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Postoperative Neurocognitive Disorders: the Legacy of Almost 400 Years of History (Review)

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Summary

The history of the study of postoperative neurocognitive disorders (PND) looks as a long and thorny path of more than 400 years. Despite all accumulated data on PND risk factors and outcomes, there's still no complete understanding of the etiology and pathogenesis of this complication. Moreover, current anesthesiology-resuscitation practice still faces challenges and has pending questions in diagnosis and classification of postoperative neurocognitive disorders.

The purpose of the review. To contemplate the evolution in the perceptions of the international medical community (IMC) regarding diagnostic approaches and algorithms in PND management. The review covers the history of development of such PND concepts as postoperative delirium, postoperative cognitive dysfunction, emergence agitation and emergence delirium. Also, the pre-existing and current international classifications of postoperative neurocognitive disorders are discussed in chronological order, supplemented by the analysis of their strengths and weaknesses. The paper also delves into current viewpoints concerning the etiology of particular postoperative neurocognitive disorders, and PND potential relevance for postoperative outcomes.

Conclusion. Current algorithms and modalities used for PND diagnosis, are novel but yet not ultimate for IMC in the context of continuous progress in medical practice. Early postoperative neurocognitive disorders remain the most poorly studied phenomena with no approved definitions and diagnostic modalities to identify. It is probably the time for IMC to undertake a joint effort to find answers to current unresolved questions regarding postoperative neurocognitive disorders.

Keywords: postoperative neurocognitive disorders; delirium; postoperative delirium; emergence delirium; agitations; postoperative cognitive dysfunction; delayed neurocognitive recovery; classifications

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Introduction

When it comes to a history of more than 400 years, it is difficult to expect recovering the exact first mention of a phenomenon. We can only assume that the first mention of acute changes in the consciousness of patients after surgery belong to the writings of Ambroise Paré (16th century). He described these complications as «a transient condition that commonly followed fever and pain due to wounds, gangrene, and operations involving severe bleeding of the patient» [1]. A similar condition, «delirium nervosum», was described by another famous surgeon, Baron de Dupuytren (XIX century): «...and finally the brain itself may be seized by pain, terror, or even joy, and reason abandons the patient at the moment when it is most necessary for his well-being that he remain calm and unperturbed» [2]. Interestingly, the first references to postoperative acute transient changes in consciousness appeared several centuries before the discovery of anesthesia. This fact invalidates the current and rather widespread notion that postoperative delirium has been and remains exclusively an anesthesiological problem.

On the other hand, it would be ridiculous to deny that postoperative neurocognitive disorders (PND) are indeed closely related to anesthesia. In 1887, G. Savage suspected a causal relationship between similar cases of «insanity» and later development of «chronic dementia» after nitrous oxide anesthesia in patients of different age groups [3]. In the same year, the American dentist S. Hayes noted the development of «dementia» as a probable complication of nitrous oxide administration without proper addition of atmospheric air [4]. This was apparently the first time that the «disreputable» role of general anesthesia in the development of PND was suspected.

The body's response to both general anesthesia and surgical stress includes changes in all vital organs and systems, but the main victim of anesthetics is undoubtedly the central nervous system [5]. In 1916, H. D. Bruns published a paper reporting postoperative delirium and subsequent «dementia» in elderly patients undergoing cataract surgery [6]. The question of whether surgery can be a trigger that stimulates the progression of a pre-existing cognitive deficit or whether it initiates cognitive impairment has continued to attract the attention of scientists and remains a relevant problem today, as researchers around the world report a relatively high incidence of cognitive impairment in the postoperative period [7].

Despite the continuing interest in the problem of postoperative neurocognitive dysfunction, a systematic approach to the study of this phenomenon emerged only in the second half of the 20th century and was marked by the emergence of a group of conditions and terms for their designation, although the terms are not widely accepted until today.

Postoperative Delirium (POD)

Background. The rapid development of cardiac surgery, which began in the mid-50s of the last century, became a major impetus for the study of PND. Clinicians discovered that cognitive deficits were particularly common after this type of surgery, significantly complicating the medical and social rehabilitation of patients [8]. The work of P. Blachy and A. Starr (1964) is considered a pioneering study in this area [9]. In addition to identifying several risk factors for the development of PND, the authors noted an extremely high incidence of delirium (57%) and introduced the new concept of «postcardiotomy delirium». The subsequent surge of research activity on risk factors and outcomes of delirium in open heart surgery [10–15] resulted in developing the first classification of postoperative recovery in terms of cognitive status (1970) [16]. S. Heller et al. distinguished 3 variants: «pure» (without abnormalities) cognitive status, early postoperative organic brain syndrome, and postcardiotomy delirium. The term «early postoperative organic brain syndrome» implied impaired orientation in space and time in patients recovering from anesthesia. Importantly, this term had 2 «strict» characteristics, such as:

(1) specific cognitive (not motor) impairment, and

(2) the absence of a lucid interval during recovery from anesthesia.

In other words, the diagnosis of «early postoperative organic brain syndrome» could be made quite accurately, avoiding overly subjective assessments.

However, the term «early postoperative organic brain syndrome» was greeted coldly by contemporaries and soon forgotten, probably for two reasons: first, it was cumbersome and inconvenient to use, and second, after its appearance in 1970, the term competed with concepts such as emergence excitement, emergence agitation (EA), and emergence delirium (ED), which had already been actively used by the medical community for more than 10 years to describe inadequate awakening after surgery [17].

Another author's concept, postcardiotomy delirium, first led researchers to focus on the relationship between cognitive impairment and the timing of surgery, defining postoperative delirium as only that which occurs after a lucid interval of 2 to 5 postoperative days (see Figure). Without adopting the term itself, the medical community adopted the definition and relegated it to the more convenient name of «postoperative delirium» (POD). For the next 10 years, this relationship between the time of onset of delirium and the time after surgery remained the only accurate definition of the condition under discussion.

Notably, the term POD remained «off the radar» of the medical community for a long time. The DSM-1 (1952) [18] and DSM-2 (1968) [19] manuals used the terms «acute cerebral syndrome» and «psychoses,» respectively, which were not widely utilized outside of psychiatry [20]. In addition, no clear diagnostic criteria were proposed to guide researchers.

The most important works of those years that considered the principles of diagnosis of postoperative delirium were the studies of G. Engel and J. Romano [21], and then the work of Z. Lipowski [20].

G. Engel and J. Romano proposed relatively simple test batteries consisting of a small number of questions/answers for the diagnosis of delirium. Some of these questions are still used in modern tests [22–25].

Z. Lipowski, in turn, created criteria for the diagnosis of delirium, which were subsequently adopted by the first clinical guidelines on the problem under discussion [20].

The year 1980 became a milestone in the history of PND research. First, the DSM-3 [26] was published, in which the term «delirium» appeared for the first time to define cognitive impairment. Clear diagnostic criteria for the condition, such as disorientation, fluctuations in cognitive status, sleep-wake cycle disturbances, and others, also appeared [26]. Secondly, Z. Lipowski in his work distinguishes two types of delirium occurring after surgery:

1. Late postoperative delirium, which occurs after a lucid interval of 24 hours after surgery (see Figure), and

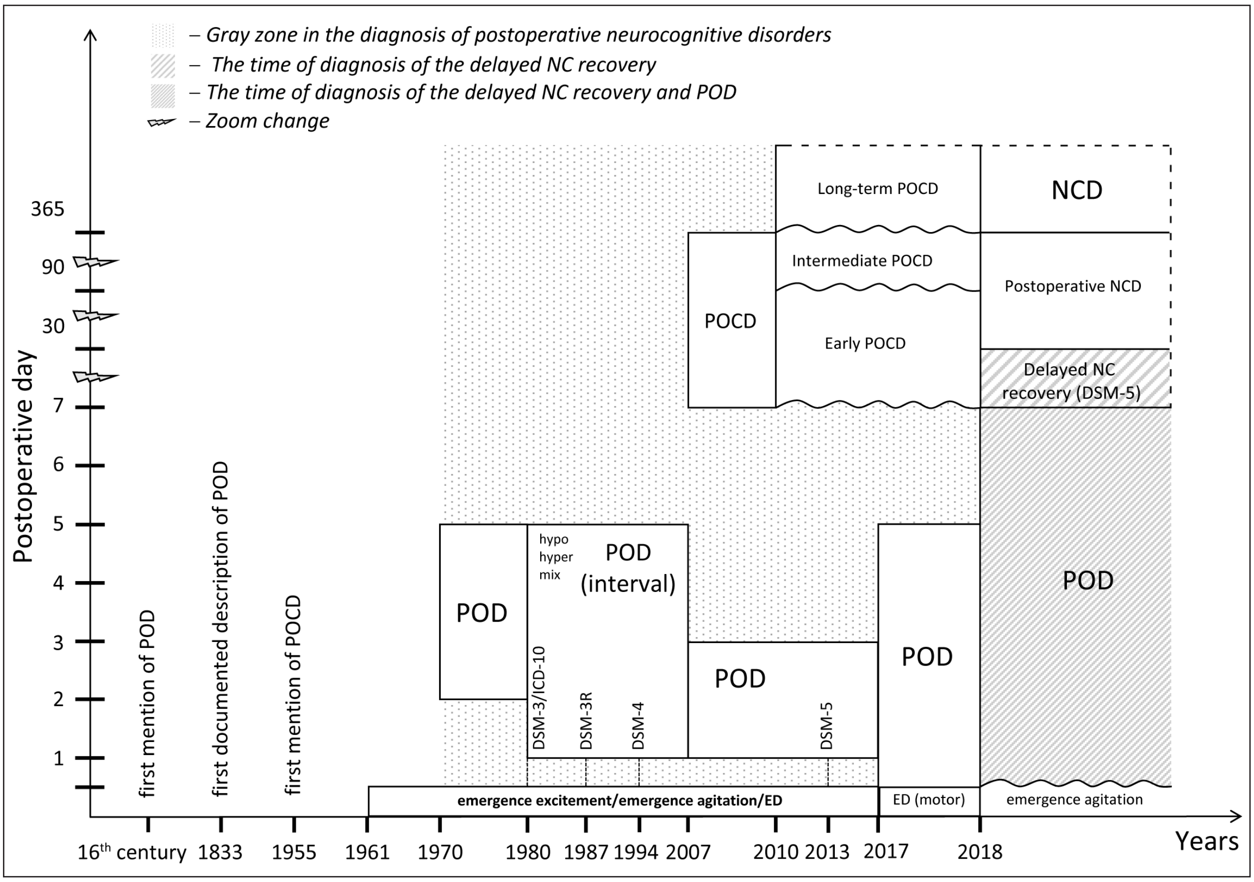

Fig. The timeline of ideas about postoperative neurocognitive disorders.
Note. POD — postoperative delirium; Hypo POD — hypoactive postoperative delirium; Hyper POD — hyperactive postoperative delirium; Mix POD — mixed postoperative delirium; POCD — postoperative cognitive dysfunction; NCD — neurocognitive disorders; NC — neurocognitive; ED — emergence delirium; ED (motor) — emergence delirium after anesthesia, diagnosed using scales to assess patients' motor signs; DSM — Diagnostic and Statistical Manual of Mental Disorders; R — Revised; ICD — International Classification of Diseases.

2. Emergence delirium, which occurs within the first 24 hours after surgery [27].

The term «emergence delirium» in Z. Lipowski's classification has not been widely used in the medical community because it has already been used for a different time interval after surgery. At the same time, Z. Lipowski's definition of late postoperative delirium will become the main definition of POD for the next 30 years. During the same period, the classification of postoperative delirium into hypoactive, hyperactive, and mixed delirium based on clinical manifestations appeared (see Figure) [27]. The emergence of relatively clear and unambiguous definitions of PND triggered the development of the first diagnostic tests, including those for POD. Thus, in 1987, the updated version of DSM-3-R [28] was published, and in 1994, in coordination with ICD-10 [29], DSM-4 [30], which clarified the concept of delirium, defining the extent of cognitive impairment, the rate of its development and evolution as the main characteristics of this condition. By the way, 1994 can be considered as the official year of appearance of the term «postoperative delirium» in the framework of international documents (ICD-10) [29]. On the basis of DSM-3, several scales for the diagnosis of postoperative delirium were created, such as the «Delirium Symptom Interview» [31] and the «Saskatoon Delirium Checklist» [32], which are currently of mostly historical interest.

At the same time, based on the DSM-3-R, the Confusion Assessment Method (CAM), one of the most popular scales for the diagnosis of delirium, was developed in 1990 [33]. This scale is currently so widespread that it has been translated into 10 languages [34]. The scale has a variant for the diagnosis of delirium in ventilated patients, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [22, 23]. The current questionnaire for rapid assessment of cognitive status in patients, 3D-CAM (3-minute diagnostic assessment for CAM-defined delirium) [24], is an improved version of the CAM scale. Other well-known delirium assessment tools include the Intensive Care Delirium Screening Checklist (ICDSC), developed in 2001 based on the DSM-4 [35], and the Nursing Delirium Screening Scale (Nu-

DESC), developed in 2005 specifically for nurses [25]. There are several other less popular scales for diagnosing and grading the severity of delirium [36].

The last decade of the 20th century was marked by the study of risk factors and methods of prevention of postoperative delirium. This focus was due to the creation in 1990 of a new method for diagnosing delirium, the Confusion Assessment Method, which was popular among perioperative physicians [33], as well as the appearance of the first significant papers demonstrating the relationship between postoperative delirium and mortality [37].

Anesthesiologists, on the other hand, were primarily concerned with studying the relationship between postoperative delirium and the type of anesthesia and surgical procedure. The key work in this direction was the review by C. Dayer et al. based on the analysis of all publications on the subject between 1966 and 1992 [38]. The authors first determined the approximate frequency of postoperative delirium development (36.8%), emphasized the absence of a unified method of diagnosing this condition, and showed that this situation leads to a high frequency of missed cases of delirium (up to 28%). In addition, the authors pointed out the lack of studies on risk factors for postoperative delirium and the need for further efforts to study this issue [39].

Meanwhile, in the first decades of the 21st century, anesthesiologists have been studying and categorizing the results of studies on different types of postoperative PND. For example, in 2007, the journal Anesthesiology published an article identifying the association of delirium with surgery only in the period up to 72 hours after surgery (see Figure) [40]. However, J. Silverstein's classification still included the presence of a «lucid interval» in the first 24 hours after surgery.

In 2017, the European Society of Anesthesiologists published guidelines that extended the time interval for the association of delirium with surgical intervention (see Figure) [41]. The authors returned the upper time limit for the occurrence of postoperative delirium to 5 days postoperatively, as it was in the classifications of S. Heller [16] and Z. Lipowski [27]. At the same time, the authors of the 2017 PND classification tried to solve the shortcoming of all POD classifications that has persisted for almost 50 years, i.e., the «gray» (unclear and unexplored) zone between the patient's awakening and the end of the minimum duration of the lucid interval. In the 1980 classification, Z. Lipowski proposed to describe the changes in cognitive status at this point as «emergence delirium», but the term had already been used to characterize the awakening of patients after anesthesia [17].

Based on the available evidence that cognitive impairment observed in the recovery room is predictive of postoperative delirium [42, 43], C. Aldecoa et al. suggested that the lower limit of the time interval for postoperative delirium may be later than the time of «arrival at the recovery room» [41]. The authors proposed that neurocognitive disturbances occurring before this (rather conventional) time point should be considered as «emergence delirium». This reasonable proposal, however, has led to even more confusion. The reasons are obvious: the lower limit of the time of onset of postoperative delirium was arbitrarily chosen and not related to the patient's condition. Moreover, it turned out that the interval could vary depending on the requirements of the patient's status, which determined whether he or she could be transferred to the recovery room, intensive care ward, or surgical ward. In a number of less «advanced» hospitals there are no recovery rooms at all, which makes the use of this classification practically impossible. This is the reason for its low popularity.

Taking into account the above-mentioned circumstances, in 2018 L. Evered proposed a new PND classification (see Figure) [44], which has 3 fundamentally important aspects:

1. The proposal to shift the lower time limit of postoperative delirium to the time of the end of the surgical procedure. Thus, any delirium after surgery should be classified as postoperative. Meanwhile, the presence or absence of a «lucid interval» is only considered an individual variation of POD.

2. The second aspect is to raise the upper time limit for the development of postoperative delirium. L. Evered et al. proposed to increase the time limit for the diagnosis of delirium to 7 postoperative days or until discharge (whichever comes first). One can only speculate about the reasons for such a proposal, as the authors did not explain their position. And finally,

3. The third aspect is the use of diagnostic criteria for delirium according to the DSM-5 [7]. The seemingly unremarkable proposal to use DSM-5 [7] criteria instead of DSM-4 [30] is in fact a significant step forward in standardizing approaches to the diagnosis of POD. The publication of DSM-5 [7] in 2013 was not a high-profile event in the anesthesiology/critical care community because of the absence of the term «postoperative delirium». However, according to L. Evered et al., postoperative delirium is a type of delirium associated with surgical intervention. Consequently, POD, as a variant of delirium, should be diagnosed according to the latest delirium criteria. Although this position is simple and straightforward, it is important to note that the DSM-5 [7] and DSM-4 [30] have a concordance rate of only 91% [45]. The presence of some inconsistency between these diagnostic criteria has made it necessary to revalidate the existing diagnostic tools for postoperative delirium, including the afore-

mentioned ICDSC, Nu-DESC, and various versions of the Confusion Assessment Method (CAM).

After validation, 3D-CAM [46], CAM-ICU [47] and ICDSC [47] confirmed high agreement with DSM-5 [7] as the new gold standard for the diagnosis of delirium. However, Nu-DESC showed a very low sensitivity (42%) during validation [48]. Based on such results, it is probably not worth considering the Nu-DESC scale as a tool for diagnosing postoperative delirium at this time.

Postoperative delirium has since been defined as «neurocognitive impairment meeting DSM-5 criteria and occurring within 7 days of surgery or before discharge (whichever occurs first)». The simplicity and precision of the definition of «postoperative delirium» make this classification successful, although not exhaustive. The time frame «within 7 days of surgery» is not substantiated in any way, which implies the possibility of subsequent changes.

Current status of POD research. According to the DSM-5 [7], delirium is currently defined as a combination of the following diagnostic criteria

A. Disturbance of attention (i. e., reduced ability to direct, focus, maintain, and shift attention) and consciousness (reduced orientation to the environment).

B. This disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity throughout the day.

C. An additional disturbance in cognition (e. g., memory deficit, disorientation, language, visuospatial ability, or perception such as delusions).

D. The disturbances in Criteria A and C are not better explained by a pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is clear evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication, or withdrawal (i. e., from a drug of abuse or medication).

Delirium itself is divided into 3 subtypes [7]:

1. Hyperactive, with increased arousal, psychomotor abnormalities, and hypervigilance (hallucinations, delusions, agitation, and disorientation);
2. Hypoactive, with lethargy and lack of interest. This type of delirium is particularly easy to overlook in clinical practice, so it often goes unrecognized or masquerades as dementia;
3. Mixed when the patient either has a normal level of psychomotor activity or can «switch» between the two types of delirium described above.

Despite the existence of the DSM-5, the only official document that currently includes postoperative delirium in the list of neurocognitive disorders is the ICD-10 [29]. According to ICD-10, postoperative delirium is defined as a nonspecific organic cerebral syndrome characterized by disturbances of consciousness, attention, perception, thinking, memory, psychomotor behavior, emotions, and sleep-wake cycle [49]. We would like to draw attention to two points:

1. This definition points to organic damage as the direct cause of POD. This observation is supported by extensive evidence of the association of delirium with underlying dementia, Parkinson's disease, and perioperative cerebral infarction [50–54].
2. The hallmark of postoperative delirium is impaired consciousness, which is not characteristic of any other PND.

Currently, the predominant concept of POD development suggests the presence of predisposing (advanced age [55–58], administration of some medications in the perioperative period [59, 60], comorbidities [61–63], etc.) and provoking (intraoperative blood loss [64, 65], depth of hypnosis [66], hypovolemia [67], etc.) factors. A combination of several predisposing and provoking factors may initiate PND. The trigger appears to be the onset of neuroinflammation as a form of systemic inflammatory response that damages brain neurons and manifests as PND. Clinical manifestations of this response are usually observed by an anesthesiologist [68].

The incidence of postoperative delirium can vary within a fairly wide range, from 15% to 53% [7]. Meanwhile, postoperative delirium is a risk factor for an unfavorable postoperative recovery period. Thus, postoperative delirium has been shown to be associated with

1. Increased mortality in adult patients [69–73].
2. Longer ICU and hospital stays in adult patients [71, 74, 75].
3. Cognitive impairment in adult patients [73, 76].

There are no specific pharmacological methods for the prevention and treatment of POD [77, 78]. Numerous recommendations to eliminate predisposing and provoking factors, to create a friendly atmosphere, to provide a protective regimen in intensive care units, etc. have limited efficacy [79]. Analysis of RCTs shows that the use of a drug with putative neuroprotective activity (dexmedetomidine) has controversial results [77]. Nevertheless, the prophylactic use of this drug is approved by some clinical guidelines [80].

Postoperative Cognitive Dysfunction

Background. As mentioned earlier, the first description of postoperative cognitive dysfunction can be found in the work of G. Savage (1887), where the author first associated the fact of anesthetic use with the development of «chronic dementia» in elderly patients [81]. However, the era of studying postoperative cognitive dysfunction did not begin until more than half a century later. It is difficult to overestimate the importance of the pioneering work of P. Bedford [82]. The author conducted a retrospective analysis of 4,250 case histories of patients over 65 years of age, 1,193 of whom had undergone various surgeries under general anesthesia during the previous fifteen years (i. e., at the age of 50 years or older), and found that in at least one third (410) of the cases, close relatives or friends noted personality changes after surgery, with the phrase «The patient will never be the same».

The next stage of research into the problem of POCD began in the 1970s, when a number of studies in the field of anesthesiology were initiated to investigate changes in psychoemotional and intellectual functioning in patients after exposure to general anesthesia [83–85]. At this point in the research, a number of unresolved problems have surfaced. The first is the lack of agreement regarding how to diagnose POCD. Guidelines that outlined a pool of questions that should be addressed in the evaluation of patients' cognitive function were published in 1995 to address this problem [86]. Additionally, these guidelines proposed a method for evaluating cognitive dysfunction based on several tests administered concurrently, allowing for a better diagnosis of cognitive impairment in postoperative patients. Unfortunately, despite the passage of nearly 30 years, there is still no single test or battery of tests specifically designed to diagnose POCD. Thus, different tests were shown to result in different rates of POCD diagnosis in 2006 [87]. Later, in 2016, R. Benson et al. attempted to conduct a meta-analysis of the development of POCD associated with aortic surgery, but differences in study methods, cognitive test batteries, and thresholds also prevented results from being pooled [88]. This issue greatly complicates the evaluation of POCD and, without a doubt, leads to interdisciplinary disagreement among neurologists, anesthesiologists, and other physicians.

Another current challenge is the very principle of diagnosing POCD. In fact, different methods of diagnosing POCD are currently used when assessing changes in scores on a scale chosen by researchers. For example, in studies without a control group, a popular criterion for the presence of POCD is a deterioration in retest scores of one standard deviation or more from baseline [89]. In studies with a control group, a popular approach is to compare the change in a given patient's score with the expected change calculated on the basis of the control group, the so-called Z-score (RCI, reliable change index) [90, 91]. Even with this approach, there are different formulas for estimating the expected change for a battery of tests [92]. Some large studies have used a third approach, which includes the assessment of the absolute change in score as a diagnostic criterion for POCD [93]. The lack of a uniform approach to the diagnosis of POCD is a major obstacle to the study of this disorder.

Uncertainty regarding the timing of the described complication's diagnosis is the third challenge. For instance, it can take anywhere between «less than 24 hours» [94] and «1 year or more» after surgery [91, 95, 96] to confirm the presence of POCD in various studies. The previously discussed classification by J. Silverstein (see Figure) [40] was developed to address this discrepancy between studies. According to the classification, postoperative cognitive dysfunction can be identified over the course of weeks and months but never over the course of days. At the same time, the scientific community established an informal classification of POCD into three stages (see Figure), including early (1 week after surgery), intermediate (during the first three months after surgery), and long-term (1 year or more after surgery) [97, 98].

Only 60 years after P. Bedford's work [82] was published, L. Evered's (2018) classification [44] was able to simultaneously solve multiple issues. It did this by first defining precisely what constitutes postoperative cognitive impairment. It was recommended that POCD should be evaluated no earlier than one month and no later than one year following surgery. Even though cognitive dysfunction can persist for much longer than a year, the terms «mild/severe neurocognitive impairment» are appropriate in this situation [44]. It is advised to refer to cognitive impairment occurring up to one month after surgery as delayed neurocognitive recovery. Second, a correlation between POCD and the most recent classifications has been made. Unfortunately, POCD is not included in any of the current official classifications, neither ICD-10 [29] nor DSM-5 [7]. However, bringing the definition of POCD closer to the DSM-5 definition of neurocognitive disorders and making the association with surgical intervention more explicit may standardize the method of studying POCD and possibly aid in its inclusion in official international documents. Third, unified diagnostic criteria for POCD have been established in accordance with the DSM-5, which include a deterioration in retest score of at least one standard deviation compared to the control group [7].

But there are still some uncertainties. On the one hand, there is currently no standard method for calculating the RCI, which is required to determine the deviation of each study patient's result from that of the control group. Contrarily, there is no approved test battery to evaluate cognitive dysfunction in patients in the documents under consideration despite the DSM-5 existing definition of neurocognitive dysfunction and the availability of approved cognitive blocks.

The exclusion of the MMSE and MoCA from the diagnostic battery for postoperative cognitive dysfunction (POCD), as recommended by the DSM-5 [44], can be interpreted as a favorable advancement due to their failure to adequately assess the required cognitive domains.

Current state of the art. The incidence of postoperative cognitive dysfunction (POCD) following major abdominal and orthopedic surgeries was investigated in the ISPOCD1 study, which involved a total of 1218 patients aged 60 years and above [90]. Postoperative cognitive dysfunction was diagnosed in 25.8% of patients one week following surgical intervention, and in 9.9% of patients three months after the surgery. Only age was a risk factor for POCD; other variables for delayed neurocognitive recovery were age, anesthetic duration, poor education level, reoperation, postoperative infections and respiratory problems, and reoperation. Nevertheless, there was no observed association between hypoxemia or hypotension and the occurrence of POCD. The authors did not provide a clear explanation of the underlying mechanisms of POCD or identify any particular risk factors that could be targeted for therapeutic or preventive interventions [90]. The association between this disorder and irreversible damage to the nervous system, characterized by structural changes in the brain and neuronal loss, remains uncertain. However, research efforts in this particular area persist [101, 102]. For instance, X. Liu et al. conducted a meta-analysis that encompassed 54 observational studies. Their findings demonstrated a positive association between elevated levels of inflammatory markers, specifically CRP and IL-6, and the occurrence of both POD and POCD [103].

POCD has been reported to occur more frequently in patients whose postoperative period was complicated by POD [104–107]. Although POCD can develop in patients without a history of POD, POD does not always progress to POCD, therefore there is no obvious causal link [108].

A small body of evidence suggests that patients with POCD have a greater risk of death [109, 110], but it is already obvious that these patients need significant and prolonged medical and social adaptation, which is becoming a major challenge for patients, healthcare providers, and social services.

Numerous investigations into the effectiveness of potential medications for the prevention and treatment of POCD have been unsuccessful. There are currently no pharmacologic treatments that have been shown to be effective in POCD patients [111].

Early Postoperative Neurocognitive Disorders

Background. The history of studying the problem of early postoperative neurocognitive disorders, which at different times included «emergence excitement», «emergence agitation», «emergence delirium», etc., probably begins with the article by J. Eckenhoff et al. (1961) (see Figure) [17]. There, for the first time, the prevalence of «emergence excitement» was studied. This complication was studied on a population of more than 14,000 patients of all ages. Unfortunately, J. Eckenhoff et al. employ three names simultaneously in their study to represent early PND, including «emergence excitement», «emergence delirium», and «emergence agitation», without describing any potential overlaps or contrasts between the conditions.

Subsequent decades of research on early postoperative neurocognitive disorders have been characterized primarily by the accumulation of data on risk factors [112–120] and their impact on clinical outcomes [42, 112, 114, 115, 118, 119, 121–125]. However, terminological issues have been ignored and authors have arbitrarily and interchangeably used the terms emergence agitation, emergence delirium, emergence excitement, PACU delirium, and recovery room delirium, which may have affected the validity of the results obtained. This seems odd because the 1980 DSM-3 provided precise definitions of delirium and agitation, stating that delirium always includes a cognitive component of impaired consciousness, whereas agitation is characterized by motor agitation alone [26].

The most recent advances in early PND classification. J. Silverstein et al. [40] made the first attempt to solve the problem of terminological chaos in early PND in 2007. The authors proposed a single term «emergence delirium» to describe early postoperative neurocognitive disorders that occur immediately after anesthesia recovery. In doing so, they suggested, paradoxically, using motor characteristics of awakening to diagnose ED. This could be why colleagues overlooked this proposal.

C. Aldecoa et al. suggested in 2017 that the term ED be used to describe all neurocognitive disorders of the early postoperative period (see Figure) [41]. To say the least, this appears illogical. Calling the emergence state «delirium» and recommending motor scales to diagnose it, despite the fact that delirium implies the presence of impaired consciousness? Combining patients «with» and «without» impaired consciousness into a single term does not appear to be the best solution.

The medical community's subsequent criticism of the inaccuracy of such diagnostic considerations prompted the development of a new classification (126, 127). Furthermore, claims have been made about the time interval used to define ED from the early postanesthetic period through «arrival in the recovery room» [41]. As previously discussed, the selection of such a time point, which is not related to the patient's condition but rather to the organization of perioperative management, became another flaw in the proposed recommendation.

The recommendations published a year later by L. Evered (2018) provided a different perspective on the issue of early PND terminology (see Figure) [44]. L. Evered et al. proposed to exclude the term «emergence delirium» from the current classification, and any condition that meets the definition of delirium according to DSM-5 during 7 postoperative days should be considered as postoperative delirium. In fact, this approach simplifies the methodology of diagnosing postoperative delirium and eliminates the problem of the «lucid interval». But the question remains, what is emergence agitation (EA)?

The problem with EA is that during the period of agitation, it is impossible to make contact with the patient to assess their cognitive status. Since there is currently no mechanism for determining cognitive status other than direct communication with the patient, it is extremely difficult to answer the question of whether agitation is purely psychomotor, as the DSM has classified it for over 40 years, or a brief episode of hyperactive delirium that resolves when the agitation subsides.

Perhaps the method proposed by E. Card et al. can help to solve this problem [128]. The authors studied the development of emergence agitation, which was diagnosed in the operating room using the RASS scale, and delirium, which was assessed by the CAM-ICU immediately after arrival in the recovery room. E. Card et al. found that of the 75 patients (19% of all participants) who had an episode of emergence agitation on recovery from anesthesia, only 60% (45 patients) had delirium on arrival in the recovery room. We would like to believe that conducting similar studies may shed light on the issue of cognitive status of patients during the period of emergence agitation after anesthesia.

Conclusion

The lack of a consistent approach makes comparing the results obtained in the study of early PND in the works of different authors extremely difficult. Thus, some anesthesiologists accept a brief disorientation with motor hyperactivity on recovery as a normal variant, attributing it to the discomfort of the intubation tube, the pain syndrome, or the erratic inhibition or recovery of various brain areas associated with the action of general anesthetics. Others define agitation as motor agitation without cognitive dysfunction, and some continue to use the terms «agitation» and «ED» interchangeably.

It is clear that anesthesiologists, psychiatrists, and neurologists must collaborate to develop an optimal classification of early PND. A classification like this will allow for a more focused search for the true prevalence of early PND and its impact on clinical outcomes. If researchers discover that early PND is more than a non-serious transient functional brain disorder and is associated with increased mortality (which is not impossible given the availability of such data for POD) or other adverse events, they will need to work hard to find ways to prevent and treat early PND.

We would like to conclude this review with a visual representation of the long history of research into postoperative neurocognitive disorders (see Figure). It also serves as a visual representation of PND's current classification. Hopefully, the scheme will be updated soon to remove inaccuracies and inconsistencies.

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