### 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  | Haloperidol only on day X |
|----------------------------------------------|--------------------------------------|---------------------------|
|                                              | n = 986                              | 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%)                     |

APACHE IV: Acute Physiology and Chronic Health Evaluation IV; mSOFA: modified Sequential Organ Failure Assessment (without central nervous system component)

*Online Resource 4 - Table 4. Characteristics of delirium days after propensity score matching; no haloperidol or clonidine versus both haloperidol and clonidine*
|                        | Group 1 | Group 2 |
|------------------------|---------|---------|
| 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%) |

APACHE IV: Acute Physiology and Chronic Health Evaluation IV; mSOFA: modified Sequential Organ Failure Assessment (without central nervous system component)