Population ageing and effects on acute health care chain

What is delirium and what are the consequences?

How can delirium be managed in older patients in hospital?

Delirium and haloperidol

Outline of this thesis
Population ageing and effects on acute health care chain

The population is ageing. Demographic features and prognosis on the population growth in the Netherlands show that the proportion of adults aged 65 and over is expected to increase with 8% in the next two decades, from 18% in 2015 to 26% in 2035.[1] An important factor contributing to this growth of the older population is an increase in life expectancy. In 2015, the average life expectancy at birth for the Dutch population was 80 and 83 years for men and women, respectively, with an expected 5-year increase for both sexes over the next 35 years.[1] This increase in life expectancy is thought to be partly attributable to a rise in healthcare expenditure, especially for older individuals.[2, 3]

With increasing age there is a higher prevalence of chronic diseases. A study using observational data from 212,902 individuals registered at 59 Dutch general practices demonstrated that 59% of those aged 75 years and over had at least two or more chronic diseases, compared with 23% to 39% of those aged 55 to 74 years.[4] As may well be expected, an increase in the proportion of older individuals with multiple comorbidities will result in a growing demand for acute and in-hospital care.[5]

Already the proportion of adults aged 70 years and over among hospitalised patients in the Netherlands grew over a 5-year period from 26.9% in 2005 to 27.9% in 2010. [6] Previous studies have shown that older individuals account for up to 22% of emergency department (ED) visits and are four times more likely to be admitted than younger adults.[7, 8] In the age group of 65 to 74 years, almost half of hospital admissions originate in the ED and this percentage further increases to 60% for the oldest old with age 85 years and over.[9] Furthermore, their length of stay (LOS) in the ED is longer and amount of resources required is higher.[7, 10] Also, early ED return visits are frequent. When discharged home, around 19% of older adults revisit the ED within one month.[11, 12] Therefore, as the Dutch population continues to grow and age, there will be an increasing demand for acute hospital care, starting in the ED.

Atypical disease presentations such as falls and delirium are common in older patients. [13, 14] The point prevalence of delirium in a general, adult, acutely admitted hospital population is approximately 20%.[15] In older surgical inpatients, delirium occurs far more frequently with prevalence rates of up to 51% in those scheduled for acute hip surgery.[16] Its high prevalence and adverse outcomes make delirium a topic of clear importance in health care for older patients.

What is delirium and what are the consequences?

Delirium is an acute, often reversible, cognitive disorder involving a disturbance of a person’s attention and awareness. The American Psychiatric Association
Introduction and Outline

(APA) Diagnostic and Statistical Manual of Mental Disorders criteria for delirium are considered ‘gold standard’ for the diagnosis, of which the fifth edition (DSM-5) is the most recent version.[17] According to these criteria, delirium is an acute disturbance in attention and awareness from baseline typically developing over a short period of time and of which symptoms tend to fluctuate during the day. Additionally, there is a disturbance in cognition. In the context of delirium, these disturbances cannot be better explained by a neurocognitive disorder such as dementia and may not occur in the setting of a severely reduced level of arousal such as coma. Furthermore, there must be evidence that the disturbances are a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or are due to multiple aetiologies. The three known subtypes of delirium based on clinical features of psychomotor activity are hypoactive-type, hyperactive-type and mixed-type delirium.[18]

Table 1. DSM-IV and DSM-5 criteria for delirium (Adapted from [19])

<table>
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<tr>
<th>DSM-IV</th>
<th>DSM-5</th>
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<td>A. Disturbance of consciousness with reduced ability to focus, sustain or shift attention.</td>
<td>A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).</td>
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<td>B. A change in cognition or development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.</td>
<td>B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.</td>
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<tr>
<td>C. The disturbance develops over a short period of time, usually hours to days, and tends to fluctuate during the course of the day.</td>
<td>C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).</td>
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<td>D. There is evidence from history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.</td>
<td>D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.</td>
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<td></td>
<td>E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.</td>
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Delirium is not a disease itself, but rather a manifestation of one or more underlying causes. As depicted in the DSM-5 criteria, delirium is assumed to be multifactorial. Particularly in older adults, delirium is likely the result of an interaction between predisposing risk factors, increasing an individual’s susceptibility to delirium, and precipitating factors, directly contributing to its onset. Previous studies have identified many of such predisposing and precipitating risk factors for delirium in older general medicine and surgery patients.[20] Predisposing risk factors include cognitive impairment, visual impairment and severe illness.[21, 22] Examples of precipitating risk factors are use of specific or multiple medications, malnutrition and events such as catheters or surgery.[23, 24] Some risk factors are potentially modifiable, for instance sleep deprivation and pain, while others such as age are not. Many of potentially modifiable risk factors have been targets for non-pharmacological intervention strategies.[25, 26]

**Figure 1.** Multifactorial model for delirium (Adapted from [24]).

The occurrence of delirium in hospitalised older patients is associated with adverse clinical and post-discharge outcomes such as prolonged LOS, functional and cognitive decline, and increased risk of death.[27-30] With the ageing population,
delirium and its associated burden will become an even greater concern for healthcare professionals. This emphasizes the importance of increasing the existing knowledge not only about its causes but also about the effective management strategies, prevention in particular.

**How can delirium be managed in older patients in hospital?**

Treatment of delirium is primarily aimed at identifying and treating the underlying cause(s). Clinical practice guidelines on delirium treatment published by the APA, National Institute for Health and Clinical Excellence (NICE) and the American Geriatrics Society (AGS) advise to limit treatment with antipsychotics to those patients who experience severe agitation or stress in the context of delirium, or for those in whom non-pharmacological interventions appear insufficient.[31-34] For the prevention of delirium, multicomponent non-pharmacological interventions targeting multiple delirium risk factors have been proven successful in reducing the incidence of delirium in older hospitalised patients.[35, 36] However, these studies have failed to demonstrate a consistent effect of these interventions on reducing severity or duration of delirium during hospitalisation.[26, 37] Also, an overall beneficial effect of these non-pharmacological interventions on relevant clinical and post-discharge outcomes such as hospital LOS and mortality has not yet been established.[35, 36] An important determining factor for the effectiveness of these non-pharmacological interventions is protocol adherence.[38] However, large variability exists in the adherence to different components of non-pharmacological intervention protocols,[26, 37-39] which could limit their success rate in everyday practice outside the setting of clinical trials. Pharmacological interventions with antipsychotics may possibly be more easily implemented in daily clinical practice, but thus far there is no strong evidence supporting their use in either treatment or prevention of delirium in hospitalised adults.[40]

**Delirium and haloperidol**

One of the main hypotheses on the underlying pathophysiological mechanisms evoking delirium is a disturbance in the neurotransmitter systems of acetylcholine (reduced availability) and dopamine (excess release) secondary to physical disruption caused by another medical condition, substance intoxication or withdrawal, exposure to toxins, or multiple aetiologies as defined in the DSM-5 criteria for delirium.[41-43] Clues for a potential role of acetylcholine deficiency in the aetiology of delirium came from clinical observations that anticholinergic
burden and serum anticholinergic activity were higher in patients with delirium.[43-45] However, other studies attenuate this association, reporting that anticholinergic activity is detectable in both serum and cerebrospinal fluid during acute illness, irrespective of anticholinergic medication use or presence of delirium.[46-48] Excess release of dopamine has long been considered an important contributor to the development of delirium.[42] Higher cerebrospinal fluid levels of the dopamine metabolite homovanillic acid are positively associated with some of the main clinical characteristics of delirium including hallucinations, cognitive dysfunction, and fluctuation of symptoms.[49] The association between intravenous dopamine administration, postoperative delirium and need for haloperidol support this hypothesis further.[50, 51] Haloperidol is a typical antipsychotic drug that primarily blocks postsynaptic dopamine D2 receptors in the mesolimbic system in the brain.[52] This mechanism underlies the idea that haloperidol may have a positive effect in the prevention and treatment of delirium. Haloperidol is generally considered the antipsychotic drug of choice in treatment of delirium symptoms. For older patients, low haloperidol starting doses (0.25-0.5 mg) for the shortest duration possible are recommended.[31, 53] Several surveys among clinicians and experts in geriatric medicine demonstrate that approximately two-third recommends haloperidol and that delirium subtype (i.e. hyperactive-type) tends to be the most important contributing factor in the decision to initiate drug treatment for delirium.[53, 54] With respect to a potential role for haloperidol in delirium prevention, current evidence is limited and the few studies performed have been restricted to specific surgical patient populations with a majority being elective admissions.[55-58] Consistently, the AGS clinical practice guideline for postoperative delirium in older adults states that the currently available evidence is insufficient to recommend the use of antipsychotic prophylaxis for prevention of delirium in older surgical patients.[32] Despite the lack of solid evidence, early prescription of haloperidol for delirium prevention is a belief in some hospitals.[59, 60] As already concluded in the NICE guideline on delirium prevention, diagnosis and management, there is need for new and large studies with at least 100 patients per intervention arm to compare the effectiveness of pharmacological interventions with placebo for delirium prevention in at risk hospitalised patients.[33, 61] Haloperidol is known to cause side-effects of which extrapyramidal symptoms and QTc interval prolongation are probably the most notorious. With respect to QTc prolongation, current recommendations on which patients are at particular risk and which actions should be taken when haloperidol is prescribed are inconclusive.[62, 63] Also, guidelines are heterogeneous with respect to their advice.[32, 33, 64] Randomised studies generally do not demonstrate an increased cardiac risk associated with haloperidol administration compared with other antipsychotics or even placebo.[57, 65] Non-randomised studies including older hospitalised adults
demonstrate that haloperidol use at an average dose of 1 to 2.6 mg per day does not result in QTc interval prolongation,[66, 67] noting that time-intervals of ECG recordings in these studies generally were not standardised and varied between 1 hour after treatment initiation to 24 hours after the final dose [66] and 1 to 6 days after hip surgery.[67] A randomised prospective placebo-controlled trial evaluating the effect of low-dose oral haloperidol on QTc interval in acutely admitted older patients is not yet available.

Outline of this thesis

Summarising the above, there is much to be learned and discovered about delirium. As for my PhD trajectory resulting in this thesis, we identified a knowledge gap that in our opinion was waiting to be filled: the need for a large study that compares the effectiveness of a pharmacological intervention with placebo for delirium prevention in at risk patients. We therefore designed and conducted the HARPOON study (Early Pharmacological Intervention to Prevent Delirium: Haloperidol Prophylaxis in Older Emergency Department Patients, registered at ClinicalTrials.gov NCT01530308): a multicentre randomised double-blind placebo-controlled trial on the efficacy and safety of haloperidol for the prevention of delirium in older patients acutely hospitalised through the emergency department.

Prior to conducting our study, we wanted to observe our target population by evaluating characteristics of older adults presenting to the ED. In Chapter 2 the trends and characteristics of older adults presenting to the ED of our university hospital in Amsterdam, the Netherlands are explored to evaluate utilisation of acute health care services and disease presentations including delirium. In order to explore the existing knowledge base of the field prior to our study, we review and discuss published results from randomised controlled trials on the efficacy and safety of haloperidol for prevention and treatment of delirium in hospitalised adults in Chapter 3. In Chapter 4 we describe and discuss the design of the HARPOON study. In Chapter 5 we show the results of our multicentre placebo-controlled trial (HARPOON study) on the prophylactic use of low-dose haloperidol on the occurrence of delirium, drug safety and important clinical outcomes in acutely hospitalised older adults. As mentioned in the introduction, haloperidol is prescribed with caution in older adults because of potential side-effects amongst which is QTc prolongation. In Chapter 6 the importance of correct QTc measurement in elderly patients treated with QTc prolonging medications is addressed. In Chapter 7 we explore the effect of a fixed low dose oral haloperidol administered in our study population on QTc interval compared with placebo. Finally, in Chapter 8 the main findings of the studies described in this thesis are discussed and clinical implications of their results are considered.
References


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