Reviewer's report

Title: The Oslo Study of Clonidine in Elderly Patients with Delirium; LUCID. The protocol of LUCID

Version: 1 Date: 24 August 2014

Reviewer: Benjamin Liptzin

Reviewer's report:

Major compulsory revisions:
1. This really should be described as a pilot or feasibility study given how complex it will be to carry out. The authors do not describe how many patients are admitted to their acute geriatrics ward. Until doing the study they do not know how difficult it will be to recruit i.e. how many patients will they have to screen to get 100 to participate. They also need to know how many patients will have or develop DSM5 delirium and subsyndromal delirium and whether they and their family will consent to participate in the study when they are admitted to the hospital for being medically ill and wanting their illness treated. They also need to know how many are admitted from a nursing home for the purposes of the stratification. As a feasibility study the authors can also figure out the right dose of study medication to use (see uncertainty on p. 6), what to do with patients who don't have informants readily available, and whether patients will tolerate all the interviews and testing. The authors acknowledge that the sample size may not be sufficient to answer the study question of whether clonidine shortens or reduces the severity of an episode of delirium.

2. For the purposes of this initial study why include subsyndromal delirium when that may make it even more difficult to find a difference between drug and placebo? This is particularly important because your endpoints are severity and duration. On p. 8 you say duration will be monitored by DSM5 criteria but how will that apply to subsyndromal delirium? In the study design on p. 9 do you mean patients will no longer meet criteria for DSM5 criteria or no longer have any symptoms of delirium?

3. On p. 12 why not measure cognitive decline or pre-existing diagnosis of dementia directly instead of using NH residence as a proxy?

Minor Essential Revisions
1. On p. 5 the discussion of use of clonidine could be shortened since its use in migraine or post-menopausal flushing or chronic fatigue syndrome doesn't seem relevant to this study.

2. On p. 6 the discussion of pharmacokinetics seems excessive except as it affects dosing in this study.
3. The discussion on p. 7 of adolescents with chronic fatigue is not relevant and can be omitted. The discussion of loading doses also seems excessive.

4. On p. 8 the Safety Review is also a dose finding study. In addition to finding out what oral dose will likely be needed tolerability should be assessed, not just blood levels.

5. On p. 10 (and p. 13) what will be done for patients who have no family or nursing home staff as informants? The definition of "acute change" is critical to the definition of delirium. How much change is required for a diagnosis of subsyndromal delirium? If the patient is off by one day on the date but usually knows it is that sufficient?

6. On p. 11, if you're using the MDAS as your measure of severity and DSM5 as your criteria for having delirium or not what's the purpose of also using the CAM daily?

7. With respect to informed consent, how "cognitively intact" can someone be and still meet criteria for delirium?

8. On p. 12 are there any restrictions on which other medications are allowed and which are not?

9. The monitoring and safety discussion on p. 12 and the lab tests described on p. 13 seem excessive and should be justified.

10. Are you aware there is a copyright on the MMSE and a royalty will need to be paid if it's used? Also on p. 13 what is the purpose of the grip strength or the data on patient distress? Are the lab tests a "fishing expedition" or are there some hypotheses about sed rate, TSH or free thyroxine? Was there consideration for measuring APOE subtypes? The discussion about safety review on p. 14 is repetitive.

11. On p. 14 is the followup 1 week after the end of treatment or discharge from the hospital? At 4 months how will you handle patients lost to follow up? Will you measure persistent delirium as defined by DSM5 or include symptoms of subsyndromal delirium or change from baseline as well?

12. On p. 15 how will you measure time to resolution of delirium from enrollment in the study to resolution for patients who are discharged while still delirious? Also on p. 15 what's the estimate of how many patients will have to be screened to get an adequate sample of willing participants? Over the 36 months how many patients will be admitted to the geriatric wards? (It would also be worth describing the types of patients admitted to these wards.) It's also not clear what "single point in time" would be used for the MDAS.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

No competing interests