

Online Resource 4 - Table 1. Association of medication exposure on day X and delirium resolution on the following day (day X+1), propensity score matching model

Exposure on day X	Mental status on day X+1	Adjusted OR (95% CI) ^{a, b}	p value
No haloperidol or clonidine	Delirium or unarousable	Reference	
Haloperidol only	Awake without delirium	0.51 (0.42-0.62)	<.001
Clonidine only	Awake without delirium	0.75 (0.60-0.94)	0.013
Both haloperidol and clonidine	Awake without delirium	0.44 (0.35-0.55)	<.001

CI = Confidence Interval; OR = Odds Ratio

^a Adjusted for age, APACHE IV score, admission type (acute surgery, elective surgery, medical reason), modified SOFA score, metabolic acidosis, use of ventilation, and administration of any antipsychotic other than haloperidol, benzodiazepines, propofol and opioids.

^b Mortality or discharge on day X + 1 was included as a competing event.

Online Resource 4 - Table 2. Characteristics of delirium days after propensity score matching; no haloperidol or clonidine versus haloperidol only

Variable	No haloperidol or clonidine on day X n = 986	Haloperidol only on day X n = 1,308
Age, years (IQR)	67.0 (59.0-74.0)	67.0 (61.0-74.8)
Admission type		
Medical, n (%)	455 (46.1%)	557 (42.6%)
Elective surgery, n (%)	200 (20.3%)	303 (23.2%)
Acute surgery, n (%)	331 (33.6%)	448 (34.3%)
APACHE IV score (IQR)	77.5 (60.0-97.3)	78 (61.0-98.0)
mSOFA score (IQR)	6.0 (4.0-8.3)	5.0 (3.0-8.0)
Metabolic acidosis, n (%)	172 (17.4%)	236 (18.0%)
Use of mechanical ventilation, n (%)	825 (83.7%)	1013 (77.4%)
Use of any antipsychotic other than haloperidol, n (%)	46 (4.7%)	60 (4.6%)
Use of benzodiazepines or propofol, n (%)	379 (38.4%)	452 (34.6%)
Use of opioids, n (%)	482 (48.9%)	566 (43.3%)

APACHE IV: Acute Physiology and Chronic Health Evaluation IV; mSOFA: modified Sequential Organ

Failure Assessment (without central nervous system component)

Online Resource 4 - Table 3. Characteristics of delirium days after propensity score matching; no haloperidol or clonidine versus clonidine only

Variable	No haloperidol or clonidine on day X n = 521	Clonidine only on day X n = 731
Age, years (IQR)	62.0 (51.0-71.0)	61.5 (52.3-69.0)
Admission type		
Medical, n (%)	264 (50.7%)	338 (46.2%)
Elective surgery, n (%)	131 (25.1%)	152 (20.8%)
Acute surgery, n (%)	126 (24.2%)	241 (33.0%)
APACHE IV score (IQR)	76.0 (56.0-87.0)	71.0 (56.0-87.0)
mSOFA score (IQR)	6.0 (4.0-9.0)	6.0 (5.0-8.0)
Metabolic acidosis, n (%)	87 (16.7%)	112 (15.3%)
Use of mechanical ventilation, n (%)	471 (90.4%)	674 (92.2%)
Use of any antipsychotic other than haloperidol, n (%)	49 (9.4%)	96 (13.1%)
Use of benzodiazepines or propofol, n (%)	285 (54.7%)	427 (58.4%)
Use of opioids, n (%)	403 (77.4%)	585 (80.0%)

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Online Resource 4 - Table 4. Characteristics of delirium days after propensity score matching; no haloperidol or clonidine versus both haloperidol and clonidine

Variable	No haloperidol or clonidine on day X n = 738	Both haloperidol and clonidine on day X n = 903
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Age, years (IQR)	65.0 (54.0-72.0)	64.0 (55.0-73.0)
Admission type		
Medical, n (%)	322 (43.6%)	371 (41.1%)
Elective surgery, n (%)	260 (35.2%)	241 (26.7%)
Acute surgery, n (%)	156 (21.1%)	291 (32.2%)
APACHE IV score (IQR)	73.0 (54.0-89.0)	72.0 (58.0-89.0)
mSOFA score (IQR)	6.0 (4.0-9.0)	6.0 (4.0-8.0)
Metabolic acidosis, n (%)	106 (14.4%)	118 (13.1%)
Use of mechanical ventilation, n (%)	651 (88.2%)	778 (86.2%)
Use of any antipsychotic other than haloperidol, n (%)	61 (8.3%)	92 (10.2%)
Use of benzodiazepines or propofol, n (%)	363 (49.2%)	456 (50.5%)
Use of opioids, n (%)	509 (69.0%)	655 (72.5%)

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Failure Assessment (without central nervous system component)