

1 **Use of Evidence in Acute Stroke Decision-Making: Implications for Evidence-Based Medicine**

2

3 **Use of Evidence in Acute Stroke Decision-Making**

4

5 **Timothé Langlois-Thérien, BSc, MPhil^{1,2}, Brian Dewar, MLIS^{1,2}, Ross E.G. Upshur, MD, MSc³,**

6 **Michel Shamy, MD, MA, FRCPC^{1,2}**

7

8 ¹Department of Medicine, University of Ottawa, Ottawa, ON, Canada

9 ²Ottawa Hospital Research Institute, Ottawa, ON, Canada

10 ³Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

11

12 **Corresponding author:**

13 **Timothé Langlois-Thérien**

14 **The Ottawa Hospital – Civic Campus, 1053 Carling Avenue, Room C2182, Ottawa, ON K1Y 4E9**

15 **Email: tlang012@uottawa.ca**

16 **Phone number: 613-761-4709**

17

18

19 **Acknowledgements**

20 The content of this manuscript was adapted from a master's thesis (MS) in the History and
21 Philosophy of Science, successfully defended at the University of Calgary in May 2014 under the
22 supervision of Dr Frank Stahnisch.

23 This work was supported by fellowship funding from Alberta Innovates Health Solutions (2012-
24 2014) and a graduate scholarship from Department of Medicine, University of Ottawa (2013-
25 2014). Dr Shamy is currently funded by a Heart and Stroke Foundation National New
26 Investigator Award.

27

28 **Data Availability Statement**

29 Data sharing not applicable to this article as no datasets were generated or analysed during the
30 current study.

31

32 **Declaration of Conflicting Interests**

33 The authors declared no potential conflicts of interest with respect to the research, authorship,
34 and/or publication of this article.

35 **Abstract**

36

37 Evidence-Based Medicine proposes a prescriptive model of physician decision-making in which
38 "best evidence" is used to guide best practice. And yet, proponents of EBM acknowledge that
39 EBM fails to offer a systematic theory of physician decision-making. In this paper, we explore
40 how physicians from the neurology and emergency medicine communities have responded to
41 an evolving body of evidence surrounding the acute treatment of patients with ischemic stroke.
42 Through analysis of this case study, we argue that EBM's vision of evidence-based medical
43 decision-making fails to appreciate a process that we have termed *epistemic evaluation*.
44 Namely, physicians are required to interpret and apply any knowledge — even what EBM
45 would term "best evidence" — in light of their own knowledge, background and experience.
46 This is consequential for EBM as understanding what physicians do and why they do it would
47 appear to be essential to achieving optimal practice in accordance with best evidence.

48

49 **Keywords:** evidence-based medicine, clinical decision-making

50 Introduction

51 Evidence-based medicine (EBM) emerged in the early 1990s as a new approach to clinical
52 medicine inspired by the seemingly pure and anti-authoritarian goal of educating clinicians in
53 the use of the published literature to optimize their practice [1]. First defined as “the
54 conscientious, explicit and judicious use of current best evidence in making decisions about the
55 care of individual patients”[2] EBM aims to position clinical practice on more solid scientific
56 grounds and rescue clinical decision-making from physicians' fallible and value-laden intuitions.
57 What rapidly became a core component of EBM's doctrine is the evidence hierarchy, which
58 privileges knowledge gained from randomized clinical trials (RCTs) — especially when
59 aggregated in systematic reviews or meta-analyses — over all other forms of knowledge,
60 including mechanistic reasoning and physicians' experiences. Yet, in order to escape a number
61 of pushbacks on the basis of reductionism, EBM was ultimately redefined as “the integration of
62 best research evidence with clinical expertise and patient values” [3].

63

64 As advocates of EBM have recognized, EBM – as a theory of physician decision-making – is
65 largely prescriptive: it is about how MDs *should* make decisions, not how they *do* make
66 decisions. Haynes and al. [3], pioneers of the EBM movement, explicitly acknowledge this
67 distinction: “[EBM] is prescriptive rather than descriptive. That is, it is a guide for thinking about
68 how decisions should be made rather than a schema for how they are made”¹. Therefore, as a
69 means of understanding how physicians will act in the course of a clinical encounter, EBM can
70 tell us little. Indeed, proponents of EBM also acknowledge that their model offers limited
71 insights into physician decision-making, for example when Djulbegovic and Guyatt recently
72 wrote that “The main challenge for EBM remains how to develop a coherent theory of decision
73 making” [1].

74

75 In this paper, we suggest that EBM's vision of evidence-based medical decision-making fails to
76 appreciate a process that we have termed *epistemic evaluation*. In Section 1, we introduce this
77 process through the case study of acute stroke decision-making, in which drastic differences in
78 interpretation of a large body of “high quality” evidence has driven decades of disagreement
79 between the emergency medicine and neurological communities. In section 2, we return to
80 EBM and identify important implications for its prescriptive mission. We contend that adopting
81 a more open and solid descriptive foundation of decision-making, and particularly of the
82 relationship between research evidence and research evidence-users, is likely to be more
83 successful in changing practice than creating ever “more” and “better” evidence. Ultimately, we
84 propose that devoting more attention to the processes of *epistemic evaluation* can lay the
85 groundwork for a theory of clinical decision-making that reconciles the prescriptive ambition of
86 EBM with what is understood about the realities of physician decision-making: that any clinical
87 evidence is necessarily situated in an epistemic, social as well as clinical context. [4,5,6].

1 ¹ Figure 2 of Haynes and al. [3] depicts a Venn diagram with three equally overlapping circles titled ‘Research
2 evidence’, ‘Clinical States and circumstances’, ‘Patients’ preferences and actions’ with an added circle titled
3 ‘Clinical expertise’ overlaying the intersected parts of the Venn diagram.

88 Section 1 | Epistemic evaluation in acute-stroke decision-making

89

90 Over the last 30 years, the field of acute ischemic stroke therapy has seen two significant
91 developments: in the mid-1990s, the identification of intravenous thrombolysis (tPA) as an
92 effective therapy for selected patients; and then in the mid-2010s, the addition of endovascular
93 thrombectomy (EVT) as an effective acute treatment for an overlapping set of patients. Despite
94 the availability of evidence from multiple RCTs in both cases, adoption of these treatments was
95 not straightforward and the way physicians engaged with this evidence tells us much about
96 real-world decision-making. In this section, we contend that the prescriptive (normative)
97 framework of EBM fails to capture relevant epistemic components of decision-making
98 surrounding acute stroke treatment, in that there is both an extensive literature of (what EBM
99 considers) "high quality" evidence as well as significant practice variation regarding these two
100 treatments. The ways in which the RCT evidence for these two treatments was applied in
101 practice can serve to demonstrate the limitations of the EBM model of decision-making in that:
102 positive RCT trials did not necessarily lead directly to practice change; negative trials did not
103 lead to abandoning treatments; and the factors that seem to have strongly influenced practice
104 change (for better or for worse) are largely cultural and contextual.

105

106 In what follows, we propose a descriptive model of physician decision-making, one based on
107 studying the decision-making we see in the case of acute-stroke treatment. Our model – which
108 we have termed *epistemic evaluation* – borrows tools from the philosophy of science to justify
109 the epistemic gap in stroke decision-making between EM doctors and neurologists.
110 Specifically, our descriptive approach highlights that different epistemic values regarding the
111 evidence, influenced by differing background mechanistic knowledge related to the evidence,
112 and different diagnostic skills necessary to apply the evidence, can better explain the gap in
113 interpretation and application that arose in the neurological and emergency medical
114 communities than can issues of evidence quantity or quality.

115

116 1.0 Treating acute stroke

117 The treatment of acute stroke can represent a (somewhat) pure case of how doctors – rather
118 than patients, or patients in combination with doctors – make decisions. Acute stroke is a
119 medical emergency and decisions about treatment must be made in a matter of minutes.
120 Moreover, the decision-making process must often be undertaken without input from the
121 patient, who is often incapacitated from a decision-making point of view. Therefore, acute-
122 stroke decision-making allows us (for the sake of this paper) to ignore aspects of *shared*
123 decision-making and focus on the relationship between the physician (or evidence-user) and
124 the research evidence.

125

126 For most of medical history, stroke was understood as untreatable [7]. A series of scientific and
127 technological advancements throughout the second half of the twentieth century helped
128 reformulate this conception [8]. In 1995, the first randomized trial demonstrating efficacy for a
129 thrombolytic agent in acute ischemic stroke was published. That trial — known as the NINDS
130 trial for its sponsors — demonstrated a modest but statistically significant benefit to the use of
131 intravenous alteplase for patients with acute ischemic stroke under 3 hours from symptom

132 onset [9]. Subsequent trials of different agents over different time windows did not reproduce
133 this result until about a decade later when the ECASS III and IST3 trials once again showed
134 benefit for tPA [10, 11]. A meta-analysis of these data demonstrated that benefit could be
135 obtained out to 4.5 hours from symptom onset, though the greatest likelihood of benefit arose
136 if treatment was administered as early as possible [12]. The neurological community was
137 energized by these results and the use of intravenous alteplase became an accepted practice,
138 as reflected by many national guidelines [13]. Moreover, legal cases in many jurisdictions have
139 awarded damages to patients who were candidates for but who did not receive intravenous
140 alteplase[14], again demonstrating that its use became a *de facto* clinical standard.

141
142 According to EBM's prescriptivist model of decision-making, there should have been little
143 variation around this practice: alteplase is effective based on the highest quality of evidence,
144 obtained from meta-analyses of multiple high quality RCTs. And yet, practice variation persisted
145 for at least a decade. Many estimates suggest that fewer than 5% of stroke patients receive
146 treatment with IV tPA. While this is largely owing to the fact that many patients do not arrive in
147 hospital quickly enough to be assessed for treatment within 3 hours, at least 50% of eligible
148 candidates did not routinely receive treatment with tPA [15].

149
150 Moreover, empirical studies demonstrated that many physicians expressed skepticism about
151 the benefits of alteplase despite the available evidence, particularly physicians from an
152 emergency medicine background. Emergency doctors are usually the first responders to
153 evaluate patients with suspected stroke. They often collaborate with neurologists in acute-
154 stroke decision-making. Yet, those two specialties would appear to interpret the evidence for
155 alteplase very differently. A survey of neurologists in 1997 showed that only 3% considered the
156 results of the NINDS "not convincing" [16], and another survey of Ontario neurologists in 2010
157 found that a mere 4% did not believe in the efficacy of tPA for stroke [17]. In contrast, in 2005,
158 a survey of over 1100 American emergency physicians reported that 40% were unlikely to use
159 tPA for stroke even "under ideal conditions" [18]. The same year, another survey of emergency
160 doctors in New York showed that only 66% considered tPA to be an "appropriate agent for the
161 treatment of acute ischemic stroke." [19] In 2010, a similar survey found that only 49% of
162 Michigan Emergency Physicians felt the scientific evidence regarding the use of tPA was
163 convincing [20]. And official guidelines from the Canadian Association of Emergency Physicians
164 (CAEP) paint a similar picture. Until 2015, the CAEP was not supportive of the use of
165 thrombolytic agents for acute ischemic stroke [21].

166
167 For EBM's prescriptive model, this variability can only be justified by a lack of research
168 evidence, or dissemination thereof, or guidelines that do not follow GRADE processes. And yet,
169 this is clearly not the case. A large body of evidence was available, with which both
170 communities of physicians were intimately aware. Indeed, evidence suggests that the
171 emergency medicine community's skepticism was based on a set of arguments grounded *within*
172 the available evidence. They were keenly aware of it, and contested it despite it being of the
173 "highest quality" as per EBM standards. We will dissect those specific arguments in order to
174 draw broader conclusions about the need to expand EBM's model of the way physicians use
175 evidence in decision-making. We argue that EM doctors and neurologists arrived at their

176 differing interpretations of the evidence because they *evaluated* it differently: they prioritized
177 different sets of epistemic values in regard to the evidence, which were themselves influenced
178 by different background mechanistic knowledge related to the evidence and distinct diagnostic
179 skills necessary to apply the evidence.

180

181 **1.1 Background mechanistic knowledge**

182 A recurring argument against the efficacy of tPA as a treatment for acute stroke questions the
183 validity of the results of by the NINDS trial in comparison to other larger clinical trials. According
184 to this criticism, benefit seen in the 624 patients enrolled in the NINDS trial is overwhelmed by
185 lack of benefit in the 1847 patients enrolled in other trials – ECASS I, ECASS II, ATLANTIS A and
186 ATLANTIS B. Indeed, these trials showed high rates of post-tPA intracerebral hemorrhage,
187 leading to excess mortality [22, 23, 24].

188 At first glance, this criticism is based on the routine statistical importance of sample size: the
189 larger the population of a trial, the more likely the results shown are valid. However, a key
190 difference between the NINDS trial and those other clinical trials reveals the subtext of the
191 criticism: the NINDS trial enrolled all its patients within 3h from the onset of symptoms while
192 the other trials used a 6h window. The selection of such a narrow therapeutic window in the
193 NINDS trial relied on animal experimentation suggesting the existence of a *penumbra* – a region
194 of the brain that could survive despite being deprived of blood flow — if only for a few hours
195 after symptom onset [25]. Interestingly, the *penumbra* is a concept commonly referenced in
196 articles defending the treatability of stroke [26,27,28] but is not mentioned in articles
197 challenging it [18, 22, 23].

198 Emergency doctors' knowledge is necessarily broader and shallower in scope. They have less
199 chance to be familiar with such physiological concepts compared to neurologists. And without
200 the concept of the penumbra, and its operational correlate of the 3-hour therapeutic window,
201 there would indeed be no grounds to distinguish between the NINDS trial and its related trials.
202 In such a case, the NINDS results would be submerged by the results of the other trials due to
203 their combined sample size.

204

205 We contend that this example demonstrates how the epistemic evaluation of “best” evidence
206 requires the integration of mechanistic concepts in the background knowledge of physicians.
207 Different relationships with mechanistic concepts – such as vascular anatomy, localization, and
208 the penumbra [8]– between neurologists and emergency doctors provides an alternate source
209 of explanation to make sense of their different epistemic evaluation and application of the
210 evidence.

211

212 **1.2 Diagnostic skills and Risk Tolerance**

213 Another argument against the treatability of acute stroke by alteplase relies on the risk of
214 intracerebral hemorrhage, the most dangerous potential side effect of tPA treatment.
215 According to the NINDS trial, 6% of patients who were treated with tPA suffered some form of
216 intracerebral hemorrhage, in contrast to only 0.6% of the patients who received placebo [9].

217 Emergency doctors have maintained that such risk is simply “unacceptable” [18]. Here, the
218 critics are not contesting the validity of the NINDS trial’s results, but are arguing about their
219 meaning. A 6% absolute risk of hemorrhage is intolerable is felt to outweigh the 35% relative
220 increased chance of benefit derived from tPA treatment. This criticism is found principally
221 among the emergency medicine community [29], and not the neurological community.
222

223 A great deal of the concern relating to the risk of hemorrhage surrounds the administration of
224 alteplase to patients who shouldn't have received it: what is seen as the risk of causing
225 unjustified harm. The risk of hemorrhage from thrombolysis for stroke is much higher than in
226 acute myocardial infarction (MI), where the risk of hemorrhage is less than 1%. Accurately
227 identifying patients who do indeed warrant thrombolysis is a key element of the decision-
228 making process, and is much more complex in stroke than in MI, where clear measures such as
229 ECG and troponins are more consistently interpreted. In the case of stroke, a CT scan is
230 primarily used to exclude other causes while the diagnosis often depends upon a clinician's
231 recognition of the pattern of symptoms. To help the physician identify patients less likely to be
232 harmed, the NINDS trial came up with a number of criteria including the 3 hour window, the
233 absence of hemorrhage on the CT scan, the absence of obvious signs of irreversible infarction
234 on the CT scan, and any feature that would predispose the patient to bleeding, such as
235 abnormalities of clotting [9].
236

237 Without the access to a CT scanner – and therefore the ability to exclude a hemorrhagic cause –
238 a physician is unable to safely initiate therapy with a thrombolytic agent like tPA. Similarly, the
239 inability to interpret correctly the history and physical examination findings of a patient with
240 acute stroke could impact a physician’s treatment decisions. While the working skill to localize
241 “focal neurological deficits” is a central focus of a neurologist’s training, emergency physicians
242 are not trained with the same rigor on such skill. The suggestion that emergency physicians are
243 less comfortable administering tPA to stroke patients is often evoked in debates about stroke
244 treatments. For instance, emergency physician Dr. Anand Swaminathan of New York University
245 raised concern about the fact that “we don’t know who to give the drug to” [30]. Physicians
246 who lack such knowledge or ability might administer tPA to patients who have more chance to
247 develop post-tPA hemorrhage, feeding into their belief that tPA is unacceptably dangerous.
248

249 Here, we see that the application of the “evidence” requires well-developed diagnostic abilities
250 (on top of access to the right diagnostic technologies). Differences in the diagnostic skills – and
251 confidence therein – between neurologists and emergency doctors can hence also help explain
252 the difference in their epistemic evaluation of the evidence.
253

254 **1.3 The case of endovascular thrombectomy**

255 In order to counter potential arguments that the phenomenon we described of *epistemic*
256 *evaluation* is idiosyncratic to emergency doctors (that they somehow take a different position
257 regarding the hierarchy of evidence) or is limited to the response to early trials of alteplase, we
258 briefly discuss the case of another recent treatment for acute stroke, namely endovascular
259 thrombectomy. Large, multicentre randomized trials published in late 2014 and early 2015
260 concluded that there was benefit to endovascular thrombectomy for stroke patients with so-

261 called large vessel occlusions, where a thrombus is visible on angiographic imaging of the brain
262 [31] doption of this novel treatment was met with no resistance by the emergency medicine
263 community. In fact, they adopted it quickly and in many cases argued that it further added to
264 the proof that alteplase was ineffective or unnecessary [32].

265

266 Yet, the 2014-2015 trials that established the efficacy of EVT were preceded by a series of
267 similarly well-conducted trials - all published in the *New England Journal of Medicine* in 2012-
268 2013 - that arrived at the conclusion that thrombectomy offered no benefit [33, 34, 35].

269 According to EBM's hierarchy, 3 large scale well-conducted RCTs should have been considered
270 definitive evidence establishing that EVT was not effective and should have halted the practice.
271 And yet, despite this evidence, the stroke and emergency communities pushed forward with
272 more trials, convinced of EVT's benefit despite their own clinical trials.

273

274 This example reinforces three important conclusions. First, that the importance of a non-
275 hierarchical interpretation of evidence is not restricted to the case of tPA or to emergency
276 physicians. If the physicians in question had followed the principles of EBM then EVT should
277 have been rejected out of hand at this point; 3 large RCTs had demonstrated that it was no
278 more effective than standard treatment. And yet, these trials only spurred a further generation
279 of trials. Second, that the reason for which the neurological community continued to believe in
280 EVT despite RCT evidence to the contrary is based in fundamental physiological (read
281 mechanistic) reasoning and individual experience. Many physicians in the community had direct
282 clinical experience of technically successful thrombectomy leading to rapid and unquestionable
283 individual patient benefit. The basis for that success was felt to be the rapidity with which the
284 treatment would successfully recanalize the affected intracerebral artery. Appropriately, much
285 of the criticism directed towards the first three negative EVT trials pertained again to the issue
286 of time — namely, that the EVT was not administered quickly enough on average to have been
287 effective. This is another example of the penumbra principle in action. Third, the emergency
288 medicine community rapidly adopted EVT as an effective treatment, a clear contrast to how
289 they had interpreted the tPA trials. Why the difference? We suspect - as some EM doctors have
290 explained to us - that this has to do with the fact that EVT-related procedures lead to the direct
291 visualization of the presence of thrombus pre-treatment (which removes doubt about the
292 diagnosis, and hence about the appropriateness of therapy) and of the absence of thrombus
293 post-treatment, thereby confirming the efficacy of the intervention. This example illustrates
294 how direct (and often personal) experience of a treatment's efficacy, alongside mechanistic
295 reasoning, inform the interpretation of RCT results, exemplifying what we have termed the
296 process of epistemic evaluation. We believe this conclusion bears important implications for
297 the future of EBM.

298 Section 2 | Implications for EBM

299

300 From our descriptive argument, we extract three implications for EBM that build on each other.

301

302 **Implication 1: Maintaining an objective unbiased view of evidence is not possible (nor** 303 **perhaps desirable)**

304

305 Our argument supports and adds to a growing body of literature contesting the possibility (or
306 even desirability) of EBM's goal to maintain an objective view of evidence. This literature –
307 powered by voices such as Upshur [5, 36, 37], Goldenberg [8, 38], and Kelly [39] – is itself
308 building on a now well-established feminist and post-positivist literature in the philosophy of
309 science.

310

311 EBM praises objectivity as an epistemic virtue. Objectivity is a scientific virtue that stands for an
312 aperspectival “view from nowhere” [38]. It underscores an emphasis towards certainty, and
313 freedom from bias and prejudice. Even if pure objectivity cannot be reasonably reached, it is
314 perceived to be an ideal worth striving for by EBM theorists and clinicians alike (e.g., see [40]).
315 Yet, the concept of underdetermination, in the tradition of Quine and Duhem, and the role of
316 epistemic values and inductive risk, as best described by Douglas [41, 42], paired with the
317 argument we advance in this paper, can help us understand the problems with holding such an
318 ideal².

319

320 In the philosophy of science, underdetermination is a key concept stating that the “evidence
321 available to us at a given time may be insufficient to determine what beliefs [or theory] we
322 should hold in response to it” [43]. In other words, the decisions we make are never
323 determined (and never can they be) solely by the evidence. As Douglas [42] puts it: “Although
324 all of the evidence may one day be in and make clear what we should think, as actual epistemic
325 actors, we are not in that position. The evidence does not clearly determine which claims are
326 the right ones, nor does it indicate that we have all the plausible options on the table for
327 consideration, nor even whether our background assumptions are adequate.” This gap between
328 theory and evidence, she proceeds to argue, is filled with values. Exemplary science has been
329 shown repeatedly to be value-laden in important ways [44, 45, 46, 47, 48]. Specifically to EBM,
330 critics have hammered this point continuously, but Kelly et al. [39] is probably the most
331 comprehensive critic showing how every aspect in the production of EBM evidence is
332 influenced by social and ethical values.

333

334 Descriptively, RCT evidence underdetermines decision-making in clinical practice [36]. In this
335 paper, we argued that such underdetermination points to the importance of other forms of
336 knowledge in applying evidence to practice – mechanistic knowledge and specialty-specific
337 cultural knowledge such as diagnostic skills. For instance, when considering the effectiveness of
338 tPA, emergency doctors caution against the hemorrhagic risk of tPA to deny its use, while
339 neurologists seem to embrace the beneficial effect tPA can bring in restoring patients' cognitive
340 abilities. This difference in prioritization can best be explained in terms of inductive risk [41,37].

4 ² For a more in-depth philosophical analysis of these concepts (and more), see [37].

341 Inductive risk refers to the risk for error that occurs when we infer broader conclusions from
342 limited data, which is omnipresent in medicine and most evident in the case of developing
343 clinical guidelines from EBM evidence. The decision-maker must balance the opposing wrongs
344 of false positives and false negatives. While one could argue that a certain optimal balance
345 could be reached, we suggested in light of our case study that idiosyncratic features of a
346 physician – such as their background knowledge or their diagnostic skills – can pull them in one
347 direction, which may be disease- or patient-specific. No matter how hard EBM attempts to
348 curate and purify the evidence, extraevidential factors and evidence-users’ assumptions will
349 necessarily guide the interpretation and use of evidence.

350

351 **Implication 2: An optimal theory of evidence-based decision-making must recognize and**
352 **include evidence-users’ assumptions.**

353

354 As pointed out earlier, EBM proponents themselves recognize a deficiency of their framework:
355 “The main challenge for EBM remains how to develop a coherent theory of decision making”
356 [1]. We suggest that one critical step in such a process is the recognition that evidence-users
357 (such as physicians) carry assumptions in their interpretation and application of the evidence.
358 Their assumptions emerge from multiple sources, whether it be mechanistic knowledge,
359 experiential skills, or social values, and nothing guarantees *a priori* that these assumptions can
360 or should be homogenized.

361

362 While EBM was developed to rescue clinical medicine from physicians’ fallibility and value-
363 ladenness, it fails to recognize – or at least convincingly acknowledge – that the relationship of
364 physicians with the evidence is itself fallible and value-laden [37]. EBM effectively maintains a
365 dichotomy between the “objective value-free” evidence and the “subjective values” of patients
366 and society [4]. While they acknowledge the ubiquity and need for values, they merely
367 encompass them in patients’ values and preferences. Therefore, they manage to keep their
368 ideal goal of objectivity, clumped into “the evidence.” By building a hierarchy restricted to
369 methodological mitigation of biases in study design, with meta-analyses, reviews, and RCTs at
370 the top, they fail to highlight and convey that values will necessarily distort every other step in
371 the production and interpretation of research.

372 As a result, our personal experience with colleagues shows us that when considering a clinical
373 question, physicians frequently ask: “What is the evidence?” [49, 50, 51]. They expect a
374 conclusive answer that can epistemically guide them. They fail to recognize the epistemic
375 evaluation they will undeniably have to perform, together with the ineradicable interpretive
376 dimension of such reasoning. EBM popularized the idea that variation in decisions must arise
377 from differences in the quality of knowledge available in the literature or possessed by different
378 individuals. In other words, either more clinical trials are needed because the sufficient
379 evidence does not exist, or it does exist but is not disseminated properly and physicians are
380 unaware of it [52].

381 Yet, this paper reveals that another line of reasoning seems probable to explain variations in
382 physician decision-making. Values, knowledge, and skills are key determinants of a physician’s

383 decision-making, and any discrepancies in those determinants between physicians might
384 impact their decision-making. As Goldenberg [6] puts it: “The appeal to the authority of
385 evidence that characterizes evidence-based practices does not increase objectivity but rather
386 obscures the subjective elements that inescapably enter all forms of human inquiry”. One
387 should think of background assumptions as playing a constitutive (and not a biasing) role in
388 epistemic evaluation [48]. Maybe that under such a premise, the CAPE guidelines that denied
389 tPA as a useful treatment for acute stroke until 2015 would have not taken so long to
390 recommend altepase treatment. Ultimately, our goal is not to incriminate the variation that
391 exist in physician’s decision-making. But, if physicians’ decision-making does not align, we need
392 a framework to help uncover and map the assumptions and values that might explain such
393 misalignment. An important first step in that direction (and towards a robust account of clinical
394 reasoning) would be to avoid hastily incriminating physicians when they do not follow
395 guidelines or practice EBM and rather examine the reasons why they may not.

396

397 **Implication 3: “More, better” evidence is not always the optimal path to bridging epistemic**
398 **conflicts**

399

400 From our descriptive analysis and the first two implications, we can deduce that EBM’s model
401 and ambition to create “more, better” evidence – best captured in their “hierarchy of
402 evidence” – might not always be the optimal path to bridging epistemic conflicts in clinical
403 medicine.

404

405 The design of a study does not confer all its epistemic ground or quality, and patients’ values
406 and preferences do not represent the only source of unavoidable (and perhaps necessary)
407 subjectivity in decision-making. As prime evidence-users, physicians are key epistemic actors.
408 While some discrepancies between physicians may be curable (gaps in diagnostic uncertainty),
409 others have no clear solutions (preferring “effectiveness” over “safety”) and would require
410 considerable discursive space to explore the optimal way forward. Adopting a more open and
411 solid descriptive foundation of decision-making (that exceeds methodological purposes), and
412 particularly of the relationship between evidence and evidence-users, is likely to yield better
413 insights into the practice-changing ambitions of EBM. For instance, acknowledging and
414 identifying differences in the education and socialization of distinct specialties may lead to the
415 possibility of acting on those areas of dis-interpretation.

416

417 In parallel, this paper brings a novel argument in support of the relevance of mechanistic
418 evidence in clinical decision-making. The fact that EBM undermines the epistemic validity of
419 mechanistic evidence has been criticized repeatedly in the literature [53, 54, 55]. The EBM+
420 approach, for instance, is a new model aimed at defending and increasing the use of
421 mechanistic evidence in clinical research [56]. While arguments put forth so far often directly
422 defend the epistemic role of mechanistic evidence in the acquisition of clinical knowledge, our
423 paper brings an “indirect” argument for the epistemic role of mechanistic evidence in the
424 interpretation of existing clinical evidence by evidence-users such as physicians. That being said,
425 it is worth pointing out that mechanistic evidence runs in the same issues with
426 underdetermination and interpretive variability. It is not a complete solution, yet incorporating

427 other forms of knowledge does provide us with a much more complex and nuanced
428 appreciation of clinical reasoning and clinical judgment.
429

430 **Conclusion**

431

432 We do not seek to reject EBM but rather acknowledge a central limitation, in that it does not
433 adequately capture what physicians do when they apply “best evidence” in the course of
434 clinical decision-making. Physicians do not simply follow best evidence, even in the most holistic
435 sense that would integrate patient values and preferences. Why? Because the process by which
436 physicians interact with evidence and decisions is more complex, dependent upon epistemic
437 and ethical evaluations of diagnosis, prognosis, treatments, and evidence for treatments.
438 Results of clinical trials are insufficient to explain treatment decisions. Variation in medical
439 decisions surrounding the same clinical scenario cannot always be traced back to a lack of
440 significant results from clinical trials, or the availability thereof.

441

442 Should physicians merely apply “best” evidence? Is the variation often seen desirable in any
443 way? Those are important and not straightforward questions that we raised but did not
444 attempt to answer in this paper. Yet, if proponents of EBM are serious when they assert that
445 “The main challenge for EBM remains how to develop a coherent theory of decision making”
446 [1], then such a theory should recognize that research evidence interacts intimately with a
447 physician’s belief system, characterized by values, background knowledge and experiential
448 skills. EBM perhaps over-emphasizes methodological ways to mitigate biases in research
449 studies. Our descriptive account of acute-stroke decision-making suggests we should shift our
450 focus from producing more evidence to defining the intricate assumptions that characterize
451 physician’s use (or lack thereof) of evidence in order to develop a robust account of clinical
452 judgement.

453

454 The benefit of unmasking the assumptions, norms, and values at play in scientific inquiry is that
455 we can now address the important socio-political question of which values ought to enter the
456 scientific arena [6]. By embracing and acknowledging values and exploring them seriously, we
457 anticipate (as others before us) that EBM will achieve a more mature, and socially useful status
458 [39].

- 460 [1] Djulbegovic B, and Guyatt GH. Progress in Evidence-Based Medicine: A Quarter Century On.
461 The Lancet 2017;390(10092):415–23.
- 462 [2] Sackett DL. Evidence-based medicine. Semin Perinatol 1997;21(1):3–5
463
- 464 [3] Haynes RB, Devereaux PJ, Guyatt GH. Physicians' and patients' choices in evidence based
465 practice. BMJ. 2002;324(7350):1350.
- 466 [4] Wieringa S, Engebretsen E, Heggen K, and Greenhalgh T. Has Evidence-Based Medicine Ever
467 Been Modern? A Latour-Inspired Understanding of a Changing EBM. Journal of Evaluation in
468 Clinical Practice 2017;23(5):964–70.
- 469 [5] Upshur R. Seven characteristics of medical evidence. Journal of Evaluation in Clinical Practice
470 2000;6(2):93-97.
- 471 [6] Goldenberg MJ. On Evidence and Evidence-Based Medicine: Lessons from the Philosophy of
472 Science. Social Science & Medicine 2006;62(11):2621–32.
- 473 [7] Pound P, Bury M, and Ebrahim S. From apoplexy to stroke. Age and Ageing 1997;26: 331-
474 337.
- 475 [8] Dewar B, Shamy M. tPA for Acute Ischemic Stroke and Its Controversies: A Review. The
476 Neurohospitalist 2020;10(1):5-10.
- 477 [9] The National Institute of Neurological Disorders and Stroke (NINDS) r-tPA Study Group.
478 Tissue Plasminogen Activator for Acute Ischemic Stroke, The New England Journal of Medicine
479 1995;333:1581-1587.
- 480 [10] Hacker W et al. (ECASS Investigators). Stroke treatment with alteplase given 3.0–4.5 h after
481 onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a
482 randomised controlled trial. Lancet Neurology 2009;8:1095-1102.
- 483 [11] Sandercock P, Lindley R, Wardlaw J, Dennis M, Lewis S, Venables G, et al. Third
484 international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke. Trials 2008;9:37
485
- 486 [12] Lansberg MG, Bluhmki E, Thijs VN. Efficacy and safety of tissue plasminogen activator 3 to
487 4.5 hours after acute ischemic stroke: a meta-analysis. Stroke. 2009; 40(7): 2438–2441.
488
- 489 [13] Lindsay P, Bayley M, Hellings C, Hill M, Woodbury E, Phillips S. Canadian best practice
490 recommendations for stroke care (updated 2008). CMAJ. 2008;179(12):S1-S25.

- 491 [14] Bhatt A, Safdar A, Chaudhari D, Clark D, Pollak A, Majid A, Kassab M. Medicolegal
492 Considerations with Intravenous Tissue Plasminogen Activator in Stroke: A Systematic Review.
493 Stroke Research and Treatment.2013;562564:6p.
- 494 [15] Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM. Utilization of
495 Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke. Archives of Neurology
496 2004;61:346-350.
- 497 [16] Katzan IL, Sila CA, Furlan AJ and HowseDC. 2001. "Community Use of Intravenous Tissue
498 Plasminogen Activator for Acute Stroke: Results of the Brain Matters Stroke Management
499 Survey," Stroke 32 : 861-865.
- 500 [17] Shamy MCF, and Jaigobin CS. The Complexities of Acute Stroke Decision-Making: A Survey
501 of Neurologists. Neurology 2013;81: 1130-1133.
- 502 [18] Brown DL, Barsan WG, Lisabeth LD, Gallery ME, Morgenstern LB. Survey of Emergency
503 Physicians About Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke. Annals
504 of Emergency Medicine 2005;46:56-60.
- 505 [19] Chan YF, Kwiatkowski TG, Rella JG, Rennie WP, Kwon RK, Silverman RA. Tissue Plasminogen
506 Activator for Acute Ischemic Stroke: A New York City Emergency Medicine Perspective. The
507 Journal of Emergency Medicine 2005;29:405-408.
- 508 [20] Scott PA, Xu Z, Meurer WJ, Frederiksen SM, Haan MN, Westfall MW, Kothari SU,
509 Morgenstern LB, Kalbfleisch JD. Attitudes and Beliefs of Michigan Emergency Physicians Toward
510 Tissue Plasminogen Activator Use in Stroke: Baseline Survey Results From the INcreasing Stroke
511 Treatment through Interactive behavioral Change Tactic (INSTINCT) Trial Hospitals. Stroke 2010;
512 41: 2026-2032.
- 513 [21] Harris D et al. Canadian Association of Emergency Physicians position statement on acute
514 ischemic stroke. CJEM. 2015;17(2):217-26.
- 515 [22] Mann J. Emergency Physician Survey: Recombinant Tissue Plasminogen Activator for
516 Stroke. Annals of Emergency Medicine 2006;48:476.
- 517 [23] Radecki. "My ACEP tPA Policy Critique," published online at
518 www.emlitofnote.com/2014/02/my-acep-tpa-policy-critique.html, (accessed April 15, 2014).
- 519 [24] ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with
520 early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials.
521 Lancet 2004;363:768-774.
- 522 [25] Lyden PD. The Ischemic Penumbra and Neuronal Salvage, in Thrombolytic Therapy for
523 Stroke.Totowa, NJ: Humana. 2001:43.

- 524 [26] Kothari R, Pancioli A, Brott T, Broderick J. Thrombolytic Therapy for Cerebral Infarction.
525 Academic Emergency Medicine 1996;3: 881-892.
- 526 [27] Thomas SH, Schwamm LH, Lev M. Case 16-2006: A 72-Year-Old Woman Admitted to the
527 Emergency Department for Change in Mental Status, New England Journal of Medicine
528 2006;354: 2263-2271.
- 529 [28] Khaja, AM. Acute Ischemic Stroke Management: administration of thrombolytics.
530 Neurology Clinics 2008;26:943-961.
- 531 [29] Milne K. SGEM #85: Won't get fooled again (TPA for CVA). Podcast. 2014. Accessed at:
532 <https://www.thesgem.com/2014/09/sgem85-wont-get-fooled-again-tpa-for-cva/>
- 533 [30] EMCrit Blog. Podcast 116 — the tPA for Ischemic Stroke Debate, emcrit.org/podcasts/tPA-
534 for-ischemic-stroke-debate, (accessed on March 14, 2014).
- 535 [31] Berkhemer OA et al. (MR CLEAN Investigators). A Randomized Trial of Intraarterial
536 Treatment for Acute Ischemic Stroke. N Engl J Med. 2015; 372:11-20.
537
- 538 [32] Goyal M et al. (ESCAPE Trial Investigators). Randomized Assessment of Rapid Endovascular
539 Treatment of Ischemic Stroke. N Engl J Med. 2015; 372:1019-1030.
540
- 541 [33] Chelsea SK et al. (MR.RESCUE Investigators). A Trial of Imaging Selection and Endovascular
542 Treatment for Ischemic Stroke. N Engl J Med 2013; 368:914-923
543
- 544 [34] Broderick JP et al. (IMS III Investigators). Endovascular Therapy after Intravenous t-PA versus
545 t-PA Alone for Stroke. N Engl J Med 2013; 368:893-903
546
- 547 [35] Ciccone A et al. (SYNTHESIS Expansion Investigators). Endovascular Treatment for Acute
548 Ischemic Stroke. N Engl J Med 2013; 368:904-913
- 549 [36] Upshur, R. Certainty, probability and abduction: why we should look to C.S. Peirce rather
550 than Gödel for a theory of clinical reasoning. Journal of Evaluation in Clinical Practice
551 1997;3(3):201-206
- 552 [37] Upshur, R. and Goldenberg, M. Countering medical nihilism by reconnecting facts and
553 values. Studies in History and Philosophy of Science (Article in Press). 2020.
- 554 [38] Goldenberg MJ. Iconoclast or Creed?: Objectivism, Pragmatism, and the Hierarchy of
555 Evidence. Perspectives in Biology and Medicine 2009;52(2):168-87.
- 556 [39] Kelly MP, Heath I, Howick J, and Greenhalgh T. The Importance of Values in Evidence-Based
557 Medicine. BMC Medical Ethics 2015;16(1):69.

558 [40] Boissy AR. IV tissue plasminogen activator use in acute stroke: What are neurologists
559 thinking? *Neurology*. 2013; 81(13):1110-1
560

561 [41] Douglas, H. Inductive risk and values in science. *Philosophy of Science* 2000;67(4):559-579

562 [42] Douglas H. Values in Science. *The Oxford Handbook of Philosophy of Science*. 2016.

563 [43] Stanford K. Underdetermination of Scientific Theory. *The Stanford Encyclopedia of*
564 *Philosophy* (Winter 2017 Edition), Edward N. Zalta (ed.), URL =
565 <<https://plato.stanford.edu/archives/win2017/entries/scientific-underdetermination/>>

566 [44] Fausto-Sterling A. *Myths of gender: Biological theories about women and men*. New York,
567 NY: Basic Books. 1985.

568 [45] Harding SG. *The science question in feminism*. Ithaca, NY: Cornell University Press. 1986.

569 [46] Harding SG. *Whose science? Whose knowledge?* Ithaca, NY: Cornell. 1991.

570 [47] Nelson LH. *Who knows: From Quine to a Feminist Empiricism*. Philadelphia. 1990.

571 [48] Longino H. *Science as social knowledge: Values and objectivity in scientific inquiry*.
572 Princeton: Princeton University Press. 1990.

573 [49] Karantzoulis S, Randolph C. Modern Chronic Traumatic Encephalopathy in Retired Athletes:
574 What is the Evidence? *Neuropsychological Reviews* 2013;4:350-360.

575 [50] Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M,
576 Kwakkel G. What Is the Evidence for Physical Therapy Poststroke? A Systematic Review and
577 Meta-Analysis. *PLOS One* 2014;9:1-33.

578 [51] Wraith DC, Goldman M, Lambert PH. Vaccination and Autoimmune Disease: What is the
579 Evidence? *The Lancet* 2003;362:1659-1666.

580 [52] Whiteley W, Sandercock P, Wardla J, Lindley R. Uncertainties About Thrombolysis for
581 Stroke Should Be Addressed With Large-Scale Randomized Trials. *Stroke* 2006;37: 2662.

582 [53] Clarke B, Gillies D, Illari P, Russo F, and Williamson J. Mechanisms and the Evidence
583 Hierarchy. *Topoi* 2014;33(2):339-60.
584

585 [54] Nardini C, Annoni M, and Schiavone G. Mechanistic Understanding in Clinical Practice:
586 Complementing Evidence-Based Medicine with Personalized Medicine: Mechanistic
587 Understanding in Clinical Practice. *Journal of Evaluation in Clinical Practice* 2012;18(5):1000-
588 1005.

589 [55] Smith G, and Pell JP. Parachute Use to Prevent Death and Major Trauma Related to
590 Gravitational Challenge: Systematic Review of Randomised Controlled Trials. BMJ: British
591 Medical Journal 2003;327(7429):1459–61.

592

593 [56] Parkkinen VP, Wallmann C, Wilde M, et al. Evaluating Evidence of Mechanisms in Medicine:
594 Principles and Procedures [Internet]. Cham (CH): Springer;Chapter 1,Introduction. 2018.

595