Dopamine Antagonists in ICU Delirium

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Perhaps the most vexing problem in a patient in an intensive care unit (ICU) is an unexpected change in mental status. Historically, "acute encephalopathy" was the term used to encompass such alterations, but "delirium" is now used to describe this state. The *Oxford English Dictionary* defines delirium as "an acutely disturbed state of mind characterized by restlessness, illusions, and incoherence that are occurring in intoxication, fever, and other disorders"; this was the concept based on the prototype of delirium tremens. With the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-4), the definition of delirium was expanded to "disturbance of consciousness and a change in cognition that develop over a short period of time,"[1] omitting the original flavor of agitation that characterized delirium tremens. In the DSM-5, the central aspects of delirium became a disturbance of attention and awareness,[2] further shifting focus to almost any form of disordered thinking. Assessments from scales that rate the level of consciousness, and possibly disordered thinking, in patients in the ICU[3] may be combined to suggest the presence of "hypoactive" delirium, which is a state of acute apathy — the obverse of the original meaning of the term delirium.[4] This categorization of delirium as hypoactive or hyperactive has implications for both treatment and clinical trials.

Girard et al.[5] now compare in the *Journal* two dopamine D_2 antagonists, haloperidol and ziprasidone, with placebo among ICU patients with delirium. Delirium was detected with the use of the Confusion Assessment Method for the ICU scale, which rates four features of delirium to determine a binary outcome of whether delirium is present or absent. Both drugs have activity at other receptors, including antagonism at 5-hydroxytryptamine$_2$ (5-HT$_2$) receptors. They are commonly used in patients who exhibit agitated and potentially injurious behavior in the ICU, such as intentionally or inadvertently removing endotracheal and gastric tubes, or who exhibit agitation that impedes mechanical ventilation. Intensivists have used these classes of drugs, often combined with sedatives, for decades and have considered them helpful in the treatment of patients with delirium.

Hypoactive delirium, seemingly less of a management problem, nevertheless hampers cooperation with nursing, physical therapy, and other activities. Over the past two decades, the notion arose that antipsychotic drugs could control delirium in patients not displaying potentially injurious behavior; approximately 85% of ICU patients with delirium have the hypoactive type. Because dopamine antagonists ameliorate thought disorders in psychotic patients, it seemed reasonable that they could help patients with disordered thinking regardless of the mechanism and independent of potentially injurious behavior in a patient.

Several trials of haloperidol for prophylaxis against delirium in the ICU have called all these suppositions into question. The Haloperidol Effectiveness in ICU Delirium (Hope-ICU) trial showed that the number of days alive without delirium or coma was not less with haloperidol than with placebo.[6] The Prophylactic Haloperidol Use for Delirium in ICU Patients at High Risk for Delirium (REDUCE) trial involved patients at risk for delirium and similarly showed no benefit for the prophylactic use of haloperidol.[7] For these reasons, some current clinical practice guidelines for the management of delirium no longer recommend haloperidol.[8]

The current trial by Girard et al. examines a different and clinically relevant question: are dopamine antagonist drugs useful for immediate treatment once delirium has begun? The primary result was that neither drug was better than placebo in the management of acute hypoactive or hyperactive delirium. Neither drug produced substantial adverse effects such as corrected QT prolongation or dyskinesias, and the drugs did not reduce the parallel use of opioids or sedatives. If they had, one might still recommend them. An interesting finding was that an added bolus of placebo was just as effective as an added bolus of an active rescue medication, perhaps because the majority of patients in the

trial had hypoactive delirium, for which the drugs may not have an effect. It would be interesting to know whether hyperactive patients were less likely to injure themselves (e.g., by unplanned endotracheal extubation) when given an active drug as a rescue agent. I would still consider using dopamine antagonists in patients at imminent risk of these types of injurious behaviors, but I would have less confidence in their benefits than I had in the past.

Why did the trial fail to show benefit? It is likely that our concept of delirium is flawed.[9] The neurochemistry of sudden alteration in mentation is complex and involves several neurotransmitters as well as structural, immunologic, and network alterations and possible brain infection that is not clinically evident.[10] The investigators deserve credit for conducting a difficult trial, but it would have been astounding if there were a single magic bullet for the restitution of normal brain function in ICU patients with delirium.

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