

The Post-traumatic Confusional State: A Case Definition and Diagnostic Criteria

Mark Sherer, Ph.D.¹, Douglas I. Katz, MD², Yelena G. Bodien, Ph.D.³, David B. Arciniegas, MD⁴, Cady Block, Ph.D.⁵, Sonja Blum, MD⁶, Matt Doiron⁷, Kim Frey⁸, Joseph T. Giacino, Ph.D.⁹, Min Jeong P. Graf, MD¹⁰, Brian Greenwald, MD¹¹, Flora M. Hammond, MD¹², Kathleen Kalmar, Ph.D.¹³, Jacob Kean, Ph.D.¹⁴, Marilyn F Kraus, MD¹⁵, Risa Nakase- Richardson, Ph.D.¹⁶, Shital Pavawalla, Ph.D.¹⁷, Amy Rosenbaum, Ph.D.¹⁸, Donald T. Stuss, Ph.D.¹⁹, Stuart A. Yablon, MD²⁰

Affiliations: ¹ TIRR Memorial Hermann, ² Department of Neurology Boston University School of Medicine, ³ Department of Neurology Massachusetts General Hospital, Harvard Medical School, ⁴ Marcus Institute for Brain Health University of Colorado School of Medicine, ⁵ Ohio State University Wexner Medical Center, ⁶ New York University Langone Department of Neurology, ⁷ Spaulding Rehabilitation Hospital, ⁸ Department of Speech-Language Pathology Craig Hospital, ⁹ Spaulding Rehabilitation Hospital, ¹⁰ Hennepin Healthcare, ¹¹ JFK Johnson Rehabilitation Institute, ¹² Department of Physical Medicine and Rehabilitation Indiana University School of Medicine, ¹³ JFK Johnson Rehabilitation Institute, ¹⁴ Department of Population Health University of Utah, ¹⁵ George Washington University Medical Center, ¹⁶ Mental Health and Behavioral Sciences James A. Haley Veterans Hospital, ¹⁷ Department of Neurology University of California Los Angeles, ¹⁸ Park Terrace Care Center, ¹⁹ Rotman Research Institute, ²⁰ Mary Free Bed Rehabilitation Hospital

This is the author's manuscript of the article published in final edited form as:

Sherer, M., Katz, D. I., Bodien, Y. G., Arciniegas, D. B., Block, C., Blum, S., Doiron, M., Frey, K., Giacino, J. T., Graf, M. J. P., Greenwald, B., Hammond, F. M., Kalmar, K., Kean, J., Kraus, M. F., Richardson, R. N., Pavawalla, S., Rosenbaum, A., Stuss, D. T., & Yablon, S. A. (2020). The Post-traumatic Confusional State: A Case Definition and Diagnostic Criteria. Archives of Physical Medicine and Rehabilitation. <https://doi.org/10.1016/j.apmr.2020.06.021>

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None of the authors have any financial conflicts of interest to report for this work.

Corresponding Author: Mark Sherer, Ph.D., ABPP, Associate Vice President for Research, TIRR Memorial Hermann, 1333 Moursund, Houston TX77030. Mark.Sherer@memorialhermann.org.

Acknowledgement

This case definition was developed under the ACRM Evidence and Practice Committee (ACRM EPC), which is supported by unrestricted grants from CARF International and Paradigm. Neither CARF International nor Paradigm were involved in any phase of the development of this case definition.

Preparation of this manuscript was partially supported by National Institute of Disability, Independent Living, and Rehabilitation Research grant # 90DPTB0016.

NIDILRR is a Center within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this publication do not necessarily represent the policy of NIDILRR, ACL, or HHS, and you should not assume endorsement by the Federal Government.

Portions of this manuscript were presented at the annual meetings of the ACRM (2015-2019) and the 4th Federal Interagency Conference on Traumatic Brain Injury (2018).

This special article was approved by the ACRM EPC on June 19, 2020 and by the American Congress of Rehabilitation Medicine Board of Governors on July 2, 2020 and published in the Archives of Physical Medical Rehabilitation. The Archives of Physical Medicine and Rehabilitation was responsible for the peer review of this article.

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The authors wish to give special acknowledgement to our coauthor Donald T. Stuss, PhD, OC, OOnt, FRSC, FCAHS, 1941-2019, for his contribution, wisdom and guidance on this paper. His previous work served as a foundation for research on PTCS and he was such an important inspiration and mentor to so many in neuroscience and neuropsychology.

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Correspondence to ACRM info@ACRM.org

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Abstract

In response to the need to better define the natural history of emerging consciousness after traumatic brain injury (TBI) and to better describe the characteristics of the condition commonly labeled Post-traumatic Amnesia, a case definition and diagnostic criteria for the Post-traumatic Confusional State (PTCS) were developed. This project was completed by the Confusion Workgroup of the American Congress of Rehabilitation Medicine Brain Injury Interdisciplinary Special Interest group. The case definition was informed by an exhaustive literature review and expert opinion of workgroup members from multiple disciplines. The workgroup reviewed 2,466 abstracts and extracted evidence from 44 articles. Consensus was reached through teleconferences, face-to-face meetings, and three rounds of modified Delphi voting. The case definition provides detailed description of PTCS (1) core neurobehavioral features, (2) associated neurobehavioral features, (3) functional implications, (4) exclusion criteria, (5) lower boundary, and (6) criteria for emergence. Core neurobehavioral features include disturbances of attention, orientation, and memory as well as excessive fluctuation. Associated neurobehavioral features include emotional and behavioral disturbances, sleep-wake cycle disturbance, delusions, perceptual disturbances and confabulation. The lower boundary distinguishes PTCS from the minimally conscious state while upper boundary is marked by significant improvement in the four core and five associated features. Key research goals are establishment of cut-offs on assessment instruments and determination of levels of behavioral function that distinguish persons in PTCS from those who have emerged to the period of continued recovery.

24 Keywords: Traumatic Brain Injury, Post-traumatic Confusional State, Post-traumatic

25 Amnesia, Confusion, Delirium, evidence-based, Delphi process, case definition

26

27 Abbreviations:

28 DoC – Disorders of Consciousness

29 CAP -- Confusion Assessment Protocol

30 DRS-98 – Disability Rating Scale

31 MCS – Minimally Conscious State

32 TBI – Traumatic Brain Injury

33 VS – Vegetative State

34 PTA – Post-traumatic Amnesia

35 PTCS – Post-traumatic Confusional State

36 UWS – Unresponsive Wakefulness Syndrome

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41

42 **Introduction**

43 Traumatic brain injury (TBI) is characterized by disturbed consciousness.¹ The degree
44 of disturbance of consciousness and the time course of recovery can vary, depending
45 on the type and severity of the injury. Those with mild injuries may have brief alterations
46 of consciousness that may or may not involve complete loss of consciousness. Patients
47 who survive severe TBI and recover consciousness, typically continue to improve to
48 states of more intact awareness. A nomenclature has been established to designate the
49 clinical conditions that can occur as consciousness recovers, including *coma*, *vegetative*
50 *state (VS)* (also termed *unresponsive wakefulness syndrome [UWS]*)², and *minimally*
51 *conscious state (MCS)*.^{3, 4} The clinical signs and criteria that define these conditions
52 have been established.³ This information is summarized in Table 1. Conversely, the
53 clinical condition observed as patients with disorders of consciousness (DoC) transition
54 to a level of consciousness higher than MCS is less well-defined and has various labels
55 including *emerged from MCS*, *Post-traumatic Amnesia (PTA)*,⁵ *traumatic delirium*,⁶ and
56 *Post-traumatic Confusional State (PTCS)*.⁷ Depending on severity of injury or differing
57 pathophysiology, this same clinical condition may be observed in patients with various
58 patterns of recovery after TBI. For example, it may occur immediately after injury,
59 without a period of unconsciousness or minimal consciousness, or in the setting of
60 deteriorating consciousness after a lucid interval.⁸

61

62 What is the clinical state of patients who have emerged from MCS? Clinical observation
63 of these patients indicates that they are not fully recovered either cognitively or

64 behaviorally. While these patients respond in a manner that indicates increased
65 awareness of self and the environment compared to MCS, it is apparent that
66 consciousness remains compromised, as indicated by impaired cognition, decreased
67 social and physical awareness, misinterpretation of social and environmental context,
68 and inappropriate or unsafe behaviors.⁹⁻¹¹

69

70 Early characterizations of this clinical state described a broad range of deficits in
71 attention, memory, orientation, and judgment, along with irritability, perceptual
72 disturbances, and agitation.¹ Some clinicians and researchers use the term PTA for the
73 clinical state characterized by these various neurobehavioral signs.⁵ Others define PTA
74 by emphasizing the anterograde amnesia observed in early recovery from TBI over the
75 other cognitive and behavioral findings. Indeed, assessment of PTA has primarily
76 focused on disorientation to time, place, and situation along with impairment of
77 recognition memory as indicated by the Galveston Orientation and Amnesia Test and
78 the Westmead Post-traumatic Amnesia Scale, measures frequently used to evaluate
79 PTA.¹²⁻¹⁴ Inconsistency in the definition of PTA used by clinicians and investigators
80 may lead to confusion while, uniform nomenclature with greater clarity of diagnostic
81 criteria will improve clinical understanding and research.

82

83 Here, we present a case definition for this condition that was developed by synthesizing
84 empirical evidence and expert opinion. We also describe the key clinical features. We
85 have chosen the term, *Post-traumatic Confusional State (PTCS)* over Post-traumatic
86 Amnesia (PTA) to emphasize the wide range of neurobehavioral features associated

87 with this condition. In 1999, Stuss et al.⁷ introduced the term PTCS and proposed that
88 PTCS was a more descriptive label than PTA for this period of recovery following TBI.
89 Stuss et al. proposed that impaired attention was the key cognitive deficit seen in
90 PTA/PTCS rather than anterograde amnesia and that in the less severe TBI patients,
91 disturbed attention may be the primary cause of the memory disturbance. These
92 investigators noted the similarity between PTCS and acute confusion or delirium.

93

94 To establish a case definition of PTCS and to distinguish the terms PTA and PTCS, the
95 Confusion Workgroup of the American Congress of Rehabilitation Medicine Brain Injury
96 Interdisciplinary Special Interest Group conducted a comprehensive review of the
97 empirical literature on PTA and PTCS and integrated these findings with a broad survey
98 of expert opinion. We believe that a case definition will contribute to several goals: (1)
99 improved understanding of the natural history of recovery from TBI, (2) improved
100 classification and uniformity of nomenclature for clinical and research purposes (3)
101 improved prognostication with better characterization of the recovery of the
102 neurobehavioral manifestations of PTCS, (4) development of structured assessments
103 that fully address the phenomenology of PTCS, (5) pursuit of a research agenda
104 including determining functional implications of PTCS, defining clinical subtypes of
105 PTCS, understanding the pathophysiologic underpinnings of PTCS, improving
106 rehabilitation management and evaluating potential treatments, and (6) comparison of
107 confusion resulting from TBI to delirium resulting from other causes.

108

109 With these goals in mind, we developed a case definition to achieve four objectives:

110

111 **(1) Clinical Features/Case Ascertainment.** The case definition provides a description
112 of the observable elements of PTCS that is sufficiently detailed to support diagnosis
113 based on clinical evaluation while also informing selection of existing measures that are
114 most useful in assessing patients at risk for PTCS. Ideally, this degree of detail supports
115 development of improved measures that provide reliable and reproducible diagnosis
116 and clinical characterization.

117

118 **(2) Description of the Pattern of Resolution of Signs of PTCS.** Previous findings
119 suggest that some signs of PTCS may resolve before others while some signs are
120 related so that resolution of one occurs close in time to resolution of the other.¹⁵
121 Improved understanding regarding these patterns of recovery may inform prognosis and
122 treatment.

123

124 **(3) Description of Functional Status.** Just as the transition from MCS to emerged
125 from MCS is described in terms of functional abilities (consistent and correct yes/no
126 answers to simple questions, correct demonstration of use of a functional object), there
127 should be functional capabilities shown by those whose confusion is resolved as
128 compared to those who remain in PTCS. Clear determination of how non-confused
129 patients are more functional than confused patients will support consistent classification,
130 indicate ability to benefit from continued therapies, and have implications for supervision
131 needs.

132

133 **(4) Comparison of PTCS to Delirium caused by other Etiologies.** Delirium is a
134 relatively common occurrence in hospitalized patients. Deliria resulting from etiologies
135 other than TBI differ from PTCS in phenomenology, duration, pattern of recovery, and
136 implications for long-term prognosis. A detailed case definition of PTCS will facilitate
137 comparison of confusion in recovery from TBI to deliria of various causes.

138

139 Below, we describe our approach to developing the case definition of PTCS and present
140 the clinical features, upper and lower boundaries, patterns of recovery, and functional
141 implications of this syndrome. We also describe how PTCS differs from deliria resulting
142 from other etiologies.

143

144 **Methods**

145 *Evidence Review*

146 The Confusion Workgroup consisted of all authors of the case definition. The
147 Workgroup included seven neuropsychologists, six physiatrists, two behavioral
148 neurologists/neuropsychiatrists, two neuroscientists, and two speech language
149 pathologists. These members met in-person and via teleconference from 2012 to 2019.
150 Key in-person meetings were held at American Congress of Rehabilitation Medicine
151 annual conferences from 2013 through 2017 and at the Galveston Brain Injury
152 Conference in 2017 and 2018.

153

154 In developing the case definition of PTCS, we focused on areas of impairment (e.g.,
155 attention, memory, orientation, fluctuation, sleep disturbance, decreased arousal,

156 agitation, and psychotic-type symptoms) as well as the lower boundary, upper
157 boundary, functional implications, and patterns of recovery. Given the long history of the
158 use of the term PTA prior to the development of PTCS, we accepted articles about PTA
159 as providing evidence regarding PTCS. We extracted data from articles in three phases.
160 First, we conducted an Ovid Medline literature search beginning in 1946 (the publication
161 date of the earliest articles indexed by OVID Medline) for abstracts published through
162 2013. We used the search criteria and keywords presented in the Supplementary
163 Materials (Supplementary Table 1). In 2018 we conducted an additional abstract search
164 for articles published from 2013 through 2017. We overlapped these reviews by several
165 months to ensure no articles were missed. Finally, we reviewed articles that were not
166 previously captured by the two abstract searches if they were identified as potentially
167 relevant to the case definition by the review teams based upon the reference sections of
168 articles retained in the first two phases. We followed the following procedure for each
169 abstract and article review:

170

- 171 1. Teams of two independent raters reviewed abstracts and determined whether each
172 abstract met the abstract inclusion criteria outlined in the Supplementary Materials
173 (Supplementary Table 2) and rated the abstracts according to the categories described
174 in the Supplementary Table 3.
- 175 2. Once all abstract reviews were completed, each pair of reviewers was unmasked and
176 reconciled their ratings for abstracts.
- 177 3. For abstracts marked as “retained” after reviewer reconciliation, teams of two
178 reviewers extracted data from the full-text articles using an online standardized form

179 (Supplementary Materials).

180 4. Information from the data extraction forms was compiled into evidence tables by the
181 first three authors (YGB, DIK, MS).

182

183 *Developing the Case Definition*

184 After the first phase of article review, and following extensive in-person and telephone
185 discussions by the Workgroup regarding the clinical presentation of confusion after TBI,
186 a subgroup (DIK, YGB, MS) of the authors developed the first draft of a six-part PTCS
187 case definition by integrating evidence from the article reviews with expert opinion.

188 Additional input from members of the Workgroup, as well as other thought leaders in
189 brain injury research and clinical care invited to the 2017 Galveston Brain Injury

190 Conference, was incorporated into the draft case definition during a session dedicated
191 to this topic. Utilizing a modified Delphi procedure, each of the six components of the

192 draft case definition was submitted to the entire author group for individual votes. The

193 modified Delphi follows a procedure commonly used to achieve expert group consensus
194 in medical science and other fields using rounds of voting, with summary of comments

195 from each participant provided anonymously back to all participants.¹⁶ Four of the six

196 components were approved on the first vote by receiving endorsement by 80+% of the

197 author group, the threshold agreed at the start of the process. Based on written

198 feedback provided as part of the vote, the other two components were edited and

199 submitted for a second vote. A fifth component received endorsement on the second

200 vote, performed online. The final component was again edited and this remaining

201 component was endorsed by the third vote, performed online. Findings from articles

202 included in our review that were published after 2013 were reviewed by a subgroup of
203 the authors and found to support the language approved by the Delphi process; thus no
204 changes were made to the definition.

205

206 **Results**

207 *Evidence Review*

208 During the first round of abstract and article reviews (published through 2013), the
209 literature search yielded 1757 abstracts, from which 154 were retained for full-
210 manuscript review. Of these 154, 53 articles met all inclusion criteria. The second
211 literature search for 2013-2017, identified 649 additional abstracts. We reviewed 14
212 articles and retained 6 that met all inclusion criteria. During the final round of review
213 (i.e., abstracts identified during the review of publication references), 60 abstracts were
214 reviewed with 13 retained. Full article reviews indicated that 10 articles met all inclusion
215 criteria. In sum, we reviewed 2,466 abstracts and 181 full text articles. Sixty-nine articles
216 met all inclusion criteria and, of these, 44 contributed directly to the evidence presented
217 in Supplementary Materials (Supplementary Tables 4-16). PTCS phenomenology was
218 best represented with 34 articles addressing various signs of confusion (Figure 1).

219

220 In the articles that addressed one or more aspects of confusion, the 4 core
221 neurobehavioral features were evident in most individuals in PTCS. In articles that
222 addressed at least 6 neurobehavioral features of PTCS, 90% to 100% had impairments
223 on cognitive measures that primarily assessed attention and some aspects of new
224 learning. Orientation was impaired in 89% to 95% and fluctuation was observed in 97%

225 to 100% (Supplementary Tables 4 - 7). Longitudinal data indicate that features of PTCS
226 may be present in patients who no longer meet criteria for PTCS (Supplementary
227 Tables 4-11). The severity of these remaining features may be decreased and no longer
228 sufficient to cause functional limitations at the level present in PTCS. A study using the
229 Confusion Assessment Protocol as a measure of PTCS found that some persons
230 emerged from PTCS remained with some of the 4 core features. However, the
231 occurrence of these feature was markedly reduced; of persons who emerged from
232 PTCS, only 35% remained with attention or memory impairment, 0% with disorientation,
233 and 45% with fluctuation.¹⁷

234

235 In articles that addressed multiple neurobehavioral features of PTCS, concurrent clinical
236 features were also observed in many patients. Greater impairment of core features of
237 PTCS such as memory and orientation was generally associated with a greater number
238 of additional features such as emotional and/or behavioral disturbances and sleep-wake
239 cycle disturbance. Behavioral and emotional dysregulation was evident in 53% to 72%
240 (Supplementary Table 8). Sleep disturbance and arousal impairment were evident in
241 58% to 83% (Supplementary Table 9). Delusions, hallucinations, or other perceptual
242 disturbances were observed in 46% to 72% (Supplementary Tables 10, and 11).
243 Notably, no articles addressed confabulation as a sign of confusion. However, the
244 Confusion Workgroup reached consensus that it should be included based on clinical
245 experience.

246

247 Only 17 of 34 articles provided evidence for more than one of the 9 features of PTCS

248 described in our Case Definition. Only 3 articles addressed as many as 6 features and
249 none addressed all 9. Consequently, conclusions regarding the co-occurrence of
250 various features depended as much on expert opinion as on evidence.

251

252 Five articles provided evidence on the lower boundary of PTCS while 6 provided
253 evidence regarding the upper boundary. These articles provide a moderate amount of
254 evidence regarding the upper and lower boundaries of PTCS. However, for almost half
255 these papers, diagnosis of PTA was accepted as a proxy for PTCS. The lower
256 boundary for PTCS was largely based on the definition of the upper boundary for MCS³,
257 however some evidence suggested that the criteria for emergence from MCS requiring
258 accurate yes-no responses for all six basic questions might be too stringent.¹⁸ The lower
259 boundary for PTCS was worded to allow some flexibility in determining the return of
260 basic communication. The upper boundary was based on evidence that the 4 core
261 neurobehavioral features occurred at a substantially lower frequency in studies that
262 measured all of these components in individuals who were no longer considered in a
263 PTCS. Other evidence supported that recognition memory and free recall of newly
264 learned information can recover after orientation and should be important components
265 in the defining the upper boundary.⁷

266

267 Ten articles provided evidence on the course of recovery of PTCS. These articles
268 provide preliminary evidence that recovery from PTCS is somewhat systematic with
269 certain signs more likely to resolve before others. One study tracked multiple clinical
270 features longitudinally and found that cognitive impairment and fluctuation were most
271 persistent, while psychotic features and sleep disturbance resolved earliest.¹⁸ One study

272 that measured aspects of attention, orientation and memory found that more demanding
273 attentional tasks, orientation and recognition memory recovered at about the same time
274 but that free recall of words after 24 hour delay recovered later.⁶ However, 7 of the 10
275 articles only assessed PTA so that information regarding the recovery of the broader
276 clinical profile of PTCS is limited (Supplementary Table 15).

277

278 Eleven articles provided general evidence that persons emerged from PTCS are more
279 functional, in both physical and cognitive domains, than those who are in PTCS.
280 However, this evidence was primarily regarding general physical and cognitive
281 functioning and did not allow determination of specific functional tasks that could be
282 used to diagnose PTCS or indicate the level of support and supervision needed by
283 individuals who have emerged from PTCS (Supplementary Table 16).

284

285 *Case Definition*

286 Following three rounds of modified Delphi voting, the group approved the six-part
287 definition of PTCS shown in Table 2. Briefly, the case definition defines the clinical
288 presentation of PTCS as requiring four core features while five associated
289 neurobehavioral features may also be present. Functional abilities in multiple domains
290 are impaired. Diagnosis of PTCS requires serial assessment and cannot be attributed to
291 causes other than head trauma. The lower boundary of PTCS is defined by at least
292 basic functional communication and/or simple, meaningful environmental interactions.
293 The upper boundary of PTCS is defined by significant improvement in the 4 core and 5
294 associated features.

295

296 **Discussion**

297 PTCS commonly occurs after TBI of all severity levels. This condition often follows
298 emergence from lower levels of consciousness, but also occurs with other patterns of
299 recovery, including those without a period of unconsciousness. While historically, the
300 term PTA has been used by some to label this phase of recovery, PTA is better used to
301 indicate the clinical impairments of anterograde amnesia and disorientation following
302 TBI. As defined by this Workgroup, PTCS encompasses multiple domains, including
303 awareness, cognitive capacity, behavioral regulation and the ability to function safely
304 and independently in daily activities and social interactions. The features of impaired
305 memory and orientation that characterize PTA are subsumed in the PTCS case
306 definition and should be considered a component of PTCS.

307

308 *Distinctions between PTCS and other types of delirium*

309 The definition of PTCS recognizes that some features of PTCS and the recovery process
310 are particular to TBI and are distinct from existing diagnostic criteria for delirium or acute
311 confusional state. The PTCS definition includes as features disturbances of attention
312 and awareness, fluctuation, and cognitive impairment that are common core features of
313 all forms of delirium as delineated in the American Psychiatric Association Diagnostic
314 and Statistical Manual of Mental Disorders 5 criteria for delirium.¹⁹ However, the
315 evolving, incremental course of recovery and lower and upper boundaries are specific to
316 PTCS and are not characteristic of other types of delirium. Indeed, the Diagnostic and
317 Statistical Manual - 5 (DSM – 5)¹⁹ criteria exclude “evolving neurocognitive disorder”
318 from the diagnosis of delirium. Anterograde amnesia, with impairment of memory

319 encoding, which is a prominent characteristic of PTCS, is not strongly emphasized in
320 DSM – 5 or other diagnostic criteria for delirium. Although PTCS after TBI is usually a
321 transitional condition leading to higher levels of recovery, delirium of other causes may
322 indicate an acute medical problem that may recover, wax and wane, or portend a grave
323 prognosis.^{20, 21}

324

325 *Features of PTCS*

326 The six-part definition developed by the Confusion Workgroup describes PTCS as a
327 clinical condition that encompasses 4 necessary core features outlined in Table 2:
328 prominent disturbances of attention, orientation, and memory, with marked fluctuation in
329 the cognitive and behavioral manifestations. These core features occur in all those with
330 PTCS but may vary in severity and time course of resolution. There are several other
331 clinical features characteristic of the condition, such as emotional problems, behavioral
332 dysregulation, sleep-wake cycle dysregulation, delusions, perceptual disturbances and
333 confabulation. These may or may not occur in addition to the core features, and they
334 present with varying frequency and severity.

335

336 *Natural History and Lower and Upper Boundaries of PTCS*

337 Evidence from our review indicates that PTCS is one of several stages of recovery that
338 may be seen in persons who sustain moderate and severe TBI. Those with the most
339 severe injuries commonly show a transition from states in which no consciousness can
340 be detected (coma, VS) to a state (MCS) that is characterized by limited, inconsistent
341 consciousness. After resolution of MCS, patients are more aware of themselves and the
342 world around them, but remain with acute confusion and other deficits. PTCS is the next

343 period of disturbed consciousness following coma, VS, and MCS as described by the
344 Aspen Work Group.²² Consequently, emergence from MCS is seen as the lower limit of
345 PTCS.

346

347 The interval from injury to transition to PTCS varies depending on injury severity, and
348 different patterns of anatomic lesions and pathophysiology.⁷ Some patients present in a
349 PTCS right after trauma, without unconsciousness or following a relatively a brief period
350 of loss of consciousness. It is more difficult to specify a lower boundary for these
351 patients. Others have a period of markedly decreased arousal following the injury, due
352 to neurologic effects of the injury or sedation, so that the full syndrome of PTCS is not
353 initially apparent or is difficult to characterize.

354

355 As with coma, VS, and MCS, PTCS duration largely varies with severity of TBI and can
356 range from short periods lasting minutes to hours, to prolonged durations, lasting weeks
357 or months.⁹ For some with very severe injuries, the core features may not fully resolve.
358 Severity and duration of PTCS are determined by various factors such as the
359 pathophysiological profile, secondary complications, age, and cognitive reserve. Greater
360 duration and severity is generally associated with worse long-term outcome.^{23, 24}

361

362 In the most comprehensive study of recovery of cognitive function in patients in
363 confusion to date, Stuss and colleagues⁷ demonstrated that patients with mild to severe
364 TBI showed recovery of orientation before recovery of 3 word recall at a 24 hour delay
365 and that attention on simple tasks recovered earlier than attention on more demanding
366 tasks. Similarly, Baird et al.²⁵ showed that recognition memory generally recovered after

367 resolution of orientation. Recovery of attention occurred concurrently with recovery of
368 orientation and recognition memory. Components of orientation and episodic memory
369 recovered at different rates. Aspects of personal orientation recovered earliest, while
370 recall of date and episodic recall of the last events before injury and first events after
371 injury were the latest to resolve.^{25, 26} Persistence of certain clinical features is more
372 strongly associated with severity and prognosis, perhaps due to differential underlying
373 pathophysiology. For instance, psychotic features, including delusions and
374 hallucinations, are more prevalent with greater severity of PTCS and indicate less
375 favorable prognosis for return to employment.¹⁵

376
377 Although individual features of PTCS may not fully normalize, with resolution of PTCS,
378 improvements in cognitive and behavioral capacity support improved ability to perform
379 activities of daily living and engage in social interactions. Safety concerns, level of
380 dependence and need for supervision lessen considerably.^{27, 28} Although cognitive
381 function improves significantly with resolution of PTCS, residual cognitive impairments
382 in aspects of attention, memory retrieval and executive functioning are common.¹⁵ More
383 profound residual impairments may be labeled by the domain(s) affected – e.g. aphasia,
384 amnesia, dysexecutive syndrome. There is no clear consensus on what to label the
385 condition if all 4 core features are still severely affected over the long term, or how to
386 mark the transition from PTCS to a residual multi-domain cognitive dysfunctional
387 condition. Possible labels include, chronic PTCS, post-traumatic dementia, and
388 persisting 'major neurocognitive disorder' per DSM - 5 criteria.¹⁹

389

390 *Functional Implications of PTCS*

391 For those in PTCS, impairments of attention, orientation, memory, and consistency of
392 behavior are so severe that the patient's functional independence is limited (Table 2,
393 Row 3). Resolution of PTCS is associated with improvements in attention, orientation,
394 memory, and consistency of behavior that are sufficient to result in greater functional
395 independence. However, unlike MCS, in which two specific behaviors provide evidence
396 that a person has emerged, there is no generally agreed upon level of functional ability
397 that indicates resolution of confusion. This is because the range of behaviors exhibited
398 by confused patients is substantially greater than for those in MCS and the variety of
399 social contexts in which these behaviors can be manifested is also substantially greater.
400 Additionally, measurement of improvement in the degree of confusion is not precise due
401 to shortcomings of current assessments.

402

403 At this point, there are no agreed upon cut-offs for the amount of improvement needed
404 to indicate that a patient is no longer in PTCS. Table 2, Row 6 provides some examples
405 of the degree of improvement that could be taken as evidence that PTCS has resolved.
406 These guidelines are related to the four core features as opposed to behaviors that
407 would occur in naturalistic settings. One could imagine more specific behavioral indices
408 of resolution of confusion such as (1) able to stay at home for periods up to 8 hours with
409 no safety concerns, (2) able to carry on an appropriate conversation with a stranger
410 even if mildly provoked by negative statements made by the stranger, or (3) able to
411 prepare a simple meal with no risk of fire or other safety issue, etc.

412

413

414 *Implications for Measurement of PTCS for Clinical and Research Purposes*

415 One key aim in developing a case definition for PTCS was to improve diagnostic
416 accuracy and reliability of assessment of PTCS for clinical and research purposes.
417 Improved measures will contribute to improved understanding of brain injury recovery,
418 care management, and prognostication. The case definition facilitates monitoring the
419 course of recovery, gauging clinical severity, and identifying clinical patterns and
420 profiles. The definition will guide development of measures to better inform prognosis
421 and clinical management.

422

423 Comprehensive clinical histories and examinations that account for the four core and
424 five associated features will be necessary for accurate diagnosis of PTCS. As has been
425 recommended for diagnostic assessment of other DoCs, serial, standardized
426 neurobehavioral assessments should be used to promote better diagnostic accuracy
427 and characterize the course of the PTCS.²⁹⁻³¹ There should be consideration of
428 confounds, such as aphasia that may compromise the accuracy and sensitivity of any
429 assessment.

430

431 Measures of core features, such as attention, orientation, and memory may include a
432 variety of established, standardized clinical assessments. However, it would be
433 impractical to rely on separate psychometrics for each characteristic of PTCS and best
434 to use assessments that collectively evaluate multiple features of PTCS. Such a
435 measure should account for all core and associated features of the condition, track
436 severity and provide suggested criteria for the upper and lower boundaries of PTCS.
437 The Confusion Assessment Protocol (CAP),¹⁷ partially based on the Delirium Rating

438 Scale-Revised 98 (DRS-98)³² and other standardized measures, was designed to
439 address the broader range of problems identified in delirium after TBI. However, neither
440 the CAP,¹⁷ nor the other currently available measures capture all PTCS features.
441 Limitations of existing tools include: 1) failure to cover all aspects of the definition; 2)
442 unknown reliability and validity; 3) subjective ratings that are vulnerable to bias and
443 inaccuracy; and 4) lack of an established comparative diagnostic reference standard
444 (psychometric, behavioral, biologic, or otherwise).

445

446 Fluctuation, a core feature of the PTCS, is challenging to measure; repeated
447 observation or measurement is required.³³ Individuals who are inconsistent in their
448 neurobehavioral presentation may manifest variability within short intervals or over more
449 prolonged periods. Severe fluctuation can be observed during bedside examination with
450 inconsistencies in presentation noted to occur over the course of minutes. In mild
451 fluctuation, patients manifest variability over longer periods of time. Variability can be
452 observed in level of arousal and/or responsiveness, behavioral disturbance, emotional
453 lability, and cognitive performance (e.g., following instructions, orientation). Significant
454 fluctuation that is consistent with PTCS results in the need for greater supervision as the
455 patient poses a safety risk. Clinician ratings are commonly used to assess fluctuation.
456 Sources of information may include direct observation (e.g., during mental status
457 examination), informant report, and medical record review. Improved standardized
458 measures are needed to assess fluctuation and other associated features PTCS (e.g.,
459 emotional and/or behavioral disturbances, sleep-wake cycle disturbance, delusions,
460 perceptual disturbances and confabulation).

461 One of the key challenges for a standardized measure is defining the upper boundary
462 and resolution of PTCS, recognizing that impairments in some of the core and
463 associated features may still be evident. At present, the best description of the upper
464 boundary of PTCS is the point at which deficits in attention, orientation, memory, and
465 behavioral consistency have improved sufficiently to no longer have major impact on the
466 patient's functional independence for basic self-care and safety awareness.

467 More research is needed to create and validate both psychometric and behavioral
468 referents of emergence from PTCS. As is the strategy in defining resolution of PTCS for
469 the Confusion Assessment Protocol,¹⁷ improvement in combinations of clinical features,
470 some weighted more than others, may better indicate resolution of PTCS rather than
471 specific cutoffs for each domain. Measures of overall function and social competence
472 may also help define PTCS resolution.

473
474 In summary, no current measure assesses the full range of core and additional
475 neurobehavioral deficits seen in PTCS (Table 3). The two measures that are closest to
476 achieving this goal are the CAP¹⁷ and the DRS- 98.³² The CAP includes a mixture of
477 clinician rated items and objective cognitive tests. Assessment of cognition is limited due
478 to failure to assess verbal declarative memory. Among clinician rated scales, agitation is
479 assessed using the Agitated Behavior Scale.³⁴ Authors of the CAP provide criteria for
480 determining whether or not a patient is confused. The DRS-98 consists entirely of
481 clinician rated items and thus the assessment may be less reliable. Further, there are
482 no clear criteria to determining whether a patient is in PTCS. Though flawed, at this
483 point, it appears that the CAP is best measure to assess PTCS.

484

485 *Implications for Treatment*

486

487 Improved characterization of the features of PTCS may result in application of
488 interventions for the various clinical features and promote improved monitoring of the
489 responses to interventions. For persons in PTCS, treatment goals include maintaining
490 safety, preventing secondary complications and restoring functional independence in
491 self-care and mobility. Patients with emotional and/or behavioral disturbances benefit
492 from environmental and behavioral interventions.³⁵ Persons in PTCS with severe
493 amnesia have the potential to acquire skills and improve performance using preserved
494 procedural memory capacity, despite profound deficits in attention and declarative
495 learning.^{36, 37} A recent randomized controlled trial demonstrated significantly greater
496 improvement in functional performance in activities of daily living on the FIM in persons
497 in PTA after severe TBI in the treatment group using retraining strategies based on
498 errorless and procedural learning principles compared to a usual treatment group.³⁸
499 Persons who have emerged from PTCS are particularly strong candidates for active
500 participation in rehabilitation interventions.

501

502 *Limitations and Directions for Future Research*

503 The case definition was derived based on the existing literature and extensive clinical
504 experience. Prior studies have largely focused on memory and orientation impairments
505 associated with PTA and few studies simultaneously examine all of the features of
506 PTCS in this case definition. There was also limited evidence to fully inform the natural
507 history and upper boundary of this condition. The natural history of PTCS has not been
508 fully characterized, as measures used in PTCS research do not capture the full array of

509 core and additional neurobehavioral features. No studies meeting inclusion criteria for
510 this review addressed confabulation and the decision to retain it in the definition was
511 based solely on the consensus of the Workgroup.

512

513 A primary goal for future research is the development of a new instrument for assessing
514 degree and pattern of confusion, with sufficient precision that natural history studies are
515 more feasible and accurate. Accordingly, new measurement tools that assess all
516 features of the PTCS should be validated, including cut-offs for the lower and upper
517 boundaries. The lack of a reference standard or biomarker for PTCS will make it
518 challenging to validate new tools. Research on functional abilities that distinguish
519 confused and non-confused patients may provide additional guidance for assessment.

520

521 Future studies may consider using this case definition to identify subtypes of PTCS and
522 patterns of recovery. The pathophysiologic mechanism of TBI recovery and PTCS
523 remain poorly understood. Identification of biomarkers with relationship to PTCS
524 subtypes, patterns, and prognosis would have substantial clinical and research utility.

525 Use of this case definition should help inform future guidelines for clinical management
526 of PTCS, including maintaining safety, promoting injury prevention, identifying
527 supervision needs, optimizing sleep, and mitigating behavioral dysregulation and
528 perceptual disturbances. This case definition is a new starting point to facilitate more
529 consistent and reliable diagnosis of PTCS for research and clinical purposes. As new
530 evidence emerges and the case definition is tested, revisions to the case definition may
531 be required.

532

534 **Figure Legend**

535

536 Figure 1: Number of articles addressing each domain of the PTCS case definition

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Table 1. Comparison of Clinical Signs of Disorders of Consciousness

Disorder	Consciousness	Sleep/wake Cycles	Command Following	Communication	Cognition	Neurobehavioral Signs	Signs of Transition to Higher Level of Consciousness
Coma	None	Absent	Absent	Absent	None detected	None exhibited	Eye opening ¹
Vegetative State	None	Present, but sleep disturbance and fluctuating arousal common	Absent	Absent	None detected	None exhibited	Visual fixation, localization to noxious stimulation, intelligible verbalizations, yes/no responses even if inaccurate, reproducible movement to command
Minimally Conscious State	Partial	Present, but sleep disturbance and fluctuating arousal common	Inconsistent, if present.	Inaccurate or inconsistent yes/no responses, if present	Some cognitive function can be discerned from command following, communication, etc. but fluctuation makes this difficult to assess	Contingent emotional response to family or familiar stimuli	Functional communication – yes and no responses are accurate and reliable, appropriate functional object use of at least 2 common objects
Post-traumatic Confusional State	Intact for internal states and external events but often does not lead to functional behavior due to disorganization, misinterpretation, etc.	Present, but sleep disturbance and fluctuating arousal common	Usually consistent, but may fluctuate	Ability to communicate generally intact, but social appropriateness and accuracy vary.	Impaired attention and memory, disorientation	Fluctuation in presentation, emotional and/or behavioral disturbance, confabulation, delusions, perceptual disturbances	Ability to attend to and process simple information, general orientation, recall of some recent events, lack of marked cognitive or behavioral fluctuations

¹ While eye opening is commonly accepted as indicating transition from coma to VS, there is no consistent evidence that this transition is associated with an improved level of consciousness

Table 3: Composite measures that assess at least two features of PTCS

Domains	CAP	DRS- R98	CAM	CTD	TOTART	NBRS	GOAT
Attention	P	O	O	P	P	O	NA
Memory	P	O	O	P	P	NA	P
Disorientation	P	O	O	P	P	O	P
Symptom fluctuation	O	O	O	NA	NA	NA	NA
Behavioral disturbance	O	O	O	NA	NA	O	NA
Sleep-wake cycle disturbance	O	O	O	NA	NA	O	NA
Confabulation	NA	NA	NA	NA	NA	NA	NA
Delusions	O	O	NA	NA	NA	O	NA
Perceptual disturbance	O	O	O	NA	NA	O	NA

Abbreviations:

P: performance-based, O: observational, NA: not assessed

CAP: Confusion Assessment Protocol⁴¹, DRS-R98: Delirium Rating Scale-Revised 98⁴⁴,

CAM: Confusion Assessment Measure⁴⁶, CTD: Cognitive Test for Delirium⁴⁷, TOTART:

Toronto Test of Acute Recovery After TBI⁶, NBRS: Neurobehavioral Rating Scale⁴⁸,

GOAT: Galveston Orientation and Amnesia Test¹⁵

Figure 1

