Summary

SUMMARY

Delirium is a common syndrome seen in adult patients admitted to an intensive care unit (ICU). Generally, these patients have difficulty sustaining attention, problems in orientation, short-term memory, poor insight, impaired judgment and a fluctuating level of consciousness. Delirium is associated with a prolonged ICU stay, a greater risk of death during ICU stay, and a poorer prognosis after discharge. Guidelines with comprehensive recommendations are available for the management of delirium in the ICU, including the management of pain and agitation, using an integrated and multidisciplinary approach. However, these guidelines are not routinely used in clinical practice despite their proven benefit. Implementation science offers tools and processes to improve the routine use of guidelines. The aim of the study described in this thesis was to investigate various aspects of the implementation of delirium guidelines. This study was coined the 'ICU Delirium in Clinical Practice Implementation Evaluation' (iDECePTIvE) study, and six ICU departments from the South-West Netherlands region participated.

Three important research components were addressed.

First, to map the extent to which the guideline had been implemented at baseline, and to describe the barriers and facilitators for guideline adherence. Second, to develop a 'tailored' implementation strategy and to implement the guideline. Third, to evaluate the effects of the implementation on guideline adherence and clinical outcomes (numbers of delirium-free and coma-free days, duration of mechanical ventilation, length of ICU-stay, and mortality) and to evaluate the implementation. Third, drug delirium treatment with haloperidol was evaluated by studying the haloperidol concentrations in blood in relation to the drug's effects on delirium symptoms and in relation to the patients' genetic profile.

The protocol of this prospective multi-center implementation study was elaborated in four phases **(chapter two)**. In phase one, we inventoried the current practice of delirium management and level of delirium guidelines adherence in the participating ICUs. In phase two, we identified possible barriers and facilitators for the implementation of delirium guidelines. In phase three, we planned the implementation strategy on the basis of the results of phases one and two. And in the final phase, we evaluated the effects of implementation. Chapter 2 is concluded with an Editorial, where we argue that there is no "silver bullet" for delirium prevention and treatment and that delirium, being a multifactorial condition, is more likely to resolve only as a result of multiple interventions, for instance in a care bundle.

To gain insight into possible barriers and facilitators, we performed a detailed analysis through focus group interviews and surveys among ICU professionals (**chapter three**). Conducted research had shown that delirium in the ICU was considered a major problem requiring adequate treatment. The professionals were aware, however, that the

approach towards delirium in general deserved to be improved. We found that the ICU nurses' and physicians' level of knowledge about screening, prevention and treatment of delirium could be improved. Furthermore, the ICU nurses systematically screened one third of the patients on delirium. There was no integral delirium prevention and treatment protocol at most of the ICUs. One of the most concerning conclusions was that ICU professionals were not confident that a better adherence to guideline recommendations could really make a difference to patient outcomes. But on the other hand, motivation for change was found a facilitator for implementation in all participating sites.

From our systematic review of implementation strategies (**chapter four**) it appeared that the use of multiple implementation strategies (more than six) aimed at changing the ICU professionals' behavior and/or use of care bundles (exemplified as the Pain, Agitation and Delirium (PAD) guidelines or the Awakening and Breathing Coordination, Delirium Monitoring, Early Mobility and Exercise (ABCDE) bundle) aimed at delirium-oriented interventions were associated with improved clinical outcomes.

Subsequently, the implementation model of Grol and Wensing was used to make an implementation program, based on the results from the phase one analysis and the systematic literature review. The implementation program consisted of different implementation strategies (**chapter five**), mainly targeted at the organizational and professional levels. These strategies were tailored to the previously identified barriers and facilitator, and confirmed by the previously performed focus group interviews. More specifically, the implementation program consisted of education about delirium (classroom education and e-learning), practical training (delirium screening), standardization of medical policies through implementation and harmonization (among the participating ICU's) of a prevention and treatment protocol, and increasing the involvement of the family of ICU patients in delirium care. Recommendations from the 2013 PAD guidelines advocating delirium and sedation screening, light sedation, analgesia first sedation, preventive measures and other treatment recommendations were included in a practical protocol and implemented in two phases. First, we did a tailored implementation of delirium screening and thereafter we implemented a delirium prevention and management protocol. Professionals from the ICUs (local champions) were involved in the development and application of the protocols to ensure a better connection with practice and to increase implementation support. Data were collected before the implementation, after the implementation of delirium screening and after the implementation of treatment protocol. Adherence with delirium guidelines was measured and changes for the different periods were calculated. A total number of 3,930 patients (more than 18,000 ICU days in total) were included in the analysis. Adherence with the delirium guideline recommendations improved after implementation. Delirium screening improved considerably after the implementation of screening and remained good after full implementation of the guideline. After the implementation, ICU nurses applied delirium screening in

more than 90% of all ICU patient days. More 'light sedation' days were noted and the use of benzodiazepines for sedation decreased. 'Analgesia First Sedation' in sedated patients improved slightly after both implementation periods. There was also improvement in the application of preventive measures such as early mobilization and physical therapy. The duration of a delirium decreased from 5.6 days before to 3.3 days after the implementation, and the proportion of 'coma days' had decreased from 14% to 9% after implementation. We did not find any improvements for the other patient outcomes such as the duration of ventilation, length of ICU-stay and mortality.

We delved deeper into the implementation process in **chapter six**. Six months after the implementation, we collected patient data for the last time to measure the sustainability of implementation among all participating ICUs. We also explored the exposure to the implementation program at the individual ICU level; impact of the implementation on barriers and knowledge; and the local implementation team experience with the implementation program. We concluded that the implementation was largely executed as planned. The implementation of delirium guidelines was feasible and successful in resolving most of the barriers encountered prior to implementation, in improving knowledge about delirium and in improving adherence to the guidelines (also six months after the last implementation activities). Nevertheless, despite a uniform implementation strategy for all participating ICUs, there were clear differences in guideline adoption between the ICUs.

To meet an important barrier to implementation, namely the doubts among some ICU health care professionals on the efficacy of haloperidol, we conducted the study on the effect of haloperidol on delirium symptoms (**chapter seven**) in one of the ICUs. None of the most recent haloperidol ICU delirium treatment trials published to date included pharmacokinetic data and thus the pharmacodynamic response of low-moderate dose haloperidol for the treatment of delirium in critically ill adults was unclear. Therefore, we sought to characterize the pharmacodynamic, pharmacokinetic, and pharmacogenetic characteristics low-dose haloperidol in critically ill adults with delirium. The 22 patients received an average daily haloperidol dose of 3.5±1.8 mg. Serum trough haloperidol concentrations were not significantly associated with either the daily haloperidol dose administered, daily presence of delirium or delirium score. Poor metabolizer CYP2D6 status was associated with significantly higher haloperidol concentrations, but an association between CYP3A4 status and haloperidol concentrations was not found. No patient experience QTc interval prolongation above 500ms.

Chapter 8 concludes with the summary of findings and General Discussion.