coined as cognitive motor dissociation (CMD; [17]).

Diagnostic Uncertainty (Second Order)

Coma and current DOC syndromes have indistinct boundaries [18]. Each clinical syndrome encompasses a broad spectrum of severity and may be produced by a variety of different neuropathological entities, it follows that these syndromes are not unitary disorders but bundles of heterogeneous mixtures of different diseases or injuries of varying severities that merely share common behavioral features [19]. To translate the point in philosophical terms, Klein has observed that since two patients can meet the criteria for being at a certain level of consciousness or DOC syndrome for completely different neurological reasons, these categories do not form projectable natural kinds [20].[2] Behavioral (un)responsiveness does not pick out natural kinds in terms of

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[2] "To say that a kind is *natural* is to say that it corresponds to a grouping that reflects the structure of the natural world rather than the interests and actions of human beings." [Bird, Alexander and Tobin, Emma, "Natural Kinds", *The Stanford Encyclopedia of Philosophy* (Spring 2018 Edition), Edward N. Zalta (ed.)].

conscious content. The recent recommendation of the European task force to abandon the term VS for UWS is acknowledging this second-order diagnostic uncertainty [21]. The 1994 multi-society task force temporal criteria applying to persistent and permanent VS have now been challenged (and the terms better abandoned) by case reports and series of patients with much later recoveries [22–24]. Another reason to abandon the term is to recognize that "Vegetative" is not a purely descriptive definition—in fact, and at purely neuroanatomical/neurofunctional level, it is often mistaken if implying *apalic* [25]—but a *thick* concept.[3] It carries dehumanizing connotations, and since for the majority of people it is associated with a life not worth living, it may serve as a heuristic (intentionally or not) to steer decision-making toward WOLST [27]. It is likely that current DOC categorization will keep evolving with potential shifts of focus to *aspects* or *modes* of consciousness [28, 29], and by combining behavior with neuroimaging and electrophysiological findings [29, 30].[4] Naccache's proposal to abandon MCS for cortically mediated state (CMS), apart from being neurologically a more accurate description, has the additional virtue of replacing another potentially thick (and see later *ambiguous*) concept, that of "minimal" consciousness.

Prognostic Uncertainty

As mentioned above, dogmas about long-term prognosis in the various DOCs have been challenged by reports of late recoveries. This, apart from terminology changes, has also revealed a potentially major confounder in prognostication, that of self-fulfilling and self-reinforcing prophecies; these are defined as predictions (that a certain outcome is likely or inevitable) that independently increase the probability of the outcome actually occurring [31]. Such phenomena have been considered to be responsible for high (and potentially premature) rates of WOLST in cohorts of patients with diverse etiologies of acute brain injury; characteristic is the example of a Canadian study, which found that 70% of traumatic brain injury deaths reported in six level I trauma centers (total of 720 patients) were attributable to WOLST, with half occurring within the first 72 h of injury, and with significant (and otherwise unexplained) variability among centers [3]. It should be understood that this may be a pervasive problem in the literature of reported outcomes for various pathologies of brain injury (from trauma, to coma post-cardiac arrest), since mode of death is not often explicitly reported and WOLST decisions are not standardized [7]. It is worth mentioning several other limitations of current prognostic models. Performance of such models in groups of patients may be reasonable, nevertheless the precision of prediction is either not routinely provided, or tends to be inadequate for decision-making in individual patients. These predictions are also mostly focused on mortality and lack granularity in terms of functional outcomes or quality of life measures. The typical assessment of outcome is at hospital discharge, or at 6 months; this temporal window is not reflective of the temporal course of recovery for many patients with PDBI, where improvements may take significantly longer to manifest [9, 32].

Saliently, one has to look at what exactly is meant by "good" and "poor" outcomes and how quality of life is understood not solely among clinicians but patients and surrogates [33]. Fear of disability in conjunction with limited imagination in terms of the ability to adapt and to have a meaningful life, can favor WOLST. This relates to the disability paradox, a significant underestimation of actual quality of life associated with a certain disability [34–36]. Examples of our limited ability to make evaluative projections in regards to quality of life after brain injury, include surveys showing a disparity between what is considered a favorable outcome among healthy adults and actual patients treated with surgical decompression for space-occupying hemispheric infarction [37], or patients in locked-in-state [38].

Experiential, Moral, and Value Uncertainties

Experiential uncertainty refers to the psychosocial or existential effects of continuing treatment or surviving with cognitive or functional disabilities. It closely interrelates with moral (the question of what ought to be done) and value (how to assign value on available courses of action and outcomes) uncertainties [10]. Fundamentally, in DOCs, the nature and quality of experiences of patients are often impossible to determine. It is stressed that the appropriate treatment and avoidance of pain is of paramount importance, nevertheless to enhance quality of life, the mere avoidance of pain is not adequate. It may be helpful to examine basic well-being theories in order to explore both the uncertainties involved, but also the relevant moral imperatives and pluralistic evaluative stances that may be available. Traditionally, the literature on well-being considers the following theories:

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[3] Thick concepts are concepts that carry evaluative and normative connotations and are not merely descriptive. The designation "thick concept" originates in Bernard Williams's Ethics and the Limits of Philosophy [26].

[4] Bayne et al. [29], consider a whole range of possible aspects that might be impaired in DOC. These include attention, different kinds of conscious content, global features like bandwidth, and accessibility of contents. They further suggest that the overall level of consciousness might be aspect-dependent—a patient might count as VS if tested on one aspect and MCS if tested on a different one. Naccache proposes changing the MCS to CMS (cortically mediated state), and creating eight categories including the source of evidence (e.g. behavioral, neuroimaging).

hedonism, desire-satisfaction, and the objective list. Plausibly, clinicians and surrogates adhere to combinations of these theories—although they may not think or speak of their views in these terms. Hedonists believe that positive well-being roughly consists in having the pleasant experiences outweigh the unpleasant. The pillars of hedonism—the avoidance of physical pain and psychological suffering in favor of comfort—are also pillars that ought to be guiding all stages of care for patients with PDBI, from emergency department to the intensive care unit (ICU), to rehabilitation [33]. Uncertainty about potential suffering can create significant distress to surrogates and clinicians in noncommunicative patients. In fact, it can serve as a potential reason to consider WOLST, especially in the face of a projected grim prognosis. This connects to the concept of a "window of opportunity," usually during the ICU stay, when WOLST is very likely to lead to death, and this can be achieved in a relatively pain- and suffering-free way [39]. The window of opportunity creates a sense of urgency regarding decisions to WOLST, since over time patients require less life-sustaining treatments and withdrawal/withholding is overall harder later rather than earlier [40, 41].

Desire-satisfaction theorists hold that a happy life is one in which enough of one's desires are satisfied. Desire-satisfaction is challenging in the context of PDBI where most patients have limited or lack capacity all together. A closely related problem is the issue of potential conflict between precedent autonomy (and pre-injury desires) with current interests. Views have been expressed in favor of either position (precedent autonomy trumping current interests and vice versa); it would take us far afield to attempt expanding on them. However, the dilemma highlights the central role that experiential uncertainty plays, and how it interacts with ethical uncertainty (to be mentioned subsequently) exemplified by the conflict between *Autonomy* and *Best Interests* [42].

Objective list proponents maintain that there is some set of goods that a life must instantiate or contain (friendship, health, intellectual achievements, as examples) for that life to be good, regardless of what the individual wants or thinks she wants. Objective list theorists claim that some things just are good for individuals, even if individuals are incapable of, or choose not to recognize their benefit. In the clinical setting, objective list theories may appear under the guise of "best interests." In many cases physicians act without any knowledge of the patient's values or desires; in certain other cases, clinicians are justified in acting according to the best interests of the patient even over the patient's requests, specifically when patients are deemed to lack medical decision capacity. Of concern here are a number of cognitive biases that may be operative unknowingly and undermine proper shared decision-making [43–45]. How implicit and explicit biases may interact toward, and with, negatively appraised uncertainty during the window of opportunity is a largely unexplored question (more on this in the second part of the manuscript) but it seems it would be important to understand as we interrogate the psychology of WOLST decision-making.[5] Returning to the objective list and considering its application in the setting of PDBI we should ask about the items that shall compose it. What may be viewed as *low-functioning* for healthy (and able-bodied) individuals could count as *high-functioning* for patients who have suffered PDBI. The issue is how appropriate is a single objective list that does not account for a person's capacities, functionings, and capabilities. Specifically, we should examine if WOLST-related judgments primarily spawn out of a version of the objective list that corresponds to ingredients of the "good life" for normal healthy adults; such lists are likely to value highly full independence in activities of daily living, return to employment, and even accomplishment of high levels professional functioning. These achievements may not be possible for a number of PDBI and DOC patients; nevertheless, it seems unjustified to subject them to the aforementioned "higher" standards.

Practical Uncertainty

The clinical course of patients with PDBI is complex and multi-staged. A resuscitative phase during emergency department and early ICU stay is often followed by a prolonged ICU course, and transitions from step-down, intermediate care units to rehabilitation and skilled nursing facilities or nursing homes. The process, criteria, and administrative requirements for these transitions can be daunting and hard to navigate for families. Surrogates may be told that a patient could benefit from specialized neurorehabilitation attention, yet information and assistance in regards to actually identifying and accessing such services can be limited, confusing or even nonexistent. Furthermore, DOC patients can be denied benefits or additional time in the hospital because of failure to meet eligibility based on lack of "medical progress" [47]. Crucially, what is defined as appropriate progress

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[5] Biases can affect shared-decision making by distorting the understanding of the nature of a certain choice or decision and the foreseeable consequences. Examples of potentially prevalent biases in cases of PDBI patients include a. *Impact:* a failure to anticipate adaptation to a new state, relates with the disability paradox (notice that it is a *paradox* only because the starting point is biased); b. *Gain framing:* reaction to a particular choice differs depending on how it is presented; e.g. as a loss or as a gain. Think of discussions where the same course of action (or intervention) is presented with an emphasis on saving life vs. an emphasis on the avoidance of survival with unacceptable quality; c. *Optimism bias:* inaccurate interpretations of physicians' prognostications by surrogates have been shown to arise partly from optimistic biases rather than simply from misunderstandings [46].

in these policies is not tailored toward the emerging natural history of potential improvement in DOCs [48]. The result of restricted benefits and coverage is to leave a heavy financial burden—including the risk of bankruptcy—on patients and families [49]. Navigating this system, let alone assuring the necessary means, to get from acute care provision to neurorehabilitation back to social re-integration harbors great obstacles and menacing uncertainty.

Ethical Uncertainty

Several of the preceding questions that affect treatment deliberations in PDBI are further nuanced by uncertainty at the normative ethical realm. The more concrete question takes the form of which ethical models or theories are most relevant for guiding the care of PDBI patients? The natural place to start would be the "four core principles" of medical ethics [50]; however, the immediate first point is that since they are nonhierarchical, when they conflict they are of limited value in providing guidance. What would be the practical deliverances of thinking in terms of beneficence and nonmaleficence in the case of PDBI? If the previous degree of uncertainty is taken seriously, these principles offer very limited guidance indeed. In fact, and under *principlism's* guise, the operation of numerous cognitive biases may be at play. For example, the combination of pessimistic (neuronihilistic) biases can easily be combined with notions of beneficence in leading to WOLST [51]. One could claim that this is the kind of response rationally called for by projections of a "life not worth living."[6] Plausibly, the exact contrary can be also occurring with optimism-biases cooperating with either beneficence or nonmaleficence (here the way these two principles are used may result into a distinction without a difference), in the prescription of inappropriately aggressive or prolonged treatment. Accordingly, an argument can be made that in the face of great diagnostic/prognostic uncertainty early in PDBI, these principles offer such limited guidance that should not be invoked in guiding treatment decisions. Furthermore, their invocation should provoke skepticism and a burden of proof that they are not fraught by numerous derailing cognitive biases and heuristics. Take another debate (already mentioned above) on what *respecting persons* would require in cases of PDBI. Leaving aside controversial metaphysical questions about personhood in individuals with PDBI or DOCs, one may ask if considerations of precedent autonomy trump considerations based on current interests.[7] This provided we are comfortable granting genuine autonomy to decisions about potentially wildly unfamiliar states such as the ones grouped under DOCs.

Finally, in terms of justice, Fins and Wright argue that DOC patients are entitled to treatment, rehabilitation, deinstitutionalization, and social re-integration, as a matter of civil and disability rights [55, 56]. These authors see as analogous (and thus required by justice) cuts in the sidewalk, ramp, or elevators to facilitate physical accessibility with reestablishing functional communication through pharmaceuticals, devices, or neuroprosthetics in DOC patients. This will have to be accomplished within health systems that have finite budgets, leading some to propose incorporating cost-effectiveness analyses on requested interventions, in the name of distributive justice [57].

Uncertainty and the Psychology of WOLST

In this section I intend to examine the potential effect of uncertainty, as a cognitive state, in the psychology of decision-making when WOLST is considered. The base model employed (albeit from a different perspective) is *the middle-range nursing theory of uncertainty in illness* theorized by Mishel [58, 59]. Mishel's theory aims to explain how patients cognitively process illness-related stimuli and construct meaning in these events. Uncertainty occurs in a situation in which the decision maker is unable to assign definite value to objects or events or is unable to predict outcomes accurately [59]. There are four concepts identified as contributors to an uncertain state—complexity, unpredictability, ambiguity and lack of information. If we were to apply each of these sources of uncertainty into the subject at hand it would become obvious that PDBI, coma, and DOC are paradigmatic cases for extreme uncertainty. It would be informative to comment on *ambiguity* and related *vagueness*; for something to be ambiguous is to be assigned a

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[6] The concern here is the involvement of an implicit bias, or an "alief"; what Gendler explains as automatically activated clusters of representations, feelings, and behaviors. So while the belief that this patient has brain injury does not have to be necessarily fixed to any particular feeling (apart from heightened attention to her care), an alief will have content like, "Brain injured! Horrible outcome! Avoid!" Gendler writes, that to have an alief, is to a reasonable approximation, to have an innate or habitual propensity to respond to an apparent stimulus in a particular way. It is to be in a mental state that is… *a*ssociative, *a*utomatic and *a*rational. As a class, aliefs are developmentally and conceptually antecedent to other cognitive attitudes, and are also affect-laden and action-generating [52, 53].

[7] Consider for example an influential philosophical position by Jeff McMahan developed in his 2002 book, *The Ethics of Killing* [54]. McMahan holds that, in order to be considered a *moral equal*, one has to be a *person*, and to be a person in the relevant sense means having "a mental life of a certain order of complexity and sophistication". Complexity and sophistication are measured in terms of psychological capacities, most importantly (according to McMahan) *autonomy* (presupposing self-consciousness and rationality). Adopting such a view, and depending how high one sets the bar in terms of cognitive sophistication, it is easy to see that there may be significant metaphysical and moral implications for patients with PDBI and DOC.

double meaning, either deliberately, or due to inexactness of expression, or due to lack of a deeper understanding and knowledge (ambiguity also results from imprecise information about outcome probabilities). The result is that information is open to interpretation. Similarly, *vague* is information couched in general, indefinite, or imprecise terms [60]. Ambiguity has been shown to promote pessimistic appraisals of risk and avoidance of decision-making, a phenomenon known as "ambiguity aversion" [61]. The magnitude of this effect is further pronounced when the source of ambiguity is conflicting versus incomplete information [62, 63]. Take as an example the terms "coma," "unresponsive wakeful syndrome," and "minimally conscious state." Unfortunately, we do not have empirical data on how these terms are interpreted by families and surrogates, neither on how the terms may interact with cognitive biases in the thinking of surrogates and clinicians. Nevertheless, it does not take far-stretched speculation to see the implicit (and explicit) ambiguity and vagueness of the language used. A direct imperative is that as we progress in our empirical/scientific knowledge we ought to re-classify nosologic states with an eye toward reduction of these sources of uncertainty. The last point was *lack of information*; that is a reality within the sciences and medicine of consciousness, however a more ominous factor is the *conflicting* information that surrogates and caregivers may be often given in clinical environments. Patients with PDBI, and at different stages, receive care by a variety of specialists with a range of expertise (and a range of biases; [6, 64]). As a result, families may be given advice and prognoses reaching the opposing ends of the spectrum. This, apart from feeding uncertainty leads to potential breakdown and loss of trust, essential features of the surrogate-clinician relationship [65, 66]. Unmet communication needs and insufficient, conflicting information can result in a rapid shift from aggressive efforts aimed at survival and recovery to treatment focused on comfort and limitation of life-sustaining measures [67, 68]. In a recent qualitative study from Canada, ICU physicians and nurses were interviewed following WOLST in comatose patients with out-of-hospital cardiac arrest treated with targeted temperature management [69]. Participants worried that the absence of clear and timely information precluded surrogates' capacities to balance hope and uncertainty about the patient's future. The study suggested that family–team communication might be an underestimated factor leading to premature WOLST.

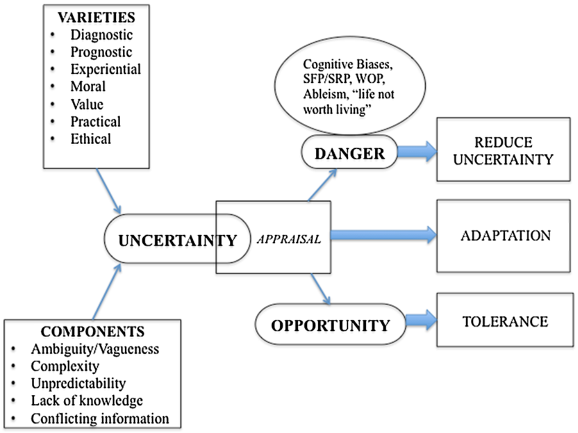

Fig. 1 A model of taxonomy, components, and appraisal of uncertainty; a paradigm shift may be called for shift appraisal early in PDBI from *danger* to *opportunity*. *SFP* self-fulfilling prophecy, *SRP* self-reinforcing prophecy; *WOP* window of opportunity

The remainder of the article offers a preliminarily sketch of the role of multi-dimensional uncertainty (exposed via the previous section's conceptual taxonomy) within an operative cognitive schema during WOLST decision-making among clinicians and surrogates (Fig. 1 illustrates this sketch via an adaptation of Mishel's model to the purposes of this manuscript). The taxonomy of uncertainty in PDBI together with Mishel's adapted model, aim to offer a unified heuristic in order to study, and understand WOLST decision-making in neurocritical care. The intended utility of this approach lies in its ability to bring to light the multidimensional nature of the uncertainty involved in conjunction with highlighting its key role—through *appraisal*—in how these decisions are made within a shared locus of clinician–surrogate uncertainty. A crucial discernment is that uncertainty is not inherently a dreaded or desired state until a phase of appraisal. It is only then that a positive (*opportunity)* or a negative (*danger)* valence is ascribed. Uncertain events evaluated as danger trigger harm-reducing strategies ultimately targeted toward a reduction of uncertainty (the risk here being a new state of false certainty).[8] Insightfully, L. Syd Johnson has observed that decisions can be often made *upstream* (early in the course of PDBI) in an effort to avoid *downstream* risks (or *danger* in Mishel's model; [41]). Specifically, upstream decisions with high-certainty outcomes (e.g., limitation on specific treatments/courses of action, or WOLST leading to death) are made to avoid uncertain—appraised as *danger*—downstream outcomes. Other experts have also proposed that clinicians' difficulties with managing uncertainty can manifest in a pessimistic tone in both verbal and nonverbal communication [70]. Lack of awareness

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[8] Uncertainty appraised as danger is not necessarily accompanied by an affective state of anxiety or emotional pressure. It could also be based on a strict probabilistic estimation of a projected poor outcome (however *poor* is defined by the people considering treatment alternatives) that is to be avoided. I would like to thank Sunil Kothari who pressed me to clarify this point.

of one's own biases or emotional state is a source of communication insufficiency and a potential mechanism of a self-fulfilling prophecy that culminates in premature WOLST [71].

On the other hand, events interpreted as *opportunity* may lead to coping strategies in maintaining uncertainty toward adaptation. Notice that adaptation does not entail elimination or even reduction of uncertainty but the opposite. It is a state of acknowledging, understanding, and embracing uncertainty. Adaptation allows, involved parties into decision-making, to maintain adequate but not extreme psychological activation, and consequently fosters goal-directed shared decision-making. Tolerance of uncertainty has the added benefit that it can be potentially properly communicated. In any given clinical circumstance, uncertainty can affect patients, clinicians, both, or neither. Exactly to what degree, and what type of uncertainty resides depends on each party's experience, cognitive and emotional capacities; importantly, however, it also depends on the extent to which their mutual interactions result in shared awareness. Uncertainty should be differentiated from a state of meta-ignorance—lacking knowledge or insight of what one does not know. In the absence of in-depth communication, there can be situations where, as an example, physicians are aware of scientific ignorance but do not inform surrogates about it [72]. Communication of uncertainty allows for its locus to become shared among health-care providers and families and to decrease meta-ignorance that can be deleterious to the goals of informed and shared decision-making. The inclusion of independent patient advocates, having experience with brain injury as survivors or caregivers, could be one measure in helping surrogates and clinicians to incorporate a crucial missing perspective that could potentially mitigate both issues of meta-ignorance, and aspects of practical and experiential uncertainty [73, 74].

Recently, and in order to enhance the decision-making process for patients with PDBI, the development of informational tools known as "decision aids" (DAs) have been proposed [66]. This is an important initiative since DAs have been shown (in other fields of medicine) to improve accuracy of risk perception, increase knowledge about possible decisions to be made, inform decisions about undergoing invasive procedures, and lead to more realistic expectations of treatment effects on disease outcomes. A caveat that should be recognized is that informational interventions such as DAs are usually built on the assumption that the successful management of uncertainty consists of processes related to the provision or acquisition of information [75, 76]; this would only mitigate reducible ignorance. The multi-dimensional taxonomy of uncertainty offered above shows though that apart from issues pertaining to lack of information, difficulty in managing uncertainty also rises from irreducible ignorance (and meta-ignorance). This requires helping decision-makers to cope with uncertainty that cannot be remediated. Such coping implies a deeper, broader acceptance of irreducible uncertainty. A suggestion based on the model described is that this broader acceptance could then motivate an intentional, conceptual, and behavioral paradigm shift toward an appraisal of uncertainty as *opportunity* rather than as *danger* (especially early in PDBI course). This suggestion, and in view of the cognitive biases mentioned earlier, has another aspect, that of moral responsibility to a changing epistemic environment with potentially serious social consequences. We are responsible for taking an active stance for likely biases that we now ought to be aware of in the management of PDBI patients and their families.

Conclusion

There are important challenges for future clinical practice and research, they include (a) increasing the empirical base that will inform more precise nosologic classifications, and prognostic models (at the same time by also limiting cognitive biases), (b) understand more precisely what appraising, coping, and adapting to uncertainty entails. In the meantime, the taxonomy offered here, in conjunction with the adapted model of uncertainty in illness may provide a conceptual framework to help clinicians start unpacking the components, and sources of uncertainty, and to bring more attention to the impact that appraisal of uncertainty can have on shared decision-making in the care of patients with PDBI.

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Dr. Lazaridis conceived the article topic, wrote and revised the draft.

Compliance with Ethical Standards

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