CHAPTER 8

Summary and General Discussion

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As mentioned in the introduction, we identified a knowledge gap with respect to evidence on pharmacological prevention of delirium using haloperidol, which still is the drug of choice in the treatment of delirium symptoms mainly based on clinical experience. As many studies have shown, delirium is highly frequent among older hospitalised patients. With respect to the use of haloperidol for delirium prevention in older hospitalised patients, there was only one randomised controlled trial (RCT) available prior to the design of our study. This RCT, also carried out by a Dutch research group, investigated the effectiveness of haloperidol prophylaxis on the incidence, severity and duration of post-operative delirium in elderly hip-surgery patients at risk for delirium.[1] In addition to the fact that there was merely one trial available, results were not generalisable due to its specific research population (mainly elective hip-surgery patients). The main goal of my PhD trajectory was therefore to design and conduct a randomised placebo-controlled double-blind multicentre clinical trial to investigate whether haloperidol prophylaxis could reduce in-hospital delirium and positively influence relevant clinical outcomes in a general acutely admitted older patient population at risk for developing delirium on admission. In addition, because haloperidol is thought to be associated with QTc prolongation, but this effect had never been studied in a placebo-controlled clinical trial, the aim was also to explore the effect of low-dose oral haloperidol on QTc interval changes in these patients.
Summary of main findings

In Chapter 2 we explore the trends and characteristics of older adults presenting to the emergency department (ED) of VU University Medical Centre (VUmc), Amsterdam, the Netherlands, in order to evaluate utilisation of acute health care services and disease presentations including delirium. We found that mean ED monthly visits and subsequent hospital admissions of patients aged 70 years and over have steadily increased over the past two decades. We furthermore describe observations from a six-week exploratory study in patients aged 70 years and older of which 63.9% attended our ED during weekday peak presentation times from 10 am to 10 pm. The majority of the patients observed were living independently at home and presented with fall-related complaints, multiple comorbidities and multiple medication use. Also, the prevalence of cognitive impairment and delirium seemed to be higher than what could be objectively determined from the medical records. More than one-third of the patients discharged from the ED to their usual residence returned to the ED within 30 days. Of these, one in five initially presented with falls.

In Chapter 3 we describe the results of a systematic literature search up to April 21, 2015 using the index terms and keywords “haloperidol”, “delirium” and “acute confusion”. Before, no systematic review of randomised controlled trials had focused on haloperidol for the prevention and treatment of delirium in hospitalised adults. This systematic search provided us with an overview of existing literature in this field and helped us to identify existing knowledge gaps. After an extensive search and screening process, we were able to include four prevention and eight treatment studies for this review. Because the aim of the HARPOON study was to investigate the efficacy of haloperidol in the prevention of delirium in a general non-intensive care unit (ICU) patient population, the non-ICU prevention studies will be the focus in this summary and general discussion section. The four prevention trials included in our review were conducted between 1999 and 2014 in Asia and Europe. Two of these studies focussed on non-ICU populations. These studies included (mainly elective) surgical populations and found that postoperative delirium incidence ranged from 15.8% to 37.8%.[1, 2] Both these studies found no significant difference in the incidences of postoperative delirium between the haloperidol and control group. However, only one of these two studies was double-blind, placebo-controlled and graded as high quality.[1] In this single-centre double-blind placebo-controlled study, primarily elective (73.5%) hip-surgery patients at risk for delirium based on visual impairments, APACHE II scores, index of dehydration and cognitive impairment (but excluding patients with profound dementia) were included. Haloperidol or placebo tablets 0.5 milligrams (mg) three times daily was initiated on admission up to a maximum of 6 days with a maximum
delay for surgery of 72 hours. This study did, however, report a significant decrease in delirium duration, delirium severity and hospital length of stay (LOS) in favour of the haloperidol group. No haloperidol-related side effect were noted in this or any of the other prevention studies included in this review.

In Chapter 4 we describe the design of the HARPOON study. As our literature review demonstrated, the effect of haloperidol prophylaxis on in-hospital delirium incidence and clinical outcomes in an older undifferentiated acutely admitted patient population had not yet been studied, leading to the design and conduct of the HARPOON study, forming the basis for this thesis. We selected an intervention period of seven days based on expected treatment response and to ensure that the days patients are most at risk to develop hospital-associated delirium were covered. The dosing strategy of 1 mg twice-daily in our study was based on previous trials and was considered optimal with respect to the primary aim of our study (reduce delirium incidence).

In Chapter 5 we present and discuss the primary results of the HARPOON study. The intention to treat analysis included 242 participants of which 118 were assigned to haloperidol and 124 to placebo. The anticipated sample size of 390 participants could not be reached, partly due to the strict exclusion criteria, but mainly because it was an investigator initiated study eventually limited by restricted financial and human resources (statistical power of current sample is 59%). In this multi-centre, randomised, double-blind, placebo-controlled trial we found no significant difference in delirium incidence between the haloperidol and placebo group. Results on clinical endpoints such as hospital LOS, readmission rate, new institutionalisation and mortality were also comparable between groups. No significant haloperidol-related treatment-limiting side-effects such as extrapyramidal side-effects and its potential for QTc prolongation were noted.

In Chapter 6 we emphasise the importance of correct QTc measurement in older patients treated with medications that may prolong the QTc interval. This letter was a response to a review article addressing the identification and management of drug-intoxicated patients who may be at risk for developing QTc prolongation, since older patients may be more prone to drug-induced QTc prolongation due to different predisposing (i.e. age, cardiac arrhythmias and myocardial damage) and precipitating factors (i.e. polypharmacy and electrolyte disturbances). No placebo-controlled trial had yet been undertaken to evaluate the effect of haloperidol on the QTc interval in elderly hospitalised patients after low-dose oral haloperidol. Therefore, this was another research focus of the HARPOON study.

In Chapter 7 we summarise the findings of an analysis of bedside 12-lead electrocardiograms (ECGs) in 72 patients before, during and after the study intervention period with haloperidol and placebo. Although Bazett formula is the most widely used to correct QT interval for heartrate (HR), it is known to be
inaccurate in the presence of low and high HR. Since the presence of abnormal HR occurs frequently in acutely ill patients, three other correction formulas were also used. We found that median (range) haloperidol serum concentration on day 4 was 0.71 (0.32 – 1.82) micrograms per litre (µg/L). For the haloperidol group, a moderate positive correlation between change in QTc from baseline and serum haloperidol concentrations on day 4 was found for Bazett ($r = 0.50$, $n = 23$; $P = 0.016$), Framingham ($r = 0.46$, $n = 23$; $P = 0.026$), and Fridericia ($r = 0.48$, $n = 23$; $P = 0.022$) correction methods. When applying these three correction methods, a maximum of 24.8% in the variability of change in QTc intervals compared to baseline was accounted for by haloperidol serum concentration at day 4. Longitudinal course of mean QTc did not significantly differ between the intervention groups for any of the automatic or manually derived QTc values.

Main findings put into context

Acutely hospitalised older patients and clinical outcomes
It is a worldwide phenomenon that older adults represent a growing proportion of the emergency care population.[3, 4] For example in Germany, one of top five most populated European countries,[5] both age and number of older patients requiring acute and rehabilitation care from geriatric clinics has steadily increased over the past 20 years.[6] In the Netherlands, adults over the age of 65 account for one quarter of all ED visitors.[7] This proportion is comparable to other countries. [8-10] During a four-week study period in 2012 in our ED, the overall admission percentage across all age groups was 23.5%.[11] A retrospective observational study of six EDs spread over the Netherlands found a slightly higher admission rate across all age groups in the year 2012: 29.2% of all ED presentations resulted in hospital admission.[7] Our observational study showed that admission rates during a six-week period at the end of 2011 were approximately 10% higher among patients aged 70 years and over.[12] Due to an increase in life expectancy and population ageing, an overwhelming growth in the number of older patients in emergency care services is expected.

Older adults presenting to the ED after a fall are prone to have repeated ED visits in the following months up to one year.[13] In our study we found that one in five of the older patients experiencing an unscheduled 30-day ED return visit had initially presented after a fall. In the Netherlands, injuries represent a major health care expenditure for emergency care, of which falls account for the largest category.[14] National estimates demonstrate that among patients visiting the ED for injuries, fall-related costs are especially high for women aged 65 years and over.[14, 15] We suggested that improvement of follow-up care for the group of older patients
discharged from the ED could perhaps reduce the number of return visits. From a patient perspective, the main reason for returning to the ED after initial ED discharge appears to be distress and uncertainty about their medical condition.[16, 17] Paying attention to these patient-related factors could perhaps reduce unplanned ED return visits after ED discharge. Similar, interventions initiated during and after hospital stay, such as educating patients about their diagnosis or treatment, scheduling of follow-up appointment or deployment of a healthcare worker for the transition process of hospital to home, may be effective in reducing ED return visits after hospital discharge, especially when these interventions facilitate better self-care for instance by increasing the patient’s control over their medical situation or reinforce their psychosocial skills.[18] The few studies investigating the effect of personal approaches and post-discharge care planning for older patients on reducing unscheduled return visits after ED discharge, reported conflicting findings. [19-21] A recent study aimed at fall prevention demonstrated that a single home visit of an occupational therapist within two weeks after discharge following an ED visit for a fall was effective at reducing both the number of fallers and falls six months after discharge.[22] Unfortunately, they did not evaluate the percentage of ED return visits within the first month after discharge.

In the HARPOON study population we found that one in five (20.2%) patients experience unplanned hospital readmissions within 3 months of discharge from the index admission. Other studies among acutely admitted patients age 70 years and over found 3 to 5% higher 3-month readmission rates.[23, 24] More than 10% of these readmissions occur within the first 30 days.[25, 26] The 33.5% lost to follow-up rate at 3 months in our study may have resulted in an underestimation of the overall readmission rate.

**Acutely hospitalised older patients and delirium**

Delirium is a frequent complication of acute illness and hospitalisation, especially in older adults.[27] In our observational study we found that delirium according to the observer-rated CAM was present in 9% of the ED patients age 70 years and over, but we only found notes on delirium symptoms in the medical records of one-third of these patients, especially when the referral question was (possible) delirium. Several studies have demonstrated that although delirium is prevalent among older ED patients, it is frequently not recognised.[28-32] As we have discussed in our paper, under-recognition and under-treatment of delirium may lead to negative patient outcomes, supporting the need to increase the knowledge and the awareness on this topic among all health care workers working in acute care, and to stimulate the introduction of a geriatric care specialist early in the acute care chain.

In the HARPOON study, 5.7% of patients were ineligible because of (suspected)
delirium. In the overall study population, delirium incidence (new onset) was 16.9%. This incidence rate is what could have been expected in older geriatric, internal medicine, hip-fracture, and general surgery patients,[33-35] although we anticipated a slightly higher incidence rate of 20%. Especially since we aimed at including patients more susceptible to develop delirium on the basis of a delirium risk tool (Dutch Safety Management Programme, Veiligheidsmanagement systeem, VMS).[36] Cognitive impairment and dementia are well-recognised delirium risk-factors that have been incorporated in many risk-stratification models for delirium.[37] Although the VMS delirium risk tool has incorporated an item on memory (“Do you have memory complaints?”), this question is rather subjective, as are the other two questions incorporated in this tool. Furthermore, delirium is a heterogeneous condition. Although there are established delirium criteria (DMS-5), screening (DOSS) and assessment tools (CAM), there is a degree of subjectivity with existing tools and ascertainment remains challenging.[38] Also, patients were only eligible for enrolment if they were able to recall the extent and nature of the study as a measure of cognitive competence, which has likely led to exclusion of patients with moderate to severe dementia who were more susceptible to develop delirium.

**Haloperidol and QTc prolongation**

Haloperidol is thought to be associated with a risk of QTc prolongation and consequent Torsade de Pointes (TdP). Most case reports on this topic involved higher doses and intravenous (IV) administration routes, which led to the release of an extended warning for haloperidol IV by the Food and Drug Administration (FDA). In response, Meyer-Massetti and colleagues stated that the available data suggests that a total cumulative dose of haloperidol less than 2 mg IV could be safely administered without continuous ECG monitoring when no concomitant risk factors are present.[39] In line with this, the Dutch delirium guideline refers to the point of view of the working group of geriatric pharmacology (in Dutch ‘Werkgroep Klinische Gerontofarmacologie’, WKGF): ECG monitoring is only recommended before and after initiation of haloperidol dosages IV above 2 mg, though medication review for other potential QTc prolonging drugs should always be conducted.[40, 41] Also, the Dutch delirium guideline mentions that past research demonstrated an increased risk of cardiac adverse events only in haloperidol dosages above 35 mg IV/day, or in patients with QTc >500 msec.[40] In conclusion, consensus seems to indicate that older patients should always be screened for additional risk factors for QTc prolongation, and haloperidol in dosages of 2 mg or lower irrespective of administration route may be administered safely without additional precautions. The HARPOON study provided the perfect opportunity to evaluate the effects of a fixed low dose of oral haloperidol on QTc interval compared with placebo. Our study results are in line with the previously mentioned recommendations: haloperidol
up to 2 mg/day did not significantly prolong QTc interval compared with placebo, neither were there any cases of TdP noted. Unfortunately, only one-third of the collected ECGs were available for analysis. Factors contributing to this downsize included initial exclusion criteria and the number of ECGs available per person (i.e. early discharge). Additionally, in accordance with previous studies on this topic we also excluded patients with ECG abnormalities such as atrial fibrillation and bundle branch blocks. This limits the generalisability of our findings. For instance, a significant amount of older adults will have pre-morbid atrial fibrillation or atrial fibrillation secondary to anaemia or hypovolemia. Also, because of our eligibility criteria and additional ECG selection criteria, we cannot add any evidence based recommendations for patients with “danger zone” QTc (men >450 – 500 msec, women >470 – 500 msec) and concurrent use of QTc prolonging medications, QTc >500 msec, heart rate abnormalities, etcetera. Any future study investigating this effect under these circumstances should be conducted in a controlled research setting under continuous monitoring by experienced specialists to ensure patient safety.

An addition to the existing literature
Prior to our systematic literature search, multiple systematic reviews on pharmacological interventions for delirium had been published, but none of them focused specifically on haloperidol in the hospitalised patient.[42-57] We found this surprising, given that surveys among clinicians demonstrate that haloperidol has been, and still is, the preferred drug for delirium treatment for both critically ill (ICU) and non-critically ill patients.[58-62] Additionally, haloperidol is already used as delirium prophylaxis in some hospitals,[63] even though evidence for this indication is ambiguous. Our literature review demonstrated that previous placebo-controlled trials report contradicting findings on the efficacy of haloperidol prophylaxis on the primary outcome delirium incidence, secondary outcomes such as severity and duration of delirium, and clinical outcomes such as hospital LOS. First, in one study, postoperative haloperidol 5 mg IV per day reduced delirium incidence, as well as the intensity and duration of postoperative delirium symptoms, in patients scheduled for elective gastrointestinal surgery and admitted to the ICU, without resulting in clinically significant complications.[64] Second, in (mostly) elective hip surgery patients age 70 years and over, perioperative low-dose haloperidol (1.5 mg per day) was not effective in reducing the incidence of postoperative delirium, but did have a positive effect on the severity and duration of delirium, reduced the length of hospital stay and was well tolerated.[1] Third, administration of haloperidol IV upon ICU admission after non-cardiac surgery reduced delirium incidence and was well tolerated without increasing risk for QTc prolongation, but had no effect on mean hospital LOS after surgery or 28-day mortality.[65] Fourth, three days
of postoperatively administered haloperidol prophylaxis (2.5 mg per day) did not reduce the incidence, severity or duration of delirium within the first 7 days after elective abdominal or orthopaedic surgery.[2] Shortly after our systematic review was published, another two reviews with a broader scope on delirium prevention and treatment in hospitalised patients were published.[66, 67] Generally, the results pointed in the same direction: there was no clear evidence that preventive treatment with haloperidol reduces the incidence of delirium. Regarding the treatment of delirium, none of the studies included in our systematic literature review demonstrated an apparent superior effect of haloperidol on delirium severity or duration over any other medication. Most of the available guidelines advise to only prescribe pharmacological agents to patients who experience severe agitation or behavioural problems that may pose a threat to themselves or others around them.[68, 69] Indeed, surveys demonstrate that both clinicians and pharmacists tend to use pharmacological agents when symptoms include agitation.[58] However, the new Dutch guideline for delirium is less stringent, leaving room for the use of antipsychotics in delirium treatment even when symptoms do not include behavioural disturbances, anxiety, or psychosis. [40] Furthermore, although the success of multicomponent non-pharmacological interventions in reducing delirium incidence is supported by strong evidence, their value in treating delirium has not yet been established.[66, 70-72]

A few years ago, an international panel of experts in the fields of methodological quality assessment and systematic reviews developed a measurement tool for the assessment of systematic reviews (AMSTAR).[73, 74] Using this tool as a starting point, strengths of our systematic review include: an ‘a priori’ research question and clearly defined eligibility criteria; a duplicate study selection by two independent reviewers and a consensus procedure in case of disagreement; a comprehensive literature search in five electronic sources with the assistance of the local librarian, defining the years and databases used, and the full search-strategy provided in a supplemental file; language (English) and publication status (full-text) as inclusion criteria were included; an all-encompassing table with all important characteristics of included studies was provided; the scientific quality of included studies was assessed and the arguments for this were provided in a supplemental file; no conflicts of interest were stated. Certain shortcomings, however, should also be noted. Data extraction was performed by one reviewer and checked by the second reviewer. The comprehensive search in online databases was not supplemented by other information sources or a complete review of the references of the identified studies. We did not provide a full list of all excluded studies, however, we did include a flowchart. Furthermore, we generally assessed heterogeneity based on study characteristics rather than performing a test to assess homogeneity and the possibility of pooling results. Also, we did not assess the risk of publication bias
using either graphics or statistical tests. However, we generally met 7 to 8 out of 11 AMSTAR criteria and therefore consider our systematic review to be of good quality.

Previously conducted research and certain practice-related differences of populations and treatment contributed to our belief that there were gaps in clinical evidence regarding the role of haloperidol in delirium prevention in older hospitalised adults, and that there was a need for a well-designed randomised placebo-controlled clinical study. The need for a large in-hospital randomised trial with at least 100 at risk participants per study arm comparing different types of pharmacological agents with placebo, having delirium incidence as the primary outcome, was already emphasized in the NICE clinical guideline for delirium.[69] During the design of our trial we attempted to tackle the issue of generalisability by including both non-critically ill surgery and general medicine patients, so the included patient population would resemble the actual patient population seen in emergency departments and acute admission units on a day to day basis. However, ethical considerations and potential haloperidol-related side effects lead to narrowing of eligibility criteria. This restricted us in the number of subjects that could be recruited, with the potential for selection bias and limited inclusions. This may have affected the external validity and the degree of generalisability of our study results negatively. For example, we excluded patients with significant cognitive impairment, likely resulting in the exclusion of patients with profound dementia. Pre-existing cognitive impairment is a well-known risk factor for developing delirium. Delirium prevalence rates in hospitalised medical and surgical populations with pre-existing dementia (‘delirium superimposed on dementia’, DSD) ranges from 32% to 89%.[75] Because delirium is such a highly prevalent and noxious complication of acute hospital admissions in older patients, especially for those with dementia, it is important for future research to be able to also focus on these patients. Unfortunately, although understandably, profound cognitive impairment poses a barrier for certain older patient populations to be included in clinical studies because of ethical considerations and informed consent related issues.

Although we attempted to overcome the concerns of small sample size and generalisability by designing a multicentre study, the non-funded investigator-initiated nature of this study and matching limited resources likely contributed to the inclusion of less participants than anticipated. Nonetheless, overall delirium incidence in our study is, although slightly lower than we expected, still in agreement with previous studies and we believe the power of 59% for the realised sample is acceptable. However, with this power there is still 41% chance that important preventive treatment differences have remained undetected. Furthermore, a multicentre design has certain obstacles of its own. Although clinicians and study
staff were repeatedly trained, incomplete observations and inter-rater differences could have led to reduced accuracy of assessment. Also, differences in local procedures had to be addressed. Although there was a strict protocol and we were able to standardise most study procedures across the participating centres, this remains a challenge in multicentre clinical research.

What the HARPOON study adds to the existing literature, is that it is the first trial on the use of haloperidol prophylaxis for prevention of delirium that focused on acutely admitted at risk older patients, and included not only non-critically ill (general) surgical patients but also medical patients. The results of our study are in line with the overall conclusions that can be drawn from past research in this field. Overall, evidence to support the use of haloperidol for prevention of delirium in older patients in hospital remains insufficient.

**Future perspectives**

One of the first questions that came into mind was ‘Why is haloperidol generally recommended for delirium treatment, but not for its prevention, while solid evidence from good quality randomised controlled trials is generally lacking for both indications?’ as we have demonstrated in our literature review in line with other systematic literature reviews on this topic.[43, 66, 67, 76] Focussing on the Netherlands, haloperidol is considered the drug of choice for delirium management in national delirium guidelines, mostly resulting from practice-based evidence rather than that it is evidence-based practice.[77, 78] The Dutch Psychiatric Association (‘Nederlandse Vereniging voor Psychiatrie’, NVvP) published their guideline in 2004.[77] The NVvP recognises that barely any high quality methodological research on the pharmacological treatment of delirium has been conducted since the introduction of the practice delirium guideline by the American Psychiatric Association (APA) in 1999.[79] Despite this, haloperidol is considered the drug of choice by both the NVvP and the APA. Furthermore, both guidelines state that haloperidol is generally used because of its favourable properties (i.e. relatively short half-life time, few active metabolites, few anticholinergic properties in common dosages, relatively low sedative properties compared to other antipsychotics, and it can be administered in different forms).[77, 80] In 2014, the Dutch Geriatrics Society (‘Nederlandse Vereniging voor Klinische Geriatrie’, NVKG) published their guideline on delirium in adults and elderly.[78] Interestingly, this guideline depicts some caution in their recommendations on haloperidol for delirium treatment, noting that although pharmacological management is an important aspect of daily clinical delirium treatment, clinicians must be aware that scientific evidence is
limited compared to practice-based evidence. On the other hand, they do state that pharmacological preventive treatment may be considered for high-risk patients, for instance who have previously developed delirium, although its routine use is not recommended.[78] International recommendations do not advise the general use of haloperidol prophylaxis to lower the incidence of delirium in a population of at risk older adults admitted to hospital.[69, 81] Despite this, some hospitals in the Netherlands as well as in other countries already use prophylactic administration of haloperidol for prevention of delirium.[63, 82]

Instead, multicomponent non-pharmacological interventions have repeatedly proven themselves to be effective in delirium prevention and should be generally applied in-hospital.[70-72] Notably, the NVKG delirium guideline positions delirium management as part of routine hospital-wide clinical care, focussing on for instance documenting certain predisposing (i.e. age, cognitive impairment or dementia) and precipitating (i.e. reason for acute admission, illness severity) risk-factors in the patient file on admission, and deployment of previously mentioned multicomponent non-pharmacological intervention strategies. Such routine implementation and facilitation of early recognition of delirium and its risk-factors is also aspired by the Dutch National Patients Safety Program (VMS) screening instrument ‘Vulnerable Elderly’, aimed at screening all patients age 70 years and over on admission for delirium risk, among other things.[36] I believe that these approaches reflect some important steps in hospital care for elderly patients, which in the near future should be further expanded. But, in order for such interventions to succeed, it is important for all clinicians involved that they receive adequate training, are motivated for intervention adherence and provide feedback to one another to complete the learning cycle.

At the time that the primary results of the HARPOON study were published, an editorial ‘Haloperidol for delirium prevention: uncertainty remains’ was published as well.[38] In addition to discussing the design and findings of our study, this editorial also addresses the important fact that delirium research is difficult and hampered by poorly understood patho-aetiology.[38] As mentioned in the introduction, numerous hypothesis on the causes, mechanisms and pathways that may lead to the development of delirium symptoms have been introduced. Perhaps there is no common final pathway. Perhaps different aetiologies lead to different delirium symptoms in different persons through different pathophysiological pathways. Perhaps genetics play a role.[83] Because its aetiology is still not clear, this provides another area for future delirium research which may result in significant and improved biomarkers or potential drug targets for delirium.[38] In the meantime, the focus should be on implementing and improving adherence of the aforementioned multicomponent nonpharmacological prevention strategies in daily clinical practice.
A search for future studies on the role of haloperidol in delirium management on ClinicalTrials.gov on December 7th, 2016 using the terms “delirium” AND “haloperidol”, resulted in 29 registered studies. Six of these studies were designed as a delirium prevention trial, four at that time with status ‘complete’. The results of only a small proportion of these studies have thus far been published. Based on this overview, our study thus far is the only one to provide data on the use of haloperidol for delirium prevention in non-critically ill, non-surgery patients. Hopefully, the findings from these registered studies, either positive or negative, will increase the knowledge base in the field and strengthen current practice recommendation guidelines.
References


Summary and General Discussion


46. Devlin JW, Al-Qadhee NS, Skrobik Y. Pharmacologic prevention and treatment of delirium


