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IMPLEMENTATION OF DELIRIUM GUIDELINES AT THE INTENSIVE CARE UNIT

Thesis

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Content

Chapter 1

Introduction

INTRODUCTION

Delirium – or: acute confusion – is a common syndrome among adults admitted at an intensive care unit (ICU). For a long time, delirium in critically ill patients has been regarded an unavoidable symptom of the critical illness, and was assumed to be reversible when the underlying disease was cured. This view has shifted, however; delirium is now seen as a form of vital organ failure, or 'brain failure', which should be prevented whenever possible, because it is strongly associated with mortality and long-term cognitive decline. Although guidelines for the management of delirium at the ICU have been issued, in clinical practice the recommendations of those guidelines are often moderately adhered to. To improve health professionals' adherence to these recommendations, we first need to identify possible factors influencing adherence and next optimize the implementation of guidelines for the management of delirium in daily practice.

What is delirium, and how does it impact patient outcomes?

Delirium is a neuropsychiatric syndrome that often afflicts hospitalized persons, especially the elderly and those treated in an intensive care unit (ICU) [1]. Different terms have been used to describe delirium (e.g. acute encephalopathy, acute confusional state, postoperative confusion, intensive unit psychosis), and case descriptions of delirium have been documented since antiquity [2,3]. In 1850, Salter proposed that delirium is "always a matter of serious consideration to the medical practitioner and the subject of diagnosis is of primary importance" [4]. As early as in the 1950s, delirium was described as a syndrome of cerebral insufficiency, and considered a form of vital organ failure or 'brain failure' that should be more frequently recognized and managed [5]. Over time, definition for this condition has evolved from 'acute encephalopathy', to cover mental alterations, to delirium – as is now mostly used. In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), delirium is defined as a disturbance in attention and awareness and a change in cognition that develops rapidly over a short period of time [6]. To distinguish delirium from other psychiatric disorders, there must always be an organic disease as underlying cause [6]. Delirium in itself is not a disease, but rather a syndrome that has to be studied as a "final common pathway of symptomatology" [3].

The pathophysiology of delirium is not well understood and a variety of etiological factors may contribute to delirium in critically ill patients. Three major hypotheses for the pathogenesis of delirium have been proposed: the immune activation hypothesis, the oxidative stress hypothesis, and the cerebral neurotransmitters disturbances hypothesis [7,8]. The wide variation in the occurrence of delirium in ICU patients is depending on the case mix; rates from 26% to 45% in a general ICU population [9,10]; 28% in a surgical ICU unit [11]; and up to 78% in ventilated ICU patients have been reported [12,13]. Contributing

factors to delirium are distinguished into predisposing factors (e.g. age, cognitive and pre-morbid functional status etc.) and precipitating factors (e.g. drugs use, infections, pain). [1] The mnemonic acronym "I Watch Death", which refers to factors such as infection, withdrawal of benzodiazepines, and hypoxia, can be used to make a differential diagnosis and detect factors which may have triggered the delirium in a specific patient [14].

Over the two past decades, we have learned that delirium is independently associated with poor outcomes for elderly patients in general and ICU patients in particular [12,15]. Furthermore, prolonged duration of ventilation, longer ICU stay and, consequently, increased healthcare costs are related to delirium in ICU patients [16,17]. Delirium is not only related to higher mortality during the ICU stay and six months after discharge [12], but also with significant cognitive impairment months after ICU stay and long-term psychological problems [18,19].

Not only the patients, but also the ICU professionals and a critically ill patient's family members consider delirium a very worrisome condition. ICU nurses characterize delirium as one of the most vexing problems due to communication difficulties [20], restless behavior and the danger of self-injury, which is associated with an increased workload [21]. And family and friends struggle to achieve contact with the patient who is mechanically ventilated and whose level of consciousness is often low [22,23]. Psychological recovery of ICU patients can improve if family participation at the ICU is facilitated by nurses, for example [24-26].

Delirium management: screening, prevention and treatment

To alleviate the adverse clinical outcomes associated with ICU delirium, professionals need to manage delirium in the best way possible. First, by applying validated bedside delirium-screening tools, like the Confusion Assessment Method-ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) [27,28], implementation of delirium screening is feasible [29,30]. The routine screening of mechanically ventilated patients may have positive effects [31]. Second, non-pharmacological prevention strategies such as orientation, environment interventions (e.g. providing glasses and hearing aids, etc.), and early therapeutic interventions (e.g. early mobilization and pain control) can reduce delirium rates [32]. Third, applying pharmacological strategies to treat delirium according to the 'ICU triad' concept, based on the idea that pain, agitation, and delirium are intertwined, may be useful [33].

Guidelines and implementation

Clinical practice guidelines are systematically developed evidence-based statements to assist healthcare professionals and patients in the decision-making about appropriate health care in specific clinical circumstances [34]. The adherence to guideline recommendations in clinical practice in general is poor and needs to be improved [35]. In other

words: "We know what we have to do, but in daily practice we do not do what we know that has to be done" (Prof. Takala, ESICM congress, 2014). On the other hand, many different recommendations have been proposed and it is challenging for staff to adhere to all of these [35]. ICU guidelines reflect the medical and nursing professional standard in intensive care medicine and can be processed into local protocols.

The Netherlands Society of Intensive Care (NVIC) has issued the "NVIC Delirium Guideline on Intensive Care" guideline [36]. The Pain, Agitation and Delirium (PAD) guidelines of the international Society of Critical Care Medicine are mostly in line with the Dutch guideline but is more updated and integrates pain, agitation and delirium better [36,37]. The most recent update is coined the PADIS (Prevention and Management of Pain, Agitation / Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU) guidelines. It includes new recommendations on sleep and immobility, but was published after the studies described in this thesis had been conducted. Screening for delirium, preventive measures and therapeutic management are the cornerstones for optimal ICU delirium management by ICU nurses and physicians, as recommended in the national and international guidelines. For unclear reasons, however, and as already stated before, the management of delirium strongly depends on local policy, individual professionals, and is often not in line with current guideline recommendations [35].

One of the most important challenges in improving the quality of care is achieving behavioral change of healthcare professionals [38]. The first step would be to identify the relevant barriers to and facilitators of delirium guidelines, professionals' knowledge about and attitude to delirium guidelines, and organizational, and patient level barriers for delirium guideline adherence. Implementation interventions tailored to identified barriers for guideline adherence seem to be more effective in improving professional practice than a "one size fits all" approach. Implementation models are helpful and necessary to develop a tailored implementation strategy based on the analysis of the context and the target group, such as the Implementation Model of Change developed by Grol and Wensing [39].

Identifying barriers to execution of ICU delirium guideline recommendations is essential [40] to develop an implementation plan that will successfully improve execution of those recommendations [41,42]. Only by merging implementation science with clinicians' knowledge and insight can the best possible outcomes for critically ill patients with delirium be achieved [43,44].

Aims and outline of the thesis

This thesis contains the reports of our studies on the implementation of delirium guidelines in daily critical care practice. For this multicenter, prospective implementation project we followed these steps: first, determining the level of guideline adherence (baseline measurement); second, describing the barriers to and facilitating factors for

adherence to the guidelines; third, developing and executing a 'tailor-made' implementation strategy; and finally, studying the effects of the implementation on compliance with the guideline and on patient outcomes before versus after the implementation. The general aims were to assess factors that influence ICU delirium guideline compliance, to develop a tailored implementation program, and to study effects of the implementation interventions on adherence to the guideline and on clinical outcomes. The above aims have been substantiated in the various studies with the following research questions:

1. What are the barriers and facilitators for implementation of delirium guidelines?
2. What is the best way to implement the ICU delirium guideline recommendations and what factors are associated with outcome improvements?
3. What is the effect of implementation on guideline adherence and clinical outcomes?
4. What is the compliance with the guideline at site level, and what are the possible explanations for the implementation effectiveness, and what are the experiences with the implementation?
5. What are the trough levels of haloperidol when haloperidol was dosed according to a protocol using a low-dose regimen?; are those trough levels associated with a decrease of delirium symptoms; and what is the influence of CYP3A4 and CYP2D6 genotype on haloperidol serum levels?

Chapter two describes the original study protocol and a letter to the editor about ICU delirium. **Chapter three** describes the barriers and facilitators based on a survey among ICU healthcare professionals about delirium, attitudes, knowledge and guideline adherence. **Chapter four** describes a systematic review of the literature on delirium guideline implementation studies. An implementation strategy based on literature review and analysis of barriers was executed and the effects were measured. **Chapter five** describes the effects of implementation on process of care and patient outcomes. **Chapter six** focuses on the evaluation of the implementation process on ICU level. **Chapter seven** describes a study on haloperidol serum concentrations and clinical response. Lastly, in **Chapter** 8 the main findings of our research, are presented, the clinical implications are discussed and conclusions are drawn.

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Chapter 2.1

Improvement of care for ICU patients with delirium by early screening and treatment: study protocol of iDECePTIvE study

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ABSTRACT

Background

Delirium in critically ill patients has a strong adverse impact on prognosis. In spite of its recognized importance, however, delirium screening and treatment procedures are often not in accordance with current guidelines. This implementation study is designed to assess barriers and facilitators for guideline adherence and next to develop a multifaceted tailored implementation strategy. Effects of this strategy on guideline adherence as well as important clinical outcomes will be described.

Methods

Current practices and guideline deviations will be assessed in a prospective baseline measurement. Barriers and facilitators will be identified from a survey among intensive care health care professionals (intensivists and nurses) and focus group interviews with selected health care professionals (n = 60). Findings will serve as a foundation for a tailored guideline implementation strategy. Adherence to the guideline and effects of the implementation strategies on relevant clinical outcomes will be piloted in a before-after study in six intensive care units (ICUs) in the southwest Netherlands. The primary outcomes are adherence to screening and treatment in line with the Dutch ICU delirium guideline. Secondary outcomes are process measures (e.g. attendance to training and knowledge) and clinical outcomes (e.g. incidence of delirium, hospital-mortality changes, and length of stay). Primary and secondary outcome data will be collected at four time points including at least 924 patients. Furthermore, a process evaluation will be done, including an economical evaluation.

Discussion

Little is known on effective implementation of delirium management in the critically ill. The proposed multifaceted implementation strategy is expected to improve process measures such as screening adherence in line with the guideline and may improve clinical outcomes, such as mortality and length of stay. This ICU Delirium in Clinical Practice Implementation Evaluation study (iDECePTIvE-study) will generate important knowledge for ICU health care providers on how to improve their clinical practice to establish optimum care for delirious patients.

BACKGROUND

Delirium, also known as 'brain failure', is a common form of vital organ failure in critically ill patients. It has an acute onset and is characterized by a combination of attention and cognitive deficits and a fluctuating consciousness [1]. Disturbed motor activity (apathy or agitation), visual hallucinations, and sleep disruption are among the most frequently observed symptoms. The reported incidence of delirium in critically ill patients ranges from 16%–89%, depending on type of intensive care unit (ICU), method of assessment, and patient population [2]. Delirium is especially common in over 65-year-old patients [3,4]. Delirium is an important, independent predictor of mortality [5-7]. Critically ill patients may develop delirium associated complications leading to serious self-harm, such as attempting to remove the endotracheal tube, central lines and catheters, or falling out of bed [8]. Many delirious patients show severe psychological distress and anxiety [8]. Delirium is a cause of longer ICU and hospital stay, and affected patients have more long-term morbidity [2,5] and a worse prognosis after discharge compared with non-delirious ICU patients. The duration of delirium is also an important prognostic indicator for various adverse outcomes. Furthermore, recent research suggests that ICU delirium independently predicts long-term cognitive impairment comparable to mild Alzheimer's disease [5,7,9-14]. The sequelae associated with delirium are a cause of increased health care costs [15].

Therefore, delirium in these critically ill patients requires adequate management, including systematic screening to prevent that the diagnosis is missed in patients who display only subtle signs of delirium ('hypoactive delirium') [16]. The importance of routine screening for delirium at the ICU was already advocated in the clinical practice guidelines for pain and sedation issued in 2002 by the American College of Critical Care Medicine (ACCM)/ Society of Critical Care Medicine (SCCM) [17] but delirium screening has not yet been widely adopted [18].

The Netherlands Society for Intensive Care (NVIC) developed and authorized a delirium guideline in 2010 [19]. The recently published 'Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium (PAD) in the ICU' from ACCM/SCCM [20] are generally in line with this guideline. Both guidelines recommend routine delirium screening in critically ill patients using a valid and reliable screening tool. Despite this, a validated delirium screening tool is not routinely used in most Dutch ICUs; the management of delirium strongly depends on local policy and is generally not in line with current recommendations [16,21]. The Netherlands is not alone in this respect; also, in other countries, the attention paid to the monitoring and management of ICU delirium has been shown to be insufficient [18].

'Get With The Guidelines' initiatives have the potential to accomplish practice changes in the ICU environment that may result in improved clinical outcomes, including mortality [22]. However, the most effective way to translate such 'paper' guidelines to real-life

clinical practice is not clear. In general, a variety of barriers may be in the way of good adherence to guidelines and interventions [23-25]. Hence, it is necessary to develop a tailored implementation strategy based on a thorough analysis of the context and target group [24].

Objective

We designed the ICU Delirium in Clinical Practice Implementation Evaluation (iDECePTIvE) study with the following aims: 1) to assess the barriers and facilitators for adherence to the Dutch ICU delirium guideline [19]; 2) based on these results, to develop a tailored implementation strategy targeting these influencing factors for successful implementation and long-term adherence to the guideline; and 3) to study the effects of tailored implementation on adherence to the guideline, clinical outcome, and costs in a prospective multi-center study. The following research questions are addressed to answer these aims:

1. What are the current practices (before-implementation) with regard to delirium management and degrees of adherence to the delirium guideline in the participating ICUs?
2. What are the influencing factors (barriers and facilitators) for the implementation of the ICU delirium guideline in the ICUs as reported by intensivists, ICU nurses, and psychiatrists?
3. What should be the content of a tailored implementation strategy to improve adherence to the delirium guideline based on the answers to the first two questions?
4. What is the effect of the tailored implementation strategy on guideline adherence, knowledge of health care providers, delirium incidence, clinical outcomes (mortality, length of ICU stay) and health care costs?
5. What are potential explanations for why the intervention was effective or not, based on ICU and health care providers' characteristics indicative of local 'culture?'

METHODS

The iDECePTIvE study is a descriptive, explorative prospective multi-center study, using a mixed method design in six ICUs in the southwest of the Netherlands. In line with the research questions, we designed the study in several phases (see detailed schedule in **Figure 1**):

A. Analysis of the current practice of delirium management and level of adherence to the Dutch NVIC delirium guideline in the participating ICUs.
B. Identification of barriers and facilitators for the implementation of the ICU delirium guideline.

C. Development of a tailored implementation strategy based on the results of phases A and B.
D. Implementation of the guideline and measurement of the effects.

We describe the methods, population, analysis, and outcomes per study phase. An overview is given in **Table 1** and **Figure 1**.

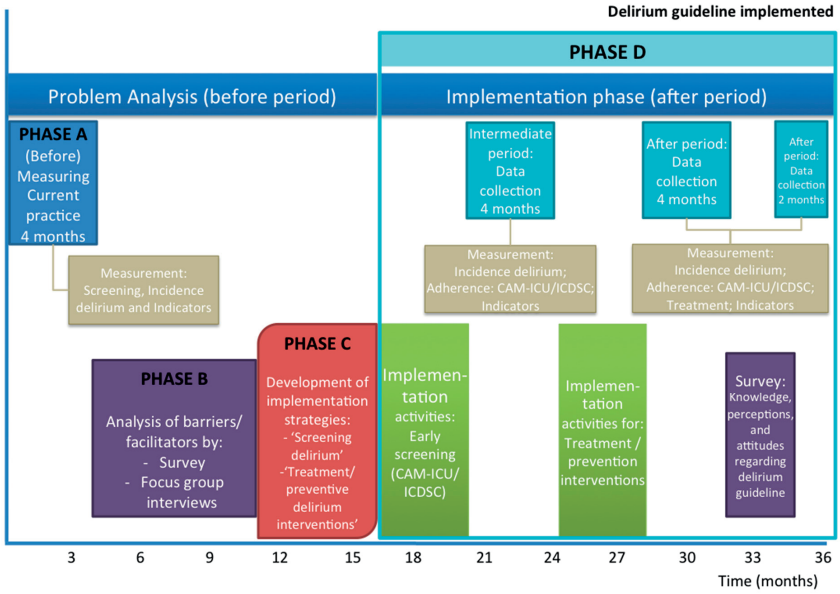

Figure 1: Study Schedule

Study sites and participants

The study will be performed in six ICUs of university, non-university-teaching, and non-university-non-teaching hospitals. Wards were selected to include several levels of intensity of intensive care practice. Inclusion criteria for patients are: age ≥18 years and admitted to an ICU for ≥24 h. Involved professionals are all ICU physicians and nurses.

Phase A: analysis of current practice of delirium management and adherence to the Dutch delirium guideline

Study design and population

Over a 4-month period, we will prospectively record the incidences of delirium, frequency of delirium assessments, types of pharmacological and non-pharmacological treatments, and documented preventive interventions. Unit staff will not be actively informed about the study, nor will they be educated on delirium, so as to avoid a Hawthorne effect as much as possible. The results of this analysis will serve as a baseline

measure to compare future practice and outcome changes in the course of the implementation project.

Measures

Adherence to and deviation from the delirium guideline will be assessed using the following indicators. The primary outcome in this study phase is the percentage of patients screened with either the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [26] or the Intensive Care Delirium Symptoms Checklist (ICDSC) [27], which both are validated for use in the ICU. Adherence is defined as screening of every eligible patient at least once per nursing shift (i.e. three times daily). The secondary outcomes are pharmacological treatment with haloperidol or other antipsychotic drugs; documented psycho-hygiene measures aimed at preventing delirium (such as use of hearing aids or glasses and stimulating a proper night-day rhythm; early mobilization and physiotherapy). Delirium is defined either as a positive CAM-ICU or ICDSC score, or if a screening tool is not used, pragmatically defined as 1) administration of haloperidol or other antipsychotic drug; or 2) delirium reported by a physician or ICU nurse in the patient record, as confirmed by a designated research nurse on site. Data on adherence to these indicators for all ICU patients will be collected by various methods: direct observations and systematic registration in the patient data management system, medical records, and 24-h ICU-care lists.

Analysis

Descriptive statistics will be used to describe the outcomes. Multivariate analysis serves to compare ICUs regarding patient mix (e.g. age, diagnosis, severity of illness [Acute Physiology and Chronic Health Evaluation, APACHE II score]) and ICU level of care. The incidence of delirium will be calculated based on screening (CAM-ICU or ICDSC) and medical notes (physicians and nurses) and consulting experts (psychiatrist, geriatrists, or neurologist).

Phase B: identification of barriers and facilitators for the implementation of the ICU delirium guideline

Study design

Barriers and facilitators will be identified with quantitative and qualitative research methods: 1) a survey and 2) in-depth focus group interviews. The main aim is to understand, and where possible explain, the opinions, attitudes, beliefs, and perceived practices of health care professionals with regard to delirium in critically ill patients [28].

Survey

ICU physicians and ICU nurses will be surveyed on their beliefs, attitudes, and practices regarding the incidence, clinical relevance, screening for, treatment, and prevention of delirium. The survey will be partly based on the instrument developed by Ely et al. [29] and expanded with self-developed questions on non-pharmacological and preventive interventions for delirium. Furthermore, the questionnaire will contain statements about the delirium guideline and attitude towards guidelines in general [30] and questions assessing knowledge [29,31,32] and demographic characteristics of responders. The survey will be repeated in a later phase (D, after implementation) to assess impact of implementation on attitudes and practice perceptions.

Focus group interviews

The uniqueness of a focus group interview is its ability to generate data based on the synergy of group interaction. This type of analysis is also essential to understand the potential barriers and facilitators in the collaboration between health care professionals, e.g. nurses and physicians. An interview framework and protocol will be developed with a series of open-ended questions, based on the framework of knowledge-attitude-behavior related barriers for guideline adherence of Cabana et al. [23]; the interdisciplinary conceptual framework of clinicians' compliance with guidelines of Gurses et al. [33]; and the framework for adherence to clinical practice guidelines in the ICU of Cahill et al. [34]. These frameworks distinguish six major categories of factors that influence adherence to evidence-based guidelines: 1) the guideline; 2) the health professionals' characteristics (e.g. knowledge and attitudes); 3) the institutional characteristics (e.g. organization, structure, resources); 4) the implementation (e.g. how the guideline is implemented); 5) the patient characteristics; and 6) the social context (e.g. ICU culture). The survey findings will be discussed in the focus group interviews to explore discrepancies between professionals' beliefs and daily practices.

Study population

All health professionals in the six ICUs, including ICU nurses, intensivists, residents, and psychiatrists or geriatrists, will be asked to complete an online survey. For the focus group interviews, we will purposefully select 8–10 professionals involved in delirium care from each participating ICU, e.g. intensivists, residents, ICU nurses, managers and psychiatrists, geriatrist, or neurologist.

Outcome measures

Barriers and facilitators for adherence to the delirium guideline in daily practice will be classified according to the six major categories of the above-mentioned frameworks [23,33,34]. Combining the findings on current practices (phase A) with the results of the

surveys and focus group interviews (phase B) will give a complete overview of current practices, attitudes, and perceptions at baseline of the study and potential barriers and facilitators for implementing the guideline.

Analysis

The different barriers and facilitators will be quantified and expressed in percentages. Continuous data will be presented as means (+/−SD), non-normally distributed as medians (interquartile range). Differences among the health care professionals and across the six ICUs will be evaluated with ANOVA or Kruskall–Wallis test depending on normality of data distributed. Data will be analyzed using IBM SPSS version 21.0. The focus group interviews will be audiotaped and transcribed in full for analysis. Qualitative analysis will be done with the software package Atlas.ti using Krueger's framework analysis approach, which provides a clear series of steps: familiarization, identifying a thematic framework, indexing, charting, and mapping and interpretation [35]. To strengthen validity of the analysis, participants will be invited to provide feedback on a summary of the focus group interview.

Phase C: development of the tailored implementation strategy

The implementation model of Grol et al. [24] assumes that the effectiveness of the implementation is enhanced if the chosen strategy is appropriate to the innovation, the setting and target group, and includes an assessment of current practice and of barriers and facilitators for guideline adherence [36]. In this study, we will use this model, which includes several steps. Step 1 involves the development and clear description of the recommended performance. Steps 2 and 3 analyze the setting and target group. Both current practice and the barriers and facilitators for guideline adherence are explored in these steps. Step 4 involves developing and choosing strategies and measures to change practice that target the previously identified barriers and facilitators. Steps 5 and 6 subsequently develop and apply the implementation to integrate changes in routine of care, and step 7 evaluates the implementation strategy [24].

Based on the results of phases A and B, a team of implementation experts, investigators, and clinicians (nurses and physicians) will develop a tailored strategy for implementation aimed at enhanced delirium guideline adherence, focusing on the barriers and facilitators most frequently encountered. The strategy should facilitate integration of the guideline in daily practice and its sustained use over time. The expert team will discuss the content of the tailored implementation strategy with local ICU teams. Two main questions should be answered in this setting: 1) Can the barriers and facilitators found be successfully translated into tailored implementation interventions?; and 2) Are the tailored interventions applicable in daily practice? Finally, the implementation

expert team will adapt the tailored strategy based on feedback provided by the local ICU teams.

Tailored multifaceted strategies are likely to be more effective than single strategies [36]. Barriers and facilitators are expected to exist at different levels. This means that the tailored strategy will consist of a combination of different interventions targeted to influence the professionals, the organization, and the structure of care. To strengthen the strategy development, we will be building upon existing theories for behavioral change like social learning or social influencing theories [37,38]. Finally, the selected implementation interventions will be matched to evidence-based interventions, described by the EPOC taxonomy [39]. We give some examples to illustrate our approach. Possible barriers at a professional level are aspects of hierarchy and lack of collaboration between nurses and doctors. A physician may have doubts and not start treatment after an ICU nurse has identified a delirious patient. This may discourage nurses to screen for delirium on a daily basis. A consistent management protocol could properly remove this barrier by linking screening results to a treatment. Another potential barrier is the perceived time-consuming nature of routine screening. ICT solutions to facilitate registration could be helpful in this regard.

Phase D: implementation study

Study design and population

The impact of implementation of a delirium guideline in six ICUs for adults will be studied in a pilot feasibility study using a prospective multi-center before-after study design (**Figure 1**). The primary aim will be to evaluate to what extent a guideline implementation program can achieve changes in ICU professionals' clinical practice with regard to delirious patients. This will be measured by the degree of adherence to the guideline recommendations. A secondary aim will be to evaluate the impact of the implementation interventions on clinical outcomes (hospital mortality and length of stay at ICU) and costs of the implementation and whether these may be linked to the practice changes achieved. A before-after study is considered a useful instrument, particularly for pilot studies in which interventions are initially evaluated and refined if necessary, before the testing of the implementation strategy on a wider scale is justified.

Implementation of the delirium guideline will be two-phased. First, we will implement delirium screening with the CAM-ICU or ICDSC. This is an essential first step because prevention and treatment of delirium will only be possible after adequate and early recognition. Second, protocolled prevention and treatment interventions (pharmacological and non-pharmacological) will be implemented. ICUs will be free to select either tool based on local preference.

Before period—intermediate period—after period

We have defined three periods (see **Figure 1**). The first is the four-month before period, during which delirium will be assessed as described earlier (phase A, current practice evaluation), i.e. on the basis of antipsychotic drug therapy and documented delirium diagnosis as a proxy for delirium incidence when no systematic screening is performed. The second period is the four-month intermediate period after implementation of delirium screening with the CAM-ICU or ICDSC. The same data as in the before period will be collected, and in addition delirium incidence as measured with the CAM-ICU or ICDSC. This period serves to assess the impact of the barrier analysis (phases A and B) and screening implementation without formal implementation of a prevention and management protocol. The third period is the after period, in which the process measures (adherence to screening, prevention, and pharmacological and nonpharmacological) and clinical outcomes will be studied in two successive four-month and one two-month period (see **Figure 1**).

Survey

Post implementation of the survey previously done in Phase B will be repeated to explore changes in knowledge, attitude, perceptions, current beliefs, and perceived practices regarding delirium management of intensivists, physicians, and ICU nurses from the participating ICUs [29,31,32].

Main outcome measures

The primary outcomes of the prospective before-after pilot implementation study are adherence to screening and (non)pharmacological treatment as described in the Dutch ICU delirium guideline. Adherence to the delirium screening procedure will be calculated as the percentage of performed assessments per day, relative to the total number of assessments that should have been performed (i.e. a minimum of three times daily in every patient). Successful implementation is defined as adherence to assessment of more than 85%. Delirium experts (expert raters) will conduct accuracy spot-checks during the intermediate and after periods on a random sample of the bedside nurses' screening assessments. The expert will then share his or her findings from the CAM-ICU or ICDSC assessment with the bedside nurse and point out any mistakes or misconceptions in the nurse's assessment. Cohen's kappa and 95% CIs will be used to analyze agreement of CAM-ICU/ICDSC assessments between the bedside nurses and the delirium experts.

Adherence to the following aspects of non-pharmacological and/or pharmacological interventions and prevention interventions (based on the guideline) will be assessed: a) pharmacological: prescription of antipsychotic drugs (e.g. haloperidol); b) non-pharmacological: attention to orientation, prevention of sleep deprivation, and the use of glasses and hearing aids; and c) prevention: adherence to early mobilization and

physiotherapy. Data on adherence indicators will be collected from systematic registration in the patient data management system and direct observations. The secondary outcomes are the process measures (as defined in the section process evaluation, e.g. incidence of delirium; delirium knowledge of nurses and physicians; interrater reliability of delirium assessment (CAM-ICU or ICDSC); hospital mortality in the before, intermediate, and after periods).

Other variables

During all measurement periods, data will be collected on: psychoactive drugs (psychiatrist, neurologist, or geriatrician consultations), complications (self-removal of endotracheal tube, central lines, feeding tubes, and falls out of bed) and length of ICU stay, length of hospital stay, mortality, and institutionalization after hospital discharge. These data are needed to explore a cost benefit analysis of completed implementation. Furthermore, severity of illness scores (APACHE II score) and ICU ward specialty (e.g. internal medicine, surgery, or combined) will be retrieved from the Dutch National Intensive Care Evaluation (NICE) registry with consent from the participating ICUs.

Analysis

Results are expressed as percentages. Adjusted analyses will be done using repeated measures analysis for binary outcome data. Finally, outcome differences between the ICUs adjustments for patient mix (e.g. age, diagnosis, APACHE II score) and ICU level will be assessed using multi-variable analysis.

Sample size

Based on the literature, the adherence rate to screening with the CAM-ICU or ICDSC could increase from 70%–85%, following implementation [31,40]. Consequently, the sample size will be 924 patients (231 patients in the before period and 693 in the after period (3 periods, Figure 1). The alpha level of significance is set at 0.01 (two-tailed) and the beta level at 0.90.

Process evaluation

A process evaluation can give insight into determinants or indicators of potential success or failure of a tailored implementation strategy [41,42]. For this purpose, process data will be collected for each of sub strategies within the 'tailored strategy'. We will conduct in-depth qualitative interviews with clinicians (n = 12) from participating ICUs to understand their perceptions of the study's effect on local practice and the effectiveness of individual components of the intervention. We will recruit these individuals by invitation letters sent to all six ICUs. A semi-structured interview guide will be developed to facilitate the interviews.

Table 1: Overview of study phases

Phase	Research question	Methods	Target population/ data resource	Measures
A	What are the current practices (before-implementation) and the adherence to the delirium guideline in the participating ICUs?	Prospective, descriptive study, analyzing variation of care	Data from 6 ICUs	Indicators e.g.: -Adherence to delirium screening -Incidence of delirium -Pharmacological treatment -Sedation practices -Non-pharmacological treatment -Knowledge
B	What are the influencing factors (barriers and facilitators) for the implementation of the Dutch ICU delirium guideline by intensivists, ICU nurses, and psychiatrists?	Survey on knowledge, attitudes and perceptions, and structured focus group interviews	Health care professionals: intensivists, residents, ICU nurses, managers and psychiatrists, geriatrist or neurologist	Barriers and facilitators classified as related to: 1) guideline; 2) provider characteristics (e.g. knowledge and attitudes); 3) institutional characteristics (e.g. organization, structure, resources); 4) implementation (e.g. how and to what extent the guideline is implemented); 5) patient characteristics; and 6) social context (e.g. ICU culture).
C	What is the content of a tailored strategy to improve the adherence to the delirium guideline?	Strategy development according to implementation frameworks by Grol and Wensing, and Cabana	Matching the data from the current practice, questionnaires and focus groups and questionnaires to construct effective implementation strategies from the literature	Tailored multifaceted implementation strategy to effectively implement current guideline-based delirium management
D	What is the effect of the tailored implementation strategy on guideline adherence, knowledge of health care providers, delirium incidence, clinical outcomes (mortality, length of stay) and health care costs?	Prospective before-after study	Data from 6 ICUs	(Process) indicators e.g.: -Adherence delirium screening -Incidence of delirium -Pharmacological treatment -Non-pharmacological treatment -Knowledge Outcomes e.g.: -Length of stay -Hospital mortality Costs
D	Explore potential explanations for why the intervention was effective or not based on ICU and health care providers' characteristics indicative of local "culture".	Process evaluation: qualitative (outcomes,) and quantitative data (survey and interviews)	Data from 6 ICUs. Frame work for process evaluation, matching outcomes with actual exposure, and experiences of the implementation strategy	Underlying mechanisms that explain the effects of the study.

The process evaluation will provide insight in elements of the tailored strategy that are less feasible and need refinement before further implementation. In a postimplementation survey, we will examine whether earlier barriers are removed and facilitators are taken up.

Process measures

a. Education: number of nurses attending per ward, duration of training per ward, evaluations of nurses attending the training, experience with the training; b. Tailored strategy: elements of the strategy are delivered as agreed; feasibility of the strategy, user experiences with the strategy, degree to which barriers are solved, and facilitators are used. Other process indicators will be defined after the strategy procedure has been developed. Data will be collected from questionnaires, interviews, and direct observations. The process indicators will be related to relevant outcomes (e.g. mortality reduction) of the 'tailored strategy' to identify elements of the strategy that were particularly associated with the success of the implementation.

Economic evaluation

Prolonged admission on the ICU due to delirium is related with increased health care costs. Therefore, strategies that focus on increasing adherence with the Dutch delirium guideline are likely cost-effective [15]. The economic evaluation compares usual care (before) and care after implementation of the guideline. The aim of this analysis is to explore whether the likely overall cost saving from the tailored guideline implementation strategy exceeds the overall cost of the tailored guideline implementation process.

Cost analysis

The economic evaluation will be performed from a health care perspective and in accordance with guidelines for such analysis [43]. Care costs of each strategy are defined as all direct medical costs associated with procedures performed within that strategy. The resources consumed by the implementation strategies will be assessed in the clinical study by collecting data on personnel costs (time spending for the strategy delivery team, for the nurses attending the strategy related activities, and for systematic screening), material costs (antipsychotic drugs), and overhead costs. Medical costs will be estimated by multiplying resource utilization with the cost per unit of resource (market prices, guideline prices, or self-determined prices based on costing methods, i.e. full costing) [43]. The implementation process and consequent costs will be estimated by focusing on activities performed with costs accumulated at the activity level(s) of the health care implementation processes. The incremental costs will be determined by the difference in resource consumption between usual care and tailored implementation. The economic analysis will be a cost minimalization analysis, in which we investigate

whether the likely overall cost saving from the tailored guideline implementation strategy exceeds the overall cost of the tailored guideline implementation process.

Ethical considerations

This study protocol was presented to the Medical Ethical Committee of the Erasmus University Medical Center (registration number: MEC-2012-063). An exemption was obtained as ethical approval for this type of study is not required under Dutch law. This study is registered in the Trial register, located at http://clinicaltrials.gov, under number: NCT01952899. Data collection will be in line with Dutch METC endorsed privacy regulations, ensuring that data collected for the analyses cannot be traced to individual patients by the coordinating investigators because the data will be anonymized by the local investigators who provide the data.

DISCUSSION

The goal of the iDECePTIvE study is to identify barriers and facilitators for adherence to a national ICU delirium guideline. We will analyze the current practice (Phase A) before executing the survey and focus group interviews to avoid a possible Hawthorne effect (attention effect) by which members of the focus groups could be influenced. Based on these results, a tailored implementation strategy targeting these influencing factors will be developed for successful implementation and long-term adherence to the guideline. Finally, a before-after multicenter study will be conducted to evaluate the impact of the implementation strategy on clinical practice including a cost-effectiveness analysis and the effects on clinical outcomes. This study is unique in that it includes all components of a multifaceted implementation in a large cohort of critically ill patients and includes measurement of important clinical outcomes based on a national database benchmarking outcome of intensive care in the Netherlands. In a systematic review of the literature, we found that ICU delirium implementation studies mainly focus on implementation of screening or assessment tools for early recognition of delirium in ICU patients and tend to ignore improvement of prevention and treatment [44]. Most implementation strategies were not based on a systematic analysis of the context, including barriers and facilitators. Studies have shown that largescale implementation of a delirium screening tool in the ICU is both feasible and sustainable with a compliance rate that may exceed 80% [31,40,45-47]. However, these studies focused only on screening and not on pharmacological and non-pharmacological treatment of delirium.

Furthermore, the analysis of the barriers and facilitators was unstructured and not focused on treatment as proposed in the current delirium guideline. In this proposed study, the multifaceted strategy will be based on theoretically underpinned mechanisms

to accomplish improved adherence to a guideline on ICU delirium. A study including all these components and of this magnitude has not been performed previously. Also, outcome assessments and cost-effectiveness analysis have not been performed on this scale.

Furthermore, the results of this study will expectedly provide us with further knowledge on effective implementation of optimal care of the delirious patient at the ICU. We will provide answers to not only the 'why should we implement' questions, but also answers to 'how to implement' question and provide clues to reproducibility. In other words, the results of this study may help persuade clinicians and nurses to put effort into formal implementation of interventions, when indeed the results confirm that these may improve outcomes of our patients.

The results of this project will therefore add to the general body of knowledge about implementation science at the ICU. The knowledge generated from this study can also be of use in other improvement projects and guidelines in the ICU that require collaboration between different health care providers [48,49].

A major limitation of this study with regard to the clinical outcomes assessment (mainly: mortality) is the before-after study design (phase D). Although changes in team behavior and clinical practices (i.e. guideline adherence; the primary outcome) related to delirium management during the course of this study are very likely to be due to the implementation itself, changes in mortality (secondary outcome) are less likely to be caused exclusively by the implementation. Other factors besides the implementation interventions that may impact on mortality include case-mix changes over the course of this study, changes in composition of the medical teams, or organizational changes (e.g. rebuilding of ICU). Such changes can only be partly accounted for in multivariable analysis because unmeasured (or unmeasurable) confounders are potential sources for bias. Therefore, results of the pilot before-after study on clinical outcomes rather than process measures should be interpreted with great caution. The generalizability is limited because concurrent changes in content or organization of care that may influence clinical outcomes may confound attribution of observed changes in outcomes to the implementation strategy. Furthermore, there is some evidence that suggests that uncontrolled before-after studies may overestimate the effects of quality improvement projects like this [24,50]. In future studies, a stepped wedge cluster randomized trial would be a more sophisticated design, in which at the end of the study all participants will have received the intervention [51]. However, the current study with the proposed design will provide details regarding the feasibility of establishing practice changes and guideline adherence improvements with a tailored implementation and provide valuable information on successful and less successful implementation interventions and the need for their refinements in future studies on a wider scale. Future implementation studies aimed at improving outcomes will likely benefit from the knowledge generated by our

study because effective interventions to change practice will be identified, which is a first essential step towards outcome improvement.

We hypothesize that the incidence rates of delirium in ICU patients will increase after implementation of early screening. One of the main reasons is that hypoactive delirium will be detected, which is ill-recognized without systematic screening. On the other hand, implementation of prevention and management of delirium is expected to decrease incidences. The balance between these opposite forces may explain why some studies found decreased incidences and others increased incidences of delirium after implementation of interventions targeted at delirium. Therefore, we propose a two-phased implementation process (Phase D: first screening implementation, thereafter prevention and treatment). After data collection for this reference period (before intermediate period), guideline-recommended treatment will be implemented. This approach prevents strong bias in the comparison of the incidence rates between the intermediate and after periods because assessment of delirium before and after implementation is similar.

The ultimate aim of our study is to reduce the incidence of delirium and improve the outcome for ICU patients and their families by implementing the national and international evidence-based guidelines on ICU delirium management. Furthermore, this study provides a framework for future efforts to stimulate guideline adherence and delirium management.

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Chapter 2.2

Untangling ICU delirium: is establishing its prevention in high-risk patients the final frontier?

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Van den Boogaard et al. [1] recently reported the recalibration of a previously developed prediction model (PRE-DELIRIC) for delirium in critically ill patients. Selecting patients for preventive measures based on PRE-DELIRIC may facilitate implementation of preventive (non-)pharmacologic measures. However, being able to identify patients at high risk for delirium may not be sufficient to facilitate implementation of preventive measures.

Although health care workers at the ICU will acknowledge that delirium is important, stimulating them to 'get with the guidelines' is more cumbersome. There often is a lack of belief that efforts to diagnose and manage delirium will translate into improved outcomes, although the contents of Awakening and Breathing Coordination, Delirium monitoring and Early exercise (ABCDE) bundle are supported by clinical trials [2]. A second problem is that probably no one has ever seen a patient die as a direct consequence of delirium. The same cannot be said about circulatory or respiratory failure, which may explain why care bundles targeted at these organ systems, may seem easier to implement. Further, delirium is still regarded by many as 'an often present but inevitable problem of intensive care'. However, recently such a perception was also common regarding central venous catheter related blood stream infections. However, we now know that prevention *is* possible, saving many lives [3].

To get care bundles aimed at ICU delirium implemented the two barriers mentioned above should be addressed. First, false perceptions about prognostic implications and preventability of delirium should be addressed when present. To this end, implementation efforts led by local champions are critical, and include attending barriers to implementation and on-going education for the complete ICU team, stimulating collaboration between nurses and physicians (nurses have a dominant role in applying preventive measures and they should be empowered to discuss a positive delirium screening test such as the CAM-ICU in the daily rounds), and regular feedback on delirium screening and incidence to the ICU team members. Second, more research is necessary into the causality between delirium and adverse outcomes. We should learn whether delirium is solely an indicator of adverse outcome or that it should be regarded as having direct intrinsic risk for the patient, and if cognitive decline is the only factor on the causal pathway to adverse outcome. The relation between contributing factors, delirium and outcome is complex (**Figure**) and treatment with antipsychotics alone seems unlikely to establish improved outcomes.

Predicting delirium at an early stage and being able to prevent it may only be a part of the solution; only when effective prevention of delirium at the ICU is accompanied by improved outcomes should it become easier to convince the medical community of the necessity of bundled care aimed at delirium. That such bundled care may indeed result in improved outcomes has only recently been shown [4,5]. Tailoring preventive measures for delirium by identification of high-risk patients that are more likely to benefit from

them may certainly help to establish more support among health care professionals for the implementation of integrated management of delirium.

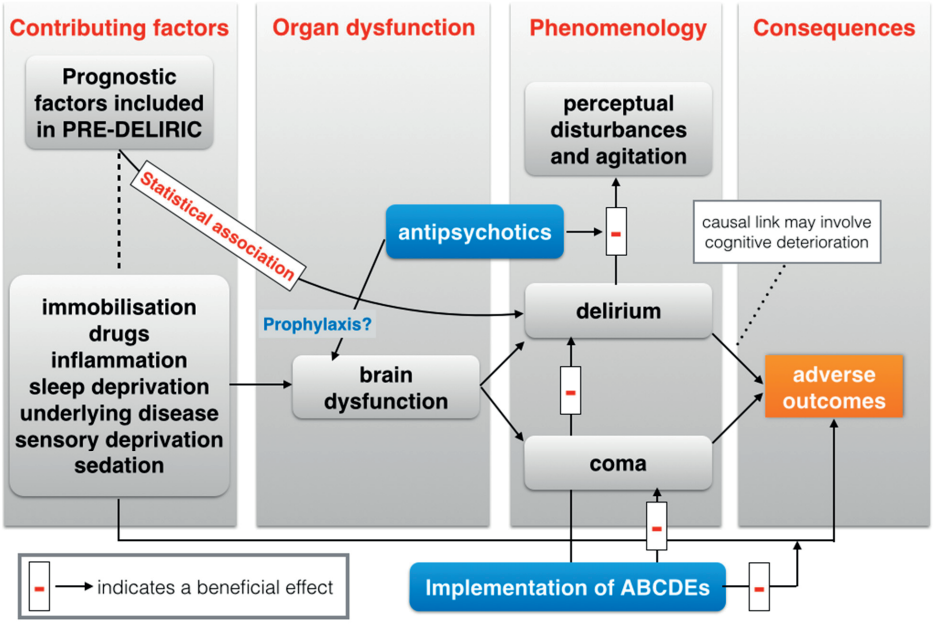

Figure: Relation between contributing factors, delirium and outcome

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Chapter 3

Attitudes, knowledge and practices concerning delirium: a survey among intensive care unit professionals

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ABSTRACT

Background

Delirium is a common form of vital organ dysfunction in Intensive Care Unit patients and is associated with poor outcomes. Adherence to guideline recommendations pertaining to delirium is still suboptimal.

Aims

We performed a survey aimed at identifying barriers for implementation that should be addressed in a tailored implementation intervention targeted at improved Intensive Care Unit delirium guideline adherence.

Design

Survey among ICU professionals.

Methods

An online survey was conducted among 360 Intensive Care Unit healthcare professionals (nurses, physicians and delirium consultants) from six Intensive Care Units in the southwest of the Netherlands as part of a multicenter prospective implementation project (response rate 64% of 565 invited; 283 (79%) were nurses).

Results

Although the majority (83%) of respondents considered delirium as a common and major problem in the Intensive Care Unit, we identified several barriers for implementation of a delirium guideline. The most important barriers were: knowledge deficit, low delirium screening rate, lack of trust in reliability of delirium screening tools, belief that delirium is not preventable, low familiarity with delirium guidelines, low satisfaction with physician-described delirium management, poor collaboration between nurses and physicians, reluctance to change delirium care practices, lack of time, disbelief that patients would receive optimal care when adhering to the guideline, and the perception that the delirium guideline is cumbersome or inconvenient in daily practice.

Conclusion

Although Intensive Care Unit professionals consider delirium a serious problem, several important barriers to adhere to guidelines on delirium management are still present today.

Relevance to clinical practice

Identification of implementation barriers for adherence to guidelines pertaining to delirium is feasible with a survey. Results of this study may help to design targeted implementation strategies for ICU delirium management.

BACKGROUND

Delirium is a common form of vital organ dysfunction in critically ill patients (up to 80% in mechanically ventilated patients) [1] and is associated with increased mortality [2], morbidity, and cognitive impairment [3]. Further, delirium is associated with increased healthcare costs [4] and hospital length of stay [1]. Therefore, adequate delirium management, including screening, prevention and treatment can have significant impact on quality of care and use of resources. Delirium management is considered an essential component of routine care in Intensive Care Unit (ICU) patients and is endorsed by national and international guidelines [5,6]. However, systematic screening for delirium is still not a part of daily routine at many ICUs [7-9] and its management varies widely [10,11]. This general lack of screening for delirium seems to persist in spite of the availability of well validated delirium assessments tools such as the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) [7,12-19] and agitation and sedation scales such as the Richmond Agitation-Sedation Scale (RASS), all of which are guideline-recommended [5].

Previous studies have shown that various barriers may exist for effective adherence to delirium-oriented measures, such as low confidence in screening tools for the ability to identify delirium [20], lack of knowledge of delirium [21,22], low perceived importance of delirium among professionals [7], fear of adverse events, communication and care coordination challenges, workload concerns, and documentation burden [23]. In general, adherence to clinical guidelines depends on the attitude of the health care professional, the guideline, the organizational context, and social and cultural factors [24-26]. The effectiveness of guideline implementation is enhanced if the strategy is appropriate for the innovation, setting and target group, and includes assessment of current practice, and barriers for adherence [27,28]. Therefore, we designed the ICU DElirium in Clinical PracTice Implementation Evaluation (iDECePTIvE) Study, which is a prospective multicenter study in the Netherlands aimed at a multifaceted implementation program to increase adherence to ICU delirium guidelines and to evaluate effects of the program on processes of care and clinical outcomes [29]. As a starting point of this project, the current knowledge, practices, and attitudes pertaining to ICU delirium have been explored with a survey among participating ICU health care professionals.

Aims and objectives of study

The aim of the survey was to identify barriers for implementation that should be addressed in an implementation intervention targeted at improved guideline adherence.

METHODS

Development and content of survey

The survey was developed according to the framework for perceived barriers for guideline adherence by Cabana et al. [24] and Grol et al. [28]. The framework provides a practical step-wise flow-chart guided approach to assess the reasons or circumstances (barriers) that may exist explaining why physicians do not adhere to guideline recommendations. Based on these publications, we identified two main headings: professional behavior (knowledge, attitude and perceptions) and guideline adherence. Most questions were constructed based on previously published surveys regarding delirium at the ICU [12-16,22,30-32] and the survey consisted of four domains: 1) demographics and other respondents' characteristics, 2) delirium knowledge; 3) attitudes, perceptions and current practices regarding delirium; and 4) guideline adherence.

Delirium knowledge was assessed by means of 18 questions about phenomenology, recognition, risk factors, prognostic implications, clinical importance and management of delirium and method of acquisition of this knowledge was explored. Per respondent a delirium knowledge score was calculated, defined as the percentage correct answers.

Attitudes towards and perceptions regarding delirium were explored through several subdomains: 1) incidence and importance; 2) screening; 3) nurse-physician collaboration; and 4) risk factors. This domain consisted of 21 dichotomous (yes/no) questions or Likert scaled statements that were dichotomized into agreement versus no agreement for analytic purposes. Current practices regarding delirium screening, prevention, treatment as perceived by the health care professionals and documentation practices were assessed by means of 8 questions.

In the part of the survey pertaining to guidelines, we stratified the assessments according to whether respondents were familiar with a Dutch delirium guideline endorsed by the Dutch Society of Intensive Care [6] or not. Respondents not familiar with this guideline were tested with respect to attitudes to guidelines at the ICU in general. This part also consisted of Likert scaled questions or statements and followed similar methodology as previously published [33] and dichotomization similar to the attitudes and perception part.

Validity

The first draft of the survey was revised by three of the authors (MJ, EI and ZT) for the face and content validity. To avoid interpretation problems, we further peer reviewed the survey prior to its dissemination. The survey was presented to the nurse researcher and the local intensivist collaborator at each participating site to test face and content validity. Any comments were incorporated in the new version. Three representatives (a nurse practitioner, nurse scientist and ICU-physician – resident), not involved in the development of the survey, subsequently independently reviewed the second version of the survey and commented on its contents before finalizing the survey. In summary, three authors, twelve local study coordinators and three independent representatives reviewed the survey before finalization.

Assessment of barriers

Barriers were defined depending on the type of question and specific domain: (1) A mean delirium knowledge score below 70% was scored as a barrier regarding knowledge at the group level (e.g. hospital, nurses, physicians), and (2) dichotomous items (yes/no or agree/disagree) were identified as a barrier if < 50% of the respondents gave an answer implicating support for the issue pertaining to that delirium-related statement.

Setting, survey distribution and ethical issues

An electronic survey was conducted among nurses, physicians, and expert delirium consultants (psychiatrists, geriatricians, neurologists) in ICUs of six hospitals in the southwest of the Netherlands [29]. Delirium consultants were only included in the survey when they were consulted on a regular basis as part of routine clinical delirium management, as per the local ICU practice. Their consultation could be requested by an ICU physician 'as needed', but some ICUs entertained regular 'delirium consultants' rounds. Consultants had a role either in determining or confirming a clinical diagnosis of delirium, or provided management advice. Three ICUs with 15 or more ICU beds were defined as high volume ICUs, and three ICUs with less than 15 ICU beds as low volume ICUs. The nurse researcher at each participating site provided the research team with an e-mail list of all healthcare professionals involved in delirium care. All 565 healthcare professionals from six hospitals were invited for the survey. The survey was announced by the local ICU newsletters. The survey was conducted by an online data management open source software program (LimeSurvey), and was available online from 5 September to 12 October 2012. Reminders were sent every week to non-responders. In total, 360 online surveys were completed (response rate 64%). Institutional approval as part of the implementation project [29] was obtained from the Medical Ethical Committee of our institution and the need for informed consent was waived according to Dutch legislation. Under Dutch law, no ethical approval is needed for research among professionals

(survey). The study protocol was reviewed and approved by a committee of the Medical Ethical Committee, in compliance with the Dutch ethical research regulations. Participation in the survey was voluntary and anonymous.

Data analysis

Descriptive statistics included frequencies and percentages of demographics and perceived barriers of participants according to the previous definitions. Knowledge scores were expressed as mean percentages as previously defined. Differences (e.g. knowledge scores) between groups were compared using Chi-square tests and ANOVA or Kruskal-Wallis test. Multivariable logistic regression analysis was used to assess the relationship (Odds Ratio) of several variables (profession, volume of ICU, working experience and working assignment) and responses that indicated barriers for implementation. A p value < 0.05 was considered statistically significant. Data analyses were performed with statistical software package IBM SPSS 21.0.

RESULTS

In total, 360 online surveys were completed (response rate 64%). The majority of respondents were nurses (n=283; 79%). Demographics are shown in **Table 1.** No significant differences were found between the participating ICUs regarding age, years of work experience and working assignment of the respondents.

Delirium knowledge

Mean delirium knowledge score of all respondents was 64% (SD=13)**.** The mean score of nurses was 61% (SD=12), of physicians 72% (SD=13) and of delirium experts 75% (SD=9)**.** There was a significant difference in the mean knowledge scores when comparing nurses, physicians and delirium experts (p<0.001). Further, significant differences existed between nurses and physicians and nurses and delirium experts (p<0.001 for both comparisons). The majority of the respondents (83%, n=298) indicated to have read something about ICU delirium in the past year, but only 37% (n=133) of all respondents had received bedside teaching about delirium. In the past three years 39% of respondents (n=140) had participated in ICU delirium related training or a teaching course. Almost half (47%) of respondents estimated that ICU delirium was associated with long-term neuropsychological deficits (n=168).

Attitudes and perceptions about delirium

Attitudes and perceptions towards delirium are presented in **Table 2(a)** (only barriers are shown). The whole survey, including the items that were not found to be barriers,

Table 1: Demographics of survey respondents

Type of healthcare professional	No.	%
ICU-physicians	53	15
• Intensivists (including fellows)	37	10
• Residents	16	4
ICU Nurses	283	79
Delirium experts (psychiatrists, geriatricians and specialized psychiatric nurses)	24	7
Years of work experience *		
< 1	47	13
1-4	64	18
5-9	72	20
≥10	177	49
Working assignment **		
<35%	7	2
35-55%	28	8
55-75%	46	13
75-90%	93	26
90-100%	186	52
Age (years) ***		
<25	16	4
25-34	109	30
35-44	87	24
45-54	99	28
>55	42	12

ANOVA, analysis of variance; ICUs, intensive care units.
Differences between 6 participating ICUs: * p=0.67, ** p=0.79, *** p=0.15 with ANOVA

is available in English as **Appendix**). The majority of respondents (83%, n=299) found that delirium is common and 84% agreed that delirium is a major problem. Only 71 (20%) of the respondents agreed that delirium was potentially preventable. Almost all (99%) respondents thought that delirium screening is useful and time investment for screening is worthwhile (98%). However, only 34% of respondents believed that nurses were capable to reliably determine delirium using a validated delirium screening instrument. Less than 50% of the physicians and nurses felt that nurses were satisfied with physician-initiated delirium management. They indicated that a better collaboration could be achieved through routine delirium discussions during clinical rounds (74% agreed) and better screening (65% agreed).

Of the sixteen optional risk factors for development of delirium, the top six mentioned risk factors as indicated by the respondents were: sepsis (93%); age >70 (86%); hypox-

emia (85%); shock (83%); acute respiratory distress syndrome (81%) and sedatives or analgesics (81%).

Current practice regarding delirium

The majority of the respondents (96%, 321/336) reported using preventive measures. The following measures were frequently performed: promotion of daytime wakefulness (81%); use of glasses when patients are visually impaired (74%); use of hearing aids when patients are hearing impaired (67%). Less frequently performed preventive measures (noted as potential barriers) included (**Table 2(b)**): allowing family visits as much as possible (50%); placing the patient bed by the window when possible (13%); the use of earplugs for the night (8%); use of eye pads for the night (<1%). Reporting of delirium management components into medical and nurses records was in general infrequent (not shown in Table 2).

All physicians (n=53) mentioned haloperidol as the first drug of choice (**Table 2(b)**). The majority of physicians (97%) reported side effects of haloperidol such as muscle rigidity, ECG abnormalities and decreased consciousness.

Fifty-eight percent of the respondents used the CAM-ICU (n=210), whereas only 51% of these respondents stated that they felt able to perform the CAM-ICU adequately (data not shown); 34% (n=72/210) found CAM-ICU easy to interpret; 30% (n=63/210) used CAM-ICU (and Richmond Agitation Sedation Scale (RASS)) during the daily rounds; 40% found CAM-ICU (and RASS) useful for daily patient management; and only 47% felt they knew what to do next when the CAM-ICU was positive. Patient screening according to CAM-ICU is only possible when RASS (sedation scale) score is higher than -4. This means that the patient is not in coma and that the level of sedation allows non-verbal communication.

Guideline adherence

Twenty-one percent of all the respondents (n=77/360) were familiar with the Dutch ICU Delirium guideline. Of the physicians, nurses and delirium experts 56%, 16% and 29% respectively was familiar with the guideline (p=0.086). **Table 2(c)** shows the results regarding the opinions of the respondents who indicated they were familiar with the Dutch ICU delirium guideline. The high agreement with the following statements indicated barriers to delirium guideline adherence: 1) low expectation that use of guidelines resulted in optimal care; 2) no wish to change delirium oriented practices regardless of the guideline recommendation's; 3) lack of time to execute the guideline in clinical practice; and 4) the perception that the guideline was cumbersome. In contrast, most of the respondents agreed that the guideline content was clinically relevant and scientifically sound. **Table 2(d)** shows the identified barriers among the respondents who rated guideline adherence in general (n=261).

Table 2: Barriers for Guideline Adherence Derived from Survey on Attitudes & Perceptions, Current practices and Guideline adherence

(a) Attitudes and perceptions	%*
Delirium occurrence and importance	
Delirium is preventable	21
Screening	%*
Is a nurse capable to identify delirium with a validated delirium screening instrument?	34
Collaboration	%*
When I as nurse suspect a patient to be delirious, I am satisfied with delirium treatment	47
When I as physician suspect a patient to be delirious, the nurse is satisfied with delirium treatment	42
Collaboration between doctors and nurses with regard to delirium at the ICU can be improved by better screening.	65
Collaboration between doctors and nurses with regard to delirium at the ICU can be improved by routinely addressing delirium in daily rounds.	74
(b) Current practices	
Delirium Screening	%*
In the ICU unit where I work the following delirium screening scale is in use:	
CAM-ICU (n=210; in only two hospitals)	58
ICDSC (n=3)	<1
Delirium Prevention	
Earplugs for the night	8
Family visits as much as possible	50
(c) Dutch ICU delirium guideline adherence (n=76)	Mean (SD)‡
If I follow the guideline recommendations, it is likely that my patients would not receive optimal care	3.1 (1.0)
I do not wish to change my delirium care practices, regardless of what delirium guideline recommends	3.7 (1.0)
I don't have time to use this Guideline	3.5 (0.9)
This guideline is cumbersome and inconvenient	3.0 (1.1)
(d) Guideline adherence in general (n=261)	Mean (SD)‡
Generally, guidelines are cumbersome and inconvenient	3.0 (0.9)
Guidelines are difficult to apply and adopt to my specific practice	3.1 (0.9)
Guidelines interfere with my professional autonomy	3.3 (0.9)
Generally, I would prefer to continue my routines and habits rather than to change based on practice guidelines	3.3 (1.0)
I am not really expected to use guidelines in my practice setting	3.7 (0.9)

** Percentage of agreement = %YES answers or % of the sum of agree and strongly agree answers (from the 5-point Likert scale statements))*

‡ Mean and standard deviation based on the 6 point Likert-scale. Mean score of ≥3 was considered to indicate agreement with statement.

The open-ended question regarding guideline adherence showed: 1) lack of a workable protocol for the delirium guideline; 2) the feeling that previous implementation was

not done properly; and 3) the feeling that there is a low rate of uniformity in delirium management by physicians.

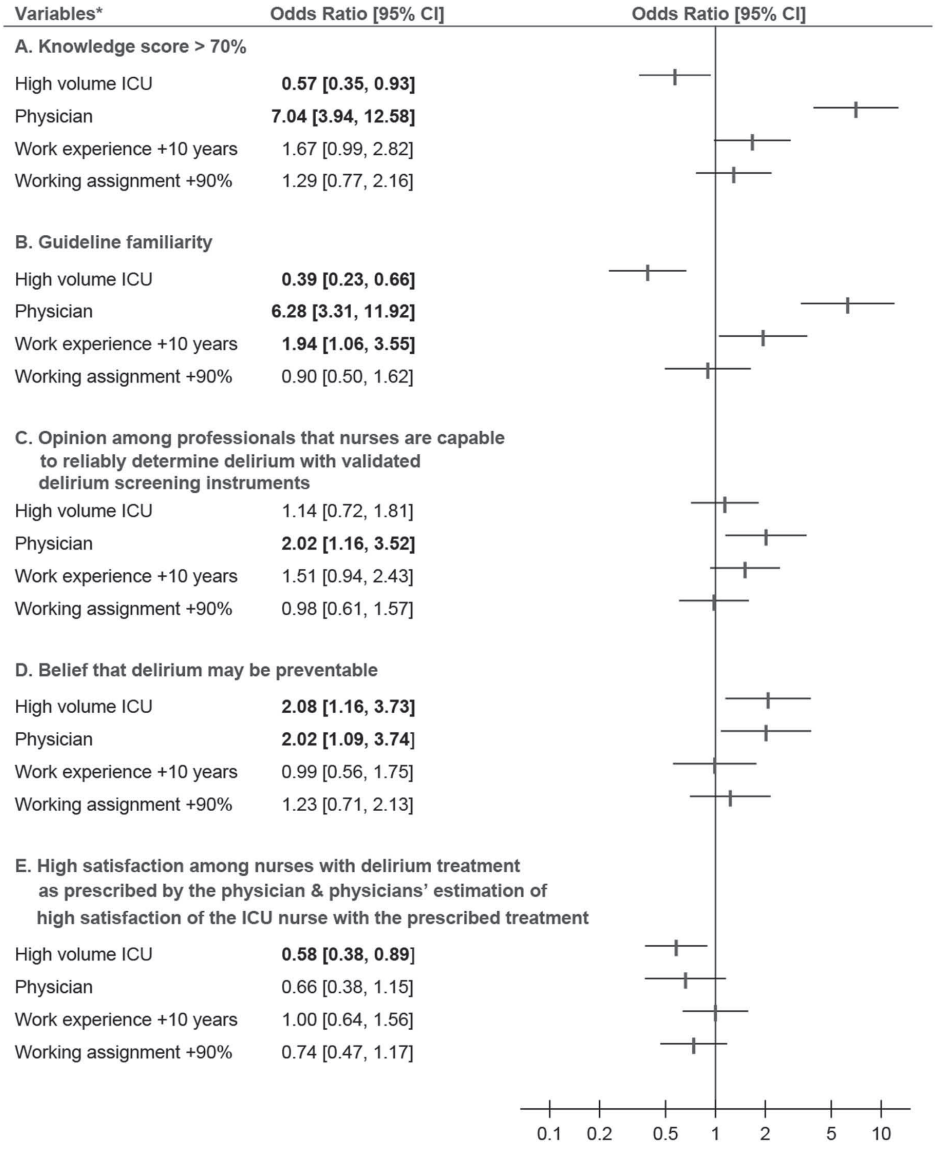

Figure 1: Determinants of perceived barriers resulting from survey results

* Outcome variables (A-E in bold) and covariables included in logistic regression analysis. Interpretation example: physicians were more likely than nurses to have a knowledge score > 70%, with an odds ratio (OR) of 7.04, after adjustment for the other covariables: high volume ICU, work experience and working assignment.

Perceived Barriers for Guideline adherence

Figure 1 illustrates the determinants of perceived barriers resulting from the multivariable analyses. Being an ICU physician (odds ratio (OR) =7.04) as compared with being a nurse and not working on a high-volume ICU (OR for high volume ICU=0.57) were associated with better (>70% correct answers) delirium knowledge. Similarly, being an ICU physician, more than ten years experience and working at a low volume ICU were associated with familiarity with the Dutch delirium guideline. ICU physicians had more trust than nurses in nurses' capability to determine the presence of delirium. Working on a high-volume ICU, and being an ICU physician were associated with the notion that delirium was preventable. Finally, not working on a high-volume ICU was associated with high satisfaction among nurses with delirium treatment by the physician and physicians' estimation of high satisfaction of the ICU nurse with the prescribed treatment.

DISCUSSION

The most important findings of this multicenter survey on delirium among ICU professionals can be summarized as follows: (1) knowledge deficits were present more clearly in nurses than in physicians; (2) although delirium is considered an important problem and is considered worthwhile to be addressed, professionals do not think delirium can be reliably determined with a screening tool or is amenable to prevention; (3) collaboration between nurses and physicians pertaining to delirium management can be improved with nurse-physicians discussions during daily rounds to enhance satisfaction on physician prescribed delirium management; (4) in spite of screening use in clinical practice, health care providers felt uncomfortable with the CAM-ICU for delirium diagnosis and management; (5) preventive measures for delirium were common; (6) there was trust in the content of guidelines and their importance, but lack of trust that patients would benefit when following the guideline, lack of motivation and time to implement guidelines; (7) compared with physicians, nurses were less confident with delirium screening tools and were less convinced that delirium can be prevented; and finally (8) the adherence to delirium guidelines seems to be less in higher-volume ICUs or among professionals with less work experience.

This study is the first survey that was performed within a formal multifaceted multicenter prospective implementation project [29] with the goal to identify barriers for delirium guideline adherence. The implications of our findings for the setting in which the investigation was performed follow directly from the resulting barriers identified based on the survey. For instance, implementation should include education (including bed-side training) on the high reliability of validated screening tools when executed by trained nurses; the lack of familiarity with guidelines in high volume centers should

translate into more efforts in education compared with low volume centers, and our findings indicate that educational efforts should target nurses to a greater extent than physicians. However, whether these findings are generalizable is not certain. It is important to note that this survey was carried out just before publication of the Pain-Agitation-Delirium (PAD) guideline [5]; therefore repeating the survey later in the same population of professionals may lead to different results.

Our findings are in line with those of Ely et al. [34] in the perceived sense of urgency of protocolled delirium management, and the fact that delirium is considered a serious problem. Furthermore, routine screening for delirium is still not broadly applied as found by others [35]. Failure to recognize delirium has previously been reported and was caused by infrequent use of routine delirium assessments tools such as the CAM-ICU or ICDSC [13,14,16,35]. On the other hand, the proven high reliability of these tools was marked as an important potential facilitator for their use by other investigators [8,9,22,36,37]. Compared to previous work [15], we found an increased knowledge (21 to 47%) of long-term cognitive dysfunction resulting from delirium, which is in line with recent findings [38]. Obviously, there is still a difference in perceived importance of delirium and motivation to invest in screening and prevention. We found only one study in which delirium was not considered as an important problem to address [7]. In line with our study, a low confidence in determination of delirium with the CAM-ICU has been found previously [20]. Deficits in delirium knowledge was also previously found, but improved after implementation of delirium-oriented measures [20,22,35,39,40]. ICU professionals, especially nurses, have previously indicated that a better understanding (education) of delirium is needed [17,20,40] justifying education as an essential implementation strategy. The creation of evidence-based toolkits to facilitate successful statewide practice changes and evaluation of their effectiveness in delirium management using an inter-professional team including nurses, physicians, and pharmacists was previously described by Dammeyer et al. [41] and may indicate that such expert-teams are important for the implementation of delirium-oriented interventions.

Our study has several strengths. First, we achieved a high response rate compared to other electronic surveys [42]. Second, next to ICU nurses and physicians we have included delirium experts. Third, to avoid interpretation problems, we peer reviewed the survey quite extensively previous to its execution. Fourth, this survey is the first to our knowledge to assess the impact of several demographic factors on important implementation adherence barriers. Finally, our study design was based on a theoretical framework.

We show that a survey-based identification of barriers is feasible. We recently found in a systematic review that use of more rather than less implementation strategies concomitantly and use of integrated management of delirium with sedation and pain protocols, were associated with potential improvements in clinical outcomes [43]. Surveys

such as these may help to identify which of the many potential barriers to target in implementation projects, which will likely result in more effective practice changes.

Limitations

Several potential limitations of our study should be mentioned. First, we have to take the potential of selection bias into account, because of the 64% response rate. On the other hand, this is a relatively high response rate. Second, socially desirable answers could be given, especially in the section of current practices and the execution of preventive measures. Finally, the fact that a pilot study was not conducted may be perceived as a limitation.

General implications and recommendations for practice

There is still a disconnection between perceived clinical importance of delirium in critically ill patients and level of implementation of delirium prevention, screening and management in daily practice. Among the key issues underlying this discrepancy may be the lack of trust in delirium diagnosis with routine delirium screening by a validated tool such as the CAM-ICU, which in turn may be explained by a general lack of knowledge both of the clinical implications of delirium and the high reliability of such screening. Nurse-physician interaction and collaboration are amenable to improvement, e.g. by means of routine delirium discussions during bedside rounds. Identification of implementation barriers for adherence to guidelines pertaining to delirium is feasible with a survey.

CONCLUSIONS

Our survey identified several important barriers for adherence to guidelines on delirium management. We found there is a disconnection between perceived clinical importance of delirium and adherence to delirium management in daily practice. We found the following barriers to stand out: screening tools are scarcely used and there appears to be an inappropriate lack of trust in routine delirium screening tools, a general lack of knowledge of delirium, a lack of effective nurse-physician collaboration with regard to routine bedside delirium discussions and a lack of protocolled treatment. Thus, in recent years little progress has been made regarding routine use of delirium-oriented measures in spite of current guidelines, but our results may help to design targeted implementation strategies for optimized delirium management.

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APPENDIX:

Survey

Demographics

1. I am working at:

(Choose one of the options below)

- Hospital 1
- Hospital 2
- Hospital 3
- Hospital 4

2. I am a:

(Choose one of the options below)

- Intensivist
- Fellow intensivist
- Physician assistant
- ICU nurse
- ICU nurse - student
- Psychiatrist
- Neurologist
- Another:_____

3. Years of work experience (at the ICU)?

(Choose one of the options below)

- <1
- 2-4
- 5-9
- 10-20
- >20

4. I have a working assignment of:

(Choose one of the options below)

- <35 %
- 35-54 %
- 55-75 %
- 75-89 %
- 90-100 %

5. My age is:

(Choose one of the options below)

- <25 years
- 25-34 years
- 35-44 years
- 45-54 years
- >55 years

1.a Delirium Knowledge Test (good answers)

1. Which form of delirium is according to you the most usual at the ICU?

(Choose one of the options below)

- Hyperactive delirium
- Hypoactive delirium
- Alternating hyperactive / hypoactive
- All forms are almost equally present

2. Features of delirium are (good only if both options are selected)**:**

(Choose what best suits. Multiple answers are possible!)

- Gradually occurrence
- Attention deficit
- Fluctuating consciousness
- Organized thinking

3. A delirium leads to:

(Please choose one of the following options)

- Increased health care costs
- Increased morbidity and mortality in the ICU
- Prolonged mechanical ventilation
- All of the above answers are correct

4. What is true?

(Please choose one of the following options)

- Only the psychiatrist / counselor psychiatry can identify delirium
- 1 time per day screening for delirium is enough
- Delirium identification by a nurse is feasible
- Delirium identification is impossible in psychiatric patients

5. What patient is delirious?

(Please choose one of the following options)

- Patient may have trouble keeping attention and cannot organize his thoughts
- Patient has some trouble with memory, but is not confused
- Patient is cooperative and calm, but hyper-alert
- Patient is plucking and picking, but can focus his attention

6-13 Specify whether you agree with the following statements (good if one of the underlined options is selected)**:**

(Select the appropriate response for each item)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Delirium is under-diagnosed				x	x
Delirium is a problem that requires adequate treatment				x	x
Delirium is in general preventable				x	x
Delirium is associated with long-term neuropsychological damage				x	x
Delirium prolongs the weaning of the patient from mechanical ventilation				x	x
Delirium assessment is needed in patients who seem alert and oriented				x	x
Delirium is associated with an increased risk of dementia				x	x
Delirium occurs only in the elderly	x	x			

14-18: Score the following statements (good if one of the underlined options is selected)**:**

(Select the appropriate response for each item)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I can identify delirium in an ICU patient				x	x
I can explain delirium to the family of a patient				x	x
Delirium is preventable				x	x
Early mobilization and physical therapy can prevent delirium				x	x
Delirium, like acute renal failure, is a form of organ failure				x	x

1.b Education evaluation

1. I have read something about IC delirium in the past year

(Please choose one of the following options)

- Yes
- No

2. How many times have you read about delirium in the past year? *

(Answer this question only if YES to previous question)

- 1
- 1-3
- > 3

3. In the past three years I have participated in training / course in delirium in the ICU

(Please choose one of the following options)

- Yes
- No

4. Statement: This training / course was useful

(Answer this question only if YES to previous question)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Indicate whether you agree with the statement above:					

5. In the last 12 months I have had bedside education about delirium by a psychiatrist or other expert:

- Yes
- No
- Not applicable

6. How often?

(Answer this question only if the following conditions are met: Answer YES to previous question)

Enter your answer here:_____

7. Statement: This has helped me to better understand delirium

(Answer this question only if the following conditions are met: Answer YES to question: Last year I have got bedside education about delirium by a psychiatrist or other expert)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Indicate whether you agree with the statement above:					

2. Attitudes, perceptions and current practices regarding delirium

1. What percentage of all your shifts do you have to deal with delirious patients at the ICU?

(Please choose one of the following options)

- Never
- <10% of shifts
- 10-30% of shifts
- 30-50% of shifts
- 50-70% of shifts
- 70-90% of shifts

2. I think that:

(Please select the appropriate response)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Delirium is a major problem in the ICU					

3. What is in jour opinion the average percentage of patients who developed delirium during their stay at an ICU?

(Please choose one of the following options)

- <10%
- 10-25%
- 26-50%
- 51-75%
- 76-100%

4. What percentage of the ventilated patients develop delirium according to you?
(Please choose one of the following options)

- <10%
- 10-25%
- 26-50%
- 51-75%
- 76-100%

5. On the ICU where I work the following instrument is used to screen for delirium:
(Select what suits. Multiple answers are possible!)

- CAM-ICU (Confusion Assessment Method ICU)
- ICDSC (Intensive Care Delirium Screening Checklist)
- DDS (Delirium Detection Score)
- DOS (Delirium Observation Scale)
- Nu-DESC (The Nursing Delirium Screening Scale)
- None of all
- Other:_____

6. How often is delirium screening performed in the department where you work?
(Answer this question only if one of delirium instruments is used at your department. Multiple answers are possible.)

- At admission
- At discharge
- Daily 1 x per day
- Daily 2 x per day
- Daily each shift
- If necessary,
- Other:_____

7. The CAM-ICU (Confusion Assessment Method - ICU)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
CAM-ICU is easy to perform					

8.We need to use the CAM-ICU in our ICU!

(Please choose one of the following options)

- Yes
- No

9. How often should the CAM-ICU be done according to you?

(Answer this question only if the following conditions are met: Answer YES to question: We need to use the CAM-ICU in our ICU! Please choose one of the following options)

- Once a day
- Twice a day
- Once a service
- One of the top plus if necessary
- If necessary

Otherwise:_____

10. What do you think is the reason that we should not use the CAM-ICU?

(Answer this question only if the following conditions are met: Answer NO to question: We need to use the CAM-ICU in our ICU!)

Please describe:

11. The screening for delirium at the ICU is useful

(Please choose one of the following options)

- Yes
- No

12. Is the time investment for delirium screening (according to you) worthwhile?

(Please choose one of the following options)

- Yes
- No

13. An ICU nurse can reliable determine delirium with delirium screening instrument when this is present?

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Please indicate:					

14. Answer the following questions:

(Answer this question only if the following conditions are met: Answer YES to question: On the IC department where I work the CAM-ICU is used to screen for delirium)

Select the appropriate response for each item:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I find that I am familiar with the CAM-ICU to perform it correctly					
I find that I am familiar with the RASS to perform it correctly					
RASS is easy to perform					
CAM-ICU is easy to perform					
RASS is easy to interpret					
CAM-ICU is easy to interpret					
I easily ask a colleague for help with CAM-ICU					
Positive or negative CAM-ICU score tells me something about delirium in my patient					
CAM-ICU score is feasible to use in discussions about delirium					
RASS and CAM-ICU are discussed with physician at daily rounds					
RASS and CAM-ICU are helpful in determining daily management					
If CAM-ICU is positive I know what to do					

15. Answer the following questions:

Answer this question only if the following conditions are met: Answer YES to question: On the IC department where I work the DOS is used to screen for delirium

Select the appropriate response for each item:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I find that I am familiar with the DOS to perform it correctly					
I find that I am familiar with the RASS to perform it correctly					
RASS is easy to perform					
DOS is easy to perform					
RASS is easy to interpret					
DOS is easy to interpret					
I easily ask a colleague for help with DOS					
DOS score <3 of same and >3 score tells me something about delirium in my patient					
DOS score is feasible to use in discussions about delirium					
DOS and RASS are discussed with physician at daily rounds					
DOS is helpful in determining daily management					
When DOS is <3 of same and >3 I know what to do					

16. In the context of psycho-hygiene at the ICU I am applying preventive measures. (Psycho-hygiene: measures to promote mental health such as day / night rhythm, hearing aids, applying orientation measures, ...)

(Answer this question only if the following conditions are met: My function is : ICU nurse, ICU nurse – student, Intensivist, Fellow intensivist or Physician assistant)

- Yes
- No

17. To promote the psycho-hygiene of my patients I apply the following measures (multiple answers are possible)
(Answer this question only if the following conditions are met: My function is : ICU nurse, ICU nurse – student, Intensivist, Fellow intensivist or Physician assistant)

- Promotion of day / night rhythm
- Earplugs for the night
- Sleep Mask for the night
- Hearing Aid
- Glasses
- Family visits as much as possible
- Placement of patients bed as close as possible to the window
- Other:_____

18.What is your first choice drug for delirium in the ICU?
(Answer this question only if the following conditions are met:
My function is: Intensivist, Fellow intensivist, Physician assistant, Psychiatrist or Neurologist)
Enter your answer here:_____

19. What is the usual dose of this drug in mg / day?
(Answer this question only if the previous question is filled in)
Lowest dosage:_____
Highest dose:_____

20. Do you ever see the side effects of this drug?
(Answer this question only if this question is completed: Which drug is for you the first choice drug as treatment for delirium?)
(Please choose one of the following options)

- Yes
- No

21. What side do you know or have you observed?
(Answer this question only if this question is completed: Which drug is for you the first choice drug as treatment for delirium?) Please describe:

22. In a difficult to treat (therapy refractory) delirium:

Select the appropriate response for each item:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Ceased all psychoactive drugs should be					
I have a feeling of powerlessness					
I have the feeling that nothing helps and that the patient should improve spontaneously over time					
The patient is getting less delirious as his physical condition improves					

23. When I, as a nurse, suspect that the patient is delirious:

(Answer this question only if the following conditions are met: My function is: Intensivist, Fellow intensivist, Physician assistant, Psychiatrist or Neurologist)

Select the appropriate response for each item:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I feel myself "herad" by the physician / intensivist					
The physician / intensivist confirms my opinion					
I am satisfied with the applied treatment					

24. When I, as a physician, suspect the patient to be delirious:

(Answer this question only if the following conditions are met: My function is: Intensivist, Fellow intensivist, Physician assistant, Psychiatrist or Neurologist)

Select the appropriate response for each item:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
I feel myself "heard" by the nurse					
The nurse confirms my opinion					
The nurse is satisfied with the applied treatment					

25. Cooperation between doctors and nurses in delirium management at the ICU can be improved with:

(Select everything that complies. Multiple answers possible!)

- Better screening for delirium
- Routine delirium discussions during daily rounds
- Better verbal transfer of delirium related information
- Better written transfer of delirium related information
- Other:_____

26. How important do you think the following risk factors are for the development of delirium at the ICU?

(Select the appropriate response for each item: 1 = not important; 5 = very important)

	1	2	3	4	5
Sepsis					
ARDS					
Surgery before the ICU admission					
Primary neurological disorder (such as SAB)					
The administration of sedatives and analgesics					
Liver failure					
Renal failure					
Heart failure					
Hypoxia					
Anemia					
Shock					
Visual impairment					
Hearing impairment					
Gender					
Age> 70 years					
Cognitive impairment					

27. Can the routine screening of delirium in the ICU be helpful according to you in order to improve the prognosis of critically ill patients (according to the current state of knowledge)?

(Please choose one of the following options)

- Yes
- No

28.I record / describe the following items in the medical / nursing records:

(Please choose one of the following options)

	Never	Sometimes	Regularly	Very regularly	Always
The interventions done to prevent delirium					
Measures to promote orientation					
The findings on screening / identification of delirium					
Consultation moments and outcomes regarding the treatment of delirium					
The result of the therapy					
Progress of delirium over time					

29. Patients with delirium are treated (next to Haldol) with other drugs, namely:

(Multiple answers are possible!)

- Olanzapine (Zyprexa)
- Other atypical antipsychotic
- Clonidine
- Propofol
- Methylphenidate
- Do not know
- Other:_____

4. Guideline adherence

1. I am familiar with the recommendations of the Dutch Socciety of Intensive Care (NVIC) endorsed guideline: "Delirium in ICU"

(Please choose one of the following options)

- Yes
- No

2. Indicate whether you agree or disagree with the following statements regarding the NVIC guideline "Delirium in ICU":

(Answer these questions only if familiar with the NVIC guideline "Delirium in ICU". Please choose one of the following options)

	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
I am familiar with the delirium guideline and its recommendations						
The delirium guideline is easily accessible						
If we follow the recommendations of the guideline, delirium should become less frequent						
If I follow the guideline recommendations, it is likely that my patients would not receive optimal care						
I have confidence in the expertise of the developer of the delirium guideline						
The guideline recommendations are relevant for my patients						
I am not really expected to use this guideline in my practice setting						
The delirium guideline is based on strong scientific evidence						
It is not really practical to follow the guideline recommendations						
I do not wish to change my delirium care practices, regardless of what the delirium guideline recommends						
I feel competent in the execution of the delirium guideline recommendations						
There are other guidelines which are conflicting with the delirium guideline						
I don't have time to use this Guideline						
This guideline is cumbersome and inconvenient						
I'm executing the guideline recommendation in my daily practice						

3. Indicate whether you agree or disagree with the statements regarding Intensive Care Unit guidelines in general:

(Answer these questions only if not familiar with the NVIC guideline "Delirium in ICU". Choose one of the options)

	Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree
I am familiar with the practice guidelines in my field						
There are so many guidelines available that it is nearly impossible to keep up						
In my field, I find practice guidelines readily available						
I don't have time to stay informed about available guidelines						
Guidelines are too "cookbook" and prescriptive						
Practice guidelines are practical to use						
Generally, guidelines are cumbersome and inconvenient						
Guidelines are difficult to apply and adopt to my specific practice						
In this organization, practice guidelines are important						
Guidelines improve patient outcomes						
Guidelines interfere with my professional autonomy						
Generally, I would prefer to continue my routines and habits rather than to change based on practice guidelines						
I am not really expected to use guidelines in my practice setting						
Guidelines help to standardize care and assure that patients are treated in a consistent way						
In my practice setting, there are sufficient administrative support and resources to allow the implementation of the practice guidelines						

4. Factors that motivate me to apply the recommendations from the NVIC guideline "Delirium in ICU":

(Answer these questions only if familiar with the NVIC guideline "Delirium in ICU". Please describe.)

5. Factors that do not motivate me to apply the recommendations from the NVIC guideline "Delirium in ICU":

(Answer these questions only if familiar with the NVIC guideline "Delirium in ICU". Please describe.)

6. Factors that motivate me to apply the recommendations from the ICU guidelines in general:

(Answer this question only if not familiar with the NVIC guideline "Delirium in ICU". Please describe.)

7. Factors that do not motivate me to apply the recommendations from the ICU guidelines in general:

(Answer this question only if not familiar with the NVIC guideline "Delirium in ICU". Please describe.)

Finally

I have filled this questionnaire out without haste and at ease.

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Please indicate:					

Chapter 4

A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes

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ABSTRACT

Introduction

Despite recommendations from professional societies and patient safety organizations, the majority of ICU patients worldwide are not routinely monitored for delirium, thus preventing timely prevention and management. The purpose of this systematic review is to summarize what types of implementation strategies have been tested to improve ICU clinicians' ability to effectively assess, prevent and treat delirium and to evaluate the effect of these strategies on clinical outcomes.

Method

We searched PubMed, Embase, PsychINFO, Cochrane and CINAHL (January 2000 and April 2014) for studies on implementation strategies that included delirium-oriented interventions in adult ICU patients. Studies were suitable for inclusion if implementation strategies' efficacy, in terms of a clinical outcome, or process outcome was described.

Results

We included 21 studies, all including process measures, while 9 reported both process measures and clinical outcomes. Some individual strategies such as "audit and feedback" and "tailored interventions" may be important to establish clinical outcome improvements, but otherwise robust data on effectiveness of specific implementation strategies were scarce. Successful implementation interventions were frequently reported to change process measures, such as improvements in adherence to delirium screening with up to 92%, but relating process measures to outcome changes was generally not possible. In meta-analyses, reduced mortality and ICU length of stay reduction were statistically more likely with implementation programs that employed more (six or more) rather than less implementation strategies and when a framework was used that either integrated current evidence on pain, agitation and delirium management (PAD) or when a strategy of early awakening, breathing, delirium screening and early exercise (ABCDE bundle) was employed. Using implementation strategies aimed at organizational change, next to behavioural change, was also associated with reduced mortality.

Conclusion

Our findings may indicate that multi-component implementation programs with a higher number of strategies targeting ICU delirium assessment, prevention and treatment and integrated within PAD or ABCDE bundle have the potential to improve clinical outcomes. However, prospective confirmation of these findings is needed to inform the most effective implementation practice with regard to integrated delirium management and such research should clearly delineate effective practice change from improvements in clinical outcomes.

INTRODUCTION

"The problem of delirium is far from an academic one. Not only does the presence of delirium often complicate and render more difficult the treatment of a serious illness, but also it carries the serious possibility of permanent irreversible brain damage".[1] –Engel and Romano

This quote, written over 50 years ago by icons in the field of medicine, would seem to be a clarion call for those caring for humans suffering from serious disease. Elsewhere in the same classic manuscript, Engel and Romano make two statements about inadequacies of the approach taken by healthcare professionals in treating delirium: 'They seem to have little interest in and, indeed, often completely overlook delirium' [1,2] and 'The deficiencies in the education of many physicians will equip them to recognize any but the most flagrant examples of delirium.' Even when armed with the wealth of information present in the literature over the past decade about the importance of assessing, preventing and managing delirium in the intensive care unit (ICU), effecting the needed changes in care through appropriate implementation programs still requires a substantial change in culture and attention to human factors that are often beyond the scope of training of most medical teams.

In the Society of Critical Care Medicine's recently released Clinical Practice Guideline for the Management of Pain, Agitation, and Delirium (PAD) in Adult Patients in the ICU current evidence is brought together on optimal management of pain, agitation, sedation and delirium [3]. A previously constructed framework to facilitate the implementation of many aspects of the evidence described in the PAD guidelines is the Awakening and Breathing Coordination, Choice of sedative, Delirium monitoring and management and Early mobility (ABCDE) bundle. The ABCDE bundle is specifically aimed at minimizing sedation, encouraging early ventilator liberation, improving delirium assessment and management and facilitating early mobilization in the ICU [4]. Importantly, both the protocols of the trial that established the value of the ABCs [5] and the seminal randomized controlled trial (RCT) that established the positive effects of early mobilization in critically ill patients [6] included routine daily delirium assessments with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), with the latter study even establishing a significant reduction in delirium incidence. Therefore, current evidence suggests that: 1) clinical effectiveness of the ABC and E within the ABCDE bundle implies routine delirium assessment with a validated tool, and, inversely, 2) delirium prevention and management requires an integrated multidisciplinary approach with standardized care processes including early mobilization, which in turn is linked to a strategy of minimizing sedation by means of 'awake(ning) and spontaneous breathing coordination'. As such, 'brain failure' (that is, delirium and coma) may be regarded as avoidable and representing an intermediate state on the pathway towards adverse outcomes, such as

death and increased length of ICU stay [7]. However, although from the ABCDE bundle or PAD guidelines it may seem evident what to aim for in everyday clinical practice, health care professionals often struggle with how to implement guidelines, especially when these include integrated care covering many domains concurrently and involving multiple care providers.

Therefore, this systematic review of the literature aims at summarizing the implementation strategies and their effectiveness to improve practices of assessment, prevention or management of delirium and clinical outcomes in the critically ill.

METHODS

Search strategy and selection criteria

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses *(*PRISMA) guidelines [8]. We searched PubMed, Embase, PsychINFO, Cochrane and CINAHL for studies published between January 2000 and April 2014 with no search filter limits. The year 2000 was chosen because a preliminary Pubmed search with the search terms "delirium", "implementation" and one of "ICU", "critically ill", or "critical care", yielded only one study that year that pertained to the subject of this review and none before [9]. A biomedical information specialist at the medical library of the Erasmus MC - University Medical Center Rotterdam guided the search. Search terms included intensive care and delirium, and were tailored to each database and its indexing system (see **Appendix** for **Additional file 1**). Reference lists of retrieved articles, reviews and books were screened to identify additional papers that met the inclusion criteria.

Selection of studies

Our search focused on clinical studies aimed at implementation of delirium screening, prevention or management in the adult ICU setting. Implementation could be focused at single components of delirium care (for example, delirium screening) or could include delirium screening, prevention and/or management as integral part of a wider bundle or guideline (for example, ABCDE bundle or PAD guideline). We considered the PAD guideline and the ABCDE bundle as similar for the purpose of this review because, next to delirium screening, they share several integrated evidence-based care components (early mobilization, awakening and breathing coordination or targeting light sedation and systematic pain assessment and treatment). We did not limit the search to specific types of ICUs. To be included in the review, the study had to contain a clear description of the implementation process (that is, an explanation of what exactly was done to implement it). We excluded studies that concerned delirium related to alcohol withdrawal and/or

were focused solely on validation of delirium screening tools. Further, the efficacy of the implementation intervention had to be reported in terms of a clearly defined outcome such as mortality, length of stay, and/or adherence to delirium screening. Reviews, opinion papers, editorials and comments on original articles were also excluded.

Two authors (ZT, EI) independently checked abstracts of retrieved articles on compliance with selection criteria. Relevant full-text articles were checked for final inclusion. Consensus on final selection was achieved by discussion with a third author (MJ).

Data extraction and synthesis

The first reviewer (ZT) extracted data on design, population, implementation strategies, and outcomes and studies were subject to further critical appraisal by two other authors (EI, MJ). The individual implementation strategies were classified into four categories: professional (for example, distribution of educational materials, reminders), organizational (for example, provider-oriented interventions, structural interventions), financial and regulatory (for example, peer review, changes in medical liability) using the *Cochrane Effective Practice and Organization of Care* group (EPOC) classification system checklist (**Table 1**)[10]. From these 4 categories, we then distinguished 17 individual implementation strategies (**Table 1**). The implementation strategies concern all phases of a formal implementation process as has been described before in the literature [11]. For instance, the strategy of 'marketing/tailored interventions' includes first performing an analysis of barriers to implementation to be able to design a subsequent implementation strategy addressing these barriers to enhance implementation effectiveness. As such, the use of more strategies concurrently may indicate a more complete implementation process.

With regard to the outcomes, we distinguished between clinical outcomes (ICU-length of stay (LOS) and mortality) and process outcomes (adherence to screening for the presence of delirium, knowledge of delirium, incidence of delirium, use of antipsychotics) [12]. Changes in these outcomes were assessed before and after implementation (or with and without implementation in the case of the only RCT included). Three authors (EI, ZT, MJ) independently scored the implementation strategies in the implementation studies reporting clinical outcomes. Differences in assessment were resolved afterwards by discussion. The studies that did not report mortality were assessed equally by two authors (ZT, MJ). We tabulated the key features deemed important for this review of all included studies: number and type of implementation strategies, care components (that is, using integrated strategy such as PAD/ABCDE or separate interventions such as only screening), implementation model and the process and clinical outcomes as previously defined.

Table 1: Implementation strategy taxonomy according to EPOC* classification system

Category	Individual strategies	Description
Professional	1.Distribution of educational materials	Distribution of published or printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials and electronic publications. The materials may have been delivered personally or through mass mailings.
	2.Educational meetings	Conferences, lectures, workshops or traineeships.
	3.Local consensus processes	Inclusion of participating providers in discussion to ensure that they agreed that the chosen clinical problem was important and the approach to managing the problem was appropriate.
	4.Outreach visits	Use of a trained person who met with providers in their practice settings to give information with the intent of changing the provider's practice. The information given may have included feedback on the performance of the provider(s).
	5.Local opinion leader	Use of providers nominated and explicitly identified by their colleagues as 'educationally influential'.
	6.Patient-mediated intervention	New, previously unavailable clinical information collected directly from patients and given to the provider; e.g., patient depression scores from a survey instrument
	7.Audit and feedback	Any summary of clinical performance of health care over a specified period of time. The summary may also have included recommendations for clinical action. The information may have been obtained from medical records, computerized databases, or observations from patients.
	8.Reminders	Patient or encounter specific information, provided verbally, on paper or on a computer screen, which is designed or intended to prompt a health professional to recall information. This would usually be encountered through their general education; in the medical records or through interactions with peers, and so remind them to perform or avoid some action to aid individual patient care. Computer aided decision support and drugs dosage are included.
	9.Marketing / Tailored interventions	Use of personal interviewing, group discussion ('focus groups'), or a survey of targeted providers to identify barriers to change and subsequent design of an intervention that addresses identified barriers.
	10.Mass media	(1) Varied use of communication that reached great numbers of people including television, radio, newspapers, posters, leaflets, and booklets, alone or in conjunction with other interventions; (2) targeted at the population level.
Organizational	11.Provider oriented interventions	Revision of professional roles e.g. expansion of role to include new tasks; Creation of clinical multidisciplinary teams who work together; Formal integration of services; Skill mix changes (changes in numbers, types or qualifications of staff); Arrangements for follow-up; Satisfaction of providers with the conditions of work and the material and psychic rewards (e.g. interventions to 'boost morale'); Communication and case discussion between distant health professionals
	12.Patient oriented interventions	Mail order pharmacies (e.g., compared to traditional pharmacies); Presence and functioning of adequate mechanisms for dealing with patients' suggestions and complaints; Consumer participation in governance of health care organization; Other categories

Table 1: Implementation strategy taxonomy according to EPOC* classification system (continued)

Category	Individual strategies	Description
	13.Structural interventions	Changes to the setting/site of service delivery; Changes in physical structure, facilities and equipment; Changes in medical records systems (e.g. changing from paper to computerized records); Changes in scope and nature of benefits and services; Presence and organization of quality monitoring mechanisms; Ownership, accreditation, and affiliation status of hospitals and other facilities; Staff organization
Financial	14.Provider or patient interventions	In summary: Patient or Provider is financially supported to execute specific actions. For detailed definitions, see reference [10]
Regulatory	15.Changes in medical liability 16.Management of patient complaints 17.Peer review or Licensure	Any intervention that aims to change health services delivery or costs by regulation or law. (These interventions may overlap with organizational and financial interventions.)

***EPOC=** Cochrane Effective Practice and Organisation of Care

Methodological quality

We rated the methodological quality of all implementation studies in an effort to ascertain a minimum quality of included studies. We used a rating system adapted from Anderson and Sharpe [13] (see Appendix for **Additional file 2**) which evaluated the impact of various types of interventions on behavior change of health care workers in line with our review. Two reviewers (ZT/EI) independently assessed each study on quality and differences in quality scores were resolved through discussion. Studies that rated less than three points were excluded because of very poor methodological quality.

Statistical analyses

Associations between study characteristics and outcomes were assessed with Pearson's Chi-square or Fisher's exact testing after dichotomization (for example, significant decrease of delirium incidence: yes/no). The number of implementation strategies used in the implementation studies was summarized as medians with IQR.

Whenever possible, for meta-analysis we quantitatively pooled the results at patient level of the included studies, when the original data were retrievable. We contacted the authors of the original articles for these data when not provided in the published paper. We expressed the effectiveness of the implementation interventions as a risk ratio (RR) for dichotomous outcomes by using a DerSimonian and Laird random effect model [14] and as a weighted mean difference (WMD) for continuous outcomes with 95% CIs. The heterogeneity among studies was tested using the Cochran Q test of heterogeneity, and Higgins and Thompson I^2 [15]. The degree of heterogeneity was defined as a value of I^2: low (25%-49%), moderate (50%-74%), and high (>75%) values [15]. Subgroup analyses were

performed for number of implementation strategies (low number = below median, high number = median or higher), and use of either PAD guideline/ABCDE bundle. Analysis was performed with Microsoft Excel 2013 and IBM SPSS 21.0. Statistical significance was defined as a *p*-value <0.05.

RESULTS

Selection of studies

We reviewed 3,981 hits and after excluding duplicates and studies not meeting inclusion/exclusion criteria, 21 studies were evaluated [16-36] (**Figure 1**). Mortality and ICU-LOS changes were reported in ten studies [16,20,24,26-28,30,32,35,36] and in one study ICU-LOS was reported but not mortality [33]. One publication was a duplicate with regard to study period and population and was therefore excluded from the analyses on clinical outcomes but included in the assessment of studies that reported process measures [27]. Sixteen of 21 included studies were before-after studies; one was an RCT, and the remaining studies were prospective or retrospective cohort studies.

Methodological quality

One study was of very low methodological quality (2 points) and was excluded [37] (see Appendix for **Additional file 3**: methodological quality rating of included studies and **Figure 1)**. This study was a randomized trial but details on randomization, interventions and assessment of delirium were insufficient with regard to reproducibility.

Implementation strategies

Implementation strategies that were used in the 21 included studies reporting process and clinical outcomes are shown in **Table 2** (strategies are explained in Table 1). These studies were published between 2005 and 2014. Professional-oriented strategies (that is aimed at changing professionals' behavior) and organizational strategies (that is aimed at changing structure of care delivery) were the most frequently used categories of implementation strategies. Of the professional-oriented strategies, education (meaning one or both of the following strategies: 'Distribution of educational material' [81%] and/or 'Educational meetings' [100%]), was used in all studies (**Tables 1 and 2**). Patient-mediated interventions, corresponding with implementation of screening for delirium with a validated tool such as CAM-ICU, was applied in 86% of the studies, whereas outreach visits, audit and feedback and local consensus processes were applied in 67%, 62% and 57% of the studies respectively (**Table 2**). Three of the 17 implementation strategies were not used at all (this is mass media, changes in medical liability and management of patient complaints). Three strategies were used in only one or two studies (provider-

oriented interventions/financial compensation [24], licensure [16] and patient oriented interventions [16,31]). Tailored interventions were used in 33% of the studies [16,20].

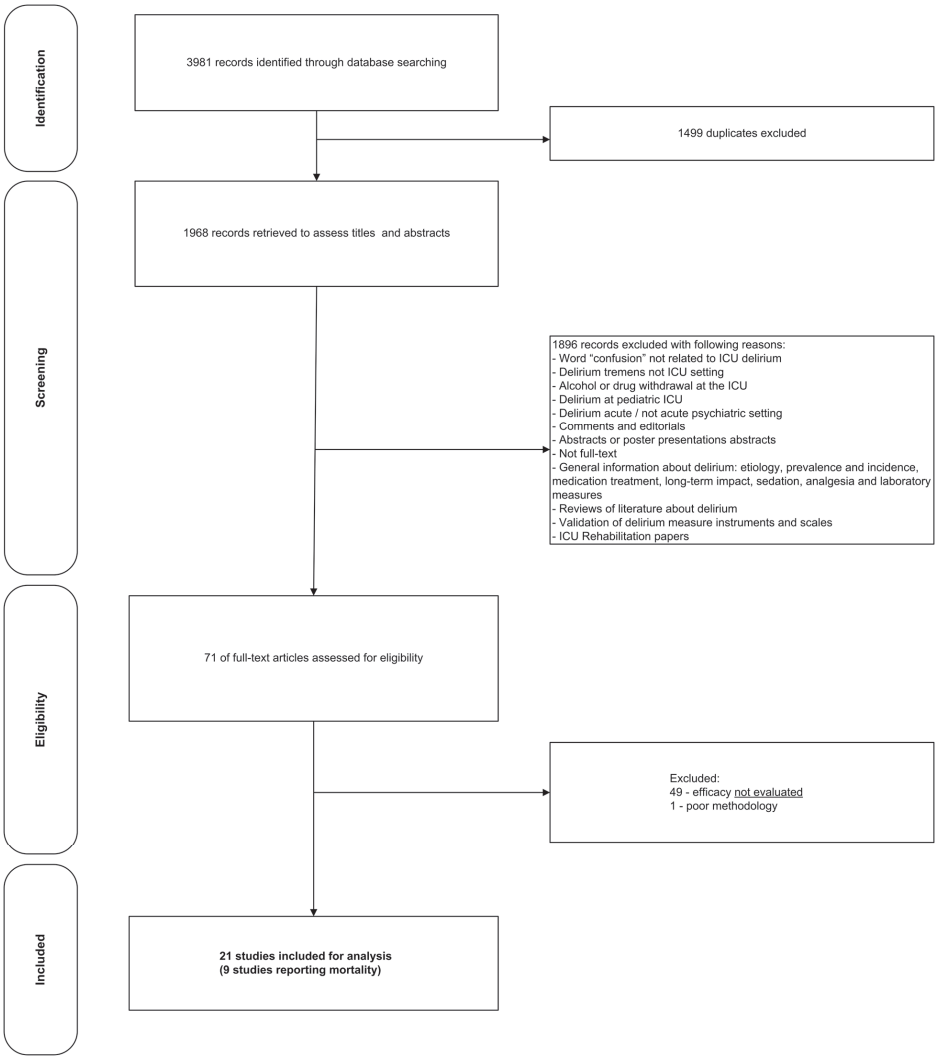


Figure 1: Selection of included studies for the review

Implementation characteristics, process outcomes and clinical outcomes

The number of implementation strategies used varied from 4 to 12 per study (**Table 3**). The overall median number of implementation strategies used per study was 7 (IQR 4.5 to 9.5). In the studies reporting clinical outcomes (n = 9) versus only process outcomes (n = 12) the median number of used strategies was 6 (IQR 4.5 to 8) and 7 (IQR 7.5 to 10) respectively (p=0.46, **Table 2**). Within the nine studies with clinical outcomes, the following implementation strat-

egies were reported only in studies with significant mortality reduction (that is, the studies by Mansouri, Skrobik, Balas): tailoring, encouragement for implementation by means of financial incentives, licensure, and audit and feedback (**Table 2**). Audit and feedback was used in all studies showing significant mortality reduction but in none without significant reduction of mortality ($p = 0.012$). In contrast, these and other strategies were used frequently in studies that reported process outcomes without clinical outcomes. The number of strategies per study belonging to the domains of organizational, financial or regulatory implementation strategies (that is, not aimed at the professional, **Table 2**) in the clinical outcome versus the process outcome studies did not differ ($p = 0.92$). However, within the nine clinical outcome studies the studies with a significant mortality reduction after the implementation [14] [24,31] used more of these non-professional oriented strategies (median 2, IQR 2 to 3) than studies without a significantly reduced mortality [26,28,30,32,35,36] (median 0.5, IQR 0.0 to 1.0, $p = 0.024$).

Delirium screening adherence was assessed in 15 of the 21 studies of which 13 showed a significantly increased adherence (**Table 3**)[16-18,21,22,24-26,29-31,33,34]. In studies specifically focused on implementation of delirium screening (n = 10), improvements in adherence to screening ranged from 14 to 92%, but the definition of adherence varied widely. These studies with focus on delirium screening typically did not report clinical outcomes (1 of 10 studies), whereas process outcomes were assessed in all of these studies (**Tables 2 and 3**). Significant improvement of screening adherence after the implementation was reported in 82% (9/11) of the studies that did not report on clinical outcomes versus 56% (5/9) of the studies that assessed clinical outcomes. Use of integrated delirium management (PAD/ABCDE) was reported in 18% (2/11) of studies without clinical outcome assessment versus in 67% (6/9) of studies with clinical outcome. Knowledge improvement was reported in 4 of 21 studies and varied both in magnitude and definition [17,18,23,29]. Knowledge improvement was reported in 36% (4/11) of studies without clinical outcome data versus 0% in studies with only process outcome data. Changes in reported delirium incidence [16,17,19,20,28,30,31,35,36] and use of antipsychotic drugs [16,17,20,24,27,30,32,36] after implementation varied between studies (some showed increased and some showed decreased incidence, **Table 3**). No significant associations existed between changes in the process measures (delirium incidence, use of antipsychotics or screening adherence) and mortality before and after the implementation. Likewise, no significant associations were found between the process measures and ICU-LOS.

In pooled analysis, we did not find differences in delirium incidence (n = 8) before versus after the implementation when comparing the studies using PAD/ABCDE versus those that did not use these frameworks or comparing those with high versus low number of implementation strategies and high inconsistency existed in such pooled analyses (see Appendix for **Additional file 4;** figures 4a,b). Implementation studies focusing on delirium screening tools did not report increased delirium incidence after the implementation compared with studies that used other frameworks (e.g. PAD/ABCDE,

Table 2: summary of implementation strategies

Implementation strategy			Studies reporting both clinical outcomes and process outcomes before vs after implementation									Studies reporting process outcomes, without clinical outcomes, before vs after implementation*											% using strategy
		Author	**Mansouri**	**Skrobik**	**Balas**	**Radtke**	**Robinson**	**Kamdar**	**Reade**	**Dale**	**Bryckz.**	**Eastwood**	**Devlin**	**Scott**	**Gesin**	**Riekerk**	**Kastrup**	**Boogaard**	**Pun**	**Hager**	**Soja**	**Page**	**Bowen**	
PO	1	Distribution**	1	1	1	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	1	1	1	81
	2	Educational Meetings	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	100
	3	Local consensus	1	1	1	0	1	1	0	1	1	0	0	0	1	1	1	1	0	1	0	0	1	57
	4	Outreach	0	0	1	1	0	0	1	1	0	1	1	1	1	1	0	1	1	0	1	1	1	67
	5	Opinion leaders	0	1	1	1	1	0	1	0	0	0	1	0	0	1	0	1	0	1	1	0	1	52
	6	Patient-mediated	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	86
	7	Audit/feedback	1	1	1	0	0	0	0	0	0	1	1	0	1	1	1	1	1	1	1	0	1	62
	8	Reminders	0	0	1	1	0	1	0	0	0	0	0	0	0	0	1	1	0	1	1	0	1	38
	9	Tailoring (barriers)	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0	1	0	1	1	0	1	33
	10	Mass media	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
O	11	Provider-oriented	1	0	1	0	0	1	0	0	0	0	1	0	0	1	0	1	1	1	1	0	0	43
	12	Patient-oriented	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	10
	13	Structural	0	1	1	1	0	0	0	0	0	0	0	0	1	1	1	1	1	1	1	0	0	48
F	14	Provider	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	10
R	15	Medical liability	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	16	Patient complaints	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	17	peer review/licensure	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
Total number IS used			**7**	**9**	**12**	**7**	**5**	**6**	**4**	**5**	**3**	**4**	**6**	**4**	**7**	**10**	**7**	**12**	**6**	**10**	**10**	**4**	**8**	
Post-implementation*																								
Mortality			↓	↓	↓	↓	↓	↓	↑	=	↓	↑	-	-	-	-	-	-	-	-	-	-	-	
ICU LOS			↓	↓	↓	↓	↓	↓	=	↓	↓	=	-	-	-	-	-	↓	-	-	-	-	-	
Screening adherence			↑	↑	↑	↑	**-**	-	-	↑	-	**-**	↑	↑	**-**	↑	↑	↑	↑	=	↑	↑	↑	
Incidence			-	↓	↓	-	-	↓	↓	↓	↑	-	-	-	-	-	↑	↑	-	↑	-	-	-	
Antypsychotics use			↓	↑	↑	-	↑	-	-	↓	↓	↓	-	-	-	-	-	↓	-	-	-	-	-	
Delirium knowledge			-	-	-	-	-	-	-	-	-	-	-	↑	↑	↑	-	↑	-	-	-	-	-	

PO = professional oriented; O = organizational; F = financial; R = regulatory; IS = implementation strategies

*Study by Eastwood concerns the same study population as the study by Reade and is therefore not used for analysis of clinical outcomes.

**for explanation of individual strategies, see Table 1

*** Only statistically significant changes are **bolded**

i.e. a more integrated program, see Appendix for **Additional file 4;** Figure 4c). Pooled analysis of relations between implementation strategies and adherence rates for screening or knowledge were not possible due to highly variable definitions for the process outcomes, and irretrievable original data allowing for pooling.

ICU-LOS

Nine of the ten studies that reported length of stay showed reduced ICU-LOS after implementation (the study by Eastwood and Reade were the same population); of which five were statistically significant (**Tables 2 and 3**). The study by Radtke et al [26] included populations from three different ICUs and were stratified according to standard or more intensive implementation strategies. Pooling all studies that reported ICU-LOS and of which data were retrieved (n=7) showed a reduction after the implementation of -1.26 days (95%CI -1.84; -0.69) (**Figure 2a**). Pooled data of four studies reporting ICU-LOS after implementation of PAD or ABCDE approach yielded significantly shorter LOS after implementation compared with not using these approaches (WMD = -1.71; 95%CI -2.45; -0.98 versus -0.55; 95%CI -1.48; 0.38) (Figure 2a). Using high (≥ 6) number of strategies showed a reduced ICU-LOS (-1.51, 95%CI -2.16; -0.86) versus no change when using less strategies (-0.36, 95%CI -1.61; 0.89) (**Figure 2b**). Within the studies using PAD or ABCDE (n=4) the signal that using more strategies reduced ICU-LOS was less evident (**Figure 2c**). None of the individual strategies were used more often in studies with versus without statistically significant ICU-LOS reduction.

Mortality

Seven of the 9 studies with mortality data before versus after implementation showed a reduction in mortality ranging from 2.9 to 12% (**Table 3**). Mortality was most often defined as hospital mortality (n = 6), but sometimes as ICU mortality [24,36] and 30-day mortality [20]. Three of these studies reported a statistically significant decrease in mortality between 6.5% (p = 0.009) and 12% (p = 0.046, **Table 3**)[16,20,24]. In the pooled analysis of all (n = 9) studies with mortality data, the mortality rates after implementation declined overall (RR = 0.82; 95% CI 0.71, 0.96, **Figure 3a**). There was no inconsistency between the studies for this association (I^2 = 0%, p = 0.526). Studies using PAD/ABCDE reported reduced mortality whereas studies that did not use these frameworks did not (RR = 0.81; 95% CI 0.69, 0.96 versus RR = 0.93; 95% CI 0.61, 1.42). However, this difference in mortality risk reduction between the pooled data in studies with and without PAD/ABCDE did not reach statistical significance (p = 0.531). Mortality risk reduction was significantly higher (p = 0.0424) in studies that used high number of implementation strategies (RR = 0.73; 95% CI 0.60, 0.88) compared with studies with low number (**Figure 3b**). Further, in the studies that used the PAD guideline or ABCDE approach (n = 6, **Figure 3c**) mortality reduction was higher (p = 0.0478) in studies that used a higher number of implementation strategies (RR = 0.73; 95% CI 0.59, 0.88 versus RR = 0.98; 95% CI 0.74, 1.30).

Table 3: Implementation characteristics and changes in important process and clinical outcomes before versus after implementation

Author, year (design)	*Implementation*			*Process outcomes*				*Clinical outcomes*	
	Number of strategies used	*Implemented care components*	*Implementation model*	*Screening adherence*	*Delirium incidence*	*Use of antipsychotics*	*Delirium knowledge*	*Mortality change*	*ICU LOS (days)*
Balas, 2014 [16] *(B/A[a] study, n=296)*	12	ABCDE[b]	CFIR[c]	**+50% (0-50%)[d]**	**-13% (62-49%), *p*=0.02**	*+12 mg (6-18 mg)[e], p=0.24*	-	**-8.6% (19.9-11.3%), *p*=0.04**	*-1[f] (5-4), p=0.21*
Van den Boogaard, 2009 [17] *(B/A study, n=1742)*	12	Delirium screening	Model of Grol and Wensing	**+14% (77-92%), *p*<0.0001**	**+13% (10-23%), *p*<0.05[g]**	**-12 mg (18-6 mg)[e], p=0.01**	**+1.2 (6.2-7.4), p<0.001**	-	*-0.3 (1.3-1)[f] p>0.05*
Riekerk, 2009 [18] *(B/A study, n=NA)*	10	Delirium screening	Structural implementation pathway	**+57% (38-95%)[d]**	**-**	**-**	**+1[d,h] (3-4)**	-	-
Hager, 2013 [19] *(B/A study, n=202)*	10	PAD[w]	4Es framework[i]	*0 (90-90%)*	**+18%[j] (20-38%), *p*=0.01**	**-**	-	-	-
Skrobik, 2010 [20] *(B/A study, n=1133)*	9	PAD	-	*+3[k] (89-92%), p=0.055*	*-0.5% (34.7-34.2%), p=0.9*	*+0.3% (39.4-39.7%), p=0.7*	-	**-6.5% (29.4-22.9%), *p*=0.009**	**-0.97[l] (6.32-5.35), *p*=0.009**
Bowen, 2012 [21] *(pilot study, n=34 nurses)*	8	Delirium screening	Diffusion of Innovations theory	**+75% (10%-85%)**	**-**	**-**	-	**-**	**-**
Soja, 2008 [22] *(Prospective study, n=347)*	10	Delirium screening	-	**+84% (0-84)[d]**	-	-	-	**-**	**-**
Gesin, 2012 [23] *(B/A study, n=20 nurses)*	7	Delirium screening	-	-	**-**	**-**	**+ 2.1 (6.1-8.2), *p*=0.001**	**-**	**-**

Table 3: Implementation characteristics and changes in important process and clinical outcomes before versus after implementation (continued)

Author, year (design)	*Implementation*			*Process outcomes*				*Clinical outcomes*	
	Number of strategies used	*Implemented care components*	*Implementation model*	*Screening adherence*	*Delirium incidence*	*Use of antipsychotics*	*Delirium knowledge*	*Mortality change*	*ICU LOS (days)*
Mansouri, 2013 [24] (RCT, n=201)	7	PAD	-	**+100%[m] (0-100%)**	-	*-2.5 mg[n] (3.2-0.7 mg), p=0.12*	-	**-12% (24-13%), p=0.046**	**-3.1 (7.1-4.0)[f], p<0.001**
Pun, 2005 [25] (Prospective study, n=711)	6	PAD	-	**+90% (0-90)[d] +84% (0-84)[d]**	**-**	-	-	**-**	**-**
Radtke, 2012 [26] (B/A[e] study, n=131)	7	PAD	Modified extended training	**+1.6 (0-1.6), p<0.01**	-	-	-	*-4.8%[o] (9.9-5.1%), p=0.16*	*-4 (18-14)[p], p=0.40* **-4 (8-4)[p], p<0.01**
Eastwood, 2012 [27] (B/A study,n=288 patients / 2368 shifts)	4	Delirium screening	-	**-**	-	**+8.5%[q] (5.8-14.3%), p<0.0001[r]**	-	*+3.2% (5-8.2)[s,t] p=0.31*	*0 (2-2), p= 0.34*
Kamdar, 2013 [28] (B/A study, n=285)	6	Multifaceted sleep promotion program	Structured QI model	-	**OR 0.46[a], p=0.02**	**-**	-	*-6% (25-19%), p=0.88[s]*	*-1.1[u] (5.4-4.3), p=0.60*
Scott, 2012 [29] (B/A study, n=119)	4	Delirium screening	-	**+78% (0-78%)[d]**	**-**	**-**	**+14%[v] (71-85%), p<0.001**	**-**	**-**
Dale, 2014 [30] (B/A study, n= 1483)	5	PAD	-	**+1.14[x] (0.35-1.49), p<0.01**	**OR 0.67, p=0.01**	**-1.7 (2.7-1.0)[y], p<0.01**	-	*0 (14-14%), p=1.0*	**-12.4%[j], p=0.04**

Table 3: Implementation characteristics and changes in important process and clinical outcomes before versus after implementation (continued)

Author, year (design)	*Implementation*			*Process outcomes*				*Clinical outcomes*	
	Number of strategies used	*Implemented care components*	*Implementation model*	*Screening adherence*	*Delirium incidence*	*Use of antipsychotics*	*Delirium knowledge*	*Mortality change*	*ICU LOS (days)*
Kastrup, 2011 [31] *(B/A study, n=205)*	7	Visual feedback system	-	**+37.5% (0.5-38%), p<0.01**	*+4% (25-29%), p=1.0*[za]	-	-	-	-
Robinson, 2008 [32] *(B/A study, n=119)*	5	PAD	-	-	-	*+14% (31-45%), p=0.25*	-	*-2.9% (17.6-14.7), p=0.64*	*-1.8 (5.9-4.1), p=0.21*
Devlin, 2008 [33] *(B/A study, n=601)*	6	Delirium screening	SCT[zb]	**+70% (12-82%), p<0.0005**	-	-	-	-	-
Page, 2009 [34] *(Retrospective study, n=60)*	4	Delirium screening	-	**+92% (0-92%)**[d]	-	-	-	-	-
Reade, 2011 [35] *(B/A study, n=288)*	4	Delirium screening	-	-	**-16% (37-21%), p=0.004**	-	-	*+3.2% (5-8.2)*[zc]*, p=0.31*	*0 (2-2), p= 0.34*
Bryczkowski, 2014 [36] *(B/A study, n= 123)*	3	Delirium prevention program	-	-	*+11% (58-47%), p=0.26*	*-1% (7-6%), p= 0.83*	-	*-4% (7-3%), p=0.31*	**-3 (9-6), p=0.04**

[a] B/A = before-after,

[b] ABCDE = awakening and breathing coordination, delirium monitoring/management and early exercise/mobilization bundle,

[c] CFIR = Consolidated Framework for Implementation Research,

[d] statistical significance not reported or assessable from data in article but presumed to be statistically significant because of strong effect. Brackets = difference (before-after). Significant changes are shown in **bold** letters. Applies to whole table,

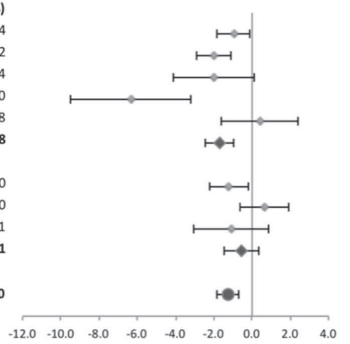
[e] total dose of haloperidol per patient,

[f] median

[g] Chi-square
[h] increase in median level of agreement on a scale of 5 (1 = totally disagree, 5 = totally agree, with 3 = neutral about statement and 4=agree) with true statements about delirium, signifying increased knowledge,
[i] 4Es framework = Engage, Educate, Execute and Evaluate
[j] % of ICU days delirium present per patient,
[k] Adherence calculated by dividing delirium assessments judged to be "possible" by total number of patients in Table 1 in reference. Adherence data to screening not explicitly provided in text
[l] Mean
[m] No explicit mention of screening adherence, but after CAM-ICU implementation as part of PAD guideline the authors mention strict adherence surveillance to the PAD protocol. 15 patients in protocol group excluded from analysis because of noncompliance with PAD guideline
[n] Mean dose of drug (haloperidol) used per patient
[o] Mortality calculated from numbers given in Table 1 in original article for combined data of ICU 1 and 2 (n=131, before-after comparison made with Chi2, df=2),
[p] This study reported different interventions (standard training versus extended training and implementation) in different ICU's. Numbers given here are those from the B/A study in 2 ICUs that received modified extended training,
[q] Percentage is total number of administered doses of either haloperidol (5 mg), olanzapine (5-10 mg) or quetiapine (25 mg) divided by the total number of 8 hour shifts in pre- and post-CAM-ICU implementation period. Study of Eastwood is duplicate report of study by Reade, therefore for analysis data were combined,
[r] Chi2 = 47, df = 1,
[s] Unstructured delirium screening vs. CAM-ICU screening,
[t] The mortality change data were not included by the analysis of all mortality data because this data are same as those of *Reade, 2011* [35],
[u] Calculated for survivors, median, frequency of delirium monitoring per day per patient,
[v] Calculated agreement with true statements about delirium and its importance increased with 14% after the implementation, signifying increased knowledge (Chi2 = 14, df=1),
[w] PAD = integrated pain, agitation/sedation and delirium monitoring and management,
[x] No. CAM-ICU assessments/day (mean)
[y] mean daily haloperidol dose (mg)
[za] Fisher's exact test,
[zb] SCT = Script Concordance Theory,
[zc] % of patients ever receiving haloperidol

Figure 2a Length of stay with (I) versus without (II) use of PAD/ABCDE as implementated care components.

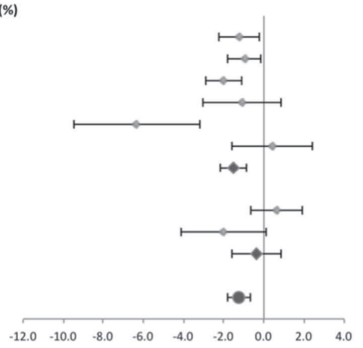
Author	WMD	(95% CI)	Weight (%)
Skrobik (2010)	-0.97	(-1.82; -0.12)	27.4
Radtke (2012) ICU1&2	-2.00	(-2.88; -1.12)	25.2
Radtke(2012) ICU3	-2.00	(-4.11; 0.11)	4.4
Mansouri (2013)	-6.35	(-9.50; -3.20)	2.0
Balas (2014)	0.40	(-1.61; 2.41)	4.8
Subtotal PAD/ABCDE	**-1.71**	**(-2.45; -0.98)**	**63.8**
van den Boogaard (2009)	-1.21	(-2.23; -0.19)	19.0
Reade (2011)	0.63	(-0.64; 1.91)	12.0
Kamdar (2013)	-1.10	(-3.06; 0.86)	5.1
Subtotal other	**-0.55**	**(-1.48; 0.38)**	**36.1**
Overall	**-1.26**	**(-1.84; -0.69)**	**100.0**
(p<0.0001)			



WMD - Weighted mean difference, CI - confidence interval

Figure 2b Length of Stay high (I) versus low (II) number of implementation strategies

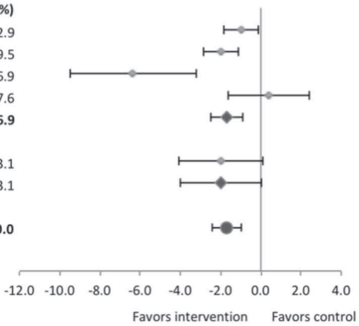
Author	WMD	(95% CI)	Weight (%)
van den Boogaard (2009)	-1.21	(-2.23; -0.19)	19.0
Skrobik (2010)	-0.97	(-1.82; -0.12)	27.4
Radtke (2012) ICU1&2	-2.00	(-2.88; -1.12)	25.2
Kamdar (2013)	-1.10	(-3.06; 0.86)	5.1
Mansouri (2013)	-6.35	(-9.50; -3.20)	2.0
Balas (2014)	0.40	(-1.61; 2.41)	4.8
Subtotal I	**-1.51**	**(-2.16; -0.86)**	**83.6**
Reade (2011)	0.63	(-0.64; 1.91)	12.0
Radtke (2012) ICU3	-2.00	(-4.11; 0.11)	4.4
Subtotal II	**-0.36**	**(-1.61; 0.89)**	**16.4**
Overall	**-1.26**	**(-1.84; -0.69)**	**100.0**
(p<0.0001)			



WMD - Weighted mean difference, CI - confidence interval

Figure 2c Length of Stay after implementation in studies using PAD or ABCDE (n=4) with high (I) versus low (II) number of implementation strategies

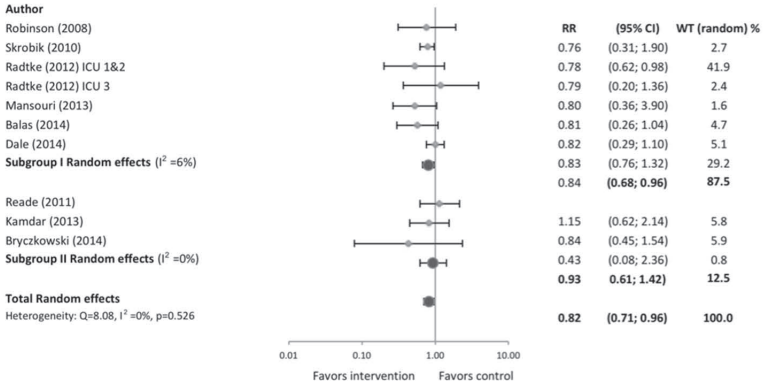
Author	WMD	(95% CI)	Weight (%)
Skrobik (2010)	-0.97	(-1.82; -0.12)	42.9
Radtke 2012) ICU1&2	-2.00	(-2.88; -1.12)	39.5
Mansouri (2013)	-6.35	(-9.50; -3.20)	6.9
Balas(2014)	0.40	(-1.61; 2.41)	7.6
Subgroup I	**-1.67**	**(-2.46; -0.88)**	**96.9**
Radtke - ICU3	-2.00	(-4.11; 0.11)	3.1
Subgroup II	**-2.00**	**(-4.03; 0.03)**	**3.1**
Overall	**-1.71**	**(-2.45; -0.98)**	**100.0**



WMD - Weighted mean difference, CI - confidence interval

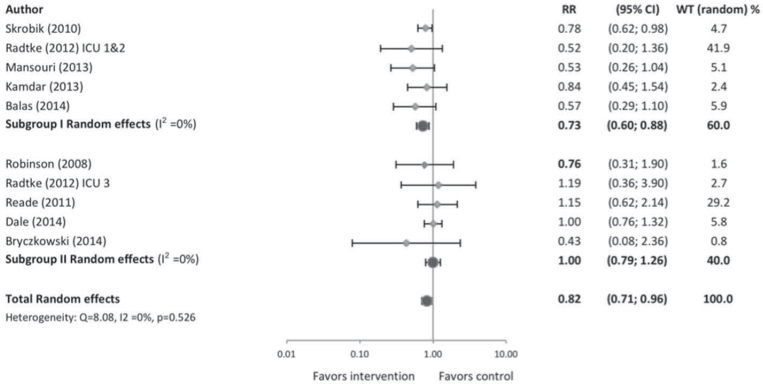
Figures 2 a,b,c: Pooled analysis of determinants of changes in ICU length of stay (days) in implementation studies (n=7) that included delirium-oriented interventions.
Determinants of ICU length of stay reduction that were studied, were: use of either PAD or ABCDE (2a) or use of high or low number of implementation strategies (2b). Figure 2c shows impact of high or low number of strategies within the studies reporting ICU length of stay and using PAD/ABCDE (n=4). See text for more details. Study by Radtke reported multiple populations and these were separately assessed.

Figure 3a Risk ratio of mortality with (I) versus without (II) use of PAD/ABCDE as implementated care components.



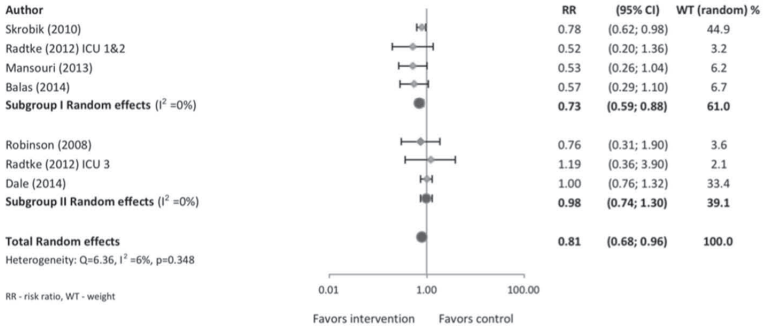
Includes all studies on implementation of delirium-oriented interventions with mortality data before and after the implementation (n=9)
RR - risk ratio, WT - weight

Figure 3b Risk ratio of mortality with high (I) versus low (II) number of implementation strategies



Includes all studies on implementation of delirium-oriented interventions with mortality data before and after the implementation (n=9)
RR - risk ratio, WT - weight

Figure 3c Risk ratio of mortality after implementation in studies using PAD or ABCDE (n=6) with high (I) versus low (II) number of implementation strategies



RR - risk ratio, WT - weight

Figures 3 a,b,c: Pooled analysis of determinants of changes in mortality (risk ratio) in implementation studies (n=9) that included delirium-oriented interventions.
Determinants of mortality reduction that were studied were: use of either PAD or ABCDE (3a) or use of high or low number of implementation strategies (3b). Figure 3c shows impact of high or low number of strategies within the studies reporting mortality and using PAD/ABCDE (n=6). See text for more details.

DISCUSSION

This systematic review and structured analysis of the literature aimed to summarize the implementation strategies and their effectiveness to change practices with regard to delirium assessment, prevention and management in the ICU and clinical outcomes. To accomplish this goal, we tried to address both the why and the how questions regarding implementation. With regard to the why, an important finding of this review indicating that multi-component implementation that included delirium-oriented interventions in critically ill patients can be useful, is that many studies reported improvements of both process outcomes (delirium screening adherence, knowledge) and clinical outcomes (short-term mortality and ICU-LOS). With regard to the how, several results of this review are worth highlighting: 1) some individual strategies such as 'audit and feedback' and 'tailored interventions' may be important to establish clinical outcome improvements, but otherwise robust data on effectiveness of specific implementation strategies are scarce, 2) using implementation strategies targeted not only at the health care professional but also at organizational, financial or regulatory domains is associated with better clinical outcomes, 3) using a higher number (that is, six or more) of implementation strategies concomitantly and delirium management being integrated according to the PAD guidelines or the ABCDE care bundle, are associated with positive effects of implementation efforts on clinical outcome, and 4) in contrast, a high number of implementation strategies and PAD/ABCDE use were not associated with reductions in delirium incidence. With regard to the third finding, it is imperative to note that the association between the use of six or more implementation strategies and mortality reductions should be regarded as a hypothesis-generating finding with regard to the effectiveness of implementation interventions for clinical outcome improvement, and therefore does not imply that using more implementation strategies will definitely result in improved outcomes.

Our results seem to be consistent with the premises of the Society of Critical Care Medicine (SCCM) guideline on management of Pain, Agitation and Delirium (PAD) [3] and the ABCDE care bundle, that: 1) integrated management of pain, agitation/sedation and delirium together with early mobilization should be a component of the plan of ICUs to improve patient safety and comfort, and 2) complying with these components of evidence-based critical care has the potential to improve clinical outcomes depending on the baseline practices of any individual ICU and the patient population. Of the evidence-based interventions mentioned, early mobilization is the only intervention that has been shown to improve both delirium and clinical outcomes, but regrettably the integrated nature of both PAD and ABCDE precluded us from studying early mobilization implementation in isolation.

Establishing such integrated management on a daily basis in all patients and by all ICU health care professionals is not an easy task, as it required consideration of an intense amount of human factors and cultural adaptions. The data from this review support that putting effort into implementation may be worthwhile, while at the same time confirming that not all programs will meet with the same success. Importantly, we cannot exclude that the positive effects of using a high number of implementation interventions on mortality may in part be explained by the Hawthorne effect, meaning that using many implementation strategies at the same time may have improved quality of care due to improved attention for specific aspects of care which may not always have been linked directly to delirium [38]. Another explanation may be that local ICU culture in these studies - which typically is unmeasured and thus unaccounted for - may have promoted successful implementation of changes into clinical practice. For instance, an ICU team consisting of professionals who are capable of adopting new practices within a limited time frame and that has acquired effective communication and collaboration across different types of health care professionals is probably more likely to implement multiple strategies successfully compared to a team that lacks these characteristics. The number of implementation strategies used may then confound the true causal association between local ICU culture and improved clinical outcome.

Although this review focused on delirium in the ICU, targeting delirium alone would not suffice to establish outcome improvements. Therefore, we argue that delirium screening alone would not likely establish mortality reduction when not embedded in an ABCDE bundle, for instance [7]. In other words, it is the circumstances leading to or sustaining brain dysfunction that should be dealt with in the first place. This view, that exclusively dealing with delirium may not suffice to improve clinical outcomes, is supported by a recent study showing that the attributable mortality caused by delirium in ICU patients is questionable and that long term sequelae may be a better clinical outcome measure for delirium-related outcomes than short-term mortality [39]. On the other hand, it is perceivable that delirium-focused management embedded in PAD or ABCDE may establish outcome improvement in spite of the fact that delirium may not be causally linked to mortality directly, analogous to lactate guided management that may improve outcome in critically ill patients, in spite of lactate not being causally linked to mortality [40].

Several methodological limitations of this review need to be addressed. First, the included studies showed strong heterogeneity with regard to design, focus of implementation (prevention, assessment or management of delirium as primary focus or delirium-oriented interventions being part of the implementation program but not the main focus), applied implementation strategies and model and whether the study was primarily aimed at studying the implementation itself or not. Definitions of process and clinical outcomes varied between studies. For instance, delirium measures varied

importantly between studies ranging from delirium incidence after admission to ICU to percentage of ICU days with delirium present per patient, which hampered comparability. Second, although early mobilization seems to be the only intervention within PAD/ABCDE that has been shown to affect both delirium and clinical outcomes, we could not isolate studies specifically reporting an implementation intervention that linked delirium and early mobilization implementation with clearly defined process or outcome measures, as per our inclusion criteria. Third, in spite of rigorous assessment of the implementation strategies that were used in included studies according to predefined EPOC definitions, a potential limitation hampering interpretation of the association between improved outcome and number of strategies is that the efforts put in to execute these implementation strategies could not be assessed. For instance, two studies using the same number of strategies may still differ with regard to the efficacy of the implementation due to ongoing educational efforts in one but only a single educational session in the other study. We speculate that when more effort is put into the implementation it may be more successful even with the same number of implementation strategies used. Fourth, there is some evidence that suggests that uncontrolled pre-post test studies as included in this review may overestimate the effects of implementation or quality improvement studies [41]. Fifth, the results on ICU-LOS should be considered cautiously because concurrent changes in mortality may affect ICU-LOS, instead of the implementation intervention itself being responsible for lower ICU-LOS, since censoring by death may bias and (theoretically) even reverse the associations found. On the other hand, strengths of this review included the systematic assessment of the implementation strategies by three independent investigators based on the description of strategies provided by EPOC, the focus on the clinical endpoints and the systematic assessment of methodological quality. Furthermore, inconsistency of the pooled analysis with regard to the clinical outcomes was low, which supports generalizability of our findings.

Summarizing the current status of implementation work that has been done to date with regard to ICU delirium reveals which implementation strategies have not yet been studied extensively in this field. For example reminders and computerized support have been previously found to mostly be effective strategies [11], whereas these strategies did not stand out in this review; assessment of these strategies in future work aimed at ICU delirium should therefore be considered. We think that our work may encourage health policy makers to invest in multifaceted implementation efforts to improve care for delirious ICU patients.

More research is necessary to elucidate which types of individual strategies and/or which combination of strategies used in implementation programs are most successful in establishing mortality reduction in delirious critically ill patients. Further, several aspects of implementation deserve further evaluation, as this review shows that these issues in implementation have lacked attention, such as cultural aspects pertaining to

the medical ICU team, nurse-physician interaction and establishing sustainability of practice changes [12]. Prospective, adequately powered before-after studies may be most suitable for evaluation of practice changes and cluster-randomized trials are conceivably the best study designs to evaluate the effect of implementation strategies on outcome improvements [42]. Therefore, an important issue to be considered is the distinction between successful practice change and clinical outcome improvements in implementation research. In our study successful implementation was evident in most studies on delirium screening implementation that showed improved adherence, even without known benefit for clinical outcomes. On the other hand cumbersome implementation may result in improved outcomes.

Finally, detailed information on extent, form and contents of implementation interventions, especially education, was often lacking in studies on implementation (data not shown). Therefore, reproducibility of delirium implementation research should also be taken into account in future investigations.

CONCLUSION

This review and meta-analysis shows that multifaceted implementation programs that included assessment, prevention and management of ICU delirium have been shown to effectively change adherence to delirium screening and delirium knowledge. Implementation programs may enhance their effectiveness when not only health care professionals are targeted for behavioral change but also organizational changes are employed. Although using more rather than less implementation strategies simultaneously and delirium management being integrated with structured pain and agitation management (PAD), awakening and breathing coordination and early mobilization (ABCDE bundle) were associated with improved clinical outcomes, these results should be regarded as preliminary and hypothesis generating with regard to the link between implementation practice and outcome improvement. Therefore, to determine whether these associations are causal our findings require confirmation and further study is needed on the most effective implementation strategies and the importance of focusing on delirium as an important form of organ failure within implementation programs aimed at practice change.

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APPENDIX:

Additional file 1: Search string and search results

Database	Search string	Identified	Duplicates excluded	Retrieved
PubMed	(Deliri*[tw] OR Confusion*[tiab] OR Psychosis[tiab] OR Psychoses[tiab] OR Psychotic[tw] OR brain failure*[tiab]) AND (Intensive Care*[tw] OR ICU*[tiab] OR critical care*[tiab] OR critically ill*[tiab])	1917	15	(1902)
Embase	('intensive care psychosis'/de OR ((Deliri* OR Psychotic OR Confusion* OR Psychosis OR Psychoses) NEAR/6 ('Intensive Care' OR ICU OR 'critical care' OR 'critically ill' OR 'critical illness')):de,ab,ti)	1232	904	(328)
PsycINFO	((Deliri* OR Psychotic OR Confusion* OR Psychosis OR Psychoses) ADJ6 ('Intensive Care' OR ICU OR 'critical care' OR 'critically ill' OR 'critical illness'))	181	125	(56)
Cochrane	((Deliri* OR Psychotic OR Confusion* OR Psychosis OR Psychoses) NEAR/6 ('Intensive Care' OR ICU OR 'critical care' OR 'critically ill' OR 'critical illness'))	15	8	(7)
CINAHL	MM "ICU Psychosis" OR SU((Deliri* OR Confusion* OR Psychosis OR Psychoses OR Psychotic OR "brain failure*") AND ("Intensive Care*" OR ICU* OR "critical care*" OR "critically ill*"))	636	447	(189)
Total:		3981	1499	2482
Total # of studies excluded before year 2000				514
Remaining # of identified studies				**1968**

Additional file 2: Adapted Rating system from Anderson and Sharpe.

Design of study or assignment rating	**Rating**
Experimental: RCT, random allocation; CCT, quasi-random allocation; three data collection points before and after the intervention	1
Quasi-experimental: CBA, comparable control sites	1
Quasi-experimental: nonequivalent control sites	0
Single group before-after tests with baseline measurement	0
Content	
Intervention, implementation strategy is clearly described	1
Sample size	
Described and justified. An n per group sufficient to detect a significant effect ($p<0.05$) with a power of 0.80 or reported Power calculation	1
Validity and reliability of instruments	
Unobtrusive observations, rater procedure described and $r>0.80$	2
Unobtrusive observations, rater procedure not described or $r<0.80$	1
Obtrusive observations, rater procedure not described or $r<0.80$	0
Test statistics	
Test statistics are described	1
Significance	
p value or confidence interval is given	1

CBA=controlled before-and-after study, CCT=controlled clinical trial, ITS=interrupted time series.

Additional file 3: Quality Rating of Implementation Studies

Author	Design of study or assignment rating	Content	Sample size	Validity and reliability of instruments	Test statistics	Significance	Total
Balas et al, 2014, USA	1	1	0	2	1	1	**6**
Bowen et al, 2012, USA	0	1	0	2	1	0	**4**
Devlin et al, 2008, USA	1	1	1	2	1	1	**7**
Eastwood et al, 2012, Australia	0	1	0	2	1	1	**5**
Gesin et al, 2012, USA	1	1	1	2	1	1	**7**
Hagar et al, 213, USA	1	1	0	2	1	1	**6**
Kamdar, et al, 2013, USA	1	1	1	2	1	1	**7**
Kastrup et al, 2011, Germany	1	1	0	2	1	1	**6**
***Khalifezadeh et al, 2011, Iran**	1	0	0	0	1	0	**2**
Mansouri et al, 2013, Iran	1	1	0	1	1	1	**5**
Page et al, 2009, UK	0	1	0	2	1	1	**5**
Pun et al, 2005, USA	1	1	0	2	1	1	**6**
Radtke , Heymann et al, 2012, Germany	1	1	0	2	1	1	**6**
Reade et al, 2011, Australia	0	1	0	2	1	1	**5**
Riekerk et al, 2009, The Netherlands	1	1	0	2	1	1	**6**
Robinson et al, 2008, USA	1	1	0	2	1	1	**6**
Scott et al, 2012, UK	1	1	0	2	0	0	**4**
Skrobik et al, 2010, Canada	1	1	0	2	1	1	**6**
Soja et al, 2008, USA	1	1	0	2	1	1	**6**
Van den Boogaard et al, 2009, The Netherlans	1	1	0	2	1	1	**6**
Dale et al, 2014, USA	1	1	0	2	1	1	**6**
Bryczkowski et al, 2014, USA	1	1	0	2	1	1	**6**

The item validity and reliability was adapted adding one extra point for first option (Unobtrusive observations, rater procedure described and r >0.80) for a better distinction when implementation procedure is well described.

* Excluded

Figure 4a Risk ratio of incidence of delirium with (I) versus without (II) use of PAD/ABCDE as implementated care components.

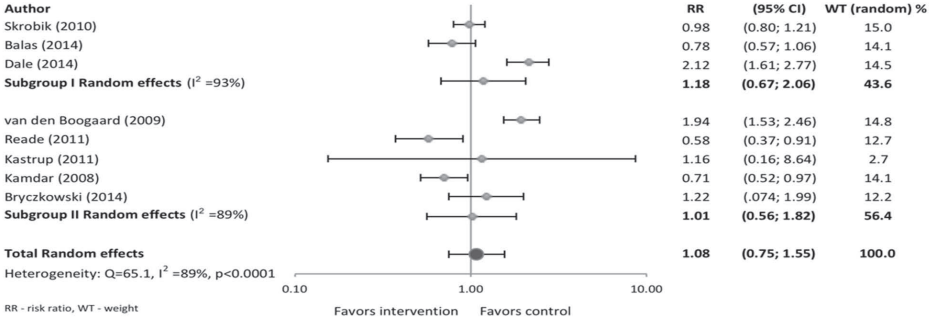


Figure 4b Risk ratio of incidence of delirium with high (I) versus low (II) number of implementation strategies

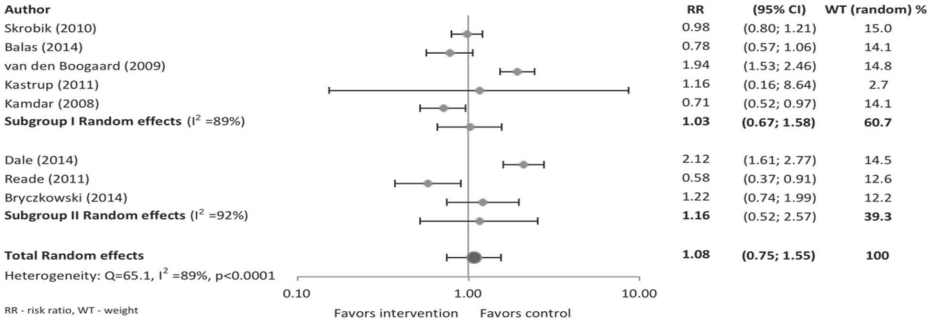
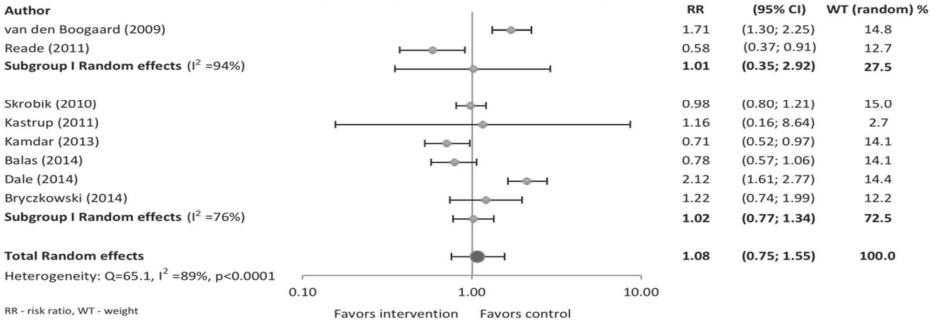


Figure 4c Risk ratio of incidence of delrium with (I) screeningtool as implementated care components versus others (II)



Additional file 4: Pooled analysis of determinants of changes in delirium incidence (risk ratio) in implementation studies (n=8) that included delirium-oriented interventions.

Determinants of delirium incidence reduction that were studied were: use of either PAD or ABCDE (4a) or use of high or low number of implementation strategies (4b). Figure 4c shows that both studies that focused on delirium screening implementation and studies that did not (but e.g. implemented ABCDE bundle), found no changes in delirium incidence after the implementation. Only two studies (van den Bogaard and Reade) on delirium screening implementation were included of which individual patient data could be retrieved from authors. See text for more details.

Chapter 5

Improved Guideline Adherence and Reduced Brain Dysfunction after a Multicenter Multifaceted Implementation of ICU Delirium Guidelines in 3,930 Patients

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ABSTRACT

Objective

Implementation of delirium guidelines at ICUs is suboptimal. The aim was to evaluate the impact of a tailored multifaceted implementation program of ICU delirium guidelines on processes of care and clinical outcomes and draw lessons regarding guideline implementation.

Design

A prospective multicenter, pre-post, intervention study.

Setting

ICUs in one university hospital and five community hospitals.

Patients

Consecutive medical and surgical critically ill patients were enrolled between April 1, 2012, and February 1, 2015.

Interventions

Multifaceted, three-phase (baseline, delirium screening and guideline) implementation program of delirium guidelines in adult ICUs.

Measurements and Main Results

The primary outcome was adherence changes to delirium guidelines recommendations, based on the Pain, Agitation and Delirium guidelines. Secondary outcomes were brain dysfunction (delirium or coma), length of ICU stay and hospital mortality. A total of 3,930 patients were included. Improvements after the implementation pertained to: delirium screening (from 35% to 96%, $P<0.001$), use of benzodiazepines for continuous sedation (from 36% to 17%, $P<0.001$), light sedation of ventilated patients (from 55% to 61%, $P<0.001$), physiotherapy (from 21% to 48%, $P<0.001$) and early mobilization (from 10% to 19%, $P<0.001$). Brain dysfunction improved: the mean delirium duration decreased from 5.6 to 3.3 days (-2.2 days; 95% CI, -3.2 to -1.3, $P<0.001$), and coma-days decreased from 14% to 9% (RR 0.5; 95% CI, 0.4-0.6, $P<0.001$). Other clinical outcome measures, such as length of mechanical ventilation, length of ICU stay and hospital mortality did not change.

Conclusions

This large pre-post implementation study of delirium-oriented measures based on the 2013 PAD-guidelines showed improved health professionals' adherence to delirium

guidelines, and reduced brain dysfunction. Our findings provide empirical support for the differential efficacy of the guideline bundle elements in a real-life setting and provide lessons for optimization of guideline implementation programs.

INTRODUCTION

Delirium is a common form of vital organ dysfunction in critically ill adults, associated with increased morbidity, mortality, and long-term cognitive deterioration [1-3]. Adequate delirium management is therefore an important component of intensive care – as substantiated in the Pain, Agitation, and Delirium (PAD) guidelines [4]. Successful implementation of guidelines into daily practice is challenging [5] although multifaceted implementation programs have the potential to facilitate success [6]. Implementation of the PAD guidelines has had beneficial effects on pain, brain dysfunction, durations of mechanical ventilation and ICU stay, early mobilization, long-term cognitive dysfunction, functional recovery and mortality in the critically ill [7-9]. Still, "real-life" prospective multicenter implementation studies focused on these delirium-oriented guidelines in hospitals with low use of the guidelines at baseline are needed to bring clinical evidence into practice on a wider scale, given the suboptimal implementation of these guidelines worldwide [10].

We therefore performed the prospective multicenter 'ICU DElirium in Clinical PracTice Implementation Evaluation' (iDECePTIvE) study [11], designed to evaluate the effectiveness of a multifaceted implementation program tailored to improving adherence to delirium guidelines, and to study patient-related benefits.

MATERIALS AND METHODS

Study design and participants

We conducted a prospective, multicenter, before-after implementation study in six ICUs in the Netherlands - one university and five community hospitals (three teaching and two non-teaching hospitals) [11]. The size of the units varied between 8 and 32 ICU beds. Consecutive ICU patients older than 18 years old or older were included. Exclusion criteria were: a primary neurological diagnosis; home mechanical ventilation for chronic respiratory insufficiency; and burn-injuries. The intervention, an implementation program focused at the implementation of the delirium-oriented recommendations derived from Dutch ICU Delirium Guidelines [12] and the PAD-guidelines of the Society of Critical Care Medicine [4] – was aimed at all ICU physicians and nurses. Results of this study were reported using the Standards for Quality Improvement Reporting Excellence guidelines [13]. The study protocol was reviewed by the Medical Ethical Committees of participating hospitals (MEC-2012-063). Patients' informed consent was not necessary according to Dutch legislation [14]. The study was registered at Clinicaltrials.Gov (Identifier: Nct01952899 2017).

Procedures, Outcomes and Data Collection

The study duration was 36 months and consisted of three measurement periods between April 2012 and February 2015 **(Figure 1).** The Implementation Model of Change of Grol and Wensing [15] was used to structure the guideline implementation. This model is a 7-steps approach, and starts with identifying the problem and defining the aim of change followed by identification of potential barriers and facilitators for implementation; development of an implementation plan based on these barriers and facilitators; and finally, execution, evaluation and sustaining of the implementation plan.

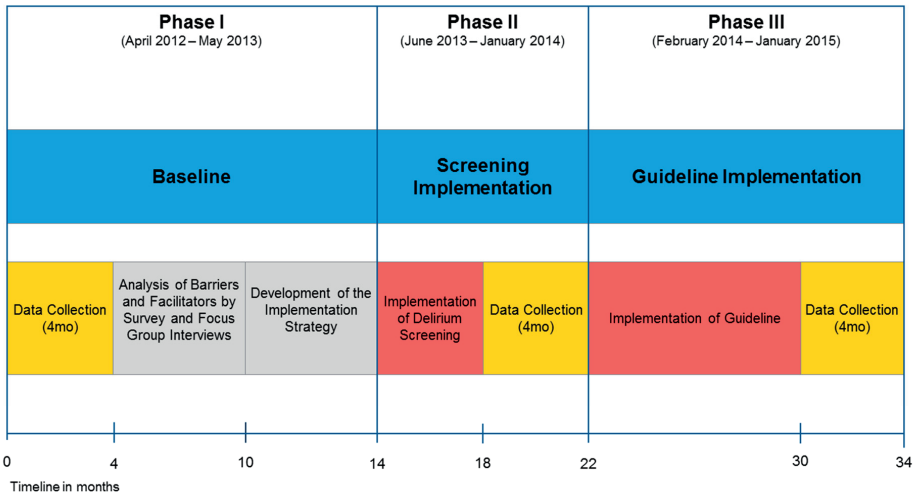

Figure 1: Timeline iDECePTIvE Study

Phase I

The baseline phase started with a 4-month data collection period. To avoid the Hawthorne effect [11], staff of the participating ICUs were not informed about the study during data collection, with the exception of the local intensivist (PI) and research nurses. Next, we performed an analysis of barriers and facilitators for delirium guideline adherence by means of a survey [16] and focus group interviews with stakeholders, and development of the implementation program **(Figure 1)**. We identified more than thirty barriers and facilitators for guideline adherence, to which we then tailored the implementation program following the model of Grol and Wensing and change theories [6,11,16,17]**(Appendix: supplemental digital content 1 and 2)**. Important facilitators were: realizing that delirium is a major problem, that treatment is essential, and that delirium is often under-diagnosed. The most important barriers were: insufficient knowledge for screening, no integral delirium protocol with a link to screening results [16]. The implementation program consisted of different implementation strategies in accordance to the Effective

Practice and Organization of Care group (EPOC) classification, mainly on organizational and professionals level [18,19]. See details in **Table 1** and **Figure 1.**

Phase II

This phase was dedicated to reliable delirium screening, for which all nurses and physicians compulsory completed an e-learning program. We formally appointed an intensivist and research nurse at each site to act as local champions during this and subsequent phases and encouraged them to involve other ICU nurses or ICU physicians as 'ambassadors'. Additional clinical lessons and bedside education were provided by the local implementation teams, which also performed delirium screening spot-checks. Three of the ICUs preferred the Confusion Assessment Method for the ICU (CAM-ICU) [20]; the other three preferred the Intensive Care Delirium Screening Checklist (ICDSC) [21]. All implementation elements are briefly explained in **Table 1** and were categorized according to the Cochrane Effective Practice and Organization of Care (EPOC) [18] and study phase.

Phase III

This phase consisted of 8-months of implementation followed by 4-months of data collection (**Figure 1**). The nurses and physicians now completed a second e-learning program focused on the guideline. Everyone received a laminated pocket-card summarizing the integrated measures based on the PAD-guidelines (Appendix: **Supplemental Digital Content 3a and b**).

Throughout the implementation phase, we regularly did bed-side reliability spot-checks on delirium screening, distributed delirium screening adherence feedback posters, issued newsletters on study progression and practical experiences, assessed the perceived level of implementation of bundle elements and the deployment of implementation elements as another feedback tool to the local implementation teams. Furthermore, experiences with the implementation program were shared in repeated focus group sessions.

Outcomes

The primary outcome was changes in adherence to guideline recommendations from before to after implementation. Secondary outcomes were: presence of brain dysfunction defined as days with delirium or coma, duration of mechanical ventilation, ICU length-of-stay (LOS), ICU and hospital mortality.

Data collection

Study data were prospectively collected by research nurses at each site, using a data handling protocol (Appendix: **Supplemental Digital Content 4**). Guideline adherence

Table 1: Description of Implementation Strategies Used, According to Effective Practice and Organization of Care classification

Implementation Strategy	Intervention	Phase II	Phase III
Audit and feedback	Repeated evaluation of implementation process strategies used and level of perceived adherence to guideline recommendations	+[e]	+
Monitoring the performance of the delivery of healthcare	Posters with delirium screening adherence and delirium incidence	+	+
Educational materials	Reader development and dissemination; Interactive website e-learning (with instructional videos, e.g. on the use of screening instruments CAM-ICU[a] / ICDSC[b])	+	+
Educational meetings	Education of expert teams at each hospital / ICU[c] Education sessions	+	+
Educational outreach visits, or academic detailing	Interactive workshop sessions: Education about the severity and impact of delirium on patient outcomes on short and long term. The importance of why screening for delirium is important and what may work as preventive measures	+	+
Clinical Practice Guidelines	Construction of general delirium guideline protocol by several "consensus group"-meetings with representatives from each ICU (physicians, nurses). During the sessions, various local protocols (if any) from each ICU would be made visible when discussing the interpretation and translation of the guideline into a workable and widely endorsed protocol among participating centers.	-[**]	+
Inter-professional education	Spot-checks for screening were first done by expert-team members, but later by all nurses, checking and discussing each other's delirium assessments	+	-
Local consensus processes	Yes, see previous point under "Clinical Practice Guidelines"	-	+
Local opinion leaders	Medical and nursing stakeholders were recruited and involved in the study and its execution. They had the task to appeal to people, encouraging colleagues to work according to the guidelines (e.g. during daily rounds / visits) We appointed participating intensivists and nurses as local opinion-leaders.	+	+
Patient-mediated interventions	Family involvement was encouraged: • delirium information poster and info booklet placed in family room • Instructions by nurses to family members on participation in daily care and communication in case of delirium	-	+
Reminders	Operationalization of existing PDMS[e] for integration of delirium guideline protocol. Reminders for screening was preferentially incorporated. One of the hospitals did not have a digital PDMS system which hampered the implementation process.	+	+
Tailored interventions	Yes: based on pre-implementation assessment of barriers and facilitators	+	+

[a]CAM-ICU: Confusion Assessment Method for Intensive Care Unit; [b]ICDSC: Intensive Care Delirium Screening Checklist; [c]ICU: Intensive Care Unit; [d]PDMS: Patient Data Management System. [e]plus (+) and minus (-) -signs indicate whether individual implementation strategies were used during: the phase II or phase III (see: Figure 1).

was measured using seven performance indicators (Appendix: **Supplemental Digital Content 5**). During phase I, the presence of delirium was defined as: treatment with any anti-psychotic drug or documentation of a delirium diagnosis in the medical or nursing chart. During phases II and III, delirium was diagnosed with the CAM-ICU or ICDSC [20,21]. Coma was defined as a sedation level compatible with a Richmond Agitation-Sedation Scale (RASS) score [22] of -4 or -5 or a Ramsay Sedation Scale score [23] less than 5 or a Critically Ill Assessment (CIA) score [24] less than 7. A "delirium day" was defined as at least one recorded delirium diagnosis in a 24-hour period. A coma-day was defined as documented presence of coma with absence of documented delirium during a 24-hour period.

Statistical Analysis

Demographics are presented as numbers and percentages; medians and interquartile ranges; or means and standard deviations where appropriate. Differences in guideline adherence between the three phases, as expressed by crude numbers and percentages, were assessed with a χ^2 test. To examine between-group differences we used Kruskal-Wallis test for non-parametric analyses. Differences in clinical outcomes between the three phases were assessed with adjusted regression models. Poisson regression was used for count data (e.g. number of delirium assessments per day), logistic regression for binary outcomes, and linear regression for continuous outcomes. Guideline adherence and presence of brain dysfunction were analyzed on day level, with random effect models with a random intercept for patient. Duration of mechanical ventilation, ICU length-of-stay (LOS), ICU and hospital mortality were analyzed on patient level with fixed effect models. The adjusted models used severity of illness score (APACHE II), hospital, age and admission diagnosis (elective or acute surgery, versus medical diagnosis) as covariables. Differences between the periods were expressed as adjusted rate ratios (aRR), odds ratios (aOR) or betas. Missing baseline data were imputed using single imputation with the AregImpute function in R. Two-sided *P* values <0.05 were considered statistically significant. All analyses were performed with computer software programs R (extension packages: foreign, lme4, and rms) and IBM SPSS Statistics version 23.0.

RESULTS

In total 4,853 patients were admitted during the three data collection periods. As 923 patients had to be excluded (Appendix: **Supplemental Digital Content 6**), data of 3,930 patients, with a total of 18,288 patient-days, were analyzed. Demographics are presented in **Table 2**. The e-learning programs in phases II and III were completed by 90% (73/81) of physicians and 91% (374/409) of nurses.

Table 2: Patient Demographics and Baseline Clinical Characteristics

Characteristic	*Data-collection period*[a]		
	Phase I: Baseline	***Phase II: Screening Implementation***	***Phase III: Guideline Implementation***
No. of patients, n	1337	1399	1194
No. of ICU[†] days, n	6527	6086	5675
Gender, n (%)			
Male	775 (58)	789 (56)	710 (60)
Female	562 (42)	610 (44)	484 (40)
Age (years), median (IQR[†])	66 (54; 75)	66 (53; 75)	65 (5; 74)
Admission status, n (%)			
Elective surgery	401 (30)	432 (31)	339 (28)
Emergency surgery	188 (14)	200 (14)	167 (14)
Medical	748 (56)	767 (55)	688 (58)
APACHE-II[b], median (IQR)	16 (11, 22)	15 (10, 21)	16 (11, 21)
Mechanically Ventilated patients, n (%)	560 (42)	541 (39)	593 (50)
Hospital, n (%)			
1	145 (11)	155 (11)	195 (16)
2	247 (19)	248 (18)	242 (20)
3	231 (17)	251 (18)	249 (18)
4	158 (12)	166 (12)	76 (6)
5	251 (19)	271 (19)	216 (18)
6	305 (23)	308 (22)	216 (18)

IQR = Interquartile Range, ICU = Intensive Care Unit.

[a] See Figure 1 for further explanation.

[b] Acute Physiology and Chronic Health Evaluation II range is 0-71.

Primary Outcomes - Guideline Adherence

Figure 2 and Appendix: **Supplemental Digital Content 7** show the crude performance indicator metrics presented as percentages. Delirium screening increased from 35% to 93% (P<0.001) to 96% (P<0.001). Continuous intravenous benzodiazepine sedation decreased from 36% to 31% (P<0.001) to 17% (P<0.001). Administration of daily intermittent benzodiazepines boluses had not consistently increased over the three phases. The amounts given (mean of 0.22-0.48 mg/day of diazepam equivalent; see legend of Supplemental Digital Content 7) seemed negligible compared with usual daily dosages of continuous intravenous benzodiazepines. While the daily use of midazolam, fentanyl and morphine had decreased, that of propofol, dexmedetomidine and remifentanil had increased (Appendix: **Supplemental Digital Content 8)**. Application of physical therapy (PT), early mobilization of patients, sedation assessments, and light sedation improved significantly. The medians of all available daily maximum RASS scores in mechanically

ventilated patients were significantly different between the study phases ($P<0.001$), indicating less deep sedation after the implementation (Appendix: **Supplemental Digital Content 9**).

Appendix: Supplemental Digital Content 10 shows the adjusted effect changes of the performance indicators. Implementation of delirium screening resulted in a significant improvement in adherence to delirium screening, sedation assessments, light sedation, less use of continuous intravenous benzodiazepine-sedation, and performing PT compared to the baseline period. These ORs indicate, for example, that for a random patient on a random admission day, the odds of getting sedated with continuous intravenous benzodiazepines was 0.5 (or 2 times smaller) after implementation of delirium screening. These improvements in adherences relative to the baseline period were maintained after implementation of the guideline. Early mobilization (as opposed to PT) only improved after guideline implementation but not after screening implementation. Guideline implementation resulted in additional improvements compared with the screening implementation phase for: delirium screening, use of benzodiazepines, performing PT, and performing early mobilization when feasible.

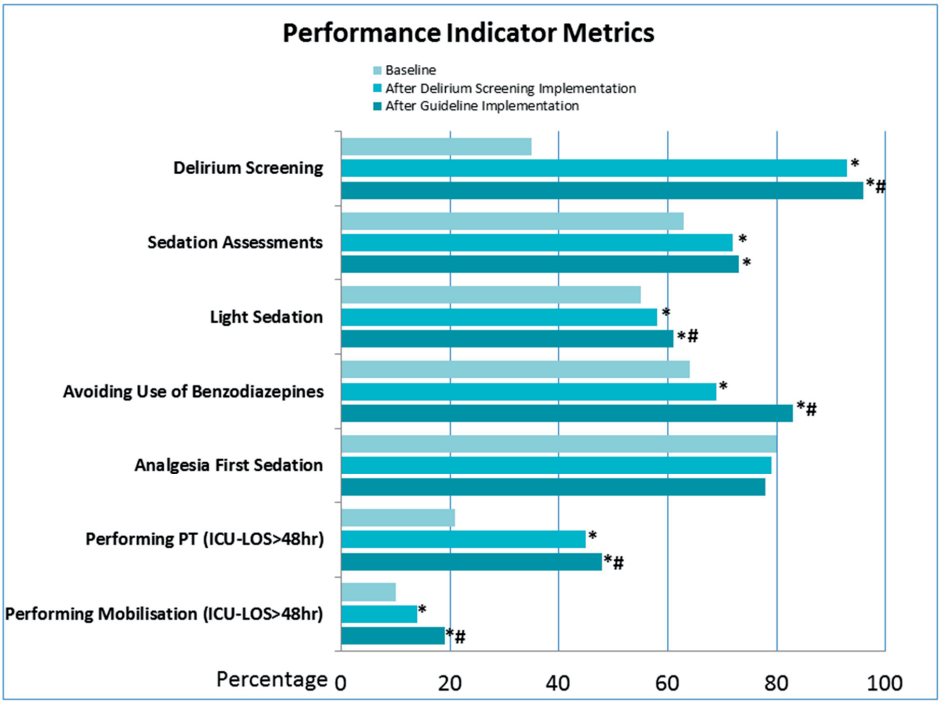

Figure 2: Adherence to Guideline Recommendations
This figure graph shows adherence percentage per performance indicator for the three data collection periods. See Supplemental Digital Content 7 for crude numbers. * Indicates a significant change relative to the baseline period. # Indicates a significant change after guideline implementation relative to the screening implementation period. For adjusted analyses: see Supplemental Digital Content 10.

Secondary outcomes - Clinical Outcomes

Table 3 shows crude and adjusted clinical outcomes changes per study phase. The duration of delirium decreased over three periods from 5.6 days to 2.9 days (Beta: **-2.6** days; 95% CI, -3.5 to -1.6 days; *P*<0.001); and to 3.3 days after guideline implementation (Beta: **-2.2** days; 95% CI, -3.2 to -1.3 days; *P*<0.001). Implementation of delirium screening resulted in 6% more patients detected with delirium in the third study period compared with the baseline period (OR **1.4;** 95% CI 1.2-1.7; *P*<0.001). Appendix: **Supplemental Digital Content 11** shows the cumulative proportions of delirium- and coma(-free) days as changes in percentages for the three study periods. In the adjusted analysis (Appendix: **Supplemental Digital Content 12**) only the coma-days were significantly reduced in phases II and III relative to phase I (from 14% to 12%; OR **0.6**; 95% CI, 0.4-0.8; *P*<0.001, and from 14% to 9%; OR **0.5**; 95%CI, 0.4-0.6; *P*<0.001). There were no significant changes for the other study outcomes.

DISCUSSION

In this study, the implementation of delirium monitoring and other elements of delirium care recommended in the 2013 PAD-guideline recommendations, was associated with modest, though significant, improvements in six of the seven studied care processes, corresponding with fewer delirium or coma days. On the assumption that the participating ICUs already applied light sedation practices in general, we decided *not* to focus strongly on safety screens for Spontaneous Awakening and Breathing Trials (SATs and SBTs), which may have precluded improvements of the secondary outcomes, such as length of ventilation, ICU stay or mortality.

We found that delirium screening resulted in slightly higher delirium detection rates, probably on account of the phenomenon that the use of a validated delirium screening tool increases the detection rate, especially of hypoactive delirium [25]. This may also explain that the cumulative number of delirium- and coma free days in the entire population did *not* decrease significantly in spite of decreased mean duration of delirium and days with coma per patient. Several previous studies on delirium screening implementation [26-29] and PAD-guidelines [7,30-32] also have reported improvement in delirium screening adherence. Further, a recent systematic review reported that adherence to delirium screening was assessed in in 15 of 21 implementation studies, thirteen of which found improved adherence, with rates ranging from 14% to 92% [6].

In a previous trial (SLEAP trial), SATs/SBTs did not have additional benefit for length of stay or mortality in settings with relatively light sedation practices [33]. The sedation levels we found (RASS -1 [IQR -3 - 0) more closely resembled those of patients in the SLEAP trial (RASS between -2 and -1) than those of patients in the ABC-trial (RASS between -4 and

Table 3: Secondary (clinical) outcomes

Outcomes	*Crude analysis*						**Adjusted[a] Effect Values**
	Phase I: Baseline		***Phase II: Screening Implementation***		***Phase III: Guideline Implementation***		***adjusted OR/RR/Beta[a](95%CI; P-value)*** ***a)Phase I vs. Phase II*** ***b) Phase I vs. Phase III*** ***c) Phase II vs. Phase III***
	Patients (n)		*Patients (n)*		*Patients (n)*		
Delirium duration (days), mean (SD)	274	5.6 (8.6)	300	2.9 (3.3)	319	3.3 (4.5)	a) -2.6 (-3.5 - -1.6; *P*<0.001) b) -2.2 (-3.2 - -1.3; *P*<0.001) c) 0.3 (-0.6 - 1.2; *P*=0.46)
Patients with delirium during ICU admission, n (%)	1337	274 (21%)	1399	300 (21%)	1194	319 (27%)	a) 1.2 (0.9 - 1.4; *P* =0.16) b) 1.4 (1.2 - 1.7; *P* <0.001) c) 1.2 (1.0 - 1.5; *P=0.*25)
Duration of mechanical ventilation (days), mean (SD)	560	4.6 (8.2)	541	4.9 (6.4)	593	4.7 (6.5)	a) 0.5 (-0.3 - 1.3; *P=0.*23) b) 0.4 (-0.4 - 1.2; *P*=0.36) c) -0.1 (-0.9 - 0.7; *P*=0.75)
ICU LOS (days), mean (SD)	1337	4.9 (6.9)	1399	4.3 (6.0)	1194	4.8 (5.9)	a) -0.3 (-0.8 - 0.1; *P*=0.19) b) -0.1 (-0.6 - 0.3; *P*=0.56) c) 0.2 (-0.3 - 0.6; *P*=0.49)
ICU Mortality, n (%)	1337	135 (10.1)	1399	140 (10.0)	1194	126 (10.6)	a) 1.3 (1.0 - 1.7; *P*=0.08) b) 1.3 (0.9 - 1.7; *P*=0.13) c) 1.0 (0.7 - 1.3; *P*=0.88)
Hospital Mortality, n (%)	1337	216 (16.2)	1399	226 (16.2)	1194	194 (16.2)	a) 1.3 (1.0 - 1.6; *P*=0.057) b) 1.1 (0.9 - 1.5; *P*=0.31) c) 0.9 (0.7 - 1.1; *P*=0.39)

ICU = Intensive Care Unit. LOS = Length of Stay.

[a] Differences are expressed as adjusted odds ratios (aOR) or adjusted rate ratios (aRR) with the Phase I: Baseline (for a and b) and Phase II: After screening implementation (for c) as the reference. Adjusted for: APACHE II; hospital; age; and admission type.

-1), which indeed found a positive effect on mortality [34]. On the other hand, the implementation studies by Balas et al [7,35], that bared many methodological similarities to our study, but was a single-center study, also had a mean RASS of -1 indicating light sedation rates, but still established lower length-of-mechanical ventilation, applying awakening and breathing trials. Our lack of focus on SATs and SBTs may also be illustrative for the tension between the premises of the PAD-guidelines (with moderate emphasis on SATs/SBTs), the ABCDE(F) concept (with strong emphasis) and more recent insights such as provided by the SLEAP study and as substantiated in the eCASH concept that has even questioned the value of daily sedation stops as opposed to goal-directed sedation [36]. Moreover, our results on patient outcomes are in line with a recent meta-analysis reporting that interventions that reduced delirium duration did not necessarily translate into reduced short-term mortality [37].

Implications of our findings

From an implementation perspective, we learned several lessons on evidence-to-practice translation. First, our implicit assumption that other improvements such as SATs and SBTs would follow next to our efforts to implement delirium-oriented measures, not specifically aimed at safety screens, has been falsified. Second, ICU teams less experienced with use of the guideline bundles or relying solely on "local champions" rather than interprofessional implementation teams should not try to implement all PAD/ABCDE bundle elements simultaneously within a limited time frame. Of note, our study deployed one or two local champions (intensivist or research nurse), but limited funding precluded appointment of full interprofessional teams (IPTs), existing of all relevant stakeholders, such as residents, respiratory therapists, physical therapists and other dedicated health care workers. Deploying such IPTs has been shown in other implementation studies to be essential for multi-bundle implementation within a limited timeframe [7,38,39]. A graded or phased implementation seems much more feasible in such relatively resource-limited settings and we learned that integration of bundle elements should not be confused with their simultaneous adoption. Third, not only the caregivers, but also the dedicated 'role models' have a learning curve for providing education and the feedback, so patience is of the essence. Fourth, successful implementation of bundle elements requires taking into account the baseline situation and contextual issues, such as existing barriers and facilitators, because many have been identified and not all are pertinent to all settings [40].

The strengths of our study include the prospective design, use of tailored multifaceted implementation strategies, the largest cohort to date outside of the United States, and the representative mix of ICU types supporting the translatability of our findings. Further, we deployed a pragmatic approach: implementation as part of daily clinical practice instead of deployment in a controlled research setting, which is also in contrast

to most published studies. Several limitations need to be addressed. First, the Hawthorne effect was not avoided, seeing that delirium screening implementation alone resulted in improved adherence to several guideline recommendations. Second, duration of delirium might be a doubtful outcome parameter due to the difference between a clinical diagnosis as assessed by chart review at baseline compared with the second and third phases (based on validated screening instruments). Long-term outcomes, such as cognition or post-traumatic stress disorder may be more relevant outcomes. Lastly, certain changes over time may have been overestimated in the presence of secular trends [41].

In conclusion, this largest pre-post implementation study outside of the US of delirium-oriented measures based on the 2013 PAD-guidelines showed that implementation had improved health professionals' adherence to delirium guidelines, which was linked to reduced brain dysfunction. Our data add to existing implementation literature due to the non-US setting, strongly enhancing translatability of findings. Furthermore, implementation lessons learned that are unique for our study pertain to: 1) the feasibility of staggered versus simultaneous implementation of bundle-elements, that seem strongly dependent on local resources (e.g. local champions, versus interprofessional implementation teams or level of previous experience with the guidelines), and: 2) the fact that our 'error of omission' of daily safety screens for SATs and SBTs may have precluded concurrently improved clinical outcomes, adding strong empirical support from a 'real-life setting' for effectiveness of individual ABCDE-bundle elements.

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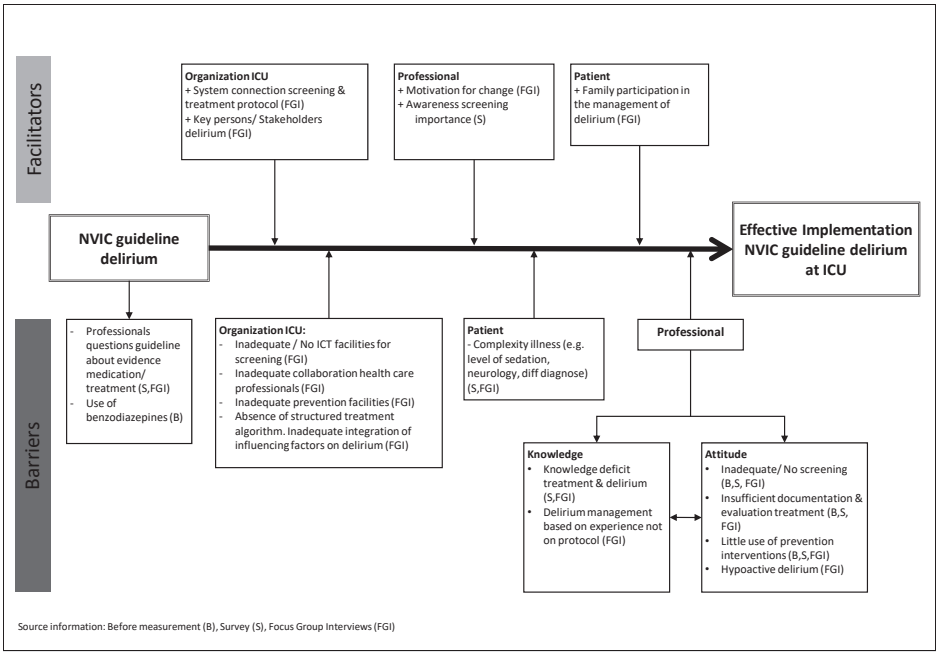
APPENDIX:



Supplemental Digital Content 1: Results Baseline analysis (compliance with guideline, facilitators and barriers)

Data about barriers and facilitators for implementation of guideline are presented below in the schematic way and more information about barriers found have previously been published by Trogrlic at al in 2016. (Reference: Trogrlic Z, Ista E, Ponssen HH, Schoonderbeek JF, Schreiner F, Verbrugge SJ, Dijkstra A, Bakker J, van der Jagt M. Attitudes, knowledge and practices concerning delirium: a survey among intensive care unit professionals. Nurs Crit Care 2016; 22: 133-140.)

Supplemental Digital Content 2: Theoretical substantiation of strategies

Theorie	Focus	Implementatie strategie
Social learning theory[1]	- Insert key figures / role models - Education	Education: - Modeling - Promoting self-efficacy - Identification
Social influence theory[2]**;** **Theorie of Leadership**	- Attitude change - Deployment of key figures / role models - Achieve consensus	- Use role models - Performance measurement / insight - Feedback - Consensus meetings
Theorie of Leadership[3]	- Leadership, coaching	- Encourage, motivate / support staff

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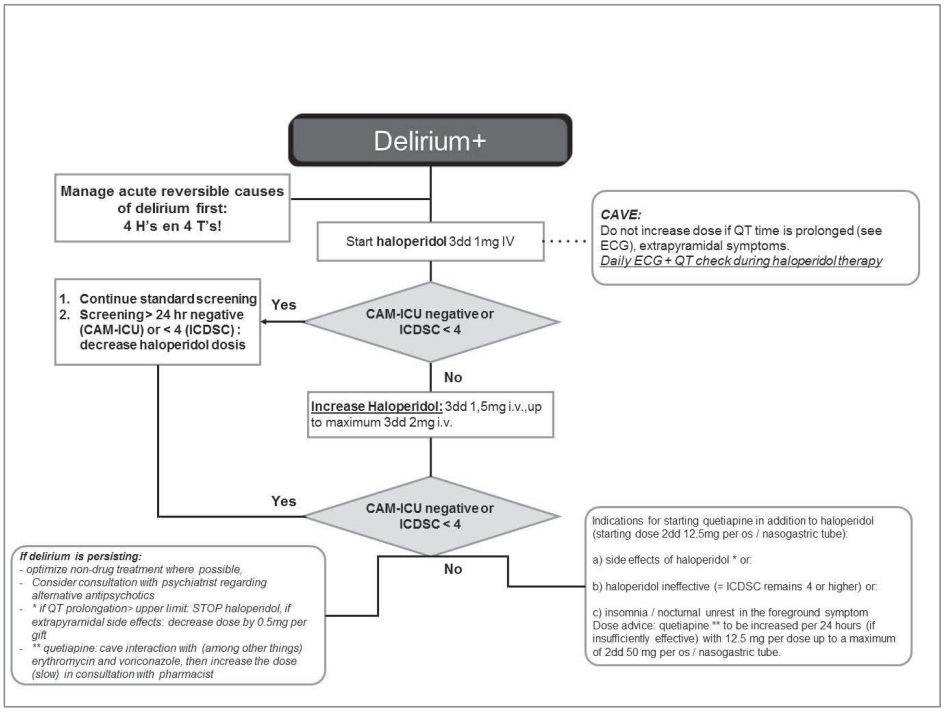
Supplemental Digital Content 3a: Daily Pain-Agitation-Delirium Care Goals Instructions



Supplemental Digital Content 3b: Flowchart antipsychotics

Supplemental Digital Content 4: Case Record Form (CRF) items for the iDECePTIvE study*
**Original CRF and data handling protocol are in Dutch and available upon request.*

Demographic

Age, Gender

Admission

Date of admission / date of discharge (Discharge to: Nursing Department, Medium care department, high care department, another ICU, another hospital, Elsewhere, Passed away)

On Admission (yes, no, not known): 1. Patient has aphasia, 2. Patient has mental disability, 3. Patient has language barrier (Dutch), 4. Patient has vision impairment (need glasses), 5. Patient has hearing impairment (hearing aid required)

Apache II, Admission status (medical, emergency surgery, elective surgery)

First 24 hours: Serum urea (highest) value, Metabolic acidosis? Is there infection? Total dose of Morphine (the first 24h)

Died during hospital admission

Daily variables during entire ICU stay

Use of haloperidol (mg), seroquel (quetiapine) (mg), olanzapine (zyprexa) (mg), another antipsychotic (mg), bolus benzodiazepines (mg)

Sedatives use per perfusion pump (for ≥2 hours / day) (yes or no): midazolam, lorazepam, propofol, clonidine, dexmedetomidine, other (specify)

Opiates use per perfusion pump (for ≥2 hours / day) (yes or no): morphine, fentanyl, remifentanil, other (specify)

Screening scales measures for: delirium (CAM-ICU or ICDSC), sedation (RASS, RAMSAY, CIA), pain (VAS, BPS, CPOT)

Renal dysfunction:

- CVVH has been applied to the patient today (yes / no)
- Creatinine (highest) (micromol/l)
- Diuresis (ml / day)

Mechanical ventilation (yes / no)

Delirium prevention (yes / no / not known / not applicable):

- Patient has had physiotherapy today
- Patient was mobilized
- Use of glasses
- Use of hearing aid
- Patient slept well last night (> 4h)
- Has the patient used earplugs?
- Patient was awakened by the staff
- Is a sleeping drug prescribed? If yes: which one? melatonin, benzodiazepines, other (specify)
- Patient was restricted due to delirium?

Patient is on the: open room or single box / room

When patient was delirious, did any adverse events occur (yes / no). If yes: what was the impact (no/ moderate/ serious):

- Patient has fallen out of bed / chair today
- Patient has removed his ET tube
- Patient has removed his nasogastric / duodenum tube
- Patient has removed his peripheral line
- Patient has removed his central line
- Patient has removed his arterial line
- Patient has removed his urinary catheter
- Patient has been removed .....drain
- Patient is aggressive

Data accuracy was ensured by the research coordinator (ZT) by checking a minimal of three CRFs of every ICU for each data collection period.

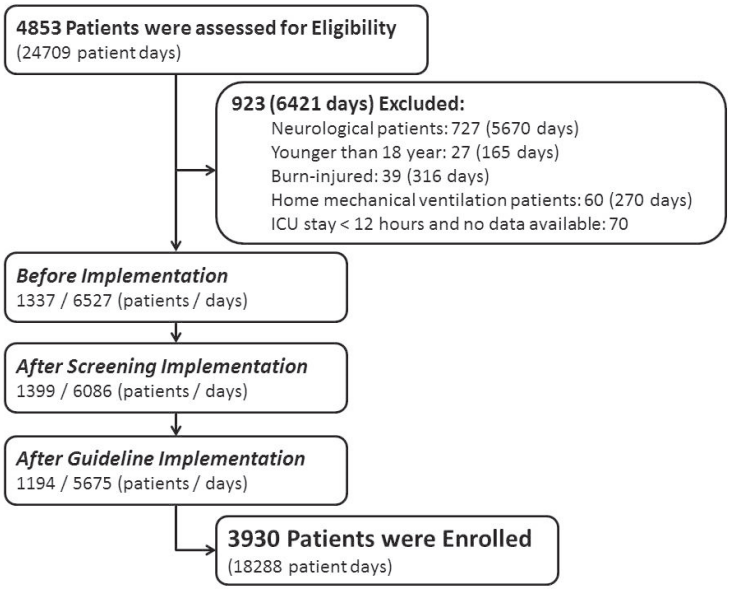
Supplemental Digital Content 5: Performance indicators assessing adherence to delirium guidelines recommendations (pertaining to delirium and based on the Pain, Agitation and Delirium guidelines)

Recommendation	Performance indicator	Indicator metric[a] %
Routine monitoring of delirium with CAM-ICU or the ICDSC should be done in all adult ICU patients	*1) Assessment of delirium with CAM-ICU or ICDSC*	*1) Total No. of CAM-ICU or ICDSC assessments / Total no. of patient-days on ICU*
Use a light target level of sedation in mechanically ventilated adult ICU patients	*2) % of sedation assessments* *3)* % of lightly sedated ventilated patients	*2) Total No. of days with at least one sedation assessment recorded / Total No. of patient-days on ICU* *3)* No. of light sedation days / Total No. of ICU days in mechanically ventilated (on one or more days) patients AND having received sedation and/or opioids *Light sedation level defined as:* • *Richmond Agitation and Sedation Scale (*RASS) *> -3 or* • *Ramsay score < 5 or* • Critically Ill Assessment Scale (CIA) *> 6*
Benzodiazepines should be avoided as routine sedative because its use may be a risk factor for the development of delirium	*4) The % of patients sedated with benzodiazepines*	*4)* No. of sedation days with benzodiazepines *(continuous IV, more than 2 hrs.)*[b] / Total No. of ICU days in mechanically ventilated (on one or more ICU days) patients AND having received sedation and/or opioids
Analgesia-first sedation should be used in mechanically ventilated adult ICU patients.	*5) The % of days on which sedatives were administered without standard analgesic medication (norm: 0%)*	*5) No. of patient no-analgesia if sedated days / Total number of patient sedation days*
Performing early PT or mobilization in adult ICU patients whenever feasible to reduce the incidence and duration of delirium by patients with more than 48 ICU-LOS.	*6) % of patients (with LOS>2 days) having received PT* *7) % of patients (with LOS >2 days) having received mobilization when feasible*	*6) No. of patients days with PT / Total No. of patient ICU days; included with LOS > 2 days* *7) No. of patients days with mobilization / Total No. of patient ICU days; included with LOS > 2 days*

CAM-ICU: Confusion Assessment Method for Intensive Care Unit; ICDSC: Intensive Care Delirium Screening Checklist; ICU: Intensive Care Unit; LOS: Length of Stay; PT: Physio Therapy; ICU: Intensive Care Unit.

[a]" numerator / denominator".

[b] Daily benzodiazepines intermittent bolus dose was also recorded and for comparison between study periods converted to diazepam equivalent according to benzo equivalence table at http://benzo.org.uk.



Supplemental Digital Content 6: Enrollment of patients

Supplemental Digital Content 7: Crude data on the Primary Outcome: Adherence to the guidelines assessed with Performance Indicators

Performance indicator	*Crude Analysis*			*P-value*[a]
	Phase I: Baseline	***Phase II: After Screening Implementation***	***Phase III: After Guideline Implementation***	***a)Phase I vs. Phase II b) Phase I vs. Phase III c) Phase II vs. Phase III***
Delirium screening [b]CAM-ICU or ICDSC assessments at least once a day / Total No. of patient-days at ICU	2284 / 6527 (0.35)	5660 / 6086 (0.93)	5431 / 5657 (0.96)	a) <0.001 b) <0.001 c) <0.001
Sedation assessments (Total No. of days with at least one sedation assessment recorded / Total No. of patient-days at ICU)	4131 / 6527 (0.63)	4389 / 6086 (0.72)	4143 / 5657 (0.73)	a) <0.001 b) <0.001 c) 0.281
Light sedation (No. of light sedation days[c] / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	1271 / 2324 (0.55)	1192 / 2050 (0.58)	1402 / 2282 (0.61)	a) 0.021 b) <0.001 c) 0.027
Use of benzodiazepines (No. of benzodiazepines[d] sedation days / Total no. of ICU days in once ventilated AND received sedation and or opioids)	835 / 2324 (0.36)	633 / 2050 (0.31)	384 / 2282 (0.17)	a) <0.001 b) <0.001 c) <0.001
Analgesia first sedation (No. of patient no-analgesia if sedated days / Total number of patient sedation days)	417 / 1935 (0.22)	356 / 1709 (0.21)	356 / 1805 (0.2)	a) 0.59 b) 0.17 c) 0.41
Performing PT (ICU-LOS >2days) (No. of patient-days with PT / Total No. of patient ICU days included with LOS > 2 days)	1013 / 4741 (0.21)	1837 / 4085 (0.45)	1928 / 4043 (0.48)	a) <0.001 b) <0.001 c) 0.014
Performing mobilisation when feasible (ICU-LOS >2days) (No. of patient-days with mobilization / Total No. of patient ICU days included with LOS > 2 days)	477 / 4741 (0.1)	583 / 4085 (0.14)	748 / 4043 (0.19)	a) <0.001 b) <0.001 c) <0.001

[a] P-values tested with $\chi 2$ test comparing: a) Phase I and Phase II; b) Phase I and Phase III; c) Phase II and Phase III

[b] "numerator / denominator".

[c] Definition of Light sedation: Richmond Agitation and Sedation Scale (RASS) >- 3 or Critically Ill Assessment Scale (CIA) >6 or Ramsay Sedation Scale <5.

[d] Benzodiazepines = midazolam and / or lorazepam as continuous intravenous sedative. Daily benzodiazepines intermittent bolus dose of all benzodiazepines were recorded and for comparison between study periods converted to 1 mg diazepam equivalent according to benzo equivalence table at http://benzo.org.uk; For conversion of diazepam to other benzodiazepines, 1mg diazepam = 1 mg bromazepam; or = 1.33 mg midazolam; or = 5 mg lorazepam; or = 0.3 mg oxazepam; or = 0.5 mg temazepam. Bolus doses diazepam equivalents differences (P < .001) were as follow: Phase I = total 3134 mg (0.48 mg/day); Phase II = total 1330 mg (0.22 mg/day); and Phase III = total 2008 mg (0.35 mg/day).

Supplemental Digital Content 8: Medication use during study

Type of Agent	***Phase I: Baseline*** (n days = 2324)	***Phase II: After Screening Implementation*** (n days = 2050)	***Phase III: After Guideline Implementation*** (n days = 2282)
Midazolam, n[a] (%)	807 (35)	633 (31)	383 (17)
Lorazepam, n (%)	30 (1)	0 (0)	1 (<1)
Propofol, n (%)	773 (33)	895 (44)	1103 (48)
Clonidine, n (%)	309 (13)	304 (15)	467 (21)
Dexmedetomidine, n (%)	0 (0)	40 (2)	117 (5)
Morphine, n (%)	485 (21)	378 (18)	191 (8)
Fentanyl, n (%)	211 (9)	142 (7)	83 (4)
Remifentanil, n (%)	1015 (44)	1039 (51)	1461 (64)
Sufentanyl, n (%)	436 (19)	43 (2)	313 (14)

[a] Number of days with use of medication *(continuous IV, more than 2 hrs. per day)* in mechanically ventilated (on one or more ICU days) patients.

Supplemental Digital Content 9: Richmond agitation-sedation scale (RASS) overview

Phase	**Selection 1[a]**		**Selection 2[a]**	
	RASS Median [IQR]	*p*-value[b]	RASS Median [IQR]	*p*-value[b]
Baseline (I)	-1 [-3 - 0]		-2 [-4 – 0]	
Screening Implementation (II)	0 [-3 - 0]		-1 [-4 – 0]	
Guideline Implementation (III)	0 [-2 - 0]		-1 [-3 – 0]	
Total (all phases)	-1 [-3 - 0]	*p*<0.001	-1 [-4 - 0]	*p*<0.001

[a]Selection 1: Median of all daily maximum RASS scores on all ICU treatment-days in patients with at least one day of mechanical ventilation during ICU stay (n= 12151; RASS missing or another sedation scale used = 3918 days); Selection 2: Median of all daily maximum RASS scores on all ICU treatment-days in patients with at least one day of mechanical ventilation during ICU stay AND having received sedation and/or opioids (n= 6656 days; RASS missing or another sedation scale used = 1833 days).
[b]Kruskal-Wallis test (non-parametric ANOVA).

Supplemental Digital Content 10: Primary Outcome (Adjusted): Adherence to the guidelines assessed with Performance Indicators

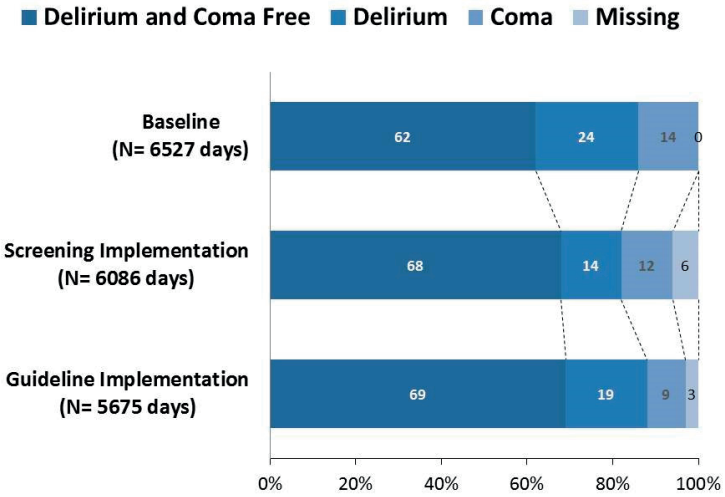
Performance Indicator	Adjusted[a] Effect Values adjusted OR/RR[a] (95%CI; *P*-value) **a)**[a]Screening Implementation vs Baseline **b)** Guideline Implementation vs Baseline **c)** Guideline Implementation vs Screening Implementation	Change		
		a)[a]	**b)**	**c)**
Delirium screening [b](Total No. of CAM-ICU or ICDSC assessments / Total No. of patient-days at ICU)	**a) 5.3** (4.9 - 5.7; *P*<0.001) **b) 5.8** (5.4 - 6.2; *P*<0.001) **c) 1.1** (1.0 - 1.2; *P*<0.001)	+[a]	+	+
Sedation assessments (Total No. of days with at least one sedation assessment recorded / Total No. of patient-days at ICU)	**a) 10.3** (7.3 - 14.4; *P*<0.001) **b) 5.7** (4.1 - 7.9; *P*<0.001) **c) 0.7** (0.5 - 1.0; *P*=0.069)	+	+	-[a]
Light sedation (No. of light sedation days[c] / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	**a) 1.3** (1.0 - 1.8; *P*=0.046) **b) 1.4** (1.1 - 1.9; *P*=0.012) **c) 1.1** (0.8 - 1.4; *P*=0.55)	+	+	-
Use of benzodiazepines (No. of benzodiazepines[d] sedation days / Total no. of ICU days in mechanically ventilated patients during at least one ICU-day AND having received sedation and/ or opioids)	**a) 0.5** (0.3 - 0.8; *P*=0.008) **b) 0.1** (0.1 - 0.2; *P*<0.001) **c) 0.2** (0.1 - 0.4; *P*<0.001)	+	+	+
Analgesia first sedation (No. of patient without-analgesia-while-sedated days / Total number of patient sedation days)	**a) 1.4** (0.9 - 2.3; *P*=0.18) **b) 1.2** (0.7 - 1.9; *P*=0.57) **c) 1.2** (0.7 - 2.0; *P*=0.53)	-	-	-
Performing PT (ICU-LOS >2days) (No. of patient-days with PT / Total No. of patient ICU days; included with LOS > 2 days)	**a) 3.9** (2.9 - 5.1; *P*<0.001) **b) 6.6** (5.0 - 8.8; *P*<0.001) **c) 1.7** (1.3 - 2.2; *P*<0.001)	+	+	+
Performing mobilisation when feasible (ICU-LOS >2days) (No. of patient-days with mobilization / Total No. of patient ICU days included with LOS > 2 days)	**a) 1.2** (0.9 - 1.6; *P*=0.31) **b) 2.1** (1.5 - 2.9; *P*<0.001) **c) 1.8** (1.4 - 2.5; *P*<0.001)	-	+	+

[a] Differences are expressed as adjusted odds ratios (aOR) or adjusted rate ratios (aRR) with either the "Baseline" phase (for a and b) or "Screening implementation" phase (for c) as the reference. Adjusted analyses included the following covariables: APACHE II; hospital; age; and admission type; plus (+) -sign indicates a significant change between a phase versus the reference; minus (-) -sign indicates no significant change between a phase versus the reference.

[b]" numerator / denominator".

[c] Definition of Light sedation: Richmond Agitation and Sedation Scale (RASS) >- 3 or Critically Ill Assessment Scale (CIA) >6 or Ramsay Sedation Scale <5, see manuscript text for references.

[d] Benzodiazepines = midazolam and / or lorazepam as continuous intravenous sedative.



Supplemental Digital Content 11: Proportion of patient-days with brain dysfunction (delirium or coma) Days shown are proportions of cumulative patient-days presenting the differences on delirium outcomes (Delirium and Coma Free Days; Delirium; and Coma) during the study phases. A small proportion of patient-day data pertaining to delirium or coma was missing due to non-adherence to delirium or sedation screening during the screening and guideline implementation phases. Adjusted analyses are shown in Supplemental Table 6 (Supplemental Digital Content 9).

Supplemental Digital Content 12: Adjusted Effect values of Proportion of patient-days with brain dysfunction (delirium or coma)

	Adjusted Effect Values (OR/RR; 95% CI; *P*-value)[a]		
	Screening Implementation vs Baseline	**Guideline Implementation vs Baseline**	**Guideline Implementation vs Screening Implementation**
Delirium- and Comafree Days	1.0 (95% CI, 0.8-1.3; *P*=0.8)	1.0 (95% CI, 0.8-1.3; *P*=0.83)	1.0 (95% CI, 0.8-1.2; *P*=0.73)
Delirium	0.9 (95% CI, 0.7-1.2; *P*=0.44)	1.2 (95% CI, 0.9-1.6; *P*= 0.28)	1.3 (95% CI, 0.9-1.7; *P*= 0.12)
Coma	**0.6** (95% CI, 0.4-0.8; *P*<0.001)	**0.5** (95% CI, 0.4-0.6; *P*<0.001)	0.8 (95% CI, 0.6-1.1; *P*=0.24)

[a] To examine the effect of the implementation on delirium outcomes (Delirium- and Coma-free Days; Delirium; and Coma), a logistic regression on day level, with random effect models, was used accounting for the repeated measures in the same patient with a random intercept for patient. A small proportion of patient-days with missing data on delirium or coma scales (due to non-adherence to delirium or sedation screening) were excluded from analysis.

Chapter 6

Prospective Multicenter Multifaceted Before-After Implementation Study of ICU Delirium Guidelines: a Process Evaluation

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Submitted for publication

ABSTRACT

Background

Implementation of delirium guidelines at ICUs is suboptimal, although their adoption may improve patient outcomes and is endorsed by international guidelines. Within a prospective implementation study, we aimed to explore: the exposure of health care workers to the implementation program; effects on guideline adherence at ICU-level; impact on knowledge and barriers, and experiences with the implementation program.

Methods

This was a mixed method process evaluation of a prospective multicenter implementation study, including data for 4,449 adult ICU patients (21,015 patient days). A tailored implementation program was executed in six ICUs. Adherence to delirium guideline recommendations at ICU-level was determined before, and after implementation of delirium screening, after subsequent implementation of delirium guidelines, and finally, six months after implementation (to assess sustainability). Knowledge of professionals and perceived barriers were measured during phase 1 and 3. Finally, interviews were done at all sites to explore experiences with the implementation.

Results

Five of six ICUs were exposed to all implementation strategies as planned. More than 85% followed the required e-learnings; 92% of the nurses attended the clinical classroom lessons; 5 ICUs used all available implementation strategies and perceived to have implemented all guideline recommendations (> 90%). Adherence to predefined performance indicators at ICU level was only above the preset target (>85%) for delirium screening. For all other performance indicators, the inter-ICU variability was between 34 and 72% indicating variable adoption of guideline recommendations among the ICUs. The implementation of delirium guidelines was feasible and proved successful in resolving the majority of barriers found before the implementation, mainly by improving knowledge about delirium (from 61 to 65%). The improvement was generally well sustained six months after full guideline implementation. Local implementation teams experienced the implementation program as very successful in changing ICU professionals' recognition of delirium as an indicator of "brain failure".

Conclusions

Multifaceted implementation interventions can improve and sustain adherence to delirium guidelines. implementation programs are feasible using local champions and can largely be performed as planned. However, variability in delirium guideline adherence at individual ICUs remains a challenge, indicating the need for more tailoring at center-level.

BACKGROUND

Delirium is strongly associated with Intensive Care Unit (ICU) length of stay, mortality and long term cognitive and functional impairments [1-4]. Previous studies have indicated that delirium can be reduced by using less sedation and avoiding use of benzodiazepines, early weaning from mechanical ventilation, and early physical therapy and mobilization [3,5,6]. Those evidence-based interventions are summarized in the 2013 Pain, Agitation and Delirium (PAD) guidelines [7] and more recently in the updated PADIS (Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption) guidelines of the Society of Critical Care Medicine [8]. Implementation of PAD guidelines in the ICU setting was mostly done in previous studies with high levels of resources, and with dedicated research personnel using the "Awakening and Breathing Coordination, Choice of drugs, Delirium monitoring and management, Early mobility, and Family engagement" (ABCDEF) bundle [9-13].

Recently, we published the results of a multicenter implementation study aimed to implement delirium-oriented recommendations derived from the Dutch ICU Delirium Guidelines [14] and the 2013 PAD guidelines [15]. In this study named the 'ICU DElirium in Clinical PracTice Implementation Evaluation' (iDECePTIvE) study, a multifaceted implementation program based on pre-implementation assessment of barriers was developed and evaluated [16-18]. The overall results showed an improved adherence to delirium guidelines and recommendations. Further, the improved adherence resulted in decreased levels of brain dysfunction, meaning reduced delirium duration and a lower number of coma days [18]. However, variable guideline adoption among different sites is a well-known phenomenon [19], which may also provide insights on factors that enhance effective implementation and guideline adoption versus factors that do not. Therefore, this process evaluation study aimed to further zoom in into the implementation interventions to get insight into the determinants and indicators of success or failure of the implementation program and to provide more detailed background information on the entire implementation process.

We explore the following four issues: 1) actual exposure to the implementation program at the individual ICU level; 2) effects of the implementation program on guideline adherence at the individual ICU level and its sustainability after six-months; 3) impact of the implementation program on implementation barriers and knowledge among ICU professionals over time; and finally, 4) the experiences of the site-specific implementation teams with the implementation program.

METHODS

Design, Setting and Participants

This was a mixed method process evaluation of a multicenter prospective pre-post implementation study (iDECePTIvE). This report adhered to the Standards for Reporting Implementation Studies (StaRI) Statement [20]. The Implementation Model of Change of Grol and Wensing was used to structure the guideline implementation [21]. The details of the study design and methods have been reported previously [16,18]. Briefly, data for performance indicators (PIs) on adherence to guideline recommendations from the PAD guidelines related to delirium were collected in four phases, defined as follows: first phase (T1, baseline period); before implementation, usual care was evaluated, second phase (T2); after implementation of delirium screening tools, third phase (T3): after implementation of delirium treatment and prevention guidelines, and fourth phase (T4); six months after completion of the implementation in the third phase, to assess the sustainability of the implementation. Whereas the findings of the iDECePTIvE study were based on the comprehensive data of all ICUs combined [18], this process evaluation is a sub-analysis of data and expands on the findings at the individual site (ICU) level and the addition of results on short term-sustainability of guideline adoption. Several methods were used. Qualitative components involved semi-structured interviews with professionals. Quantitative components were surveys and data on seven performance indicators (PIs) to measure guideline adherence. Definitions of these performance indicators were previously defined [18].

The major implementation strategies of the implementation program were education, audit and feedback, and reminders, as previously described [18]. In brief, education was provided in the form of web-based e-learning. Education was provided first in phase II during implementation of screening for delirium and thereafter in phase III, where it focused on the contents of delirium prevention and management guidelines. In addition to e-learning, classroom educational sessions for nurses were held, aimed to discuss the questions raised about delirium screening and protocols, and to provide more information about the implementation and practical application of the protocols. The physicians were not required to be present at the clinical classroom lessons. During study phase II educational spot-checks of delirium screening (target was four spot check moments per nurses versus local experts) were performed. Audit and feedback were applied in two ways during phase II and III: 1) using posters with delirium screening adherence and prevalence of delirium of the individual ICU (phase II), which were presented to the ICU staff of the separate ICU every quarter [16]; and 2) using a so-called Implementation Readiness Test (IRT, phase three; explained in next paragraph). During phase II, posters on delirium screening were presented to the ICU staff of the separate ICUs every quarter. These posters presented the actual adherence rates of the individual

ICU and the mean of all centers to delirium screening for comparison and visualized the predefined adherence level-aim of 85% [16]. To further facilitate the use of the guidelines in daily practice and to sustain the implementation, an ICU Delirium App was developed as an implementation facilitator (link: http://icudelierapp.nl). The App was focused on the health care professional who received advice on additional management regarding delirium in a certain patient using a step-wise evaluation of the current status of the patient and current management. The App was released in January 2015. Reminders were used as the standard notifications and flowcharts for delirium screening and management in the electronic patient files system. An information leaflet and a poster for family members of ICU patients were used to inform them about the identification, prevention and treatment of delirium in an attempt to further enhance and stimulate structural attention for delirium by next-of-kin and stimulate discussions with care providers.

Data collection

1. Actual exposure to implementation program

To be able to follow the implementation progress at different sites and to provide the sites with implementation feedback, we drafted an implementation process check tool, which we named the "Implementation Readiness Test" (IRT)**.** The IRT was applied three times in eight months during the audit visits in Phase III to evaluate the current status and progress of implementation as perceived by the local implementation team. The IRT consisted of two parts: 1) assessment of application of the number of implementation strategies by the local study team; and 2) the local study team's perception of the extent to which the guideline recommendations were actually implemented into clinical practice. This enabled us to generate feedback for the local implementation teams. Based on the IRT, an action plan at site level including the priorities for each site, was made. Follow-up IRTs were done twice approximately every three months. The study team also used IRTs to monitor the progress of implementation at all sites, by giving each item one point for each site if a particular item was implemented. As such these scores were used to monitor and semi-quantitatively assess implementation progress. Of note, the IRT is not a validated tool and meant to monitor and stimulate the implementation progress in a pragmatic and face-valid manner.

2. Effect of the implementation program on guideline adherence at ICU level

All consecutive adult ICU patients were included. Adherence rates to the guideline recommendations at site-level were assessed with seven performance indicators (PI) [18]. In addition to the previous paper [18], we now added the data on the sustainability of the adherence changes 6 months after implementation phase III.

3. Impact of implementation program on knowledge and implementation barriers
Beliefs, attitudes, practices, knowledge, guideline implementation barriers and facilitators for nurses and physicians of the ICUs were assessed twice, both before T1, and after the guideline implementation (T3). Details of the questionnaire were previously published [17].

4. Experiences with the implementation program
In order to explore the experiences of local implementation teams, we organized interviews at each site after completion of phase III. The interviews were semi-structured with predefined questions about the experiences with the implementation program and its components **(Additional file 1)**. We also asked the members of local implementation teams to provide the study implementation management team with feedback and to give their opinions on the success of implementation, barriers perceived during execution of the implementation program and the satisfaction with the program. All interviews were audio-recorded and conducted by the same moderator (ZT).

Data analysis

Quantitative data
Data regarding the actual exposure to the individual elements of the implementation strategies were presented as percentages or absolute numbers. The questionnaires were distributed before phase I and after implementation. For the questions about 'attitude and perceptions' and the 'current practices' we used the questions with dichotomous answer options yes / no or agree / disagree (from the 5-point Likert scale statements where options: 1= strongly disagree; 2= disagree; 3= neutral; were marked as disagree and options 4= agree; 5= strongly agree) where marked as agree. Barriers for this dichotomous questions were considered to be present if <50 % of the respondents gave an answer implicating support for the issue pertaining to that statement. Barriers for delirium guideline and guidelines in general adherence were assessed with 6-point Likert-scales (no agreement = 0, and maximum agreement = 5). Mean scores of ≥ 3 were considered to indicate agreement with statements and was considered as a barrier [17]. A delirium knowledge score was calculated per respondent, defined as the percentage of correct answers. A mean delirium knowledge score below 70% was considered as a barrier regarding knowledge at the group level (e.g. ICU, nurses, physicians). Student t-test (for two groups) and one-way ANOVA (for three groups) was used to test the differences per ICU before versus after implementation. Frequencies and proportions were used to describe the adherence to the seven PIs and were described at ICU level and stratified by the four periods. The relative change in adherence difference between the baseline (T1) and the follow-up (T4) for each ICU and each guideline recommendation was given as ΔT4-T1 and the crude adherence numbers for T1 and T4 were reported.

Qualitative data

Associations between guideline adherence and exposure to implementation strategies was explored qualitatively by visual inspection. The interviews were transcribed verbatim and summaries of the interviews were sent to the participants to check for accuracy and validity of transcriptions. The moderator of the interviews (ZT) had also analyzed the data through reading and rereading interviews in order to obtain the essence of the whole. Thematic content analysis approach was used in searching themes [22]. Next, themes were labeled, coded and defined as: factors of implementation success, experience in collaboration with study implementation team (EI, MvdJ and ZT), and lessons learned for future implementations. Reliability checks were done by a second researcher (EI), and discussed and resolved in case of any unclarities.

RESULTS

All available staff working at the ICUs, 81 physicians (range within ICUs: 5 to 31) and 409 nurses (range: 35 to 125 per ICU), was targeted to participate in the implementation program. Depending on the number of ICU beds, the local implementation expert teams consisted of 2 to 11 ICU professionals. All ICUs were visited by the study management team at least seven times. One site (ICU4) was visited ten times due to challenges in the implementation caused by changes in RNs involved.

1. Actual exposure to implementation program

The average self-recorded time spent on both e-learnings was about 45 minutes per person per e-learning. Classical clinical lessons for delirium screening and PAD recommendations were repeated several times (about 45 minutes for each lesson). The majority of nurses (n = 375; 92%) attended the clinical classroom lessons. During study phase II educational spot-checks of delirium screening (nurses versus local experts) were performed as intended (four spot check moments per nurse).

Table 1 shows an overview of three completed IRT forms (filled in approximately three months apart), just before the T3 data collection period. Total score just before the start of T3 data collection was for both parts of IRT between 90 and 100% and had overall improved compared to the first assessment 6 months earlier. Five ICUs used all implementation strategies and implemented all guidelines recommendations, as estimated by the local intensivist or RN involved in the study. Only ICU 4 lagged behind and used 81% of the available implementation strategies and implemented only 67% of the advised protocol recommendations in daily practice.

Table 1: Implementation Readiness Test (Exposure in number of ICUs)

Part 1: Execution of Implementation Strategies				
Implementation strategy	Norm / requirements	IRT[1] 1	IRT 2	IRT 3
Education: Learning Part 1 screening	≥75% of nurses have completed the e-learning?	6[2]	6	6
Education: eLearning Part 1 screening	≥75% of physicians have completed the e-learning?	4	5	6
Education: e-learning Part 2 - treatment and preventive protocol	≥75% of nurses have completed the e-learning?	2	2	6
Education: e-learning Part 2 - treatment and preventive protocol	≥75% of physicians have completed the e-learning?	2	3	6
Clinical lessons screening	New employees are trained around delirium management?	3	4	4[3]
Educational outreach				
Spot-checks screening	There are at least 4 spot checks done by a nurse?	5	5	5
Quality control screening	This is scored by the experts? (Interobserver variation)?	3	4	5
Local implementation teams				
	Local implementation team is multidisciplinary (at least: intensivist, IC nurse, and possibly: psychiatrist / neurologist / geriatrician / physical therapist)?	6	6	6
	There were at least 2 consultations between local implementation team members (since beginning of the study) and there are agreements on implementation?	4	5	6
	It was agreed (preferably also recorded) who is responsible for which part of the implementation.	6	6	6
Local opinion leaders	It is clear who the implementation team members are and who is a contact for delirium in general and the study in particular?	5	5	6
Audit and feedback				
Indicators poster screening and incidence	1) Are the posters visible? 2) Are those discussed in the management team?	5 2	6 5	6 6
Decision support				
Laminated pocket cards screening CAM-ICU or ICDSC	Are pocket cards present for nurses and physicians?	5	6	6
	Pocket cards are used in practice?	3	4	5[4]
Reminders	There are reminders regarding screening and management of delirium (if available, popups PDMS for screening)	6	5	6
Focus groups / barrier analysis	Bottlenecks are discussed in local multidisciplinary meetings at the ICU level and is the implementation aimed to address them?	2	3	5

Table 1: Implementation Readiness Test (Exposure in number of ICUs) (continued)

TOTAL (of max 99)		**69 (70%)**	**80 (81%)**	**96 (97%)**
Part 2: Implementation of Protocol				
PDMS (patient demographic management system)	Is PDMS modified and helpful for delirium screening?	5	5	5[5]
Treatment delirium	Are the 4HS 4TS used in practice regularly if delirium screening result is a positive one (new delirium) ?	0	3	5
	Is it clear what the drug treatment for delirium (according to protocol) is?	4	6	5
	Is medication sometimes modified following the screening?	5	6	6
	Are the non-pharmacological measures optimized before starting medication?	2	3	5
Prevention of delirium: Physical therapy and early mobilization	Physical therapy: there are structural arrangements with physical therapist and there is agreement about how to provide early physical therapy and mobilization?	2	3	6
	Mobilisation of patients Is basically addressed daily patient rounds and this is implemented in the daily rounds?	4	5	6
	Its department policy in such a way that seeks to mobilize ventilated patients next of bed if possible?	3	4	5
Prevention: sleep hygiene	Is there a protocol regarding sleep promotion?	3	6	6
	Used this protocol and regularly followed in practice?	0	5	5
	Sleep protocol contains at least the next recommendations: lights off or muted overnight, strive for sleep (no standard rounds running if not necessary), and use of earplugs?	5	5	6
Prevention: psycho hygiene (among other, reducing sensory deprivation)	Is there a structural focus on using eyeglasses / hearing aid if the patient used normally in all patients / days?	4	5	6
Evaluation of pain-sedation-delirium	Daily delirium screening is implemented and "going well"?	3	4	6
	The coordination of delirium, sedation and pain management is implemented in any way in the daily rounds (eg. visit form)?	4	5	6
	Daily rounds checklist is implemented and used?	3	4	5
Sedation	Sedation with midazolam (or other benzodiazepines) by continuous infusion is avoided, and alternative sedation (analgo-sedation with opiate and possibly clonidine / dexmedetomidine / propofol targeting addressable patient comfortable?) is used?	4	5	6
Family engagement	Is there a leaflet about delirium for family?	4	4	6

Table 1: Implementation Readiness Test (Exposure in number of ICUs) (continued)

	Family of the ICU patient is getting the opportunity to contribute in identifying and / or treatment of delirium (eg. To help with washing, etc.)?	3	5	6
	Poster about family engagement by delirium is presented in the family room?	1	2	5
TOTAL (of max 113)		**59 (52%)**	**84 (74%)**	**106 (94%)**

[1] IRT = Implementation Readiness Test, drafted to measure the actual exposure to implementation strategies as perceived by the local study team. All three IRT overviews were made in Phase III during the implementation of guideline (total time = 10 months). The last one IRT overview was made just before the start of third data collection period (T3).

[2] The numbers indicates the number of sites which has implemented the item in daily practice.

[3] Not Applicable for two ICUs because there were no new employees at previous period.

[4] Not Applicable for one ICU because the information as given on Pocket cards was integrated in PDMS

[5] Not applicable for one ICU because no PDMS system was available.

2. Effect of the implementation program on guideline adherence at the level of participating ICUs and sustainability

The fourth data collection period served to assess sustainability of the implementation, and included an additional 519 patients (2727 days) next to the 3930 patients from the previous three phases. Only the percentage of mechanically ventilated patients was higher (51%) than in the preceding three phases (resp. 42%; 39%; 50%) as previously published [18]. See **Additional file 2** for patient demographics in phase T4.

Figure 1 displays the changes on adherence to the performance indicators in the different ICUs over time. Absolute numbers for all four measurement periods are given in **Additional file 3**. Adherence to the seven performance indicators improved overall and this improvement was sustained 6 months after active implementation support by the study management team had been terminated. Four PIs improved by more than 10%. The adherence to Delirium Screening (ΔT4-T1) improved most significantly with +57%, followed by avoiding benzodiazepines sedation (+18%); performing PT (+17%); and performing mobilization (+13%). Sedation assessments were improved during implementation, but the improvement of +8% was not sustained after implementation and dropped to the initial adherence level of 86%. Performing physical therapy initially improved by 27%, but dropped to 17% in T4. Light Sedation improved slightly by 7%.

Despite the overall improvement on process indicators, not all ICUs succeeded in adherence improvement for all performance indicators. In contrast and remarkably, decreases in adherence of more than 10% were measured on four performance indicators between baseline and follow up (**See Additional file 3** for ΔT4-T1). These were: Sedation Assessments (ICU 3 = -15%; and ICU 6 = -20%); Light sedation (ICU 1 = -13%); Avoiding Benzodiazepines Sedation (ICU 4 = -13%); and Performing Physical Therapy (ICU 1 = -26%; and ICU 4 = -35%).

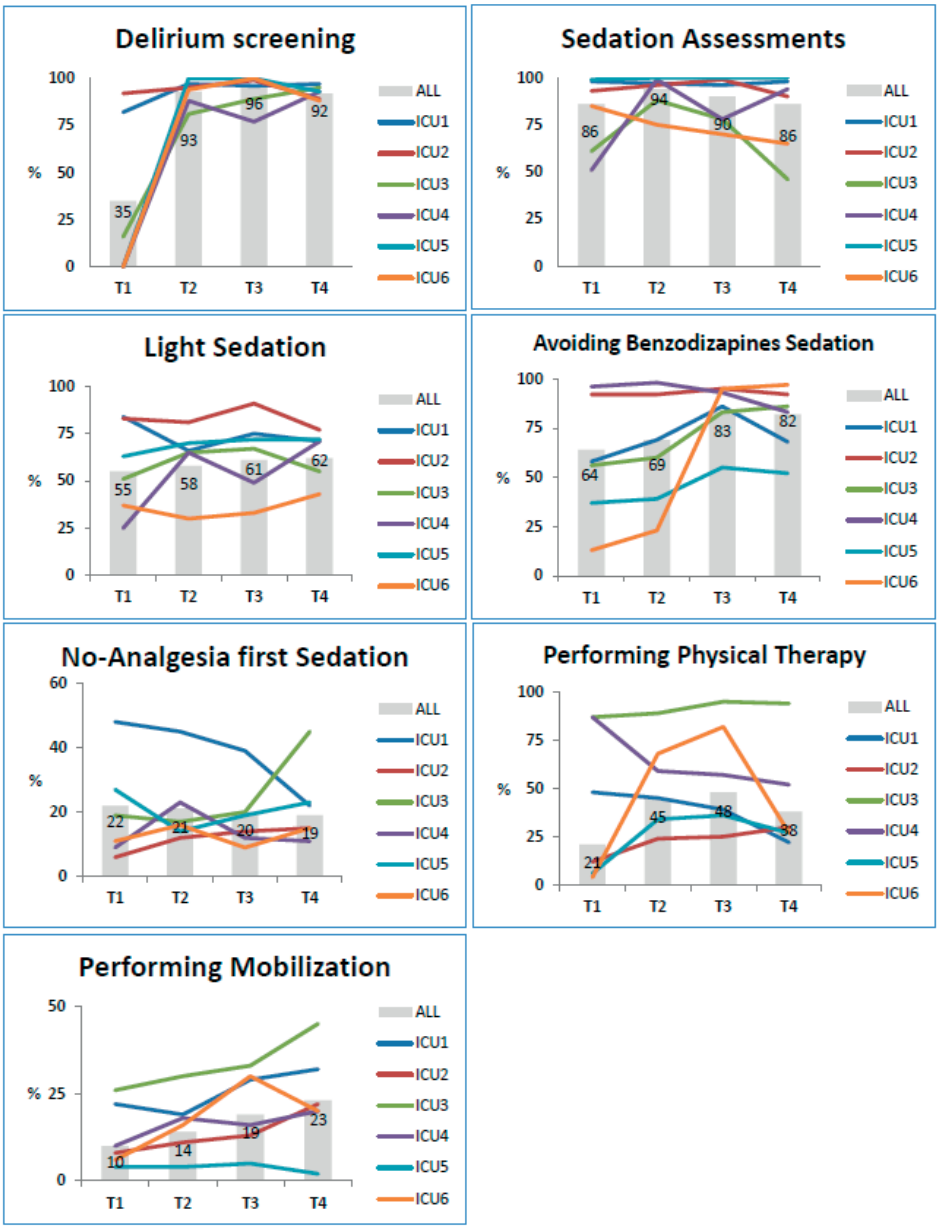

Figure 1: Adherence to Process Indicators over the study periods

There was no clear relationship between center specific adherence changes and clinical outcomes changes per ICU, similar to the overall results. **Additional file 4** shows the changes of clinical outcomes per ICU per study phase.

3. Impact of the implementation program on knowledge and implementation barriers

In total, 360 (69%) and 264 (50%) healthcare professionals completed the survey at T1 and T3 respectively. There were no differences between the participants at T1 and T3 in years of experience, work assignment, and age **(See Additional file 5)**. Delirium knowledge test scores improved from 62.9 (SD = 13.3) before to 65.1 (SD = 13.1) after the implementation (p = 0.037). However, significant differences were established by only three of the ICUs (ICU 1: from 65 to 67 %; ICU 2: from 62 to 64 %; and ICU 6: from 60 to 66 %) that succeeded in obtaining improved knowledge scores, while we found no differences in exposure to education for this three ICUs.

From all barriers identified through the survey before the implementation a quarter was not resolved by the implementation program. The perception that "delirium is not preventable" was not resolved. This may have affected, for example, the use of earplugs for the night. Also, the perception that "routinely addressing delirium in daily rounds can still be improved after the implementation" was not resolved, and finally, the satisfaction of nurses about delirium treatment did not improve **(Table 2)**.

4. Experiences with the implementation program

Overall, the members of the local implementation teams experienced the implementation program as very successful. The most important themes were the encouragement of the local implementation team by the implementation management team, change of culture with regard to the attitude of professionals towards delirium as a form of brain failure, and the improvement in collaboration with other (not ICU) disciplines due to the implementation. Despite the believe that a positive change in practice around delirium management had been made, the application of delirium preventive interventions still deserved more attention. A more detailed report of the semi-structured interview findings about experiences with the implementation program is given in **Additional file 6.**

DISCUSSION

In this process evaluation of a multicenter delirium guidelines implementation program, we found that all ICUs, except for one, were exposed to more than 90% of the implementation strategies. The implementation of the delirium guideline using the tailored implementation program was feasible and successful in resolving the majority of barriers found before the implementation. It resulted in improved knowledge about delirium, and it improved the daily process of care at six ICU sites as defined by seven performance indicators (PIs), which generally proved sustainable when measured after 6 months. However, the results on the PIs showed a considerable variation in guideline adoption across the six ICUs. Experiences with the implementation support from the

Table 2: Comparison of barriers found by first survey versus the results of second survey

	BEFORE	AFTER
(a) Attitudes and perceptions	**%**[a]	
Delirium occurrence and importance		
Delirium is preventable	21	15
Screening	%[a]	
Is a nurse capable to identify delirium with a validated delirium screening instrument?	34	80
Collaboration	%[a]	
When I as nurse suspect a patient to be delirious, I am satisfied with delirium treatment	47	40
When I as physician suspect a patient to be delirious, the nurse is satisfied with delirium treatment	42	11
Collaboration between doctors and nurses with regard to delirium at the ICU can be improved by better screening.	65	30
Collaboration between doctors and nurses with regard to delirium at the ICU can be improved by routinely addressing delirium in daily rounds.	74	78
(b) Current practices		
Delirium Screening	%[a]	
In the ICU unit where I work the following delirium screening scale is in use:		
CAM-ICU (Before: n=210; in only two hospitals / After: n=119)	58	45
ICDSC (Before: n=3 / After: n=104)	<1	39
Delirium Prevention		
Earplugs for the night	8	24
Family visits as much as possible	50	61
(c) Guideline adherence (n=136)		
If I follow the guideline recommendations, it is likely that my patients would not receive optimal care [b]	3.1 (1.0)	1.9(1.1)
I do not wish to change my delirium care practices, regardless of what delirium guideline recommends [b]	3.7 (1.0)	1.4(1.0)
I don't have time to use this Guideline [b]	3.5 (0.9)	1.7(1.0)
This guideline is cumbersome and inconvenient [b]	3.0 (1.1)	2.0(1.1)
(d) Guideline adherence in general (n=128)		
Generally, guidelines are cumbersome and inconvenient [b]	3.0 (0.9)	2.2(0.9)
Guidelines are difficult to apply and adopt to my specific practice [b]	3.1 (0.9)	2.0(0.9)
Guidelines interfere with my professional autonomy [b]	3.3 (0.9)	1.7(0.9)
Generally, I would prefer to continue my routines and habits rather than to change [b] based on practice guidelines [b]	3.3 (1.0)	1.9(0.9)
I am not really expected to use guidelines in my practice setting [b]	3.7 (0.9)	1.4(1.0)

[a] = % agreement (= %YES answers or % or the sum of agree and strongly agree answers (from the 5-point Likert scale statements)). Barriers depends on the question formulation. For positive formulated the barrier is ≤50% and negative formulated the barrier is ≥50%.[b] = mean and standard deviation based on the 6 point Likert-scale. Mean score of ≥3 was considered to indicate agreement with statement = Barrier

research coordinators were favorable, but continued support and coaching was deemed necessary to support the implementation interventions throughout the study.

Despite the general improvements in process of care outcomes, our data do not allow for conclusions regarding an association of individual implementation strategies and adherence changes because all sites largely executed the implementation as intended. Different entry levels of adherence and variation in time also make it difficult to compare the changes in time. However, the wide variation in guideline adoption, may be an argument that there is still room for more center-level tailoring.

We have identified relevant differences in the "dose" of implementation for individual PIs. Only for delirium screening the norm (goal ≥ 85%) was set before the implementation and repeated feedback about performance on this PI was given during the implementation phase. In daily practice there was more focus and education on this topic (separate e-learning and classical lessons, and spot-checks), and there were specific Patient Data Management System (PDMS) adjustments and delirium screening quality checks. This difference between the efforts made for the Performance Indicator for delirium screening and the rest of the Performance Indicators concerning other guideline recommendations from the PAD guidelines, resulted in the highest adherence (changes) on delirium screening PI during the implementation. Setting a clear adherence-level goal in combination with using audit and feedback for all PIs may have resulted in an increased level of adherence. Positive effects of audit and feedback on professionals intentions to improve practice have been empirically evaluated [23]. In our study the feedback data were collected and given only for delirium assessment and incidence of delirium. We suggest this was a facilitator in improving adherence in combination with electronic reminders to create continued awareness for delirium assessment and presence of delirium. However, we did not use the same feedback for the other PIs which may have hampered adoption of other guidelines than the screening for delirium. Otherwise, we could have intervened on time through providing feedback to those sites with deteriorating adherence on four PIs as described above.

Even though all sites were exposed to the same implementation program there were differences in the adherence changes across the sites. Based on the results of this process evaluation we cannot easily explain the variability within and between the sites. One of the possible explanations in the variability in adherence to the implementation program is the fact that there were other implementation projects, and organizational changes going on at the different sites which diverted the attention of the physicians, nurses and managers. During the study, two ICUs underwent organizational changes such as opening a medium care unit at the ICU, and separating medium care and ICU care patients at different units (ICU 1 and ICU 6). Such changes could be the reason behind the increased number of mechanically ventilated patients over the four study periods (baseline 42% to 51% in follow-up). But more importantly, we did not assess culture, organizational

aspects, and other context related factors before implementation across multiple sites which may have shed light on the variable adoption. Retrospectively, the Consolidated Framework For Implementation Research (CFIR) [24] could have been a helpful implementation model: in contrast to the implementation model of change of Grol and Wensing [21], the CFIR model operationalized the organizational context by two dedicated domains: "inner setting" (local culture, leadership engagement, implementation climate, etc.), and 'outer setting' (patients' needs and resources, cosmopolitanism, peer pressure and external polices and incentives). Readiness for implementation with the self-designed IRT was only one construct of 'inner setting' we used to get an overview of implementation progress across the sites. Local implementation teams experienced the implementation program as very successful in changing the culture of ICU professionals about delirium as indicator of brain failure and a problem that needs to be actively addressed, but that was not directly related to the degree of local implementation success.

One of the problems when comparing the degree of adherence with other guidelines implementation studies relates to the definitions of different PI measures [11] and the measurement of total or partial compliance in relation to hospital survival [13]. The question remains: when are we satisfied with the degree of adherence? We defined a target level for the PI for delirium screening only, and did not define this for other PIs or overall implementation success in advance. The definition of targeted adherence-level in advance is not a common practice in implementation studies, but we suggest that this may provide more clarity on the goals of implementation, which may facilitate adherence and, ultimately, quality of care [25].

Limitations of the study particularly relate to lacking assessment of the implementation context e.g. ICU culture and context of organization in advance, which impedes obtaining general insights from the implementation at large. Second, assessment of exposures of the ICUs to the implementation program partly depended on self-reported assessments, which may not have been entirely accurate. For example, when we assumed that the e-learning was executed as intended because the self-evaluation forms were filled in correctly, we cannot guarantee that knowledge indeed was conveyed optimally to every health care professional, because this depends on how serious the education was done. Third, predefined knowledge level of >70% was a choice and may not have represented sufficient knowledge. Apart from this predefined knowledge level, the survey was, although based on previously published studies, not a validated questionnaire and may not have had the most optimal validity to test knowledge. Fourth, our design was not appropriate for measuring the association between the individual implementation strategies and adherence changes. Finally, experience with implementation was measured only among the local implementation team members, and not among all involved health care professionals at the participating units. Also, the managers were not involved during the implementation whereas previous studies have shown that

healthcare managers may play an important role in facilitating implementation [26] and buy-in from medical staff seems essential. More inclusive assessment of experiences of both healthcare professionals and managers with the implementation could have provided more information about the "why" of non- (or suboptimal) adherence.

CONCLUSIONS

Multifaceted implementation interventions such as performed in this study can improve delirium guideline adherence in the ICU, moreover the improvements of these implementation interventions can be sustainable on the short term. Delivering multifaceted implementation interventions is feasible within the ICU setting, where these interventions can largely be performed as planned. Indicators of success or failure of the implementation remains very challenging to identify in an observational study as ours, because implementation success may be variably defined or perceived and because of the multitude of factors influencing both guideline adherence and clinical outcomes, including ICU culture which we did not formally assess. In spite of a general level of tailoring, variability in delirium guideline adherence at individual ICUs remained in this study. For future quality improvement, this could possibly be resolved with investing in a higher degree of tailoring implementation interventions to ICUs' local inner and outer context.

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ADDITIONAL FILES

Additional file 1: Semi structured interview for the assessment of experiences of local implementation teams with the implementation

1. Do you think that the implementation of delirium directive (generally) was successful?
- If not, why it was not successful?

2. Which components of the implementation were successful?
- If yes, which:
- If not, which:

3. Are the barriers identified at the beginning of the study for your center / ICU sufficiently resolved with the chosen implementation interventions?

4. Which individual components of the strategies have been effective and which ones (i.e. why the implementation was less successful (open question thus, and own opinion about this, will also provide additional information)?

5. Did you have a local project team / delirium expert team,
- Who was involved?
- How were the roles / responsibilities distribution inside the local team?
- Had we had to tackle different things (study team and ICs) differently?

6. Describe Part 1: implementation of screening and

7. Describe Part 2: Implementation of prevention and treatment.

8. Is the guideline delirium sufficiently guaranteed, and what does this prove?

9. What are the thoughts about Feedback on delirium incidence and delirium screening?

10. Control for screening of delirium: Are you going through this and how?

11. Nursing - doctor cooperation?

12. Is the delirium App applicable in practice?

Question about project organization:

1. Were the objectives of the coordination team (study team / we) clearly / concretely formulated?

2. What do you think of time investment (e.g. to implement screening)?

3. Sufficient support from coordinating team to achieve goals?

4. What did this project teach you for future implementation projects (such as protocols, guidelines)?

- Organization,
- Material,
- Communication,
- Staff,
- time

What combinations of strategies have been essential to your practice (what has been the key to success?)
Process
Finally, complete the completed IRT table of the relevant hospital and complete it at the end the interview.
Also check for any structural changes to the IC have been made. E.g.
1.

Additional file 2: Patient Demographics and Baseline Clinical Characteristics in T4

Characteristic	***Data-collection period[c] T4 / Sustaining***
No. of patients, n	519
No. of ICU[a] days, n	2727
Gender, n (%)	
Male	300 (58)
Female	219 (42)
Age (years), median (IQR[a])	66 (55, 76)
Admission status, n (%)[b]	
Elective surgery	135 (26)
Emergency surgery	55 (11)
Medical	271 (52)
APACHE-II[a], median (IQR)	16 (12, 22)
Mechanically Ventilated patients, n (%)	261 (51)
Hospital, n (%)	
1	73 (14)
2	117 (23)
3	103 (20)
4	37 (7)
5	124 (24)
6	65 (13)

[a]Acute Physiology and Chronic Health Evaluation II range is 0-71, IQR: Interquartile range; ICU: intensive care unit

[b] Admission status missing's for Sustaining period = 1

[c] Data about previous three phases were published previously[1]

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Additional file 3: Changes in Pain Agitation Delirium (PAD) Guidelines Performance Indicators at ICUs level across study

Performance Indicator (PI)[1]	ICU	T1[2] baseline	T2	T3	T4 follow-up	Δ T1 - T4% (T4% - T1%)
Delirium Screening (Total No. of days with at least one CAM-ICU or ICDSC assessment recorded / Total No. of patient-days at ICU)	1	82	97	96	97	+15 (97 - 82)
	2	92	95	99	89	-3 (89 - 92)
	3	16	81	89	95	+79 (95 - 16)
	4	0	88	77	93	+93 (93 - 0)
	5	0	100	100	93	+93 (93 - 0)
	6	0	94	100	88	+88 (88 - 0)
	ALL	35	93	96	92	+57 (92 - 35)
Sedation Assessments (Total No. of days with at least one sedation assessment recorded / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	1	98	97	96	98	0 (98 - 98)
	2	93	96	99	90	-3 (90 - 93)
	3	61	88	78	46	-15 (46 - 61)
	4	51	99	78	94	+43 (94 - 51)
	5	99	100	100	100	+1 (100 - 99)
	6	85	75	70	65	-20 (65 - 85)
	ALL	86	94	90	86	0 (86 - 86)
Light Sedation (No. of light sedation days[3] / Total No. of ICU days in ventilated patients receiving sedation and /or opioids)	1	84	66	75	71	-13 (71 - 84)
	2	83	81	91	77	-6 (77 - 83)
	3	51	65	67	55	+4 (55 -51)
	4	25	65	49	71	+46 (71 - 25)
	5	63	70	72	72	+9 (72 - 63)
	6	37	30	33	43	+6 (43 - 37)
	ALL	55	58	61	62	+7 (55 - 62)
Avoiding Benzodiazepines Sedation (No. of benzodiazepines[4] sedation days / Total no. of ICU days in mechanically ventilated patients during at least one ICU-day AND having received sedation and/or opioids)	1	58	69	86	68	+10 (68 - 58)
	2	92	92	95	92	0 (92 - 92)
	3	56	60	83	86	+30 (86 - 56)
	4	96	98	93	83	-13 (83 - 96)
	5	37	39	55	52	+15 (52 - 37)
	6	13	23	95	97	+84 (97 - 13)
	ALL	64	69	83	82	+18 (82 - 64)
No-Analgesia first sedation (No. of patient without-analgesia-while-sedated days / Total number of patient sedation days)	1	48	45	39	22	-26 (22 - 48)
	2	6	12	14	15	+9 (15 - 6)
	3	19	17	20	45	+26 (45 - 19)
	4	9	23	12	11	+2 (11 - 9)
	5	27	14	19	23	-4 (23 - 27)
	6	11	16	9	15	+4 (15 - 11)
	ALL	22	21	20	19	-3 (19 – 22)

Additional file 3: Changes in Pain Agitation Delirium (PAD) Guidelines Performance Indicators at ICUs level across study (continued)

Performance Indicator (PI)[1]	ICU	T1[2] baseline	T2	T3	T4 follow-up	Δ T1 - T4% (T4% - T1%)
Performing Physical Therapy (No. of patient-days with PT / Total No. of patient ICU days; included with LOS > 2 days)	1	48	45	39	22	-26 (22-48)
	2	12	24	25	30	+18 (30 - 12)
	3	87	89	95	94	+7 (94 - 87)
	4	87	59	57	52	-35 (52 - 87)
	5	6	34	36	27	+21 (27 - 6)
	6	4	68	82	27	+23 (27 - 4)
	ALL	21	45	48	38	+17 (38 - 21)
Performing Mobilization (No. of patient-days with mobilization / Total No. of patient ICU days included with LOS > 2 days)	1	22	19	29	32	+10 (32 - 22)
	2	8	11	13	22	+14 (22 -8)
	3	26	30	33	45	+26 (45 - 26)
	4	10	18	16	20	+10 (20 - 10)
	5	4	4	5	2	-2 (2 - 4)
	6	6	16	30	20	+14 (20 - 6)
	ALL	10	14	19	23	+13 (23 - 10)

[1] Predefined Performance Indicator(s) were used to assess the Pain Agitation Delirium (PAD) guidelines recommendations. For performance Indicators metrics see In and defined.

[2] T1= Baseline measurement (Before the start of implementation); T2= After delirium screening implementation; T3= After PAD guidelines implementation; T4= follow-up 6 months after implementation.

[3] Definition of Light sedation: Richmond Agitation and Sedation Scale (RASS) >- 3 or Critically Ill Assessment Scale (CIA) >6 or Ramsay Sedation Scale <5, see manuscript text for references.

[4] Benzodiazepines = midazolam and / or lorazepam as continuous intravenous sedative.

Additional file 4: Clinical Outcomes at ICUs level across the study

Outcomes		*Crude analysis*											
	ICU	**T1**		**T2**			**T3**			**T4**			
		Patients, n		*Patients, n*		*p-value (T1 versus T2)*[a]	*Patients, n*		*p-value (T1 versus T3)*[a]	*Patients (n)*		*p-value (T3 versus T4)*[a]	*p-value ALL*[b]
Delirium duration (days), median (IQR)	1	59	3 (2, 6)	38	1.5 (1 - 5.3)	*0.03*	44	3 (1 - 4)	*0.11*	24	4 (2 - 6.5)	*0.19*	*0.08*
	2	71	3 (2, 10)	83	2 (1 - 5)	*0.006*	99	3 (1 - 6)	*0.036*	36	4.5 (2 - 11)	*0.007*	*0.002*
	3	44	2 (1, 3)	60	2 (1 - 3)	*0.35*	54	2 (1 - 3)	*0.49*	23	2 (1 - 4)	*0.63*	*0.78*
	4	29	2 (1, 3)	30	2 (1 - 4)	*0.68*	15	2 (1 - 4)	*0.68*	7	2 (1 - 6)	*0.82*	*0.85*
	5	39	4 (2, 6)	38	1.5 (1 - 2)	*<0.001*	59	1 (1 - 3)	*<0.001*	27	1 (1 - 2)	*0.53*	*<0.001*
	6	32	3 (1, 4.8)	51	1 (1 - 2)	*0.001*	48	1 (1 - 2)	*<0.000*	18	2 (1 - 3)	*0.28*	*0.001*
	ALL	274	3 (2, 5)	300	2 (1 - 3)	*<0.001*	319	2 (1 - 3)	*<0.001*	135	2 (1 - 5)	*0.92*	*<0.001*
Patients with delirium during ICU admission, n (%)	1	145	59 (41%)	151	38 (25%)	*0.004*	188	44 (23%)	*0.001*	72	24 (33%)	*0.10*	*0.003*
	2	247	71 (29%)	242	83 (34%)	*0.19*	240	99 (41%)	*0.004*	108	36 (33%)	*0.16*	*0.036*
	3	231	44 (19%)	223	60 (27%)	*0.046*	240	54 (23%)	*0.36*	102	23 (23%)	*0.99*	*0.26*
	4	158	29 (18%)	150	30 (20%)	*0.71*	73	15 (21%)	*0.69*	36	7 (19%)	*0.89*	*0.98*
	5	251	39 (16%)	271	38 (14%)	*0.63*	216	59 (27%)	*0.002*	121	27 (22%)	*0.31*	*0.001*
	6	305	32 (11%)	297	51 (17%)	*0.017*	216	48 (22%)	*<0.001*	62	18 (29%)	*0.27*	*<0.001*
	ALL	1337	274 (21%)	1334	300 (21%)	*0.21*	1173	319 (27%)	*<0.001*	501	135 (27%)	*0.92*	*<0.001*
Duration of mechanical ventilation (days), median (IQR)	1	47	2 (1 – 3.6)	75	3 (2 – 6)	*0.005*	84	3 (2 – 5)	*0.020*	34	3 (2 – 9)	*0.40*	*0.023*
	2	193	1 (1 – 3)	176	2 (1 – 5)	*0.006*	192	2 (1 – 5)	*<0.001*	96	3 (1.5 – 8)	*0.048*	*0.003*
	3	57	1 (1 – 3)	76	2 (1 – 3.5)	*0.10*	58	2 (1 – 3)	*0.28*	23	3 (2 – 5.5)	*0.06*	*0.06*
	4	50	1 (1 - 2.5)	38	2 (2 – 6)	*0.002*	41	3 (2 – 8)	*<0.001*	12	4 (1 – 5)	*0.56*	*<0.001*
	5	120	2.6 (1 – 6.7)	103	3 (2 - 6)	*0.12*	118	3 (1 - 6)	*0.62*	59	3 (1.5 – 5)	*0.72*	*0.42*
	6	93	2.2 (1 – 6.4)	73	3 (2 – 7)	*0.15*	100	2 (1 - 4)	*0.31*	37	2 (2 – 4)	*0.39*	*0.08*
	ALL	560	1.5 (1 – 4.6)	541	2 (1 - 6)	*<0.001*	593	2 (1 - 5)	*<0.001*	261	3 (2 – 6)	*0.042*	*<0.001*

ICU LOS (days), median (IQR)	1	145	3 (2 – 6)	155	3 (2 - 5)	*0.033*	195	3 (2 – 5)	*0.04*	73	4 (2 – 6)	*0.01*	*0.004*
	2	247	3 (2 – 6)	248	3 (2 - 6)	*0.94*	242	3 (2 – 7)	*0.65*	117	3 (2 – 8)	*0.45*	*0.98*
	3	231	2 (2 - 3)	251	2 (2 – 4)	*0.84*	249	2 (2 – 4)	*0.12*	103	2 (2 – 3)	*0.49*	*0.43*
	4	158	2 (2 – 4)	166	2 (2 – 3)	*0.003*	76	3.5 (3 – 6.5)	*<0.001*	37	3 (2 – 5)	*0.05*	*<0.001*
	5	251	3 (2 – 6)	271	3 (2 – 4)	*0.028*	216	3 (2 – 5.5)	*0.98*	124	3 (2 - 4)	*0.07*	*0.038*
	6	305	2 (2 – 4)	308	2 (2 – 3)	*0.40*	216	3 (2 – 4)	*0.020*	65	4 (3 – 6)	*<0.001*	*<0.001*
	ALL	1337	3 (2 - 5)	1399	2(2 – 4)	*<0.001*	1194	3 (2 - 5)	*0.003*	519	3 (2 -5)	*0.21*	*<0.001*
ICU Mortality, n (%)	1	145	14 (9.7%)	155	15 (9.7%)	*0.99*	195	18 (9.2%)	*0.90*	73	9 (12.3%)	*0.45*	*0.90*
	2	247	51 (20.6%)	248	42 (16.9%)	*0.29*	241	41 (17%)	*0.31*	117	14 (12%)	*0.21*	*0.23*
	3	231	9 (3.9%)	251	26 (10.4%)	*0.006*	249	18 (7.2%)	*0.11*	103	8 (7.8%)	*0.86*	*0.06*
	4	158	10 (6.3%)	166	11 (6.6%)	*0.91*	75	8 (10.7%)	*0.25*	37	5 (13.5%)	*0.66*	*0.34*
	5	251	24 (9.6%)	271	23 (8.5%)	*0.67*	216	28 (13%)	*0.24*	124	21 (16.9%)	*0.32*	*0.06*
	6	305	27 (8.9%)	307	23 (7.5%)	*0.54*	216	13 (6.0%)	*0.23*	65	7 (10.8%)	*0.19*	*0.52*
	ALL	1337	135 (10.1%)	1398	140 (10%)	*0.94*	1192	126 (10.6%)	*0.70*	519	64 (12,3%)	*0.29*	*0.49*
Hospital Mortality, n (%)	1	145	32 (22.1%)	155	25 (16.1%)	*0.19*	195	27 (13.8%)	*0.048*	69	9 (13%)	*0.88*	*0.18*
	2	247	59 (23.9%)	248	49 (19.8%)	*0.27*	242	55 (22.7%)	*0.76*	85	15 (17.6%)	*0.33*	*0.53*
	3	231	17 (7.4%)	251	45 (17.9%)	*0.001*	249	30 (12%)	*0.08*	101	11 (10.9%)	*0.76*	*0.005*
	4	158	21 (13.3%)	166	20 (12%)	*0.74*	76	14 (18.4%)	*0.30*	26	6 (23.1%)	*0.61*	*0.32*
	5	251	45 (17.9%)	271	50 (18.5%)	*0.88*	216	46 (21.3%)	*0.36*	120	33 (20.3%)	*0.20*	*0.14*
	6	305	42 (13.8%)	308	37 (12%)	*0.51*	216	22 (10.2%)	*0.22*	63	10 (15.9%)	*0.21*	*0.53*
	ALL	1337	216 (16.2)	1399	226 (16.2)	*0.99*	1194	194 (16.2)	*0.95*	464	84 (18.1%)	*0.36*	*0.77*

[a] P-values are calculated as difference between two independent groups with Mann-Whitney Test for continue outcomes and Pearson Chi-Square Test was used for bivariate outcomes.

[b] P-values are calculated as difference between four independent groups (marked as ALL) with Kruskal-Wallis Test for continue outcomes and Pearson Chi-Square Test was used for bivariate outcomes.

Additional file 5: Demographics of survey respondents

Survey	**BEFORE n (%)**	**AFTER n (%)**
Type of healthcare professional		
ICU-physicians	53 (14)	53 (20)
· Intensivists (including fellows)	37 (10)	38 (14)
· Residents	16 (4)	15 (16)
ICU Nurses	283 (79)	201 (76)
Delirium experts (psychiatrists, geriatricians and specialized psychiatric nurses)	24 (7)	10 (4)
Years of work experience [a]		
< 1	47 (13)	22 (8)
1 to 4	64 (18)	50 (19)
5 to 9	72 (20)	63 (24)
≥10	177 (49)	129 (49)
Working assignment [b]		
<35%	7 (2)	3 (1)
35-55%	28 (8)	19 (7)
55-75%	46 (13)	49 (19)
75-90%	93 (26)	76 (29)
90-100%	186 (52)	117 (44)
Age (years) [c]		
<25	16 (4)	2 (1)
25-34	109 (30)	87 (33)
35-44	87 (24)	63 (24)
45-54	99 (28)	72 (37)
>55	42 (12)	33 (13)
missing	6 (2)	7 (3)

Differences between 6 participating ICUs in first survey (before): [a] p=0.67, [b] p=0.79, [c] p=0.15
Differences between 6 participating ICUs in second survey (after): [a] p=0.26, [b] p=0.29, [c] p=0.0

Additional file 6: Experiences with the implementation program

Overall, the members of the local implementation teams experienced the implementation program as very successful. More in detail, this was mainly due to constant attention given to the different parts of the guideline by the implementation teams. The implementation management team was able to encourage local implementation teams to stay focused on implementation at their ICUs. Initially, attention from the implementation management team was sometimes perceived as intrusive, but this feeling waned over time. The feeling that delirium is a form of *"vital organ failure"* was an important message which was embraced by the ICU professionals. Gradually, delirium was seen as a problem that needs as much attention as other forms of organ failure in critically ill patients, such as renal failure, respiratory (lung) failure, etc. This was perceived as a '*change of culture*'. Two ICUs had tried to implement delirium screening in the past. However, the local team members stated that "*this round was much more successful,*" (than previous attempt and relating this mainly to the analysis of barriers for screening being done before the implementation program). Further, bedside-teaching (practical training of delirium screening), creating a firm basis for acceptance and support, optimizing ICT facilities for screening and treatment, developing a comprehensive protocol and acceptance into daily rounds of the ICU were regarded facilitators for the implementation in some centers that succeeded in these items. The lack of ICT facilities and Research Nurses turnover were regarded crucial factors that limited the implementation at ICU 4. The respondents indicated that the implementation process sometimes faltered in their organization. For these local implementation leaders, the Implementation Readiness Test (IRT) was a very useful tool and worked for them as an "*implementation thermometer*" to accelerate the process. In addition, although the implementation took considerable time investment from the local teams, it had obviously translated into a concrete change of practice. At times, it was felt the local teams could have been addressed more actively by the implementation management team, referring to more directive and clearer clues on what to do and when. On the other hand, the project in different ICUs also had spin-off effects like optimizing collaboration with other disciplines. The implementation of other guideline recommendations can be picked up in the future because of the experience with this implementation (e.g. use of champions, opinion leaders (formally appointed an intensivist and research nurse at each site) and the use of IRT. Most people interviewed believed that delirium screening and drug treatment had been guaranteed in their ICU but that non-pharmacological interventions (such as earplugs) and other preventive measures still required attention for the future.

Chapter 7

Pharmacogenomic Response of Haloperidol in Critically Ill Adults with Delirium

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ABSTRACT

Objective

To characterize the pharmacogenomic (PG) properties of low-dose haloperidol for delirium treatment of critically ill adults.

Design

Single-center, prospective cohort study.

Setting

A mixed ICU at an academic medical center.

Patients

Critically ill adults with delirium [Intensive Care Delirium Screening Checklist (ICDSC) score ≥ 4] admitted to the ICU ≥ 48 hours and administered low-dose IV haloperidol using an institutional treatment protocol [1mg IV q8h; increased by 0.5mg IV q8h daily if delirium persisted up to 2mg IV q8h].

Measurements and Main Results

Each patient was evaluated with the ICDSC every 8 hours by a trained nurse. The QTc interval was calculated daily from a 12-lead ECG. Serum haloperidol concentrations were collected before each morning dose on days two through six and analyzed using standard liquid chromatography-mass spectrometry techniques. At baseline, CYP2D6 and CYP3A4 genotypes were determined and patients were categorized as extensive (EM), intermediate (IM) or poor (PM) metabolizers. The 22 patients (age 67 [48,77] years; APACHE III 81[54,181]; CYP2D6 [EM=12, IM=7, PM=3], CYP3A [EM=18, IM=4]) 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 ($p = 0.3$), daily presence of delirium ($p = 0.2$) or cumulative ICDSC score ($p = 0.4$). PM CYP2D6 status was associated with significantly higher haloperidol concentrations ($p = 0.017$); an association between CYP3A4 status and haloperidol concentrations was not found. No patient experience QTc interval prolongation (≥500ms).

Conclusions

This pilot study, the first to evaluate the pharmacogenomics properties of low-dose haloperidol in critically ill adults with delirium, suggests trough serum haloperidol are lower in patients with a CYP2D6 PM status but, overall, are not associated with the daily dose administered, delirium occurrence, or changes in delirium symptoms.

INTRODUCTION

Haloperidol is frequently administered at low (4 to 8 mg/day) or moderate (9-20 mg/day) dose to critically ill adults to either prevent or treat delirium despite evidence from randomized, controlled trials that it neither prevents or resolves delirium nor improves important outlines like mortality or post-ICU cognition [1-5]. The achievement of low, and potentially inadequate, serum haloperidol concentrations has been postulated as a reason why low-dose haloperidol failed to prevent delirium in the recent REDUCE trial [6]. However, none of the most recent haloperidol ICU delirium treatment trials published to date [3-5] included pharmacokinetic data and thus the pharmacodynamic response of low-moderate dose haloperidol for the treatment of delirium in critically ill adults remains unclear.

Haloperidol is metabolized through both the CYP2D6 and CYP3A4 isoenzyme systems [7]. CYP2D6 and CYP3A4 polymorphisms are common and the activity of each may be affected by critical illness and the administration of any medication that is metabolized by one or both of these pathways [8]. Pharmacogenomic variability may therefore be an important contributor to haloperidol's pharmacodynamic response in a critically ill adult with delirium however the pharmacogenomics of haloperidol in this setting has never been evaluated. Although the pharmacodynamic, -kinetic, and -genetic characteristics of very high-dose haloperidol has been evaluated in patients with major psychiatric disorders [9], these properties have not been evaluated in critically ill adults receiving low-dose haloperidol for the treatment of delirium [1,4]. This data is important for the design of haloperidol dosing interventions in future studies and may help ICU clinicians individualize haloperidol dosing regimens for patients with clinically important delirium symptoms where its use may be warranted [10].

We therefore sought to characterize the pharmacogenetic characteristics low-dose haloperidol in critically ill adults with delirium.

METHODS

Study Enrollment

This single-center prospective observational pilot study was conducted in the adult intensive care units Erasmus University Medical Centre, Rotterdam, NL. The study was approved by the Institutional Review Board and informed consent was obtained from each patient or their next-of-kin. Consecutive adults (≥ 18 yrs.) expected to be admitted to the ICU ≥ 48 hrs with delirium [Intensive Care Delirium Screening Checklist (ICDSC≥4) [11] and administered haloperidol according to a preexisting institutional delirium protocol were evaluated for study participation between October 2014 and April

2017. Exclusion criteria included: treatment with haloperidol in the 24 hours prior to ICU admission; ICDSC not evaluated due to coma or severe hearing loss; end stage liver failure; primary neurologic diagnosis; a history of severe dementia; history of parkinsonism and/or psychosis; a baseline QTc interval ≥ 450msec; concurrent use of a medication with the potential to induce CYP2A6 and/or CYP3A4 isoenzyme concentrations (i.e., bosentan, carbamazepine, efavirenz, etravirine, phenobarbital, phenytoin, nevirapine, rifabutin, lopinavir, ritonavir, rifampicin); acute alcohol withdrawal; pregnancy; or no informed consent.

Data Collection

The following baseline data was collected: gender, age, APACHE III score, Body Mass Index (BMI), serum blood urea nitrogen, ICDSC score, QTc interval (based on ECG evaluation) and CYP2D6 and CYP3A4 isoenzyme concentrations. The following daily data was collected: daily change in ICDSC score, dose of haloperidol administered, SOFA (Sequential Organ Failure Assessment score, QTc interval, use of medications used in the ICU and known to inhibit CYP2D6 (amiodarone, cimetidine, fluoxetine, metoclopramide, metoprolol, paroxetine, and propranolol) and/or CYP3A4 (alprazolam, amiodarone, aripiprazole, clozapine, diazepam, erythromycin, fluconazole, melatonin, midazolam, quetiapine, risperidone, verapamil, voriconazole, zolpidem, and zopiclone) activity [12,13].

Delirium screening (by the ICU bedside nurse using the ICDSC every 8 hours) and reduction efforts were well-established in all study ICUs [14,15]. The investigative team conducted regular spot-checks of nurse ICDSC assessments, offering additional training to nurses when required. The ICU delirium treatment protocol advocated the use of haloperidol when the bedside nurse identified delirium and the physician agreed with nurse's assessment. Haloperidol was initiated at 1mg IV q8h [0.5 mg IV q8h if age ≥ 80 years old; 2mg IV q8h if agitation present] within 12 hours of delirium detection. On a daily basis, if delirium was still present, each dose of IV haloperidol was increased by 0.5mg to a maximum of 2mg IV q8h.

Blood samples for haloperidol concentration determinations were drawn from an arterial line before the administration of each morning dose on days 2, 3, 4, 5, and 6 (end of study) or until haloperidol was stopped before day 6 due to protocol, patient death or ICU discharge. Each blood sample was immediately sent to the hospital pharmacy laboratory, centrifuged, and the serum was stored at -80^{o}C until haloperidol quantification using validated, FDA-approved, liquid chromatography-mass spectrometry methods [16]. All serum concentrations were corrected for the most recent haloperidol dose administered.

CYP3A4 and CYP2D6 patient genotyping was performed using a validated method by the clinical chemistry laboratory at the study center. For each isoenzyme, patients were classified according to the number of active enzyme alleles present: poor metabolizers

(PM; two defective alleles), intermediate metabolizers (IM, 2 decreased activity alleles or 1 active and 1 inactive allele), extensive metabolizers (EM) and ultra-rapid metabolizers (UM, gene duplication positive in absence of a CYP2D6 null allele).

Data Analysis

The following analyses were conducted: 1. efficacy- association between daily haloperidol dose administered and highest ICDSC score, 2. safety- association between daily haloperidol dose administered and QTc intervals ≥ 500msec. 3. association between daily haloperidol dose administered and daily haloperidol trough concentrations, 4. association between highest daily ISCDC score and daily haloperidol trough concentrations. 5. Haloperidol pharmacogenomics: a. CYP2D6: association between CYP2D6 metabolizer status and daily haloperidol trough concentration, b. CYP3A4: association between CYP2D6 metabolizer status and daily haloperidol trough concentration and c. Association between CYP2D6 (and CYP3A4), haloperidol dose, and serum haloperidol concentrations over time. Additional analysis were conducted to account for use of co-medications known to inhibit one or both isoenzymes.

A convenience sample of 20 patients was chosen for this study given its pilot nature and the lack of published ICU data to provide a standard deviation for any of the outcomes evaluated. Data was presented as percentages, median (IQR) or mean (SD). To compare the daily mean haloperidol dose and QTc interval, a Student's t-test was used. To investigate the association between haloperidol dose, CYP2D6 and CYP3A4 metabolizer status, and serum haloperidol concentrations, a linear mixed model was constructed with haloperidol serum concentrations as the outcome of interest and haloperidol dose, baseline metabolizer status, patient age, ICU day, and the daily SOFA score as other covariates. To investigate the association between serum haloperidol concentrations and the presence of delirium, we constructed a generalized linear mixed model. Two-sided p values <.05 were considered statistically significant. Outliers were excluded from analysis. All analyses were performed using R (additional packages: foreign, lme4, and rms; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

Baseline characteristics

Twenty-two patients (55% male, median 67 [48,77] years old, BMI of 27 [18, 39] kg/m^2, APACHE III 81 [54,181], serum BUN 18±13 mmol/L) were enrolled. The primary reasons for ICU admission included: surgery (7, 32%), respiratory failure (3, 14%), sepsis (3, 14%) and vascular aneurysm (2, 9%). The median length of stay of ICU stay was 16.5 [2, 63] days. Eleven patients died (50%); six patients during the ICU stay, four after ICU discharge, and

one after transfer to another hospital. Thirteen patients (59%) completed the maximum six days of data collection.

Haloperidol dose outcomes

Average haloperidol dose, ICDSC score, SOFA score and QTc interval across each study day are presented in **Table 1**. The average daily dose of haloperidol administered was 3.5 ± 1.8 mg. The distribution of daily haloperidol doses is presented in **Figure 1**. The average day 2 (3.3 ± 1.7 mg) and day 4 (4.2 ± 2.9) administered haloperidol doses were not different (p = 0.28). The daily distribution of serum haloperidol concentrations per patient are presented in **Figure 2.** The average daily haloperidol concentration among the 81 drawn was 1.9 [0 to 62] µg/L. Among four patients, seven concentrations exceeded 10 µg/L. An association between daily haloperidol dose and the haloperidol serum concentration was not found after adjustment for ICU day, age and daily SOFA score (p = 0.30).

Table 1: Average haloperidol dose, ICDSC score, SOFA score and QTc interval across each study day.

Parameter	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Daily haloperidol dose (mg)	2.6 (1.9)	3.2 (1.9)	3.3 (1.7)	3.6 (1.5)	4.2 (2.9)	3.8 (1.5)	4.2 (1.8)
Daily ICDSC[B] score	3.8 (1.4)	5 (1.1)	4.7 (1.5)	4.9 (1.6)	4.3 (2.1)	4.5 (1.7)	4.5 (1.8)
SOFA[B] score	10 (3.1)	9 (3.8)	9.3 (4.3)	10 (5.1)	9.8 (5.1)	8.4 (5.1)	9.7 (5.3)
QTc interval (msec)	413 (34)	423 (33)	425 (27)	418 (23)	413 (20)	414 (36)	423 (36)

[A]Data presented at mean ± SD

[B]ICDSC = Intensive Care Delirium Screening Checklist, SOFA = Sequential Organ Function Assessment

An association between the haloperidol serum concentration and delirium severity was not found (p = 0.20). An association between the haloperidol serum concentration and cumulative ICDSC score was also not found after adjustment for ICU day, age and daily SOFA score (p = 0.4).

Among the 92 ECGs performed, the QTc interval ranged from 318 and 486 ms; none exceeded 500 ms. The average QTc interval was not different between day 1 (423 ± 33 ms) and day 5 (413 ± 20 ms) (p=0.48).

Pharmacogenomic outcomes

The CYP2D6 genotype analysis revealed: extensive metabolizers (EM) (12, 54%), intermediate metabolizers (IM) (7, 32%), and poor metabolizers (PM) (3, 14%). No ultrarapid metabolizers were detected. We found that CYP2D6 PM status was significantly associated with higher haloperidol concentrations (p = 0.017) (**Supplemental Digital Content Figure 1**). The CYP3A4 genotype analysis revealed: EM (18, 82%) and IM (4, 18%). No ultrarapid metabolizers or PMs were detected. The association between CYP3A4 me-

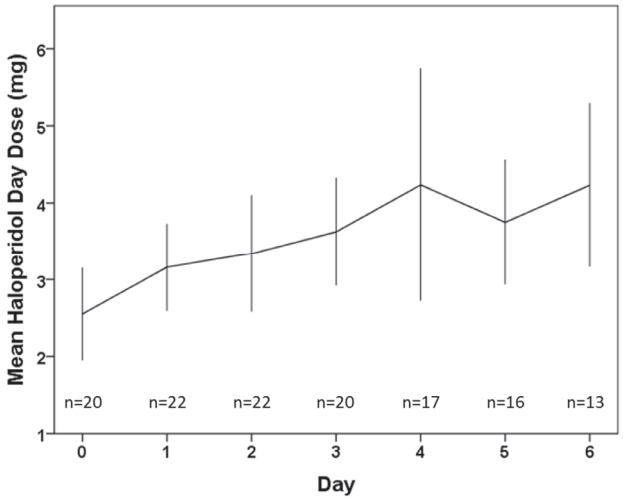


Figure 1: Average haloperidol dose administered each study day
Error Bars: 95% CI

tabolizer status and haloperidol serum concentrations was not found to be significant (p = 0.98) **(Supplemental Digital Content Figure 2).**

Most (18, 82%) patients received CYP2D6 inhibitors (often in combination) as follows: Metoprolol (10), amiodarone (8), metoclopramide (9) times. Many (13, 59%) received CYP3A4 inhibitors (also often in combination): erythromycin (5), amiodarone (7), voriconazole (2) and fluconazole (2).

The very high serum haloperidol concentrations (patient 1: 39.4; 54.4; 15.8; patient 2: 12.1; 10.1; patient 3: 59.9; patient 4: 62,2 µg/L) observed in four patients could be accounted for in two patients by a combination of new onset liver failure, CYP2D6/CYP3A4 genotype status and the administration of medications known to inhibit CYP2D6 and/or CYP3A4. In the other two patients, no clear reason for the high serum haloperidol concentrations observed were found and thus the two samples were excluded from the analysis. Theoretical explanations could be that samples were drawn from same central line haloperidol had recently been administrated through, or an error in the haloperidol measurement.

DISCUSSION

This single-center prospective observational pilot study is the first to evaluate the pharmacogenomics of low-dose haloperidol in critically ill adults with delirium. Scheduled IV haloperidol at dose of up 2mg q8h does not appear to affect delirium symptoms based

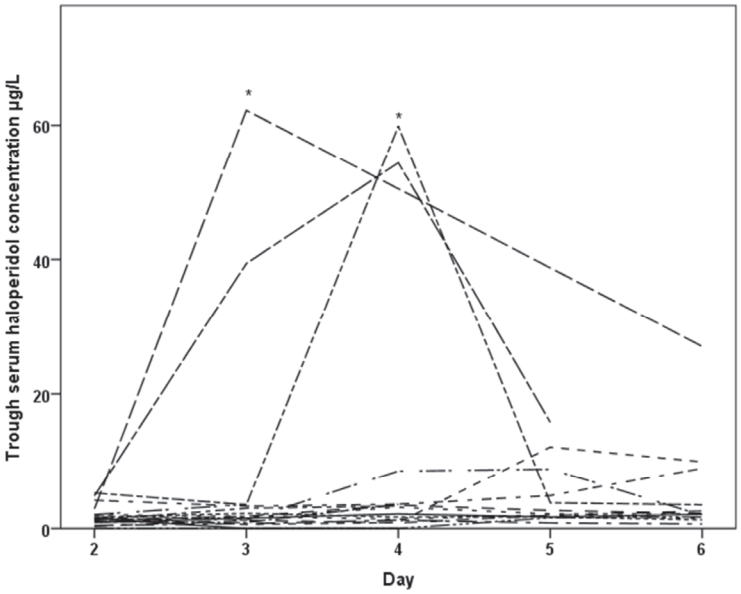


Figure 2: Observed haloperidol through concentrations per patient per day
Two outliers are marked with * and are excluded from statistical analyses

on the ICDSC assessments evaluated. The lack of relationship we observed measured serum haloperidol concentrations and the dose of haloperidol administered suggests that important factors other than age, severity of illness and day of administration account for the haloperidol concentration variability observed. While our results suggest CYP2D6 is an important contributor to this variability future research is required to define all factors that affect the pharmacodynamics response of low-dose haloperidol in critically ill adults.

While our data is consistent with a recent pharmacokinetic sub study from the REDUCE trial, it is important to recognize that the analysis in REDUCE trial was based on haloperidol use in patients without delirium and did not assess pharmacogenomic considerations like cytochrome P450 isoenzyme genotype [6]. It remains unclear if the lack of haloperidol benefit observed in our cohort is simply a result of the subtherapeutic haloperidol concentrations being achieved or reached or an intrinsic lack of response of delirium to haloperidol.

The results of two recent clinical trials in critically ill patients receiving low-dose haloperidol therapy have also reported a lack of effect on delirium resolution, and suggest – subtherapeutic serum concentrations are an important reason for a lack of effect [1,4]. However, the MIND trial [3], where haloperidol was administered at a dose of 15 mg/day, reported an average study day two serum haloperidol trough concentration of 4.5 [2.9,5.8] µg/L - nearly three-times the concentration we report – and also reported no

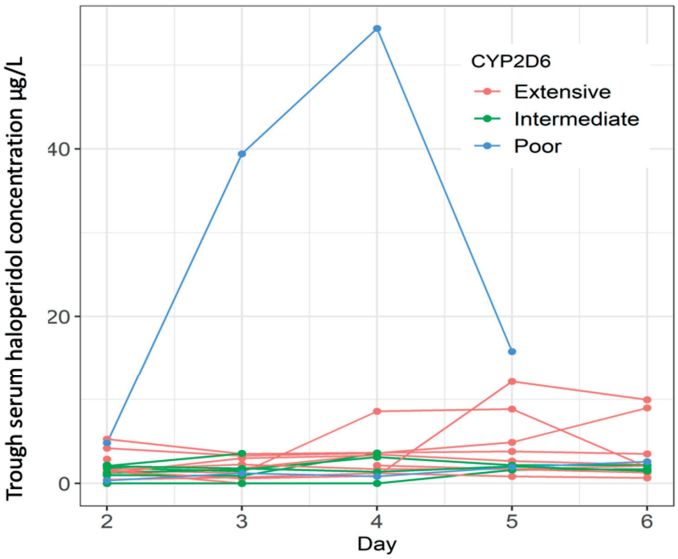
clinical benefit with haloperidol use. Importantly, with the recent MIND-USA trial finding even higher doses of IV haloperidol (20mg/day) not to be associated with improved delirium resolution or other clinical benefit, suggests that haloperidol has an intrinsic lack of effect on delirium [17].

Outside the ICU setting in patients with acute schizophrenia the therapeutic window for positive effects of haloperidol therapy has been reported to be in the range of 5.6 to 16.9 µg/L with a recommended target concentration of 10 of µg/L [9]. Whether the therapeutic haloperidol doses in schizophrenia patients compare with doses needed in an ICU-delirium remains unclear. A recent paediatric ICU study suggested, contrary to our study, that haloperidol is potentially effective but had higher risk for adverse events, despite low haloperidol plasma concentrations (0.005-0.085 mg/kg/d, equal to approximately 0.35 – 5.95 mg/day for an adult weighing seventy kilo) [18].

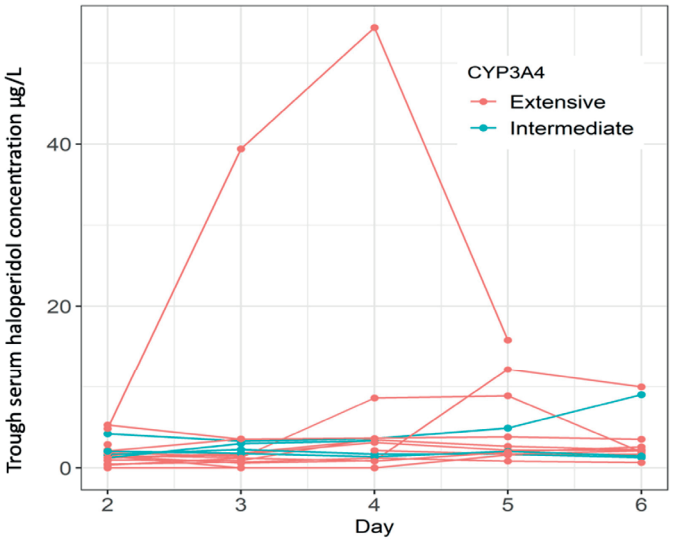
Our study has several limitations. Our analysis was neither controlled nor blinded. Although patients with factors that could influence the clinical, pharmacokinetic or genomic outcomes evaluated were excluded, the heterogenous nature of any ICU population like our population may have confounded the results we report. Our study was a pilot and considering the variability between patients we report; future investigations should focus on evaluating larger numbers of patients and at a greater range of haloperidol dose administration. Although we wanted to keep our analysis as pragmatic as possible, many patients received 1 or more medications known to affect haloperidol serum concentrations. Future studies on PK/PD of haloperidol in critically ill adults should aim to describes clearance, AUC. and distribution volume of haloperidol to test clinical efficacy. Furthermore, more extensive PK studies, e.g. on steady state kinetics and more extensive pharmacogenetics studies are clearly indicated. Finally, future studies may focus more on individual delirium symptoms rather than delirium either being present or absent, given the results of recent trials with haloperidol for ICU delirium.

CONCLUSIONS

This report represents the first prospective study to evaluate the pharmacogenetic parameters of low-dose intravenous haloperidol for the treatment of delirium in critically ill adults. We observed a lack of effect on delirium in a population of patients with stable disease severity during the study may be related to lower than expected serum concentration and the presence of important pharmacogenomic confounders. Our results may explain the lack of clinical efficacy of recent randomized trials of low-dose haloperidol. Further studies on genetic subgroups effects on haloperidol serum through levels and effect on individual delirium symptoms (or delirium as a graded syndrome of brain insufficiency rather than delirium being either present or absent) are needed.



Supplemental Digital Content Figure 1: CYP2D6 metrabolizers distribution of haloperidol serum levels across days



Supplemental Digital Content Figure 2: CYP3A4 metrabolizers distribution of haloperidol serum levels across day

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Chapter 8

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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Chapter 9

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.

Chapter 10

Samenvatting

SAMENVATTING

Delirium is een vaak voorkomend syndroom bij volwassen die zijn opgenomen op een intensive care (IC) afdeling. Een delirium wordt onder andere gekenmerkt door aandacht stoornissen, problemen met oriëntatie en kort termijn geheugen, slecht inzicht en een slecht beoordelingsvermogen en een wisselend bewustzijnsniveau. Patiënten met een delirium verblijven langer op de IC, hebben een groter risico op overlijden in ziekenhuis en hebben een slechtere prognose na ontslag. Voor de optimale zorg met betrekking tot delirium bij IC-patiënten zijn richtlijnen beschikbaar voor de behandeling van pijn, agitatie en delirium bij kritiek zieke patiënten, met toepassing van een geïntegreerde en multidisciplinaire aanpak. De huidige richtlijnen worden echter niet voldoende routinematig gebruikt, ondanks het bewezen nut van de aanbevelingen. De implementatiewetenschap biedt ons de hulpmiddelen en processen om het routinematig gebruik van richtlijnen te verbeteren. Het doel van dit proefschrift was om verschillende aspecten van de implementatie van deliriumrichtlijnen te onderzoeken. Deze studie werd "ICU Delirium in Clinical Practice Implementation Evaluation" (iDECePTIvE) studie genoemd. Drie belangrijke componenten daarvan zijn beschreven.

Eerst is de omvang van de implementatie van de richtlijn in de praktijk in kaart gebracht en zijn de belemmerende en bevorderende factoren voor het naleven van richtlijnen beschreven. Ten tweede is een 'op maat' gemaakte implementatiestrategie ontwikkeld en is de richtlijn geïmplementeerd. Ten derde zijn de effecten geëvalueerd van de implementatie op de naleving van richtlijnen en klinische uitkomsten (aantal delirium- en coma-vrije dagen, duur van mechanische ventilatie, ICU verblijfsduur en mortaliteit) geëvalueerd. Ten slotte is de deliriumbehandeling met lage-dosis haloperidol geëvalueerd door het et meten van de bloedspiegels van haloperidol en deze te relateren aan genetisch profiel van de patiënt.

In **hoofdstuk twee,** is de methode van deze prospectieve multicenter implementatiestudie in vier fases uitgewerkt. In de eerste fase is de huidige behandeling van delirium beschreven evenals het niveau van de naleving van de delirium richtlijnen in de deelnemende IC's. In fase twee zijn de analyse belemmerende en bevorderende factoren voor de implementatie van delirium richtlijnen beschreven. In fase drie is de implementatiestrategie opgezet op basis van de resultaten van fase één en twee. En in de laatste fase is de implementatie van de richtlijnen beschreven samen met de beoordeling van de effecten van implementatie. Hoofdstuk twee sluit af met een Editorial waar we beweren dat er geen 'zilveren kogel' is voor deliriumpreventie en -behandeling en dat delirium, als een multifactoriële aandoening, eerder zal verdwijnen als gevolg van meerdere interventies, bijvoorbeeld in een zorgbundel.

Om inzicht te krijgen in belemmerende en bevorderende factoren hebben we een gedetailleerde analyse uitgevoerd door middel van focusgroep interviews en enquêtes

(**hoofdstuk drie**) onder IC-professionals. Uit het onderzoek was gebleken dat men delirium in de IC als een groot probleem vond, waarvoor een adequate behandeling nodig was. Men was zich echter van bewust dat de aanpak van delirium in het algemeen zou kunnen worden verbeterd. We merkten inderdaad dat de kennis van IC-verpleegkundigen en artsen over screening, preventie en behandeling van delirium voor verbetering vatbaar was. Bovendien werd systematische deliriumscreening door IC-verpleegkundigen slechts bij een derde van de patiënten uitgevoerd. Op de meeste IC's werd geen integraal protocol voor de preventie en -behandeling van delirium gehanteerd. Een van de meest zorgwekkende conclusies was dat IC-professionals er aan twijfelden dat een betere naleving van de richtlijnen echt een verschil zou kunnen maken voor de uitkomsten van de patiënt. Maar aan de andere kant vormde de algehele motivatie voor verandering een bevorderende factor voor richtlijn implementatie.

In **hoofdstuk vier** hebben we een systematische literatuur review beschreven, gericht op het evalueren van implementatie strategieën en hun effecten op klinische uitkomsten betreffende delirium preventie en -management richtlijnen. Uit deze review van de literatuur bleek dat het gebruik van meerdere implementatiestrategieën (meer dan zes) gericht op het veranderen van het gedrag van IC-professionals en / of het gebruik van zorgbundels (bijvoorbeeld de Pain, Agitation and Delirium (PAD-richtlijnen) of de Awakening and Breathing Coordination, Delirium Monitoring, Early Mobility and Exercise (ABCDE-bundel) gericht op delirium interventies was geassocieerd met verbeterde klinische uitkomsten.

Vervolgens hebben we het implementatiemodel van Grol en Wensing gebruikt om een implementatieprogramma te maken gebaseerd op de uitkomsten van de eerste fase (enquête en focus groep interviews) en de bovengenoemde review. Het implementatieprogramma bestond uit verschillende implementatiestrategieën (**hoofdstuk vijf**), voornamelijk samengesteld uit strategieën op organisatieniveau en op professioneel niveau. Deze waren afgestemd op de eerder gevonden belemmerende en bevorderende factoren. In het bijzonder bestond het implementatieprogramma uit voorlichting over delirium (klassikaal onderwijs en e-learning), praktische training (delirium screening), standaardisatie van medisch beleid door implementatie van een preventie- en behandelprotocol en vergroting van de betrokkenheid van de familie van IC-patiënten. Aanbevelingen uit de PAD-richtlijnen van 2013 die pleiten voor delirium- en sedatiescreening, lichte sedatie, analgesie bij sedatie, preventieve maatregelen en andere behandel aanbevelingen werden opgenomen in een praktisch protocol en geïmplementeerd in twee fasen. Eerst hebben we een op maat gemaakte implementatie van deliriumscreening uitgevoerd en daarna hebben we een protocol voor de preventie en behandeling van delirium geïmplementeerd. Professionals van de IC's waren hierbij betrokken om een betere aansluiting op de praktijk te bewerkstelligen en om de doeltreffendheid van de implementatie te vergroten. Gegevens werden verzameld vóór de implementatie, na de

implementatie van delirium screening en na de implementatie van het behandelprotocol. De naleving van deliriumrichtlijnen werd gemeten en de veranderingen werden berekend voor de verschillende perioden. In totaal 3.930 patiënten (overeenkomend met meer dan 18.000 IC-dagen) werd opgenomen in de analyse. Het opvolgen van de richtlijnaanbevelingen verbeterde na de implementatie. Deliriumscreening verbeterde aanzienlijk na de implementatie en bleef op peil na volledige implementatie van de richtlijn. Na de implementatie hebben IC-verpleegkundigen deliriumscreening toegepast tijdens meer dan 90% van alle patiëntdagen. Meer dagen met 'lichte sedatie' werden gemeten en het gebruik van benzodiazepinen voor sedatie nam af. 'Analgesie bij sedatie' bij gesedeerde patiënten verbeterde na beide implementatieperioden. Er was ook een verbetering in de toepassing van preventieve maatregelen zoals vroege mobilisatie en fysiotherapie. De duur van het delirium nam af van 5,6 dagen naar 3,3 dagen, en het percentage coma-dagen nam af van 14% naar 9% na de implementatie. Voor andere patiëntuitkomsten, zoals de duur van de beademing, de duur van ICU-verblijf en de mortaliteit, vonden we geen verbeteringen tussen de meetperioden.

In **hoofdstuk zes** zijn we dieper ingegaan op het implementatieproces. Zes maanden na de implementatie, zoals beschreven in hoofdstuk vijf, hebben we voor het laatst patiëntengegevens verzameld om de duurzaamheid van de implementatie bij alle deelnemende IC's te meten. We onderzochten ook de uitvoering van het implementatieprogramma op individueel IC-niveau; de impact van de implementatie op belemmerende factoren en de kennis van professionals; en de ervaringen van de lokale implementatieteams met het implementatieprogramma. We hebben vastgesteld dat de implementatie volgens plan is uitgevoerd. De implementatie van deliriumrichtlijnen was haalbaar en de meeste belemmerende factoren waren weggenoen. De kennis over delirium was toegenomen en de naleving van de richtlijnen was verbeterd (ook zes maanden na de laatste implementatieactiviteiten). Ondanks een uniforme implementatiestrategie voor alle IC's waren er echter duidelijke verschillen in het opvolgen van de richtlijn tussen de IC's.

Om tegemoet te komen aan een belangrijke belemmerende factor voor implementatie, namelijk de twijfels bij sommige IC-professionals over de werkzaamheid van haloperidol, hebben we de studie uitgevoerd naar het effect van haloperidol op deliriumsymptomen (**hoofdstuk zeven**) in een van de IC's. Geen van de meest recente haloperidol IC studies die tot op heden zijn gepubliceerd, bevatte farmacokinetische gegevens en daarom was de farmacodynamische respons van een lage dosis haloperidol voor de behandeling van delier bij ernstig zieke volwassenen onduidelijk. Daarom hebben we geprobeerd om de farmacodynamische, farmacokinetische en farmacogenetische karakteristieken van een lage dosis haloperidol behandeling op de IC te karakteriseren. De betrokken tweeëntwintig patiënten kregen een gemiddelde dagelijkse dosis haloperidol van 3,5 ± 1,8 mg. Serum dal haloperidol concentraties waren niet significant geassocieerd met

de dagelijkse toegediende haloperidol dosis, dagelijkse aanwezigheid van delirium of delirium score. Een langzame CYP2D6 metaboliet was geassocieerd met significant hogere haloperidolconcentraties, maar er werd geen verband gevonden tussen de CYP3A4-metabolieten en haloperidolconcentraties. Er zijn geen verlengde QTc-intervallen boven 500 ms gemeten.

In **hoofdstuk 8** worden de belangrijkste bevindingen van ons onderzoek samengevat, en uitgebreid bediscussieerd (algemene discussie).

Appendices

PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

Name PhD student: Z. Trogrlić Erasmus MC Department Intensive Care Research School: COEUR	PhD period: 2012 – 2019 Promotor(s): prof. dr. J. Bakker Supervisors: dr. E.Ista and dr. M. van der Jagt

1. PhD training			
	Year	**Workload (Hours)**	**ECTS**
General academic skills			
- Biomedical English Writing and Communication	2012	112	4.0
- Research Integrity	2012	5	0.2
- BROK course - Erasmus MC; Rotterdam	2012	40	1.5
- EndNote Course	2012	14	0.5
- Atlas.ti course - Qualitative data analysis	2012	28	1.0
- LimeSurvey administrator training	2013	28	1.0
- NFU – re-registration BROK	2017	5	0.2
Research skills / In-depth courses			
Causal Inference and Data Analysis – Erasmus Summer program	2012	56	2.0
Methodology implementation – iBGM	2012	14	0.5
Erasmus Winter Programme: Regression Analysis for Clinicians	2015	28	1.0
International conferences			
Brussel ISICEM	2013 & 2014	84	3.0
	2013	84	3.0
EDA symposium – Leuven	2014	16	0,6
BHAAS symposium Bosnia	2016	14	0.5
ESICM LIVES – Milano – Symposium		84	3.0
Seminars and workshops			
PhD-day 2012; Erasmus MC Rotterdam	2012	8	0,3
Schakels in de zorg	2013	28	1.0
	2014	28	1.0
Delirium consortium NL – Leeuwarden	2013	5	0.2
Symposium Kwaliteit en Implementatie: Durf de uitdaging aan!	2013	3	0.1
Delirium consortium NL	2014	5	0.2
Symposium "Een dag om nooit te vergeten" Gelre Ziekenhuizen Apeldoorn	2014	5	0.2
Topics in IC congress – Presentation Euridice trial	2017	5	0.2
Topics in IC congress – Presentation iDECePTIvE study	2018	5	0.2
Intensivistendagen Symposium 2019 - Rotterdam	2019	8	0.3
Didactic skills			
Supervision nurse student	2013	42	1,5
Supervision research nurses (multicentre)	2014	168	6.0
Implementation EMC / lectures	2013 - 2019	67	2,4

Other			
Self-study Webdesign RapidWeaver	2013	12	0,4
NVIVO qualitative research software self-study	2013	12	0,4
European Resuscitation Council: Immediate Life Support	2017	8	0,3
Lecturing			
- Supervision Nursing scientist student	2013	42	1.5
- Supervision Research Nurse's 5 hospitals	2012 - 2014	112	4.0
- Supervision Erasmus MC ICU / implementation	2013	40	1.5
- Presentations ICU Erasmus MC	2013 - 2019	31	1.1
- Lecture implementation Zorgacademie	2013 - 2019	11	0.4
- Lecture Pain – Agitation – Delirium guideline (ICU nurses, ICU physician assistants)	2014 - 2019	28	1.0
Other			
IC-Bulletin (ICU research newspaper): design and redaction	2013 - 2015	56	2.0
Chairman TopicsinIC congress	2015 - 2019	112	4.0
TOTAL		1453	**52.2**

LIST OF PUBLICATIONS

Publications related to this thesis

- Ista E, Trogrlić Z, Bakker J, Osse RJ, van Achterberg T, van der Jagt M. Improvement of care for ICU patients with delirium by early screening and treatment: study protocol of iDECePTIvE study. Implement Sci. **2**;9:143 (2014)
- van der Jagt M, Trogrlić Z, Ista E. Untangling ICU delirium: is establishing its prevention in high-risk patients the final frontier? Intensive Care Med **40**(8):1181-2 (2014)
- Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PH, Ista, E. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care **9**;19:157 (2015)
- Trogrlić Z, Ista E, Ponssen HH, Schoonderbeek JF, Schreiner F, Verbrugge SJ, Dijkstra A, Bakker J, van der Jagt M. Attitudes, knowledge and practices concerning delirium: a survey among intensive care unit professionals. Nurs Crit Care **22**(3):133-140 (2017)
- Trogrlić Z, van der Jagt M, Lingsma H, Gommers D, Ponssen HH, Schoonderbeek JFJ, Schreiner F, Verbrugge SJ, Duran S, Bakker J, Ista E. Improved Guideline Adherence and Reduced Brain Dysfunction After a Multicenter Multifaceted Implementation of ICU Delirium Guidelines in 3,930 Patients. Crit Care Med **47**(3):419-427 (2019)

Publications unrelated to this thesis

- Z. Trogrlić, L. Brouwer, M. Hoogendoorn, R. van Linge, NAS score: Nursing Activities Score: onderzoek naar de responsiviteit van de NAS items Open access via de Utrecht universiteit: http://dspace.library.uu.nl/handle/1874/178792?_ga=1.148475639.1509501775.1449813312
- Speksnijder H, Trogrlić Z, Lima A, Bakker J, dos Reis Miranda D. Endotracheal suctioning with nonsterile gloves and only when necessary! Intensive Care Med **41**(8):1500-1. (2015)
- Z. Trogrlić, M. van der Jagt, E. Ista, Implementatie van Deliriumrichtlijn op volwassen Intensive Care. Vip Science (Wetenschappelijk magazine voor verpleegkundigen in het Erasmus MC), November 2016

CURRICULUM VITAE

Zoran Trogrlić was born on October 19th 1974 in Zenica, Bosnia and Herzegovina. He graduated from Medical Secondary School "Desanka Todić", Zenica as a registered nurse in 1993. During this time the Bosnian civil war was ongoing and he worked almost two years as a nurse at the department of intensive care at Zenica hospital. During this time, he attended the Emergency Medical Course, provided by International Medical Corps (ICM), and has become skilled for emergency situations like airway management and intubation, cardiopulmonary resuscitation, bleeding control, and the triage of mass trauma victims. After coming to the Netherlands as a political refugee in 1993 following the civil war, he assimilated in the Netherlands by following different language and literature courses and has obtained his diploma "Dutch as a Second Language" at 1996. From 1996 to 2000 he studied Nursing at "Rotterdam University of Applied Sciences – formal "Hoge School Rotterdam" and he received his Bachelor of Nursing degree in 2000. Directly after receiving his Bachelor of Nursing degree he followed the specialization for intensive care unit nurse and has received his degree as ICU nurse at 2001.

From 2007 to 2010 he studied Nursing Science at the Utrecht University and received his Master of Science degree in 2010, while working as intensive care nurse at the Department of Intensive Care for adults at the Erasmus MC, University Medical Center, Rotterdam. From 2001 until present he works as intensive care nurse and from 2010, he combines his nursing work with a research at the Department of Intensive Care for adults at the Erasmus MC, University Medical Center, Rotterdam. In 2012 he started as a PhD student under the supervision of prof. dr. J. Bakker resulting in this thesis.

From 2015 he is a chairman of multidisciplinary Intensive Care congress named "Topics in Intensive Care". He actively participates in the training of ICU nurses, medical students, and surgery and anesthesia assistants by teaching about delirium, sedation, pain management and implementation in general.

Zoran is married to Danijela Dilber, they have two children Marja and Gabriela.

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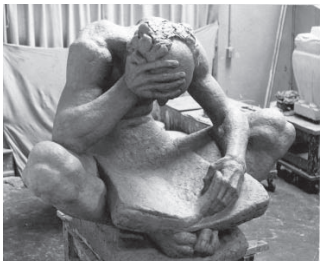

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