Critical Review Form
Therapy

Godet T, Louis C, Rieu B, et al. Dexmedetomidine for treatment of hyperactive delirium in non-intubated ICU patients: the 4D randomized clinical trial. Intensive Care Med. 2025;51(12):2305–2317.

Objectives: **To determine "Whether dexmedetomidine improves the control of hyperactive delirium in non-intubated intensive care unit (ICU) patients as compared with placebo remains uncertain." (p. 2305).**

Methods: **This multicenter, double-blind, placebo-controlled randomized trial was conducted in 9 French ICUs between December 2017 and February 2022. Adults (≥18 years) admitted to a participating ICU who were not on invasive mechanical ventilation, with a Richmond Agitation Sedation Scale (RASS) score ≥ +1 and a positive Confusion Assessment Method for the ICU (CAM-ICU) were eligible. Patients recently extubated or on tracheostomy pressure support within 24 hours, or who had received dexmedetomidine and/or haloperidol within 72 hours, were excluded.**

Patients were randomized in a 1:1 fashion to dexmedetomidine or placebo. Dexmedetomidine was infused at 0.2–0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (titrated up to 1.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$) or matching saline, targeting a RASS of 0 to −1. On enrollment, patients with RASS ≥+2 received an immediate 2.5-mg IV haloperidol bolus, with repeat doses (up to 30 mg/day) allowed if agitation persisted; beyond that, open-label rescue (preferentially clorazepate) was at the physician's discretion. Infusion continued for at least 36 hours after delirium resolution (four consecutive negative CAM-ICU assessments) or until ICU discharge.

The primary outcome was a composite or duration of agitation (hours with RASS ≥ +1), duration of delirium (days with positive CAM-ICU), and need for intubation with deep sedation for delirium control. Secondary outcomes included each primary component separately; ventilator-free and/or delirium-free days at day 30; ICU length of stay; mortality at days 7 and 30; septicemia, pneumonia, delirium recurrence, reuse of dexmedetomidine, use of rescue medications, and adverse respiratory, neurologic, or cardiovascular events.

Study enrollment stopped in February 2022 after an interim analysis with 168 patients enrolled. Of 344 screened patients, 168 were randomized; 17 (7 dexmedetomidine, 10 placebo) were excluded after randomization. The intention-to-treat analysis included 151 patients (77 dexmedetomidine, 74 placebo); the per-protocol analysis included 145 patients (74 and 71, respectively). Median ages in the placebo and dex groups were 72 and 69 years, respectively, and 24% and 18% were female.

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Guide	Comments
Are the results valid?	
Did experimental and control groups being the study with a similar prognosis?	
Were patients randomized?	Yes.
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	Yes. "Participants were randomly assigned 1:1 to receive dexmedetomidine or placebo via a web-based system. To ensure the blinding of study drug administration, opaque reinforced envelopes were available, identified by a unique number, each containing a study drug vial." (p. 2307) This system should ensure that allocation concealment was maintained.
Were patients analyzed in the groups to which they were randomized?	Yes. "An intention-to-treat analysis was considered for the primary analysis. Secondarily, a per-protocol analysis was also considered, including all randomized patients except those having one or more major protocol violations defined as trial inclusion and exclusion criteria (Supplementary Appendix)." (p. 2308)
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, most coexisting conditions, admission type (medical vs. surgical), SAPS 2 score, delirium phenotype, and median RASS score at enrollment. There were some differences in coexisting conditions (e.g. 51% with history of hypertension in the placebo group vs. 38% in the dex group).
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	No. "Study drug preparation was performed in a dedicated, secured preparation area within the participating ICUs by a nurse and/or a physician independent of the study protocol and not responsible for the enrolled patient to ensure double-blinding." (p. 2307)
Were clinicians aware of group allocation?	See above.
Were outcome assessors aware of group allocation?	Uncertain. It is not specifically mentioned whether outcome assessors were blinded to study group allocation (observer bias).
Was follow-up complete?	Yes. Excluding 17 patients who were randomized but later withdrew consent, outcome data was available for all 151 patients who remained in the study.
What are the results?	
How large was the treatment effect?	• Patients received similar median durations of study drug (4 days in each group), but those allocated to dexmedetomidine were less likely to receive haloperidol (40.5% vs 23.4%) and required fewer open-label rescue medications both on the inclusion day and over 30 days (58.4% vs 81.1%). • The jointly modeled primary outcomes significantly favored dexmedetomidine (median difference −30.9 points; 95% CI −49.4 to −12.4; p=0.001), with a shorter agitation duration (median 1.0 vs 2.0 hours; p=0.001). • There was no clear difference between dexmedetomidine and placebo in time to resolution of delirium (negative CAM-ICU), need for intubation, or 30-day mortality (13.5% vs 18.1%; RR 0.75; 95% CI 0.35–1.60). • Subgroup and multivariable analyses supported a beneficial effect of dexmedetomidine on the primary outcome, particularly in patients aged 65 years or older, and findings were consistent in the per-protocol cohort.

	• The frequency of adverse events and clinically significant events requiring treatment was similar in the dexmedetomidine and placebo groups.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above.
How can I apply the results to patient care?	
Were the study patients similar to my patient?	No. While this study was conducted exclusively at centers in France, where there were likely differences in ethnic make-up and medical comorbidities, it seems unlikely that this would have significantly affected outcomes. However. This study was conducted in the ICU, where care is quite different from that provided in the ED (external validity).
Were all clinically important outcomes considered?	Mostly yes. The authors considered a wide array of outcomes, including duration of agitation, duration of delirium, mortality, need for mechanical ventilation, days alive without delirium, and ICU length of stay. They did not consider need for restraint or patient or provider comfort as outcomes.
Are the likely treatment benefits worth the potential harm and costs?	Yes. In this trial of ICU patients with agitation and delirium, conducted at 9 sites in France, dexmedetomidine—when compared with placebo—reduced agitation duration and the need for haloperidol and rescue sedatives, improved the composite primary outcome (especially in patients ≥65 years), but did not clearly affect delirium resolution, intubation rates, mortality, or overall adverse events.

Limitations:

1. **Despite a planned sample size of 150 patients group (300 total patients), only 151 patients were included in the intention-to-treat analysis as the study was stopped early for perceived benefit.**

2. **The primary outcome, for which there was benefit, was a composite outcome without significant differences in all but one of the included components.**

3. **The authors do not specifically mention whether outcome assessors were blinded to study group allocation (observer bias).**

4. **This trial was conducted exclusively at centers in France, where there were likely differences in ethnic make-up and medical comorbidities (external validity).**

Bottom Line:

Yes. In this trial of ICU patients with agitation and delirium, conducted at 9 sites in France, dexmedetomidine improved the composite primary outcome (median difference −30.9 points; 95% CI −49.4 to −12.4; p=0.001) and reduced agitation duration median 1.0 vs 2.0 hours; p=0.001) when compared to placebo. While there was also a decrease in need for haloperidol and rescue sedatives, dexmedetomidine did not clearly affect delirium resolution, intubation rates, mortality, or overall adverse events.