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# Research progress of esketamine and postoperative delirium

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**Abstract**: Postoperative delirium (POD) is a common complication in elderly patients after surgery, significantly affecting prognosis and increasing mortality rates. The underlying mechanisms of POD remain unclear, with diverse risk factors making prevention difficult and treatment outcomes unsatisfactory. Esketamine is a high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist known for its anesthetic and analgesic properties. Besides its widespread use in perioperative anesthesia and pain management, esketamine has shown promising clinical applications across various disciplines including psychiatry and critical care. This review summarizes recent advances and mechanisms of esketamine in preventing and treating POD, offering new insights for clinical practice.

**Keywords**: Esketamine; Postoperative delirium; Elderly patients; Mental illness; Induction of anesthesia; Pain treatment; Pain management

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The recommendations released by the Perioperative Cognition Nomenclature Working Group classify delirium into emergence delirium (ED) and postoperative delirium (POD) [1]. ED refers to delirium diagnosed within minutes or hours after surgery, including the stage of awakening in the post-anesthesia care unit. POD refers to delirium diagnosed within a few days, up to one week, or until discharge after surgery. It is an acute brain dysfunction characterized by attention disorders, memory disorders, fluctuations in consciousness levels, confusion in thinking, sleep cycles disturbances, and emotional disorders, typically occurring within 24-72 h post-surgery. A meta-analysis indicated that POD was an independent risk factor for long-term cognitive impairment and short-term mortality in hospitalized patients, potentially leading to increased medical costs, decreased recovery quality and prolonged recovery time, higher complication rates, extended hospital stays, and increased readmission rate [2]. POD is more common in elderly patients over 65 years old, with a 1.15-fold increase in the risk of delirium for every 1 year of age [3]. In comparison, patients over 80 have a higher probability of experiencing delirium. Studies reported that 11% to 51% of patients undergoing surgery experience POD, with the highest incidence seen in elderly patients undergoing cardiac and major non-cardiac surgeries [4]. According to "expert consensus on prevention and treatment of postoperative delirium in elderly patients in China", the incidence of POD in cardiac surgery patients is 5.5% - 46.0%, in non-cardiac surgery patients over 65 years old is 6.1% - 57.1%, with an overall incidence of 11.1%. Among them, the incidence of POD in neurosurgery surgery is the highest, reaching 57.1%, followed by upper abdominal surgery, with a incidence rate of 18.1%, and 16.3% in thoracic surgery and 15.2% in spine and joint surgery [5]. A study conducted abroad investigated more than 2 0000 elderly patients over 65 years old, and showed that the overall incidence of POD was 12.0%, with the lowest incidence of gynecological surgery at 4.7% and the highest incidence of cardiothoracic surgery at 13.7% [6].

POD is classified into three types based on clinical presentation: (1) High-activity delirium, which accounts for about 25% of cases, is characterized by varying degrees of agitation, incoherent speech, aggressive movements, and directional disorders, which are generally more likely to be noticed by medical staff or family members. (2) Low-activity delirium, comprising about 50% of cases, is characterized by clinical manifestations such as quietness, silence, bradykinesia, drowsiness, and reduced interaction, which are often overlooked by medical staff and family members. (3) Mixed delirium, about 25% of cases, displays characteristics of both high-activity and low-activity delirium, showing agitation or drowsiness at different times.

Delirium patients often have poor prognosis due to related complications. Short-term delirium can increase the risk of acute respiratory distress syndrome, unplanned extubation, and other issues. Long-term delirium can lead to cognitive impairment, mental health issues, decreased quality of life, and may result in severe psychological conditions such as post-traumatic stress disorder, depression, and anxiety.

## 1 Diagnosis, prevention, and treatment of POD

To date, there is no definitive laboratory diagnostic standard for POD. Internationally, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition

(DSM-V) and the International Classification of Diseases (ICD-10) are recognized as diagnostic criteria. However, these diagnoses require experienced psychiatric physicians to conduct detailed bedside interviews and observational neuropsychiatric evaluations. The diagnosis mainly depends on clinical symptoms, such as attention deficits, abnormal consciousness, and cognitive impairment, accompanied with acute onset and fluctuating course. Due to the complexity of the diagnosis for POD, researchers in the U.S. developed the Confusion Assessment Method (CAM), which is now the most widely used diagnostic tool worldwide [7]. CAM has a sensitivity of 94%-100% and specificity of 90%-95%, making it user-friendly for non-psychiatric physicians and nurses, and convenient for delirium screening. CAM evaluates four key aspects: (1) Acute onset or fluctuating changes in consciousness; (2) Inattention or difficulty focusing; (3) Disorganized thinking; (4) Altered level of consciousness. A diagnosis of POD is made if (1) and (2) are present along with either (3) or (4). Various derived scales have been developed for specific contexts, such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM).

Despite the high incidence of POD, research showed that up to 40% of cases could be prevented through active multi-faceted interventions. The consensus in academia emphasizes that prevention is more important than treatment, with prevention being crucial for reducing the incidence of POD. During the perioperative period, patients are under stress, and stimuli from changes in the environment and physiological responses are significant triggers for POD. Implementing necessary measures to control adverse factors during the perioperative period can reduce the incidence of postoperative delirium. The comprehensive prevention and treatment measures recommended by the "Consensus on the Prevention and Treatment of Postoperative Delirium in Elderly Patients in China" include: (1) An active preoperative assessment of the risk of delirium. For high-risk patients, proactive intervention measures should be taken. (2) During surgery, special attention should be given to the management of the surgical procedure and anesthesia. For elderly patients, minimally invasive and shorter-duration surgical methods should be chosen whenever possible, with minimal interference with the body's normal physiological functions. (3) Postoperatively, effective pain management, rehabilitation, and prevention of complications are essential. Early mobilization and active participation in rehabilitation exercises are encouraged [5]. Currently, there is no mature and effective treatment plan for POD in elderly patients. Although a randomized, double-blind, placebo-controlled clinical trial for non-cardiac surgery in elderly patients showed that prophylactic administration of low-dose dexmedetomidine significantly reduced the incidence of delirium within the first 7 days after surgery [8], the clinical effectiveness of pharmacological treatments for POD is limited. It is recommended that multidisciplinary teams provide comprehensive non-pharmacological interventions, primarily focusing on removing triggers, correcting underlying causes, ensuring adequate sedation and analgesia, controlling mental status, and improving sleep [9].

## 2 Mechanisms of POD

Numerous hypotheses have been proposed to explain the mechanisms of POD, but most are based on animal models, and direct evidence from human studies is very limited. Overall, delirium is the result of multiple interacting factors. Mechanistic hypotheses reported in the literature include neuroinflammation theory, neurotransmitter theory, oxidative stress theory, sleep-wake cycle disturbance theory, gut microbiota dysbiosis theory, genetic theory, suppression of electroencephalographic bursts theory, and changes in brain network connectivity theory [10]. A single mechanistic hypothesis may not fully explain the onset and development of POD. Instead, interactions among several different hypothesized factors may lead to widespread disruption of neural networks in the brain, resulting in acute cognitive dysfunction and subsequently delirium. Perioperative stress from surgery and anesthesia triggers acute inflammatory responses in the body. Abnormal stress responses leading to a pro-inflammatory shift in the innate immune system can further cause central nervous system inflammation, leading to POD. Elevated levels of white blood cells, tumor necrosis factor-alpha (TNF-α), interleukins (IL)-6, IL-8, IL-10, C-reactive protein, and the pro-inflammatory/anti-inflammatory ratio have been observed [11]. Among these, TNF-α and IL-6 production are considered major contributors to POD-related cognitive impairment, and this process may be exacerbated in elderly individuals. Munster *et al.* [12] conducted a postmortem case-control study and found increased microglial activity and elevated IL-6 levels in the brains of delirium patients, further supporting the inflammatory mechanism of delirium. Some researchers also believed that changes in DNA methylation levels might be an initial molecular mechanism of delirium [13]. Anesthesia and surgical stress not only activate inflammatory cascades in peripheral and central systems, but also cause oxidative stress damage. Peripheral oxidative stress can disrupt the integrity of the blood-brain barrier, promoting the entry of inflammatory cytokines and peroxides into the brain, thus inducing or exacerbating central nervous system inflammation and leading to postoperative delirium [14]. Cholinergic input in the basal forebrain plays a key role in many higher functions, including memory, attention, arousal, and sensory processing. Anticholinergic substances were initially observed to cause delirium in some patients. Lin *et al.* [15] found that various neurotransmitters in the brain, including acetylcholine, dopamine, glutamate, and γ-aminobutyric acid, were closely related to the occurrence of POD, supporting the neurotransmitter hypothesis. Qin *et al.* [16] investigated the regulation of melatonin on NOTCH3/NF-κB signaling pathways and found that sleep-wake cycle disturbances and brain ischemia/ hypoxia lead to brain metabolic

disorders, causing brain dysfunction. The brain-gut axis theory, involving the nervous, endocrine, and immune systems, suggests that routine preoperative bowel preparation may disrupt the composition and activity of normal gut microbiota, thus increasing the incidence of POD through the brain-gut axis. Further research identified *Bacteroides* and *Veillonella* genera as potential risk factors for POD, while *Eucommia* genus may serve as a protective factor [17]. The theory of suppression of electroencephalographic bursts suggests that the occurrence of POD is related to the depth of anesthesia during general anesthesia. Excessive anesthesia depth increases electroencephalographic burst suppression, thereby increasing the risk of POD [18]. The brain is a highly restructured and interconnected structure that allows for complex integration of sensory information and motor responses. Delirium represents variable failures in the integration and proper processing of sensory information and motor responses. Studies on the electroencephalograms of POD patients support this theory [19]. Recent genetic susceptibility hypotheses for delirium have opened new research directions. A meta-analysis found associations between POD and genes such as APOE4, dopamine transporter gene SLC6A3, dopamine receptor 2 gene, glucocorticoid receptor, melatonin receptor, and mitochondrial DNA haplotypes, as well as two insightful long non-coding RNA genes [20].

## 3 The relationship between esketamine and POD

Esketamine exerts anesthetic and analgesic effects not only through non-competitive binding to the phenylcyclohexyl site of NMDA receptor, inhibiting glutamate activation of the receptor, thereby reducing neuronal activity, but also by binding to μ and δ receptors in opioid receptors to produce analgesia. It can also inhibit hyperalgesia, with an affinity for NMDA receptors 3-4 times that of ketamine, and its analgesic effect is 2-2.5 times that of ketamine. The pharmacological action sites and mechanisms are fundamentally consistent with those of ketamine.

A prospective, nested case-control study from Poland investigated the mechanisms of POD from the perspective of genetic polymorphisms and found that genetic variations and functional disorders in the NMDA receptor NR3A subunit may be one of the mechanisms leading to POD [21]. A phase IV clinical trial involving 160 healthy male volunteers indicated that esketamine increased glucose and lactate levels in the brain, reduced branched-chain amino acids and tyrosine expression, while increasing serotonin and norepinephrine effects, and was helpful in improving depression and cognitive disorders. Therefore, it is used in the prevention of POD [22]. Luo *et al.* [23] found that a low dose (0.5 mg/kg) of esketamine not only reduced the incidence of POD within 7 days post-surgery in elderly patients under general anesthesia, but also decreased the usage of intraoperative opioid analgesics and vasoactive drugs. In elderly patients undergoing hip replacement under general anesthesia, Ren *et al.* [24] discovered that esketamine reduced the incidence of delirium after general anesthesia in older patients by inhibiting inflammation and alleviating brain damage. An orthopedic study using combined spinal-epidural anesthesia with fascia iliaca block showed that continuous infusion of a low dose (0.3 mg/kg) of esketamine during surgery could provide better perioperative analgesia and sedation for elderly patients with hip fractures and reduce the risk of early postoperative POD (within 3 days) [25]. A study comparing dexmedetomidine and esketamine in elderly patients undergoing thoracic surgery found that both could be used to prevent delirium and adverse allergic reactions after anesthesia. However, esketamine was superior to dexmedetomidine in terms of analgesic effect, improvement of mood and sleep, and stabilization of hemodynamics during surgery. Therefore, the authors believed that esketamine was more effective in preventing post-anesthesia delirium and nociceptive sensitization [26]. Researchers found that administering a low dose of esketamine in elderly frail patients undergoing gastrointestinal cancer surgery reduced the incidence of POD [27]. Yang *et al.* [28] used 0.2 mg/kg esketamine combined with midazolam for induction before anesthesia in elderly hip replacement patients, and found that this combination could reduce the incidence of postoperative delirium, which might be related to the combination's ability to reduce glutamate-induced HT22 cell apoptosis and necrosis. Wang *et al.* [29] studied 80 elderly patients undergoing esophagectomy and found that perioperative use of esketamine could lower the levels of S100B calcium-binding protein β (S100β) and neuron-specific enolase (NSE), as well as the incidence of POD. This effect might be related to suppression of inflammatory responses of esketamine. Similarly, Cao *et al.* [30] also applied a low dose of esketamine during the induction phase of gastrointestinal surgery anesthesia and found that it not only alleviated hemodynamic fluctuations during anesthesia induction, but also reduced the incidence of POD.

Esketamine is used not only in elderly patients but also in pediatric patients. A study found that administering 0.2 mg/kg esketamine at the end of anesthesia safely and effectively reduced the incidence and severity of delirium during the recovery period and postoperative pain in preschool children undergoing tonsillectomy and/or adenoidectomy [31]. However, a study involving 230 children reached the opposite conclusion, indicating that a single dose of esketamine (0.46 mg/kg) might increase the incidence of delirium during the recovery period in preschool children undergoing general anesthesia [32]. In a comparative study of pediatric endoscopy with nalbuphine, the esketamine combined with propofol group had a higher success rate for endoscope placement, required less total propofol, and had more stable hemodynamics compared to the nalbuphine group. However, the esketamine group had a higher incidence of adverse reactions such as agitation and double vision during recovery [33]. These studies also indicate that the role of esketamine in children is still unclear and requires more clinical evidence.

## 4 Summary and Outlook

As a common postoperative neuropsychiatric complication in elderly patients that can be prevented and is influenced by multiple factors, POD still lacks a clear pathogenesis, and related exploratory research is in the early stages. However, proactive screening and intervention measures can effectively reduce the incidence of POD and minimize potential adverse clinical outcomes. Currently, the effectiveness of esketamine in preventing and treating POD in elderly patients remains inconclusive, with limited high-quality clinical evidence available. There is an urgent need for large-scale, multi-center, and prospective randomized controlled clinical trials to explore new approaches for preventing and treating POD.

**Conflicts of Interest** None

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· 研究进展 ·

# 艾司氯胺酮与术后谵妄的研究进展

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**摘要**：术后谵妄（POD）是老年患者手术后常见的一种并发症，严重影响患者的预后，增加病死率。POD 的发病机制目前仍未明确，其危险因素繁杂，预防困难，治疗效果不佳。艾司氯胺酮是一种高亲和性的 N-甲基-D-天冬氨酸（NMDA）受体非竞争性抑制药，同时具备麻醉和镇痛作用，除了广泛应用于围术期麻醉诱导与维持、急慢性疼痛的治疗与管理外，艾司氯胺酮在精神疾病和急危重症诊疗等多学科领域同样有较好的临床应用。本文将近年来国内外应用艾司氯胺酮防治 POD 的作用机制和研究进展进行综述，为临床提供新的思路。

**关键词**：艾司氯胺酮；术后谵妄；老年患者；精神疾病；麻醉诱导；疼痛治疗；疼痛管理
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## Research progress of esketamine and postoperative delirium

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**Abstract**: Postoperative delirium (POD) is a common complication in elderly patients after surgery, significantly affecting prognosis and increasing mortality rates. The underlying mechanisms of POD remain unclear, with diverse risk factors making prevention difficult and treatment outcomes unsatisfactory. Esketamine is a high-affinity N-methyl-D-aspartate (NMDA) receptor antagonist known for its anesthetic and analgesic properties. Besides its widespread use in perioperative anesthesia and pain management, esketamine has shown promising clinical applications across various disciplines including psychiatry and critical care. This review summarizes recent advances and mechanisms of esketamine in preventing and treating POD, offering new insights for clinical practice.

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**Fund program**: Qinghai Provincial Science and Technology Plan Fund (2019-ZJ-7085); Key Project of Qinghai Provincial Health System (2023-wjzdx-86)

2018 年围术期相关认知命名工作组发布的建议将谵妄分为苏醒期谵妄（emergence delirium, ED）和术后谵妄（postoperative delirium, POD）[1]。ED 指在手术后几分钟或几小时内诊断出的谵妄，包含了在复苏室苏醒的阶段。而 POD 是指在术后几天内、最长 1 周或直到出院前诊断出的谵妄，它是以注意力障碍、记忆障碍、意识水平波动、思维混乱、睡眠周期和情绪障碍为特征的急性脑功能障碍，主要出现在术后 24～72 h。一项 Mate 分析指出 POD 是住院患者发生远期认知功能障碍和短期病死率的独立危险因素，能够导致患者医疗费用增加、术后恢复质量下降和时间延长、并发症发生率增加、出院时间延长以及再次入院的可能性增加[2]。POD 多发生在 65 岁以上的老年人，年龄每增长 1 岁，发生谵妄的风险增加 1.15 倍[3]。相比较而言，超过 80 岁的老年人发生谵妄的概率更高。据研究报道，接受手术治疗的患者中 11%～51%的患者都会发生 POD，特别是接受心脏手术和重大非心脏手术的老年患者发生率最高[4]。《中国老年患者术后谵妄防治专家共识》显示心脏手术患者 POD 发生率为5.5%～46.0%，65 岁以上非心脏手术患者 POD 发生率为6.1%～57.1%，总体发病率为 11.1%，其中神经外科手术发病率最高，达到了57.1%，紧随其后的是上腹部手术，发病率为 18.1%，胸科手术和脊柱与关节手术的发病率分别为 16.3%和 15.2%[5]。国外一项研究调查显示，大于 65 岁的老年患者 POD 总体发生率为12.0%，其中妇科手术发生率最低（4.7%），心胸外科手术发生率最高（13.7%）[6]。根据临床表现将 POD 分为 3 种类型，（1）约占

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1/4 的高活动型谵妄：患者的临床表现多为不同程度的躁动、胡言乱语，多伴有攻击性动作和定向障碍，一般比较容易被医护或家属关注。（2）约占 1/2 的低活动型谵妄：临床表现多以安静不动、沉默不语、运动迟缓、嗜睡和互动减少为特点，临床症状不典型，常被医护人员及家属忽视。（3）约占 1/4 的混合型谵妄：同时具有高活动型和低活动型的部分临床表现，可在不同时间分别表现为躁动或嗜睡。谵妄患者易产生相关并发症进而引起不良预后，短期谵妄可增加患者急性呼吸窘迫综合征、非计划拔管等风险；长期谵妄会导致患者认知功能障碍、精神心理健康受损、生活质量下降。谵妄患者及其家属承受着巨大的痛苦，甚至可能导致创伤后应激障碍、抑郁和焦虑等心理疾病。

## 1　POD 的诊断、预防及治疗

到目前为止 POD 尚无明确的实验室诊断标准，国际上将美国精神病学会第 5 版《精神障碍诊断和统计手册》（DSM-V）和《国际疾病和相关健康问题统计分类》第 10 版（ICD-10）作为公认的诊断依据，美中不足的是需要有经验的精神科医师，通过床旁详细的访谈性和观察性神经精神评估。确诊依据主要是临床表现，包括注意力障碍、意识状况异常和认知功能障碍，伴随急性起病、病程波动的特点。由于 POD 金标准的诊断过于专业复杂，Inouye 等[7]建立了目前应用最广范的诊断方式——意识模糊评估量表（the confusion assessment method，CAM）。该评估量表具有 94%～100% 的敏感性和 90%～95% 的特异性，对于非精神心理专业的医师和护士比较友好，容易掌握，方便筛查谵妄。CAM 评估分为 4 个主要方面：（1）急性起病或意识状态的波动性改变；（2）注意力不集中或集中困难；（3）思维混乱；（4）意识水平改变。同时具（1）和（2），以及具备（3）或（4）其中一项，即可诊断 POD。在临床使用过程中，根据不同场景特殊患者需要，又发明了不同的衍生量表，如针对重症监护室患者的谵妄评估法（CAM-ICU）、基于 CAM 的 3 分钟诊断法（3D-CAM）等。虽然 POD 的发生率高，但研究发现高达 40% 的谵妄通过积极的多手段干预是可以预防的，预防是降低 POD 发生率的关键。住院患者在围术期处于相对应激的状态，在此期间周围环境变化和身体内部应激改变带来的刺激是发生 POD 的重要诱因。尽可能在围术期通过必要措施控制相关的不良诱因，可以降低 POD 的发生率。《中国老年患者术后谵妄防治专家共识》建议的综合性防治措施包括：（1）术前积极评估谵妄发生的风险，对于高风险患者，应积极采取相应的干预措施；（2）术中应重点关注手术和麻醉方面的管理。针对老年人应尽可能选择创伤小、时间短的手术方式，尽量不干扰人体的正常生理功能；（3）术后完善疼痛管理、术后康复和并发症的防治，鼓励早期下床活动，积极配合康复运动[5]。目前对于老年患者 POD 的治疗还没有成熟有效的治疗方案，尽管一项针对老年患者非心脏手术的随机、双盲、安慰剂对照临床试验显示，预防性给予低剂量右美托咪定可显著减少老年患者术后前 7 d 内谵妄的发生率[8]。但临床中药物治疗 POD 的效果有限，推荐多学科团队提供综合性非药物干预，主要措施是去除诱因、纠正病因、充分镇静镇痛、控制精神状态、改善睡眠为主[9]。

## 2　POD 的发病机制

目前关于 POD 的发病机制有众多的模型假说来解释，但大多数假说来自于动物模型，而直接来自人类的研究证据非常有限。总的来说，谵妄是多种因素共同作用的结果。研究报道的机制假说主要包括神经炎症学说、神经递质学说、氧化应激学说、睡眠-觉醒周期障碍学说、肠道菌群紊乱学说、遗传学说、脑电暴发抑制学说以及大脑网络连接变化学说[10]。单一的机制假说可能无法完全阐明 POD 的发生发展，相反，几组不同的假说因素相互作用会导致大脑中大规模神经元网络的破坏，从而导致急性认知功能障碍，进而发生谵妄。围术期手术、麻醉等应激使机体产生急性炎症反应，异常的应激反应导致先天免疫系统促炎性转变，可进一步引起中枢神经系统炎症反应从而导致 POD，并且白细胞水平、肿瘤坏死因子 α（TNF-α）、白细胞介素（IL）-6、IL-8、IL-10、C 反应蛋白水平升高[11]。其中 TNF-α 和 IL-6 的产生被认为是 POD 认知障碍的主要原因，并且这一过程在老年人中可能会加剧。Munster 等[12]进行了尸检病例对照研究，发现谵妄患者脑内小胶质细胞活性增高，IL-6 水平增加，进一步证明了谵妄的炎症机制。也有研究者认为 DNA 甲基化水平的变化可能是谵妄风险增加的最初分子机制[13]。麻醉与手术产生的应激性创伤不仅能够激活外周和中枢系统的炎症级联反应，还能产生氧化应激损伤，外周氧化应激能够破坏血脑屏障的完整性，促进炎性细胞因子及过氧化物进入大脑，从而诱发或加重中枢神经系统炎症而引起术后谵妄[14]。Lin 等[15]的研究结果表明脑内许多神经递质包括乙酰胆碱、多巴胺、谷氨酸、γ-氨基丁酸等与 POD 的发生密切相关，支持了神经递质假说。Qin 等[16]通过对褪黑激素调节细胞 $NOTCH_3$/NF-κB 信号通路的研究发现，睡眠-觉醒周期障碍及脑缺血、脑缺氧导致脑代谢紊乱引发了脑功能障碍。由神经、内分泌、免疫系统参与组成的脑-肠轴理论认为，术前常规的肠道准备可能会干扰正常肠道微生物群的成分和活性，增加患者 POD 发生率，进一步发现拟杆菌属和韦荣球菌属可能为 POD 的危险因素，欧陆森菌属可能是 POD 的保护因素[17]。脑电暴发抑制学说认为 POD 的发生与全身麻醉术中的麻醉深度相关，麻醉过深会增加脑电暴发抑制，从而增加 POD 风险[18]。大脑是一个高度重组和相互关联的结构，其功能允许感觉信息和运动反应的复杂整合，谵妄代表感觉信息和运动反应的整合和适当处理方面的可变故障，POD 患者脑电图的研究结果支持这个理论[19]。近年来基于谵妄的遗传基因易感性提出的遗传假说开辟了新的研究方向，一项荟萃分析发现基因 APOE4、多巴胺转运体基因 SCL6A3、多巴胺受体 2 基因、糖皮质激素受体、褪黑激素受体和线粒体 DNA 单倍型与 POD 存在一定联系[20]。

## 3　艾司氯胺酮与 POD 的相关研究

艾司氯胺酮发挥麻醉和镇痛作用，不仅是通过非竞争性

结合 NMDA 受体的苯环己哌啶位点抑制谷氨酸对该受体的激活，从而使神经元活动减弱，还可以与阿片类受体中的 $\mu$ 受体和 $\delta$ 受体结合产生镇痛作用，同时能够抑制痛觉过敏，对 NMDA 受体的亲和力是氯胺酮的 3~4 倍，镇痛效果是氯胺酮的 2~2.5 倍，药理作用位点和机制与氯胺酮基本一致。波兰的一项前瞻性、嵌套式病例对照研究从基因多态性角度研究术后谵妄的发病机制，结果表明 NMDA 受体 NR3A 亚基的遗传变异和功能紊乱可能是发生 POD 的机制之一[21]。一项纳入 160 名健康男性志愿者的Ⅳ期临床药物试验表明，艾司氯胺酮可以增加大脑中葡萄糖和乳酸含量，减少支链氨基酸和酪氨酸表达量，同时增加血清素和去甲肾上腺素的作用，并有助于改善抑郁和认知障碍，因此可被用于预防 POD[22]。罗静雅等[23]研究发现，小剂量（0.5 mg/kg）艾司氯胺酮不仅能够降低全身麻醉老年患者术后 7 d 内 POD 的发生率，还能降低术中阿片类镇痛药和血管活性药的使用量。任红等[24]研究发现，在全麻下行髋关节置换术的老年患者中，艾司氯胺酮可能通过抑制炎症反应、减轻脑损伤来减少老龄患者 POD 的发生。一项蛛网膜下腔阻滞联合髂筋膜神经阻滞的骨科研究显示，术中持续泵注小剂量（0.3 mg/kg）艾司氯胺酮可为老年髋部骨折患者围术期提供更完善的镇痛和镇静，降低术后早期（3 d 内）POD 的发生风险[25]。一项研究对比了右美托咪定和艾司氯胺酮的效果，发现两者均可用于预防老年胸外科患者麻醉后的谵妄和伤害性过敏反应，但艾氯胺酮在镇痛效果、改善不良情绪和睡眠、稳定术中血流动力学方面均优于右美托咪定[26]。有研究者发现在老年衰弱患者行胃肠道肿瘤根治术中给予小剂量艾司氯胺酮，可以降低衰弱患者 POD 的发生率[27]。杨子健等[28]在老年髋关节置换麻醉前用 0.2 mg/kg 艾司氯胺酮复合咪达唑仑进行诱导，可以降低患者 POD 的发生率，可能与减轻谷氨酸引起的 HT22 细胞凋亡和坏死有关。王妮等[29]在 80 例行食管癌根治术的老年患者中研究发现，围术期应用艾司氯胺酮可降低食管癌根治术后老年患者的钙结合蛋白 $\beta$（S100$\beta$）、神经元特异性烯醇化酶（NSE）水平及 POD 发生率，其机制可能与艾司氯胺酮的抑制炎性反应有关。同样的，曹彬等[30]也将小剂量艾司氯胺酮应用在胃肠道手术麻醉诱导期，发现其不仅可以减轻手术患者麻醉诱导中的血流动力学波动，还能降低 POD 的发生率。艾司氯胺酮不仅应用于老年患者，也被应用在儿童患者中。有研究发现麻醉结束时给予 0.2 mg/kg 艾司氯胺酮安全有效地降低了接受扁桃体切除术和/或腺样体切除术的学龄前儿童 ED 的发生率和严重程度以及术后疼痛[31]。然而，一项纳入 230 名患儿的研究得出了相反的结论，给予单次全麻诱导量（0.46 mg/kg）艾司氯胺酮可能增加全身麻醉学龄前儿童 ED 的发生率[32]。在儿童内窥镜检查中，与纳布啡对比，艾司氯胺酮联合异丙酚组内窥镜置入成功率较高，所需异丙酚总量较少，血流动力学较纳布啡组更稳定，但艾司氯胺酮组苏醒期躁动、复视等不良反应发生率较高[33]。这些研究也说明，艾司氯胺酮在儿童中的作用尚不明确，需要更多的临床证据。

## 4　总结与展望

尽管到目前为止 POD 确切的发病机制尚不明确，相关探索研究仍处于早期阶段，但是通过采取积极的筛查与干预措施可以有效地减少其发生，减少可能带来的不良临床结局。目前在老年患者中使用艾司氯胺酮防治 POD 的效果尚无定论，相关的高质量临床证据较少，急需大样本、多中心、前瞻性的随机对照临床试验，为防治 POD 探索出新的道路。

**利益冲突**　无

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