Title

The Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial

Short title

Clonidine in Elderly Patients with Delirium

Keywords

Delirium treatment, clonidine, RCT

Author names

Karen R. Hov MD[1,2,#], Bjørn Erik Neerland MD[1,2,#], Øystein Undseth MD[3], Vegard Bruun Bratholm Wyller, MD, PhD[2,4] Alasdair MJ MacLullich, MD, PhD[5], Eirik Qvigstad, MD, PhD[6], Eva Skovlund, MSc, PhD[7], Torgeir Bruun Wyller MD, PhD[1,2]

[1] Oslo Delirium Research Group, Department of Geriatric Medicine, Oslo University Hospital, Oslo, Norway

[2] Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3] Department of Acute Medicine, Oslo University Hospital

[4] Department of Pediatrics, Akershus University Hospital, Lørenskog, Norway

[5] Edinburgh Delirium Research Group, Geriatric Medicine, University of Edinburgh, UK

[6] Department of Cardiology, Oslo University Hospital, Oslo, Norway

[7] Department of Public Health and Nursing, NTNU, Trondheim, Norway

[#] shared first authorship

Corresponding author

Dr. Bjørn Erik Neerland, Oslo Delirium Research Group, Department of Geriatric Medicine,

University of Oslo, P.O.BOX 4956 Nydalen, N-0424 Oslo, Norway.

Phone: +47 90078979

E-mail: bjorn.erik@neerland.net

Word count

Abstract: 238 words

Main text:3166 words

Number of Tables: 3

Number of Figures: 2

Abstract

Objectives: The aim of this double-blinded randomised placebo-controlled trial was to investigate the efficacy of clonidine for delirium in medical inpatients > 65 years.

Methods: Acutely admitted medical patients > 65 years with delirium or subsyndromal delirium were eligible for inclusion. Included patients were given a loading dose of either placebo or clonidine; 75 µg every 3rd hour up to a maximum of 4 doses to reach steady state and further 75 µg twice daily until delirium free for 2 days, discharge or a maximum of 7 days of treatment. The primary endpoint was the trajectory of the Memorial Delirium Assessment Scale (MDAS) for the 7 days of treatment. Presence of delirium according to the DSM-5 criteria and severity measured by MDAS were assessed daily until discharge or a maximum of 7 days after end of treatment.

Results: Due to slower enrolment than anticipated, the study was halted early. Ten patients in each group were studied. The low recruitment rate was mainly due to the presence of multiple patient exclusion criteria for patient safety. There was no significant difference between the treatment group in the primary endpoint comparing the trajectory of MDAS for the 7 days of treatment using mixed linear models with log-transformation, ($p=0.60$). The treatment group did not have increased adverse effects.

Conclusions: No effect of clonidine for delirium was found, though the study was under-powered. Further studies in less frail populations are now required.

Key points:

- This randomised placebo-controlled study aimed to investigate the effect of clonidine for delirium in geriatric medical patients.

- More than 4000 eligible patients were screened for inclusion.

- Ten patients in each group were studied.

- No effect of clonidine for delirium was found, though the study was under-powered.

Background

Delirium is an acute disturbance in attention, awareness and cognition triggered mainly by acute medical disorders, trauma, surgery, or drugs. It affects at least 20% of hospitalised patients [1] and is associated with poor outcomes [2]. The pathogenesis is poorly understood, but one hypothesis is that delirium may in part result from exaggerated and/or prolonged stress responses [3]. No validated pharmacological treatment options exist [4,5], but still medications are widely, though variably, used [6,7].

Geriatric populations are poorly represented in drug trials [8], despite their being the bulk of patients in clinical medicine. Ageism is a possible cause, but there are likely also other factors including heterogeneity due to different stages of aging, comorbidities and polypharmacy. The lack of evidence informing medical decisions in older patients is a major challenge.

Dexmedetomidine is a parenterally administered alpha-2-adrenergic receptor agonist which attenuates sympathetic nervous system activity [9] and shows promise as treatment of delirium in intensive care units (ICU) [10-15] and dexmedetomidine is now in clinical use for delirium in ICUs [16]. However, the vast majority of patients with delirium are outside of ICUs, where dexmedetomidine use is not feasible. An alternative agent could be orally administered clonidine. This drug has very similar pharmacological properties to dexmedetomidine [17], but lower alpha-2-adrenergic selectivity [18]. Clonidine in delirium is little studied, but a pilot study showed that the use of clonidine infusion during the weaning period after surgery for type-A aortic dissection might reduce the severity of delirium [19].

The Oslo Study of Clonidine in Elderly Patients with Delirium (LUCID) aimed to investigate the potential superiority of clonidine vs. placebo in decreasing delirium severity and duration

in geriatric medical patients [20]. The primary endpoint was the trajectory of delirium severity over time (measured by Memorial Delirium Assessment Scale).

Methods

LUCID is a randomised, placebo-controlled, double-blinded, parallel group study with 4-month prospective follow-up [20]. Patients were recruited at the Oslo University Hospital, Oslo, Norway between April 2014 and February 2017. Independent data monitoring was performed. Acutely admitted medical patients > 65 years with delirium or subsyndromal delirium were eligible for inclusion. Included patients were randomised to treatment with oral clonidine or placebo for a maximum of 7 days. The goal was to include 100 patients, but according to the protocol, pharmacological analysis of clonidine and safety of the treatment would be assessed in the first 20 patients. As it turned out that inclusion rates were much lower than anticipated (for details on recruitment rates, see Results section and Figure 1), the Principal Investigator (T.B.W.) and study physicians (B.E.N. and K.R.H.) decided against further inclusion and the study was halted. This paper presents the results of these 20 patients.

Screening and inclusion

The main goal of the screening process was to find patients who fulfilled the selection criteria (see Table 1). Initially, all patients in the acute geriatrics ward were screened with a combination of the Single Question in Delirium (SQiD) [21] combined with two simple attention tests (reciting the days of the week and months of the year backwards). If any of these tests were positive, if the patient was drowsy, or if the nurse and/or the treating physician for any other reason suspected delirium, formal ascertainment of delirium or subsyndromal delirium was performed according to the DSM-5 criteria.

7

Due to low inclusion rates, the screening sites were expanded from January 2015 to all patients >65 years from the other medical wards. The screening was adjusted to initial information from staff and charts of any signs of delirium (i.e. change in mental state, drowsiness/change in arousal or other symptoms associated with delirium) or any knowledge of exclusion criteria present. If there were no known exclusion criteria, and the patient was described to have symptoms suggestive of delirium or being at moderate to high risk of delirium development; the investigators (B.E.N. and K.R.H.) performed delirium diagnostic tests according to DSM-5 criteria as previously published [20].

Due to the complexity of assessing both the inclusion and strict exclusion criteria, the ethics committee judged that the screening could be performed prior to consent, on condition that as soon as any positive exclusion criteria were found, no further confidential patient information was obtained.

Randomisation and blinding

The block randomisation was based on computer-generated random numbers, and was carried out by a statistician (E.S.). The randomisation schedule was distributed to the producer of the study medication, and capsules made accordingly. The randomisation was initially stratified with respect to whether or not the patient was admitted from a nursing home, in order to balance the groups with respect to pre-admission cognitive decline, an important prognostic factor. However, as the inclusion rate was slow and only two patients from nursing homes were eligible, to assist in reaching recruitment of the first 20 patients the stratification was cancelled. This was a double-blinded study where the study physicians (B.E.N. and K.R.H.) who evaluated the primary endpoint (delirium), the patients and the treating physicians all were blind to whether the patient is allocated to clonidine or placebo.

Intervention

The study drug was produced and labelled by "Kragerø tablettproduksjon A/S" and each capsule (CAPSUGEL) contained either 75µg Catapresan (clonidine hydrochloride) or placebo. After inclusion and randomisation to treatment group, patients were given a loading dose of one capsule every 3rd hour up to a maximum of 4 doses. Further dosage was one capsule twice daily (8 am and 8 pm) until delirium free for 2 days, discharge or a maximum of 7 days treatment, whichever came first. Blood pressure (BP) and heart rate (HR) were measured just before every dose for safety. The capsule was not given if the systolic BP (SBP) was < 100 mmHg or the HR < 50 beats per minute. Serum creatinine, blood glucose, ECG, a clinical assessment of hydration and the Richmond Agitation Sedation Scale (RASS) [22] were scheduled for daily assessments for safety reasons. If other medications were indicated for the treatment of delirium, the treating physician would prescribe this as was found necessarily, without interference from the study physicians. All patients received standard care following the ward routines.

Outcomes

The objective was to explore the potential superiority of clonidine vs. placebo in decreasing delirium duration and severity; measured by Memorial Delirium Assessment Scale (MDAS) [23] in patients diagnosed with delirium or subsyndromal delirium (according to Diagnostic and Statistical Manual of Mental Disorders, DSM-5 [24]). The primary endpoint was the trajectory of delirium measured by MDAS over time. Several secondary endpoints were also assessed, as detailed in the published protocol [20]. With the early termination of the study and thus very low power for any analyses, all analyses were considered exploratory. The most important secondary endpoints were considered to be time to delirium resolution (both first resolution

and final resolution), length of stay and use of rescue medications.

Data collection

All patients were assessed daily by a study physician for delirium diagnostics (according to DSM-5 criteria) and severity (MDAS). Scores were made based on a brief interview with tests of cognition, attention and alertness; including the digit span test (forward and backward), orientation and delayed recall, the Observational Scale of Level of Arousal (OSLA) [25] and RASS [22]. Also information from staff, charts and family members were obtained. All MDAS scores reflected the development from one MDAS score to the next (i.e. the last 24 hours). On some weekends the on-call geriatrician would see the patients and perform the tests/interview before the DSM-5 and MDAS scores were filled out on Monday in cooperation with the study physicians and also using chart review from the weekend. Details of the diagnostic process have previously been published [20].

Pre-existent functional and cognitive status were assessed by asking the patient's primary caregiver (the best available source) to complete questionnaires to assess the patient´s functional and cognitive state two weeks prior to hospital admission. Functional status was assessed using the Barthel ADL Index [26] and the Nottingham Extended ADL Index (NEADL) [27]. To ascertain prior long-term cognitive decline we used the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [28] using a recently published cut-off of IQCODE >3.82 for pre-existing cognitive impairment [29]. The severity and number of comorbidities were scored using the Cumulative Illness Rating Scale (CIRS) [30]. The level of physiological disturbance was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) [31].

Statistical methods

A statistical analysis plan (SAP) was developed (and published online at http://folk.uio.no/tbwyller/research.htm) prior to unblinding of the data. Based on power calculations and choice of statistical methods, the study aimed for 100 included patients. Therefore, when ending the study after 20 patients it was not sufficiently powered to precisely estimate effects, and it was thus not expected to be possible to draw conclusions about the primary outcome. However, the SAP stated that we would adhere to the original plan as described in the protocol, but consider the analyses (of both primary and secondary endpoints) as exploratory. The statistician (E.S.) carried out the analyses blind to allocation.

For comparison between the groups of the repeated measures of continuous variables (i.e. MDAS and OSLA), we used mixed linear models [32]. Estimated slopes for each individual's trajectory were based on all available data, thus tolerating a few missing single time-point evaluations. Data regarding our primary endpoint were available from all patients, and the three patients who died during the hospital stay or shortly after discharge were also included in all analyses. There was no linear relationship between the MDAS (and OSLA) scores and time, and data was log-transformed to better fit a linear model. For time to resolution of delirium and length of stay, the Kaplan Meier method and the logrank test were applied.

Statistical analyses were performed in SPSS Statistics version 22 and 24 (IBM, Armonk NY) and Prism v7 (GraphPad Software Inc, La Jolla, CA, USA).

Ethics

The study was undertaken in accordance with the Declaration of Helsinki. The data and plasma samples were collected after informed consent from the patient and/or proxy (if

patient was lacking capacity to consent due to delirium and/or dementia), as approved by the Regional Committee for Ethics in Medical and Health Research (South-East Norway) REK: 2013/525. Due to the importance of rapid inclusion, the proxy would give verbal consent (by phone) before inclusion to the study, and written consent was obtained as soon as possible afterwards. None of our 20 patients had capacity to consent to this study, so next of kin gave consent in all cases. Still, all patients were informed to the level of their capacity and all tests were voluntary at all times. ClinicalTrials.gov NCT01956604. EudraCT Number: 2013-000815-26. Approved by The Norwegian Medicines Agency.

Results

Screening and inclusion

Of 4282 inpatients screened, 4262 were ineligible (see flowchart, Figure 1). Out of these, 3110 were considered to have no delirium or other inclusion criteria were not fulfilled, while 1152 patients had at least one exclusion criterion present (delirium status unknown in 813 of these). Twenty patients fulfilled the selection criteria and were included in LUCID between April 2014 and February 2017 and randomised to either clonidine (n=10) or placebo (n=10). No patients were lost or excluded after inclusion and all 20 patients are included in our analyses. Median age was 86 years (range 66-95), and 13 (65%) were women. See Table 2 for background characteristics.

Primary endpoint

Comparing the trajectory of MDAS for the 7 days of treatment using mixed linear models with log-transformation, there was no statistically significant difference in the reduction of log(MDAS score) over time (p=0.60) between the two groups. See Figure 2 for all individual MDAS trajectories in both treatment groups.

Secondary endpoints

There was no difference in time to first delirium resolution (i.e. first day without delirium) between the groups (placebo group median 3.0 (95%CI 1.8-4.2) vs. clonidine group median 3.0 (95%CI 2.1-4.0)), p=0.59. There was also no significant difference in time to final delirium resolution (i.e. first delirium free day without known consecutive delirium episodes); placebo group median 8.0 (95%CI 4.7-11.3) vs. clonidine group median 5.0 (3.8 - 6.3), p = 0.40. Median length of stay was 7 days in both groups. For the delirium element arousal (measured with OSLA) the trajectories were similar to those of MDAS, and using mixed linear models there was no significant difference between the groups (p= 0.37). The use of rescue medications is described in Table 3. As the study was halted early and no effect of clonidine could be detected on primary or main secondary outcomes, no exploration of data from the 4-month follow-up was performed.

Safety, haemodynamic responses and plasma concentrations

Plasma concentrations of clonidine and haemodynamic responses were measured and have been reported [33]. Briefly, plasma concentration levels were within the higher end of our target range, suggesting that loading doses are not necessary to achieve adequate early therapeutic effect. There was extensive individual BP and HR variation in both the clonidine and placebo groups, but there were no episodes of clinically significant hypotension or bradycardia in any patient in any group.

Other events

On the 5th day of treatment, one patient in the clonidine group developed a hypertensive pulmonary oedema (SBP 238 mmHg). According to the study protocol, the study drug was

halted and a report of a possible Serious Unexpected Serious Adverse Reaction (SUSAR) was filed routinely to The Norwegian Medicines Agency. The patient died two weeks later. The acute hypertensive episode was treated effectively, and hypertension was not a reoccuring problem when the patient's status deteriorated further. After careful consideration, it was assessed that the episode was not related to the study drug; nor that withdrawing clonidine aggravated the situation. In the placebo group two patients died during the hospital stay or shortly after discharge.

Regarding minor side effects, two patients in both the clonidine and the placebo group reported dry mouth. One patient in the clonidine group experienced a fall during the treatment, but it was not considered related to hypotension (there was no orthostatic hypotension found in this patient). There were no significant episodes of sedation or alterations in blood-glucose in either treatment group.

Discussion

Enrollment in LUCID was more difficult than anticipated. The low recruitment rate was mainly due to a combination of a frail target population and the presence of rigorous exclusion criteria. After the twentieth patient was included, an assessment by the Principal Investigator (T.B.W.) and Study Physicians (B.E.N. and K.R.H.) decided against further inclusion to this study as the time frame to achieve 100 patients was clearly unrealistic. Additionally, with such a small percentage of eligible patients included the results would not be considered generalizable to the population in question. It was, however, in line with the protocol to halt the trial after the first 20 patients to evaluate feasibility. The following results are considered exploratory.

There were no statistically significant differences between the treatment groups with regard to our primary endpoint (MDAS trajectory) or secondary endpoints (e.g. time to delirium resolution). Due to the low power, however, the results do not imply that clonidine does not have a beneficial effect on delirium. Likewise, there is a possibility that clonidine is not effective. Based on our exploratory analysis, there is no trend in either direction. Thus, the study is inconclusive, and the main finding is that strict exclusion and inclusion criteria made the present study infeasible. Further evaluation of this drug in a more robust population and with altered exclusion and inclusion criteria is warranted.

As seen in the flowchart (Figure 1), there were many delirious patients, but the ineligibility rates were very high. Most commonly, exclusion criteria for patient safety were present and several patients had more than one exclusion criterion. The ethics committee accepted that the screening could be performed prior to consent, provided that once it was recognised that a patient was not eligible for the study, no further confidential patient information could be obtained. Due to this, many patients being registered with one exclusion criterion might in fact have more than one criterion present. For the same reason delirium status was unfortunately not assessed in all patients and is unknown for a large proportion of the patients not included. Our impression is that many of the patients who had to be excluded had in fact delirium. Even though no evidence exists regarding the need for dose adjustments based on renal dysfunction, such adjustment seems reasonable based on the renal elimination [34].

The major recruiting problem was the high prevalence of exclusion criteria in our frail and multimorbid population. One solution could have been to adjust the exclusion criteria, but since the benefit of clonidine for delirium treatment is uncertain, it was not acceptable to take

higher risks in order to improve recruitment. A lower dosage of clonidine could have been considered, but our challenge was that certain exclusion criteria were considered necessary for any dosage of clonidine. Also, lower dosages might not be expected to reveal any beneficial effect. So for future studies of clonidine for delirium; trials in more robust populations are probably more realistic; and feasibility studies in the chosen population would be helpful. Still, as the potential beneficial effect of clonidine in delirious patients is unknown, focus in such trials should be on feasibility and safety.

A strength of our study was the structured and comprehensive delirium diagnostics performed according to a published algorithm. However, this approach is work-demanding. Balancing the difficult task of delirium diagnostics with what is do-able must be considered for future studies. As inclusion rates are often low in delirium treatment trials, multicentre studies have often been more successful and the use of delirium detection tools already established in the wards might be feasible in these studies. Another practical issue is related to the need for informed consent. Our procedure with proxy-consent by phone worked very well.

The overall impression from the clinical assessments was not that the exclusion criteria were too strict, but rather that the population at hand was indeed very frail and multi morbid, as illustrated by a 15% short term mortality. Thus any introduction of new drugs needs to be well indicated and carefully considered regarding potential side effects.

The study included a real life control group in the assessment of hemodynamic changes. The patients were monitored very closely; safety and best care of the patients was a priority. As expected in this population, some evaluations are missing. Over all, because of strict exclusion criteria, the external validity of our findings is potentially limited.

In conclusion, enrollment in LUCID was considerable more difficult than anticipated and the low inclusion rate was mainly due to the frail population and the presence of exclusion criteria for patient safety. The study was halted after 20 patients had been included, and no statistically significant difference between the clonidine and placebo was detected. It is however important to emphasize that this apparent lack of effect should not be misinterpreted as evidence of no therapeutic potential for clonidine in delirium. Further studies of clonidine for delirium are called for, but should be performed in a more robust patient population.

References

1. Ryan DJ, O'Regan NA, Caoimh RO, et al. Delirium in an adult acute hospital population: predictors, prevalence and detection. *BMJ Open.* 2013;3(1).

2. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA : the journal of the American Medical Association.* 2010;304(4):443-451.

3. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *Journal of psychosomatic research.* 2008;65(3):229-238.

4. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *Journal of the American Geriatrics Society.* 2016;64(4):705-714.

5. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* 2014;383(9920):911-922.

6. Carnes M, Howell T, Rosenberg M, Francis J, Hildebrand C, Knuppel J. Physicians vary in approaches to the clinical management of delirium. *Journal of the American Geriatrics Society.* 2003;51(2):234-239.

7. Morandi A, Davis D, Taylor JK, et al. Consensus and variations in opinions on delirium care: a survey of European delirium specialists. *International psychogeriatrics / IPA.* 2013;25(12):2067-2075.

8. Briggs R, Robinson S, O'Neill D. Ageism and clinical research. *Ir Med J.* 2012;105(9):311-312.

9.   Smith H, Elliott J. Alpha(2) receptors and agonists in pain management. *Current opinion in anaesthesiology.* 2001;14(5):513-518.

10.   Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA : the journal of the American Medical Association.* 2007;298(22):2644-2653.

11.   Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA : the journal of the American Medical Association.* 2009;301(5):489-499.

12.   Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;50(3):206-217.

13.   Shehabi Y, Grant P, Wolfenden H, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). *Anesthesiology.* 2009;111(5):1075-1084.

14.   Mo Y, Zimmermann AE. Role of dexmedetomidine for the prevention and treatment of delirium in intensive care unit patients. *The Annals of pharmacotherapy.* 2013;47(6):869-876.

15.   Zhang H, Lu Y, Liu M, et al. Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. *Crit Care.* 2013;17(2):R47.

16.   .

16.   Bajwa S, Kulshrestha A. Dexmedetomidine: An Adjuvant Making Large Inroads into Clinical Practice. *Annals of medical and health sciences research.* 2013;3(4):475-483.

17. Pichot C, Ghignone M, Quintin L. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? *Journal of intensive care medicine.* 2012;27(4):219-237.

18. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia.* 1999;54(2):146-165.

19. Rubino AS, Onorati F, Caroleo S, et al. Impact of clonidine administration on delirium and related respiratory weaning after surgical correction of acute type-A aortic dissection: results of a pilot study. *Interactive cardiovascular and thoracic surgery.* 2010;10(1):58-62.

20. Neerland BE, Hov KR, Bruun Wyller V, et al. The protocol of the Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID: a randomised placebo-controlled trial. *BMC geriatrics.* 2015;15:7.

21. Sands MB, Dantoc BP, Hartshorn A, Ryan CJ, Lujic S. Single Question in Delirium (SQiD): testing its efficacy against psychiatrist interview, the Confusion Assessment Method and the Memorial Delirium Assessment Scale. *Palliative medicine.* 2010;24(6):561-565.

22. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *AmJRespirCrit Care Med.* 2002;166(10):1338-1344.

23. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *Journal of pain and symptom management.* 1997;13(3):128-137.

24. Association AP. *Diagnostic and Statistical Manual of Mental Disorders, 5th edn. DSM-5.* . Arlington, VA: American Psychiatric Association; 2013.

25. Tieges Z, McGrath A, Hall RJ, Maclullich AM. Abnormal level of arousal as a predictor of delirium and inattention: an exploratory study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2013;21(12):1244-1253.

26. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Maryland state medical journal.* 1965;14:61-65.

27. Lincoln NB, Gladman JR. The Extended Activities of Daily Living scale: a further validation. *Disability and rehabilitation.* 1992;14(1):41-43.

28. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychological medicine.* 1994;24(1):145-153.

29. Jackson TA, MacLullich AM, Gladman JR, Lord JM, Sheehan B. Diagnostic test accuracy of informant-based tools to diagnose dementia in older hospital patients with delirium: a prospective cohort study. *Age and ageing.* 2016;45(4):505-511.

30. Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. *Journal of the American Geriatrics Society.* 2008;56(10):1926-1931.

31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Critical care medicine.* 1985;13(10):818-829.

32. Tahir TA, Eeles E, Karapareddy V, et al. A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. *Journal of psychosomatic research.* 2010;69(5):485-490.

33. Hov KR, Neerland BE, Andersen AM, et al. The use of clonidine in elderly patients with delirium; pharmacokinetics and hemodynamic responses. *BMC pharmacology & toxicology.* 2018;19(1):29.

34. Gagnon DJ, Fontaine GV, Riker RR, Fraser GL. Repurposing valproate, enteral clonidine, and phenobarbital for comfort in adult ICU patients: a literature review with practical considerations. *Pharmacotherapy.* 2017.

Tables

Table 1. Selection criteria

Table 1. Selection criteria
Inclusion criteria

- Patient > 65 years old admitted to an acute medical ward

- Delirium or subsyndromal delirium within the last 48 hours

- Signed informed consent from patient or relatives and expected cooperation of the patients for the treatment and follow up must be obtained and documented

Exclusion criteria

- Symptomatic bradycardia, bradycardia due to sick-sinus-syndrome, second- or third-degree AV-block (if not treated with pacemaker) or any other reason causing HR <50 bpm at time of inclusion

- Symptomatic hypotension or orthostatic hypotension, or a systolic Blood Pressure <120 mmHg at the time of inclusion

- Ischemic stroke within the last 3 months or critical peripheral ischemia

- Acute coronary syndrome, unstable or severe coronary heart disease (symptoms at minimal physical activity; NYHA 3 and 4) and moderate to severe heart failure (NYHA 3 and 4). (Acute coronary syndrome is defined according to international guidelines)

- A diagnosis of polyneuropathy, phaeochromocytoma or renal insufficiency (estimated GFR<30 ml/min according to the MDRD formula)

- Body weight <45 kg

- Considered as moribund on admission

- Unable to take oral medications

- Current use of tricyclic antidepressants, monoamine reuptake inhibitors or ciclosporin

- Previously included in this study

- Adverse reactions to clonidine or excipients (lactose, saccharose)

- Not speaking or reading Norwegian

- Any other condition as evaluated by the treating physician

- Admitted to the intensive care unit

AV = Atrioventricular; HR = Heart Rate; NYHA = New York Heart Association; GFR = Glomerular Filtration Rate; MDRD = Modification of Diet in Renal Disease

Table 2 Characteristics of study participants, n=20

Characteristic	Clonidine, n = 10	Placebo, n = 10
Age, years, median (range)	85 (73-94)	88 (66-95)
Female, n/N (%)	6/10 (60)	7/10 (70)
Body mass index, kg/m^2, median (range)	23 (19-29)	24 (17-28)
Creatinine at baseline, median (range)	78 (34-128)	88 (32-140)
Pre-existing cognitive impairment (IQCODE ≥ 3.82), n/N (%)	5/9[†] (55)	6/10 (60)
Barthel ADL Index, median (range)	18 (10-20)	16 (5-20)
Independent in ADL[‡], n/N (%)	4/10 (40)	3/10 (30)
The Nottingham Extended ADL Index (NEADL), median (range)	33 (17-60)	28 (1-48)
Admitted from nursing home, n/N (%)	0/10	2/10 (20)
Acute Physiology and Chronic Health Evaluation II (APACHE II), median (range)	10 (8-16)	11 (7-19)
Cumulative Illness Rating Scale (CIRS), total score	17 (8-21)	18 (7-31)

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; ADL = Activities of Daily Living

[†] IQCODE missing in one patient, [‡] Barthel Index score ≥19

Table 3 Use of rescue medication

Rescue medication	Clonidine, n = 10	Placebo, n = 10
Prticipants who received rescue medication, n/N (%)	4/10 (40)	6/10 (60)
No rescue medications	6 (60)	4 (40)
Only sedatives (benzodiazepines and/or clomethiazole)	2 (20)	4 (40)
Only antipsychotics	0	0
Both sedatives and antipsychotics	2 (20%)	2 (20%)

Legends

Figure 1. Flow chart of study screening, inclusions and exclusions

Figure 2. The figure shows the individual trajectories of the individual Memorial Delirium Assessment Scale (MDAS) scores in the clonidine and placebo groups (upper and lower panels of the figure, respectively).