Still Delirious after All These Years

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1987 on the basis of its effect in lowering LDL cholesterol levels, but the first outcomes data for pravastatin did not become available until 1995. But if a drug were put on the market and subsequently found to be ineffective or unsafe, patients would have been exposed to unnecessary and perhaps unforeseen risks. The FDA would then have to take action to remove the drug — a problem that is avoided if data showing convincing clinical benefit are required before approval.

Vascepa represents an important example of a drug whose clinical outcome benefits have not

yet been established, and we do not yet fully understand its safety profile. The FDA's decision about Vascepa may not set a firm precedent, however, since the estimated likelihood and magnitude of both benefits and risks are unique to each new candidate drug.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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HISTORY OF MEDICINE

Still Delirious after All These Years

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Related article, p. 444-54

Doctors have recognized delirium for centuries. Transient alterations in consciousness, attention, orientation, perception, or behavior were well known with malaria and alcohol withdrawal or after surgery. Delirium became more prominent in the 1950s and 1960s with the emergence of intensive care. Intensive care units (ICUs) made it possible for patients to survive more severe illnesses and for doctors to attempt more aggressive interventions that required physiological monitoring, respiratory support, and intensive nursing. Delirium, “the ‘new madness of medical progress,’”¹ became more prevalent and more visible. Doctors set out to understand and prevent it, but, as the Critical Care Medicine article by Reade and Finfer (pages 444–454) shows, this effort is a work in progress.

Delirium results from so many sources that decisive understanding remains elusive.

The first intensive research on delirium associated with intensive care focused on cardiac surgery. These studies demonstrate the strategies and struggles of doctors who worked to understand delirium. Open-heart surgery had developed rapidly in the 1950s and 1960s, in parallel with — and dependent on — intensive care. Patients who underwent such surgery often had frightening delirium. Consider one patient who underwent mitral-valve replacement.² On postoperative day 5, she began to hear rock-and-roll music with laughter in the background, as if at a party. First she believed that her friends had hidden a record player under her mattress. As her paranoia deepened, she perceived insult-

ing voices in the music and thought it was part of a plot to torture her. She suspected that one of her nurses was dating one of her married physicians (definitive proof of her delirium, at least for the authors). Whenever she closed her eyes, she felt as if her bed were moving and feared that she was being taken back to surgery. The delirium cleared 2 days after she was transferred out of the ICU.

In 1965, Donald Kornfeld and his colleagues at Columbia–Presbyterian Medical Center published one of the first major studies of the problem.² Kornfeld's team studied 99 adult patients after open-heart surgery. Chart review revealed evidence of perceptual distortions, disorientation, hallucinations, or paranoia in 38%. Interviews of 20 patients found delirium in more — 70%.

A follow-up study of 100 patients refined the analysis.³ One group of patients (9%) exhibited an “organic brain syndrome,” with disorientation, impaired consciousness, and neurologic signs, immediately on awakening from surgery. A second group (24%) had “postcardiotomy delirium” like that described in the first study.

The researchers blamed organic brain syndrome on damage that occurred during surgery. This attribution made sense, given the limitations of early heart-lung machines. Patients had cerebral emboli (caused by air, cholesterol, platelet aggregation, or debris from silicone or other plastic tubing), blood-pressure fluctuations, and altered permeability of the blood-brain barrier.

Delirium posed a more difficult problem. These patients awoke intact after surgery, only to have delirium several days later; the symptoms usually cleared after transfer out of intensive care. Kornfeld’s team ruled out many variables, including age, diagnosis, and duration of surgery. Some of the risk could be attributed to preoperative factors: sicker patients, as assessed in terms of anesthesia risk or New York Heart Association functional classification, were more likely to become delirious. Some of the risk could be attributed to operative factors: the longer the duration of cardiopulmonary bypass, the greater the risk of delirium. Other researchers had speculated that changes in blood chemistry, possibly an increase in serotonin levels, contributed to the delirium, but Kornfeld’s team was skeptical: “Although it is possible that some metabolic or toxic effect does occur and then sponta-

neously subside in this postoperative period no present evidence exists to identify it.”²

Even though the Columbia team knew that cardiac surgery could injure the brain, they focused their analysis on the conditions of postoperative intensive care. How else could they explain the emergence of delirium after several days of lucidity? They suspected that the preoperative liabilities and operative insults produced an “impaired brain” that was “most susceptible to the stressful effect of the open-heart recovery-room environment.”² The stressors were not hard to identify. Patients were kept in oxygen and cooling tents that produced a background drone of humming and hissing. They were immobilized, if not by pain then by the tangle of electrocardiography leads and intravenous catheters. Hourly nursing checks made good sleep impossible. Patients described their stay “as a disturbing experience.”² Another review was even starker: “the oxygen tent, cooling blanket, monitoring devices, monotonous noise background, painful and weakened physical state, relative immobilization, and frequent interruptions of sleep — all superimposed on the usual clouded, postanesthetic mental state — combine to form a unique variety of psychological torture, rivaled only by the brainwashing techniques portrayed in recent science fiction thrillers.”⁴ Delirium was “a complex and multidetermined phenomenon.”⁵

Amid this abundance of possible causes, psychiatrists in the 1960s and 1970s looked even further afield, seeking psychodynamic causes of delirium associated with intensive care. Korn-

feld’s team studied 142 patients and arrived at a “new, suggestive finding”: that “a specific personality type may contribute to delirium.”⁵ Patients who exhibited “dominance, aggressivity, and self-assuredness” experienced “intense conflicts” with the “passive, immobilized patient role in the recovery room.” Summing up a decade of work, Kornfeld’s team concluded that delirium was “a psychosomatic condition, being the final common path for a variety of pathogenic factors ranging on a continuum of organic to symbolic.”⁵ Yet even as they wrote with confidence about delirious personalities, they admitted that delirium remained mysterious: “there are patients who have passive-submissive personalities, who have neither received tranquilizers nor been depressed preoperatively who nevertheless develop delirium. Indeed, delirium does occur in patients having no known physical or psychological risk factors, indicating that the etiology of delirium is not yet fully understood.”⁵

Not everyone was convinced that intensive care itself was the root of the problem. Psychiatrists at Massachusetts General Hospital, led by Thomas Hackett, studied 50 patients admitted to the coronary care unit (CCU) after myocardial infarction.¹ The CCU was “a cramped, essentially windowless place, as cheerless and drab as a room in a tenement.” Its apparatus, “especially cardiac monitoring devices, is almost universally regarded as conducive to the patient’s psychological decline.” And yet only 10% of the patients had delirium despite sleep deprivation, lurches between monotony and terror, and “constant threat of death.”¹ Why was

the incidence lower than among patients who had undergone cardiac surgery? Hackett's team offered three explanations. First, surgical units were noisier, brighter, more crowded, and had "more rush and turmoil." Second, surgical patients were "apt to be more obtunded and uncomfortable." Third, the residents who staffed the CCU undermedicated their patients for pain, anxiety, and sleep, inadvertently protecting their patients from the delirigenic effects of those medicines. Delirium had many causes, but Hackett's team did not think that it was an inevitable part of intensive care.¹

Since the 1960s, nurses and doctors have worked to make intensive care more tolerable for patients. They have implemented changes to improve sleep, minimize stressful interruptions, and

orient patients to time and date. Reade and Finfer also credit better ventilators and drugs, especially shorter-acting sedatives and analgesics. Yet delirium remains prevalent — seen in up to 89% of critically ill patients — and puzzling. Reade and Finfer speculate about γ -aminobutyric acid (GABA), acetylcholine, dopamine, and the neurotoxic effects of unspecified inflammatory cytokines but admit that the pathophysiology of delirium "remains largely uncharacterized." When patients become delirious, doctors cast a wide net to catch the likely cause, including withdrawal syndromes, hypoxia, hypoperfusion, hypoglycemia, hyperthermia, hypothermia, infections, poisoning, and many other possibilities. Although no one worries about delirigenic personalities anymore, no simple answers or solutions have

emerged. Continuing work is needed to understand the problem and minimize its consequences.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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