General Discussion

The papers presented in this thesis basically concern the question how to effectively implement delirium guidelines for critically ill adults admitted to an intensive care unit (ICU) – with an important role for the ICU nurse.

The overall aims of this thesis were to assess factors that influence adherence to ICU delirium guidelines, to develop a tailored implementation program, and to study effects of the implementation interventions on guideline adherence and clinical outcomes.

In this final chapter, I reflect on the main findings, discuss possible difficulties and pitfalls of implementation of ICU guidelines in relation to knowledge of implementation science, and give directions for future research.

Implementation of delirium guidelines, barriers and implementation strategy

According to the Implementation Model of Change of Grol and Wensing [1] a survey (**chapter 3**) and focus group interviews (**chapter 5**) were performed to identify the barriers and facilitators for delirium guidelines adherence. Several previously reported barriers were confirmed and were in general comparable to those reported in the literature about delirium guideline adherence [2-9]. The most important barriers found were: knowledge deficit about delirium management, low delirium screening rate, lack of trust in the reliability of delirium screening tools, belief that delirium cannot be prevented, collaboration problems among ICU healthcare providers, lack of routine use of delirium management protocols, and discrepancy between the perceived significance of delirium in the ICU and the current practices of delirium management and treatment with antipsychotics. One of the additional key features that stood out compared with other literature was that professionals were not confident that attending the needs of delirious patients will really make a difference for the patient outcomes. Currently, there is a growing awareness that delirium should not be assessed as an isolated problem, but that it must be placed in a wider context. Attention has therefore shifted from isolated implementation of delirium guidelines to implementation of pain-agitation-sedation (PAD) guidelines [10], linking them to the 'Awakening and Breathing Coordination, Delirium Monitoring, Early Mobility and Exercise' (ABCDE) bundle [11], preferably with preceding analysis of barriers [12-17]. In our study, we assessed the barriers for delirium guidelines implementation, but did not heavily focus on the role of physiotherapists and did not assess the barriers regarding early mobilization. Therefore, in hindsight, we did a limited barrier analysis – i.e., rather focused on delirium instead on all the bundle elements. Important barriers for early mobilization are, for example, lack of an early mobility program/protocol, and limited resources (staffing and equipment), and we did not solve these issues beforehand [18]. In addition, the analysis of unit-specific barriers prior to ABCDE implementation can be assessed with a comprehensive checklist consisting of 107 barriers to ABCDE delivery, and this might have helped in our multi-center study, but this systematic review was published after our implementation study [19]. When trying

to improve performance and increase adherence to guideline recommendations, it is important to conduct a barrier analysis before applying implementation strategies. This may reveal why performance is bad in the first place. If this is overlooked, we are setting ourselves up to fail [20]. Next to using the above-mentioned checklist, one of the recommendations for more effective implementation programs is to explore the cultural and contextual factors of the individual sites in more detail [12, 21], which we did not do in our study. Individual ICUs may be able to implement guidelines more effectively by local inner and outer context analysis [21] exploring factors such as safety culture, quality improvement culture, excessive turnover issues, and staff morale issues, which may foster or hinder the implementation [12]. According to the Implementation of Change Model, the next step was to identify implementation strategies for changing professionals' behavior which match with the identified barriers. Therefore, we performed a systematic review (**chapter 4**) on effects of implementation strategies which have been used to improve ICU professionals' adherence to guidelines, including delirium management. We found that the improvement of clinical outcomes was based on the combination of two key components [22]. The first was the use of care bundles targeting ICU delirium assessment, prevention and treatment as integrated within the PAD guidelines [10] or ABCDE bundle [11]. The second component was the use of multifaceted implementation strategies; especially using six or more of these seemed associated with improved outcomes.

These findings supported that the scope of delirium management implementation in our study was broadened from implementation of a Dutch ICU delirium guideline to the implementation of the 2013 PAD guidelines recommendations as a bundle of clinical delirium management. In our implementation strategy, we mainly focused on knowledge improvement and behavior change of nurses and physicians. However, we did not incorporate implementation strategies that targeted non-delirium recommendations from the PAD guidelines and/ or ABCDE bundle from the beginning of the project because a comprehensive analysis of barriers related to these and the context of individual ICUs was not our focus. In phase III of the project (full guideline implementation), we have tried to implement the integrated measures based on the PAD guidelines by using laminated pocket cards summarizing the PAD guidelines recommendations, by involving physical therapists, and by assessing the perceived level of implementation of the PAD guidelines using the Implementation Readiness Test checklist as feedback tool to the local implementation teams (**chapters 5 and 6**). A more integrated approach may have been necessary in the case of implementation of a complex bundle. An example from the mental health services shows that an integrated approach to policy formulation at different levels of 'Policy Ecology' [23] and five key organizational level constructs (leadership, vision, managerial relations, climate, and absorptive capacity) are necessary to achieve a successful implementation of evidence-based practice [24].

The second key component of our implementation strategy was the use of multifaceted implementation strategies. Sinuff and colleagues [25] found in their systematic review that multiple implementation strategies did not appear to be better than single interventions for implementation of protocols, bundles, guidelines in the ICU. Importantly, they found that single strategies might help to improve processes of care rather than clinical outcomes. We agree with Sinuff et al. [25] that in most implementation projects, lack of knowledge is an important barrier and could be resolved by education only. But it is unlikely that education only can work well if multiple barriers are found. In general, multiple implementation strategies were likely more effective than single strategies [26, 27]. Further, tailored implementation is more successful [28], also in the ICU setting [29]. The conceptual clarity, relevance, and comprehensiveness of implementation strategies that can be used have been advanced and the recommendations of multifaceted strategies taxonomies have been endorsed [30, 31]. A refined compilation of implementation strategies can be used to help researchers, decision makers and other stakeholders to prioritize which strategies to use when planning an implementation initiative [32].

Evaluation of effects of guideline implementation

In our study (iDECePTIvE-study, **chapter 5**), we have primarily measured the effects of the implementation program on clinical guideline adherence, based on performance indicators that we constructed for this study. We found that the implementation was successful to improve processes of care as measured with the performance indicators. Next, an important question was: did improved adherence to guideline recommendations (performance indicators) lead to improved patient outcomes? We found that the duration of delirium decreased from 5.6 days to 3.3 days after guideline implementation, and the proportion of coma days decreased from 14% to 9%. To our surprise, however, these improvements did not result in improved clinical outcomes (e.g. length of ICU stay, or hospital mortality). I will discuss these findings below.

Implementation of guidelines is a complex affair, as reported by several authors [33, 34]. When looking at seven performance indicators that measured processes of care related to the guideline recommendations from the PAD guidelines, these recommendations may be related with delirium in different ways, both qualitatively and quantitatively. In the implementation strategies (applied as different kinds of education, feedback, appointing local champions, etc.) we paid great attention to delirium screening. This approach paid back with a great improvement in adherence to delirium screening. However, the statistically significant improvements in most other performance indicators were in fact clinically moderate improvements, which may explain why 'delirium and coma' days improved moderately and the length of mechanical ventilation or ICU stay and mortality not at all. An implementation study by Balas et al. [35], which was methodologically similar to our study (pre-post design), did find reduced mortality.

Another study, by Barnes-Daly and Pun et al. [36, 37], with a different design (studying the association between level of adherence to the ABCDEF bundle and mortality) also found inverse associations between level of adherence and mortality. Our study differed with these studies in that: 1) it was a multicenter study in 'real-life'; 2) all screenings and activities were done by regular bed-side ICU nurses instead of dedicated research personnel; 3) we did a pre-implementation barrier assessment and tailored the implementation to these barriers, but did not execute a comprehensive barrier analysis of all ABCDE bundle components (which is different from the Balas et al. study); 4) we did not extensively focus on, nor sufficiently implemented, the safety screens for spontaneous awakening and breathing trials (SATs and SBTs). Based on our systematic review, using care bundles and more than six implementation strategies, as we pursued in our pre-post implementation study, would have had the potential to lead to better patient outcomes such as a lower mortality rate, but this was not confirmed after the implementation. Despite all efforts made and the moderate but significant improvements in many processes of care related to the guideline recommendations, we could not translate these findings in our setting into reduction of the duration of ventilation, ICU-LOS or mortality rate. The most conspicuous differences between our study and the studies of Balas et al. [14] and Barnes-Daly et al. [38], which may help explain the lack of effect on the clinical outcomes, are: 1) the resources and personnel available to facilitate the implementation (e.g. broad and dedicated stakeholder involvement as in interprofessional teams and 2) the design of the Barnes-Daly study. The deployment of a multidisciplinary and dedicated team of implementation personnel rather than just one or two local champions probably raises the chance of success of simultaneous implementation of all guideline recommendations as conceptualized in the bundle elements. This might be the reason why the implementation translated into outcome improvements. On the other hand, we think that staggered implementation (versus simultaneous multi-bundle implementation) should be considered when the ICU team has little experience with bundle elements and has limited personnel resources available, as in our study. Further, the Barnes-Daly study seems difficult to interpret, since the significant associations with level of adherence to the bundle elements and mortality might, at least in part, be explained by confounding by indication: the higher adherence might also be due, on a patient level, to lower disease severity. Early mobilization, for example, will be more successful in less sick patients. This notion should result in at least some reluctance to accept the results of that study as robust evidence. Further, our implementation was tailored to general barriers that were common to all ICUs, and although it was nice to see that this implementation had effect, a more flexible process – e.g., through 'linking evidence to action' [38] – could lead to better results by starting the change, measuring and adding or adjusting the strategy, which is also how the Model of Change of Grol and Wensing is intended. In short: there is no magic bullet for the best implementation strategy. Furthermore, a

concept known as the 'learning healthcare system' can be used as the 'next generation' of implementation efforts. It seamlessly integrates implementation work into daily practice by exploring more innovative approaches such as the application of principles from behavioral economics and bio informatics [39]. To understand how to implement in daily practice, the implementation strategies have to be fully described with all their components and how they should be used [40]. The comparative effectiveness of implementation strategies in general will be advanced if implementation outcomes are conceptualized and measured during the implementation research [41]. More recently, the importance of patient outcomes is shifting from ICU-LOS and mortality to long-term outcomes as long-term cognitive impairment [42-44]. Recently, it was stated that there is low-quality evidence to suggest that single or multicomponent non-pharmacological interventions are effective in improvement of delirium outcomes. In the future, robust research is needed and should focus on the feasibility of multicomponent interventions, and should clearly describe interventions and outcome measures [45]. Translated to our study, the long-term cognitive outcomes of survivors could have been a more relevant outcome than survival.

Six months after the implementation (**chapter 6**), we have concluded that the implementation program was mainly executed as intended. The implementation of delirium guidelines was feasible and successful in resolving the majority of barriers found before the implementation. Staff knowledge about delirium as well as guideline adherence had improved. Guideline adoption was quite variable among the participating ICUs, in spite of a uniform implementation strategy. The most difficult and perhaps the most important challenge of our research was integrating the quantitative and qualitative outcomes in the process evaluation, to understand the difference in adherence between the ICUs. This is in line with previous research [46]. On the basis of our experiences in our setting, we argue that next steps for implementation for our setting (with relatively low resources and – at best – one or two local champions per ICU) would be: implementation of nurse-driven SATs and SBTs and earlier extubation to decrease length-of-mechanical ventilation and more extended early mobilization programs including a strong role for physiotherapists. In doing so, continuous efforts should still be directed at improving and maintaining delirium management.

To ensure that the guideline is more patient- and family-centered, but also feasible for health care providers, the 2013 PAD guideline was updated in the newest Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines: the topics rehabilitation / mobilization and sleep disruption were added. Furthermore, patient representatives were added to the author group as collaborators; experts from Europe and Australia were added; more than 70% of guideline recommendations were new; and the focus was shifted to post-ICU and patient-centered outcomes [46]. Only 2 of 37 recommendations rated as strong evidence. As previously elaborated on, such extension

of the guidelines may be comprehensive from a scientific point of view, but even more challenging from an implementation point of view. To enhance early adoption, teaching hospitals in particular, where future physicians and nurses are trained, must provide education about the (updated) guidelines. Furthermore, since guideline knowledge was found to be an important facilitator for physicians and nurses, they should receive training on delirium guidelines and practices at the time they enter clinical practice. E-learning has practical advantages, and should be strongly considered as an effective and modern implementation strategy for physicians and nurses in particular, since the use of E-learning was particularly feasible for and appreciated by the healthcare providers in our studies.

Delirium treatment

During the study, ICU professionals were questioning the effectiveness of low dose haloperidol in resolving delirium symptoms. The PAD guideline did not recommend the use of haloperidol as there was little evidence that it resolves delirium. Nurses had expressed their dissatisfaction with pharmacological delirium treatment as one of the most important barriers in adherence to the delirium protocol. Before studying the effectiveness of haloperidol for the treatment of delirium, it is important to understand the pharmacology of haloperidol in the ICU patient population. To characterize the pharmacology of therapeutic low-dose haloperidol in critically ill adults with delirium, we conducted a single-center prospective study at our academic medical center (**chapter 7**). Twenty-two patients were administered an average daily haloperidol dose of 3.5 mg/day (SD: 1.8). The through haloperidol serum levels (median = 1.9 µg/L) were lower than those measured in studies in patients with schizophrenia or in the scarce studies in ICU patients. There was no significant association between haloperidol dosage and the measured haloperidol serum through levels ($p = 0.30$); haloperidol serum levels and the presence of delirium ($p = 0.20$); haloperidol serum levels and cumulative ICDSC scores ($p = 0.13$). Only one significant association was found between genotype (CYP2D6 metabolizer group) and haloperidol trough serum levels ($p = 0.028$).

We concluded that the blood serum level of low dose haloperidol as measured in our study may be too low to reduce delirium symptoms. Delirious patients bothered by lack of sleep during the evening or night are at risk to receive sedatives or opioids such as remifentanil, dexmedetomidine, propofol or clonidine, which may not be conducive to good sleep and further deteriorate delirium. Previous studies on prophylactic use of haloperidol showed no benefits on patient outcomes [47, 48]. A recent systematic review of randomized controlled trials showed no outcome improvement in patients treated with haloperidol versus placebo [49]. The question 'Does this critically ill patient with delirium require any drug treatment?' [50] is a good one. We think that the answer can be found in the first place in the dose that should be given. Previous studies, especially prophylactic

studies, probably used too low doses of haloperidol (like in our study) and the blood serum levels were not measured. In a recent new trial, a higher dose of haloperidol [51] had not any effect on delirium outcomes. We are currently enrolling critically ill patients for a multicenter RCT to assess whether a moderate dose of haloperidol can reduce the duration of delirium. The new insight of our pharmacological study is that the question about the effectiveness of haloperidol treatment may be tested by giving a higher daily dose and possibly titrating haloperidol on the basis of a patient's genotype.

General perspectives on the research performed

There are two major problems when implementing delirium guidelines at ICUs. The first relates to implementation and the second to the guidelines. Almost two decades back, the Institute of Medicine made an urgent call for fundamental change to close the quality gap between health care in America by publishing 'Crossing the Quality Chasm' [52]. One of the main messages is that we have to move from 'the care that is' to 'the care that could be'. But the question was raised: "What gets in the way to better management of delirium and related problems experienced by ICU patients?" Optimal care is complicated by resources, policies, knowledge, rigidity, behavior, systems, habits, guidelines, awareness, and so on. In the United States, delirium management improvement is embedded in quality improvement projects and many tools and information are available for dissemination and implementation research in this area. This information can be found at the websites such as www.iculiberation.org and www.icudelirium.org. In the Netherlands, prominent and leading research is conducted by the Dutch Delirium Consortium, but there is no platform to disseminate the research findings. The website of the Netherlands Society of Intensive Care (NVIC) provides 28 guidelines with medical care content and three guidelines with organizational content, but as yet there is no formal guidance or document concerning the implementation of guidelines. Given the gap that generally exists between guideline recommendations and their application in daily practice, implementation knowledge seems in need of more widespread dissemination, also in the Netherlands.

In the future, more attention must be paid to the implementation of guidelines in the ICU setting. Certainly, for hospitals and healthcare professionals, many new or revised guidelines are released every year. In the new guidelines that are issued in the Netherlands, implementation is becoming more and more central, as exemplified for instance by the HARING tools [53]. In addition, even more attention to and knowledge of implementation may be necessary within the organization of health care. In the Dutch quality standard of ICU care organization ('Kwaliteitsstandaard Organisatie Intensive Care') [54] there is no explicit attention for the implementation nor involvement of implementation experts who can support the ICUs in their efforts to bring evidence to practice. In this document, performance indicators are mentioned with a reference to the national

intensive care evaluation (NICE) registration system [55]. These indicators should be used as: 1) start point for quality improvement; and 2) monitoring tools for quality improvement initiatives and guidelines implementation feedback, as mentioned by van der Veer at al. [56].

The barriers related to implementation of quality improvement indicators were listed as behavioral factors [57], but in my opinion there is also room for improvement in the contextual and organizational barriers. Given this information, I think that implementation science can be of added value in this important area of healthcare (namely ICU) to give the best possible care to the critically ill patients in the Netherlands.

Future steps and research

Further implementation research should include extended analysis of contextual factors and more center-tailored strategies to overcome local barriers. Staggered implementation of guideline bundle components should be considered when dedicated multidisciplinary implementation teams are not available, as is the case in most Dutch health care settings, including ICUs. The ICT systems have to be more integrated and be optimized to provide a feedback on process indicators and to decrease the registration burden. A set of process indicators per ICU bundle has to be described, and a minimum required adherence has to be determined for indicators to become relevant. Finally, the advantages or disadvantages of staggered versus simultaneous implementation of complex ICU bundles have to be explored because they may differ depending on the topic. Implementation interventions should be fitted with the contextual situations of individual ICUs and be embedded in larger quality improvement projects to ensure the involvement and support of 'higher management'. New forms of implementation research design and evaluation like 'action research', as referred to above, should be used and tested.

Future research should focus on the best pharmacological management of delirium. We are currently enrolling patients in a multicenter RCT with a moderate dose of haloperidol (max 15 mg/day). However, since delirium is highly multifactorial, non-pharmacological management strategies also require further evaluation.

Conclusions

The stepwise approach to implementation intervention development, as described in this thesis, could be applied to other hospital guidelines and in particular for guideline/protocol adherence at the ICU. Using a survey to identify barriers for adherence to delirium guidelines is essential and feasible. The methodology we applied enables to develop effective interventions targeting the crucial points of non-adherence. 'Guideline bundles' and 'implementation strategies' are different constructs that both need attention when aiming to improve delirium outcomes. Applying these implementation insights to the

ICU setting can help improve patient safety and further improve ICU healthcare. Implementation of delirium guidelines in the ICU requires an interprofessional and dedicated team approach with continued and periodic attention by local champions and education. To optimally facilitate the implementation process, consideration should be given to staggered versus simultaneous multi-bundle-elements implementation, depending on the availability of dedicated local implementation personnel. Tailored implementation of delirium guidelines does not preclude a high variability in guideline adoption by different ICUs – a variety which possibly is related to the level of center-specific tailoring.

This thesis has added insight into the barriers and facilitators of delirium guidelines adherence in ICUs and how interventions could target these barriers. The research presented shows that a combination of implementation strategies tailored to the barriers can improve knowledge and eventually the behavior of healthcare professionals at the ICU. Successful implementation is often not defined by improved clinical outcomes but rather relates to improved processes of care.

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