Article

Scoping review of the use of virtual reality in intensive care units

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Hill, James Edward ORCID: 0000-0003-1430-6927, Twamley, Jacqueline, Breed, Hetty, Kenyon, Roger, Casey, Rob, Zhang, Jennifer and Clegg, Andrew ORCID: 0000-0001-8938-7819 (2021) Scoping review of the use of virtual reality in intensive care units. Nursing in Critical Care . ISSN 1362-1017

Scoping review of the use of Virtual Reality in Intensive Care Units

Abstract

Background

A wide range of reviews have demonstrated the effectiveness and tolerability of Virtual Reality (VR) in a range of clinical areas and subpopulations. However, no previous review has explored the current maturity, acceptability, tolerability, and effectiveness of VR with intensive care patients.

Aims:

To identify the range of uses of VR for intensive care patients, classify their current phase of development, effectiveness, acceptability, and tolerability.

Methods

A scoping review was conducted. A multi-database search was undertaken (inception to January 2021). Any type of study which examined the use of VR with the target application population of intensive care patients were included. Screening, data extraction and assessment of quality was undertaken by a single reviewer. A meta-analysis and a descriptive synthesis were undertaken.

Results

Six hundred and forty-seven records were identified, after duplicate removal and screening twenty-one studies were included (weak quality). The majority of studies for relaxation, delirium and Post Traumatic Stress Disorder (PTSD) were at the early stages of assessing acceptability, tolerability and initial clinical efficacy. Virtual Reality for relaxation and delirium were well-tolerated with completion rates of target treatment of 73.6%, (95%CI:51.1%–96%, I^2=98.52%) 52.7% (95%CI:52.7–100%, I^2=96.8%). The majority of reasons for non-completion were due to external clinical factors. There were some potential benefits demonstrated for the use of VR for relaxation, delirium and sleep.

Conclusion

Virtual Reality for intensive care is a new domain of research with the majority of areas of application being in the early stages of development. There is great potential for the use of VR in this clinical environment. Further robust assessment of effectiveness is required before any clinical recommendations can be made.

keywords: Virtual reality, intensive care, acceptability, effectiveness, tolerability.

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Introduction

During admission intensive care units (ICU) patients can experience multiple periods of intense pain (1), anxiety (2), depression (3), delirium (4), sleeping disorders (5) and hallucinations (5). These experiences can leave them facing the possibility of long-term physical, cognitive, and quality of life impairments (6-9) and a psychological legacy (5, 10). This psychological legacy can manifest in many forms, causing anxiety (11), depression (11, 12) and post-traumatic stress (13) disorders, which may have wider negative impacts (e.g. long-term unemployment) (14, 15). Prevention is a priority, and it is thought that virtual reality (VR) may offer a unique therapeutic benefit (16-19).

The concept of VR as an intervention has developed over time, with early VR definitions referring to a virtual representation of self in a digital environment, to more recent definitions which refer to the specific use of 3D-generated environments viewed through VR headsets (20). Alongside the use of a VR headset other sensory channels can be used such as vision, hearing, touch, smell, and taste to increase the realism of the environment (21). As well as being able to create a realistic virtual environment, VR also provides a method of real-time feedback allowing direct monitoring of patients' performance and outcomes (22). Due to this diverse functionality and the reducing costs of VR technology, VR research and development is gaining popularity for clinical applications (19).

Background

The use of VR has been assessed in a range of diverse clinical populations such as dementia (23), cerebral palsy and Down's syndrome (24), chronic neck pain and shoulder impingement syndrome (25), dental anxiety and phobia (26), and Parkinson's Disease (27). Multiple reviews have been undertaken demonstrating the effectiveness of VR for pain (28), morbidity, (29), post-traumatic stress (30), anxiety (31) and depression (31) in the general public. These reviews all demonstrate the potential efficacy that VR may provide in preventing and managing some of these long-term impairments for ICU patients. To the best of our knowledge there has not been a systematic review exploring any aspect of VR use for the specific population of ICU patients. As ICU patients have unique clinical and environmental needs, which may substantially affect the types of application of VR and acceptability, it is important to assess the use of VR for this specific population. This review has been carried out as part of a larger project looking at developing the use of VR for ICU patients to prevent post-traumatic stress disorder (PTSD). Thus, this scoping review will help to identify the current maturity, potential effectiveness, acceptability, and tolerability of VR use for ICU patients. With the focus of providing recommendations for future research and potential areas for further development.

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Aims

The aim of this review was to identify the range of uses of VR for ICU patients and classify their current phase of development. The secondary aims of this review were to identify evidence of effectiveness, acceptability and tolerability of the use of VR with ICU patients.

Design and methods

The methodology of the scoping review was based on Peters et al (2015) and Levac et al (2010) guidance on how to undertake a scoping review (32, 33). All stages of this review have been undertaken with patient engagement, (XX) who has helped design and undertake the scoping review. This was both in the writing of the manuscript and attendance at fortnightly meetings to discuss findings and focus of the review.

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Search

A multi-database search was undertaken on Medline, Embase, CINAHL, PsycINFO, Cochrane Library and WoS from date of inception to January 2021 (see supplementary electronic file 1 for search strategy). Additional studies were identified through screening of all included studies and relevant systematic reviews' reference lists. Duplicate removal was undertaken using EndNote. No language restrictions were used.

Study selection

We included any type of study which explored the use of VR with a target population of ICU patients. We defined VR as an artificial environment which is experienced through sensory stimuli (such as sights and sounds) and in which one's actions partially determine what happens in the environment (34), delivered through a head-mounted headset display. We classified an ICU as a unit which provides a spectrum of monitoring and life support technologies and serves as a resource for the care of critically ill patients (35). No specific outcomes were set as an inclusion criterion.

We excluded any discussion papers or commentaries. Any review/systematic review which met the inclusion criteria were not included, but were screened for any additional papers. Study selection occurred through two stages. A single reviewer screened titles and abstracts using EndNote software (JH) and then screened the full manuscripts of any citations meeting our inclusion criteria (JH).

Data extraction and quality assessment

Data extraction was carried out by a single reviewer using a pre-piloted form (XX or XX). The data items which were extracted were Date of publication, Study type, Country of study, Population, Number of patients, Attrition rate, Age, Focus of intervention, Intervention type, Technology used, Comparator (if applicable), Outcomes, Results (including Acceptability) and Phase of development. The phase of development was coded using a three-tiered approach, this was:

- VR1 studies which focused on content development by working with patient and provider end-users through principles of human-centred design.

- VR2 trials that conducted early testing with a focus on feasibility, acceptability, tolerability, and initial clinical efficacy.
- VR3 trials which were randomized controlled trails that compared clinically important outcomes between intervention and control condition.

This coding system was used to identify the stage of development for which VR was being used in different situations in ICU (36). The focus of the use of VR was defined by the primary aim of the study. Assessment of quality was undertaken by a single reviewer (xx or xx) using the quality assessment tool Effective Public Health Practice Project (EPHPP) (37). Only studies which reported effectiveness outcomes were quality assessed. No studies were excluded based on quality.

Data synthesis

Studies were synthesized through a structured narrative summary and tabulation of findings, based on both the clinical focus of studies and the phase of development of VR (38). Outcomes assessing effectiveness were not meta-analysed due to heterogeneity associated with the outcomes measured and tools used. Treatment acceptability was assessed through a narrative review of patient perceptions and adverse events (e.g. motion sickness). Rates of treatment acceptability were meta-analysed. This was defined as the proportion of people who received the full proposed number of sessions defined within the methods or if provided protocol. Through a random effects model (DerSimonian-Laird) of the proportion of participants who completed the target number of treatment sessions (39). Heterogeneity was assessed through visual inspection of forest plots and the I-squared statistic (I^2). Meta-analyses were undertaken using OpenMeta [Analyst](40).

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Results

Our search strategy identified 647 records which, after duplicate removal, resulted in 432 records. Screening of title and abstract identified 42 records for paper screening, with 21 individual studies presented in 25 papers included in the review. No additional papers were identified through screening of citations of included studies. Most studies were excluded on full paper screening due to the target population for the use of VR not being ICU patients. The remaining papers were excluded due to not using VR headsets or being a commentary piece (see Figure 1 for PRISMA flow diagram (41)). This resulted in 15 completed published studies and six registered trials being identified (18, 42-65).

All included studies were published between 2017 to 2020 (18, 42-65) with the majority published in 2020 (18, 47, 50-52, 55-57, 60, 63, 64). The country of study varied with studies taking place in France (54, 55), Netherlands (57, 58, 62), Singapore (59), South Korea (50, 51), Switzerland (44-46, 56), United Kingdom (52, 53) and the United States (18, 42, 43, 47-49, 60, 63, 64, 66). The mean age of included participants ranged from 21 to 66.42 years (42, 43, 48, 50, 51, 67). There were seven different primary uses of VR in ICU (defined by primary aim of study), specifically relaxation, delirium, PTSD, sleep, lower limb function, early neurocognitive stimulation and orientation (See Table 1 for full study characteristics).

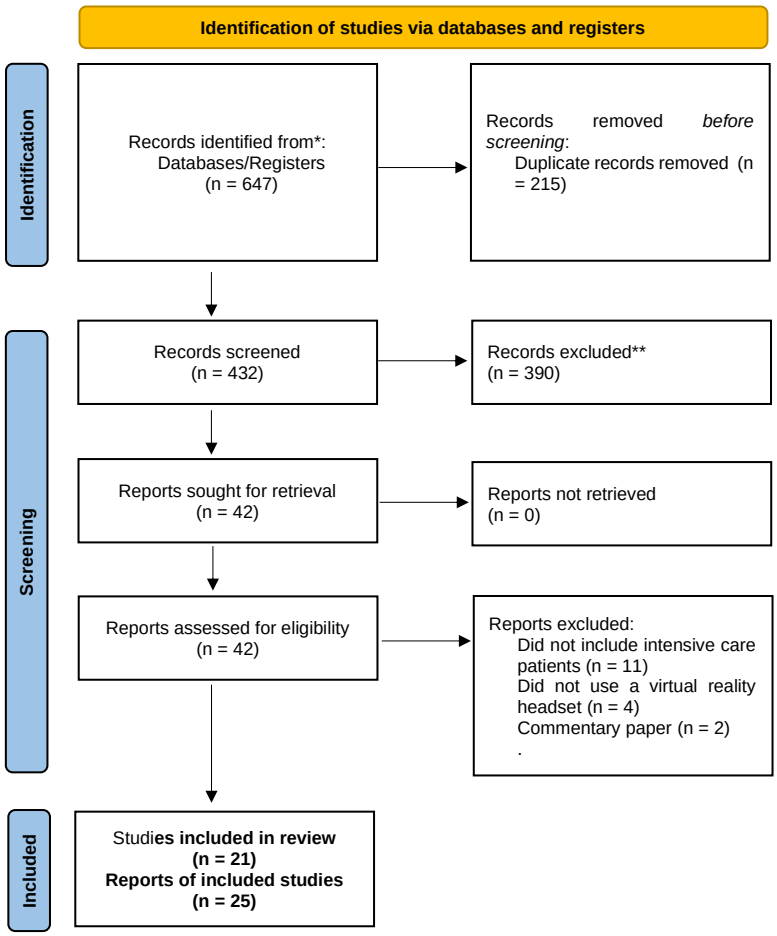

Figure 1 PRISMA 2020 flow diagram for systematic reviews

Table 1: Study Characteristics

Study name	Study type	Country of study	Population	Number of patients who are exposed to VR	Attrition rate[a]	Mean age	Intervention	Hardware	Relaxing environment with audio	Level of research
Gerber et al (2017) (46)	Single arm prospective repeated measures design study	Switzerland	ICU patients (critically-ill)	37	37	48	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR2
Gerber et al (2019a) (45)	Single arm prospective repeated measures design study	Switzerland	healthy subjects	45	45	NR	VR for Relaxation (anxiety)	HTC Vive VR Headset 1080 x 1200	Relaxing environment with audio	VR2
Gerber et al (2019b) (44)	Single arm prospective repeated measures design study	Switzerland	ICU patients	57	33	63	VR for Relaxation (anxiety)	Noise-cancelling headphones	Relaxing environment with audio	VR2
Jawed et al (2020) (47)	Single arm prospective study	USA	ICU patients and providers (current)	15 patients and 21 providers	NR	61	VR for Delirium	Samsung Gear	Relaxing environment with audio	VR2
Kapil et al (2020), Blair et al (2019, 2018) (42, 43, 48)	Case report	USA	ICU patients (critically-ill)	1	1	21	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR2

Study name	Study type	Country of study	Population	Number of patients who are exposed to VR	Attrition rate[a]	Mean age	Intervention	Hardware	Relaxing environment with audio	Level of research
Krogg et al (2018) (49)	Developmental/ commentary	USA	ICU patients (current)	NR	NR	NR	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR1
Lee and Kang (2020), Lee et al (2020) (50, 51)	RCT	South Korea	ICU patients (current)	26	24	66.42	VR for sleep	NOON PRO	Relaxing environment with audio	VR3
Lynch and Jones (2020) (52)	Protocol: Single arm prospective study	United Kingdom	ICU patients (current)	25	NR	NR	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR2
Munby et al (2019) (53)	Development/ commentary	United Kingdom	ICU patients Pre and current	NR	NR	NR	VR For orientation	NR	Virtual reality ICU Ward	VR1
NCT03569358 (ClinicalTrials.gov) (65)	RCT	Malaysia	ICU patients (critically-ill)	20	NA	NA	VR for potential early neurocognitive stimulation	FOVE VR VR headset 2560 x 1440	Relaxing environment with audio	VR3
NCT04017299 (ClinicalTrials.gov) (54)	RCT	France	ICU patients (current)	60	NR	NR	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR3
NCT04441164 (ClinicalTrials.gov) (55)	RCT	France	ICU patients (previous patient)	NR	NR	NR	VR for lower limb function	NR	Relaxing environment with audio	VR3

Study name	Study type	Country of study	Population	Number of patients who are exposed to VR	Attrition rate[a]	Mean age	Intervention	Hardware	Relaxing environment with audio	Level of research
NCT04498585 (ClinicalTrials.gov) (56)	RCT	Switzerland	ICU patients (current)	NR	NR	NR	VR for Delirium	NR	Relaxing environment with audio	VR3
NL8835 (WHO) (57)	RCT	Netherlands	ICU patients (previous patient)	80	NR	NR	VR for PTSD	NR	Relaxing environment with audio	VR3
NTR6795 (Netherlands Trial Register) (58)	RCT	Netherlands	ICU patients (previous patient)	50	NA	NA	VR for PTSD	NR	Relaxing environment with audio	VR3
Ong et al (2020) (18)	Single arm prospective pre- and post-test design study	USA	ICU patients (current)	59	46	50	VR for, Delirium	Google Daydream with a smart phone Bluetooth headphones	Relaxing environment with audio	VR2
Quah et al (2019) (59)	RCT	Singapore	ICU patients (critically-ill)	11	NR	NR	VR for potential early neurocognitive stimulation	NR	Relaxing environment with audio	VR3
Suvajdzic et al (2019) (66)	Single arm prospective pre- and post-test design study	USA	ICU patients (not intubated)	37	10	56.9	VR for Delirium	Google Daydream with a smart phone	Relaxing environment with audio	VR2

Study name	Study type	Country of study	Population	Number of patients who are exposed to VR	Attrition rate[a]	Mean age	Intervention	Hardware	Relaxing environment with audio	Level of research
								Hand-held controller		
Van et al (2017) (62)	Single arm retrospective study	Netherlands	ICU patients (previous patient)	67	NR	NR	VR for PTSD	NR	Relaxing environment with audio	VR2
Wacker and Haley (2020) (63)	Single arm prospective pre- and post-test design study	USA	ICU patients (critically-ill)	10	10	NR	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR2
Zheng et al (2020), Schecter et al (2020) (60, 64)	Single arm prospective pre- and post-test design study	USA	ICU patients (current)	60	9	61	VR for Relaxation (anxiety)	NR	Relaxing environment with audio	VR2

Key: a) The number of people who received the full proposed number of sessions defined within the methods or if provided protocol. VR1: studies focus on content development by working with patient and provider end-users through principles of human-centred design, VR2: studies conduct early testing with focus on feasibility, acceptability, tolerability, and initial clinical efficacy. VR3: trials are randomized controlled trails that compare clinically important outcomes between intervention and control condition.NR: Not reported. NA: Not applicable, RCT: Random controlled trial.

Assessment of quality for included effectiveness studies

All 11 quantitative evaluation studies were judged to be of weak quality due to a wide range of methodological issues, with the most common issue being the lack of blinding of both patients and outcome assessment. The second most common issue was concerns of confounding variables. This was only assessed between groups in two randomized controlled trials (RCTs) and one single arm prospective repeated measures design study which assessed possible effect of age. All of the studies reported key possible confounding variables, but no detailed assessment was carried out. The majority of studies were of weak methodological design, with only two RCTs being identified. Six registered protocols for ongoing RCTs were identified, indicating that more robust evidence on effectiveness may be published in the future. Many of the concerns identified were due to poor reporting of study methods.

Table 2: Assessment of quality using the quality assessment tool for quantitative studies (EPHPP) (35).

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal & Drop outs	Intervention Integrity	Analysis	Agreed Rating
Gerber (2017) (46)	3	2	2	2	2	1	2	2	3
Gerber (2019a) (45)	2	2	3	3	2	1	2	2	3
Gerber et al (2019b) (44)	2	3	3	3	2	2	1	2	3
Jawed et al. (2020) (47)	3	3	3	3	2	3	3	3	3
Kapil et al (2020), Blair et al (2018, 2019) (42, 43, 48)	3	3	3	3	3	1	2	3	3
Lee and Kang (2020), Lee et al (2020) (50, 51)	1	1	1	3	3	1	2	1	3
Ong (2020) (18)	3	2	3	3	1	2	2	1	3
Quah et al (2019) (59)	1	1	1	3	3	3	2	2	3
Suvajdzic et al (2019) (66)	3	2	3	2	2	2	2	2	3
Wacker and Haley (2020) (63)	3	3	3	3	3	3	3	3	3
Zheng et al (2020), Schecter (2020) (60, 64)	3	3	3	3	3	3	2	1	3

Key: Quality assessment rating - 1 Strong, 2 Moderate, 3 Weak.

Table 3: Effectiveness for VR for relaxation, delirium, sleep and early neurocognitive stimulation

Effectiveness VR for Relaxation					
Study	**Study type**	**Number of patients exposed to VR**	**Attrition rate (number of patients who received full target number of sessions)**	**Interventions**	**Results**
Kapil et al. (2018) (48)	Case report	1	1	Relaxing environment with audio	The patient reported improvements in her anxiety levels post virtual reality therapy (VRT). The clinical team also noted a reduction in her vital signs after each session of VRT.
Wacker and Haley 2020 (63)	Single arm prospective Pre-and post-test design study	10	10	Relaxing environment with audio	Following 5-minute VRT sessions all but one of their participants reported a reduction in their anxiety levels post intervention. It is important to note that no further detail on the participants of this study or the analysis methods used are reported in this publication.
Zheng (2020), Schecter et al (2020) (60, 64)	Single arm prospective Pre-and post-test design study	60	9	Relaxing environment with audio	Anxiety levels were reduced in all three of the sessions: in session one by – 1.7cm (95% CI – 1.1 to –2.2, $p < 0.0001$, N=60) in session two by –1.2cm (95% CI – 0.5 to –1.8, $p = 0.0008$, N=29); and in session three by –1.1cm (95% CI –0.6 to –1.7, $p = 0.0002$, N=9). A significant difference was also observed in the recorded pain scores in session one (decreased by – 1.1cm, 95% CI -0.6 to –1.7, $p = 0.016$, N=60) and session two (decreased by – 1.0, 95%CI –0.4 to –1.5, $p = 0.0015$, N= 29), however no significant difference was seen during session three (n=9). These scores

					were support by results of a 5-point Likert scale of agreement, in which 42/60 (70%) of participants reported that they felt less anxious after session one, 18/29 (62%) following session two and 5/9 (56%) after the third session. Furthermore 27/60 (45%) reported that they were in less pain after session one, 18/29 (62%) after session two and 3/9 (33%) after the third session.
Gerber et al 2017 (46)	Single arm prospective repeated measures design study	37	37	Relaxing environment with audio	A significant reduction in the vital signs of participants over the time during the VRT sessions, including a reduction in heart rate (time effect (t)=-2.704, p=0.007, N=37), respiratory frequency (RF) (t=-2.020, p=0.044, N=37), and mean arterial pressure (MAP) (t=-1.981, p=0.049, N=37). The participants who had higher baseline measurements seemed to benefit the most, as their RF and MAP had significantly higher time effects than those with low baseline measurements.
Gerber et al.(2019a) (45)	Single arm prospective repeated measures design study	45	45	Relaxing environment with audio (Three exposures of 10 minutes of dynamic, virtual, natural, and urban)	Analysis showed the nature themed VR simulation had a significant negative correlation of respiration rate and time (negative time effect) (45) rate of the participants (95% confidence interval (CI) Infinity (-Inf) to -0.024; t_{42}=-2.13; p=0.02). In contrast, neither the urban simulation or ICU TV simulation had any significant effect. Again when analysing the time effect of the VR simulation on heart rate the nature VR again had a significant negative time effect (95% CI - Inf to -0.177, t_2=-7.53; p<0.001), this

					was also observed in the urban VR simulation (95% CI –Inf to 0.161; t_{40}=−7.35; P<.001) and in the ICU TV simulation (95% CI –Inf to 0.141; t_{38}=1.31; P<.001). The nature VR simulation was shown to have a relaxing effect on heart rate (95% cI -Inf to 0.141; t_{38} = 1.31; P<0.001). No significant changes were observed in blood pressure of the participants during the intervention.
Gerber et al.(2019b) (44)	Single arm prospective repeated measures design study	57	33	Relaxing environment with audio	Although the focus of the study was the acceptance of the VR device, they reported a significant difference in the vital sign parameters measured. Respiratory rates were measured at two points, in the first 15 seconds of the therapy session and the last 15 seconds in each of the three VRT sessions, a reduction in respiratory rate was observed in each of the individual sessions. However, on further analysis no significant difference was seen when the sessions were compared. Likewise, no significant difference was reported when comparing heart rate or blood pressure.

Effectiveness VR for Delirium					
Study	**Study type**	**Number of patients of those who are exposed to VR**	**Attrition rate (number of patients who received full target number of sessions)**	**Interventions**	**Results**
Ong et al (2020) (18)	Single arm prospective Pre-and post-test design study	59	46	Relaxing environment with audio (once daily for up to 7 days)	Of the 46 subjects that participated in a VR session, 13 were delirious for at least 1 day during their admission. 81% of participants agreed with the following statement, "I feel that I experienced less pain yesterday because of the DREAMS". However, results from the Defence and Veterans Pain Rating Scale (DVPRS) did not support this as no statistical significance was found. A statistically significant decrease in anxiety was observed by the reported Hospital Anxiety and Depression Scale (HADS) scores (anxiety: –2.17; 95% CI, –4.23 to –0.106, N=46) and (depression: –1.25; 95% CI, –2.37 to –0.129, N=46)) when comparing scores before initial exposure and following third exposure. It is important to note that only 12 of the participants had three or more exposures. No statistically significant differences were observed from pre- to post-intervention for systolic and diastolic blood pressure, mean arterial pressure, heart rate and respiratory.

Jawed et al. 2020 (47)	Single arm prospective study	N/R	61	Relaxing environment with audio (15-minute daily sessions)	The reporting for their effectiveness results is difficult to comprehend and lacks statistical analysis. However, they state of their 15 participants, six reported an improvement in their anxiety, while eight participants felt no change in their pain or discomfort levels. The study population was however small and restricted to relatively stable patients on the ICU, due to the lack of repeats and statistical analysis conclusions made from this study should be considered weak.
Suvajdzic et al 2019 (66)	Single arm prospective pre-and post-test design study	37	10	Relaxing environment with audio (5-min family-friendly VR Films + 5-10-Minute beaches, forests, famous locations	After one hour session pain scores were seen to decrease (m=3.50 1 hour before the session, m=2.78 one hour after, N=10), however began increasing two hours after the session. Statistical analysis by paired t-tests showed no significant difference in the pain scores recorded one hour before and one hour after the session. Unfortunately results for the outcome measures affect and sleep were only reported for two participants. Vital signs were recorded at hourly intervals and showed no differences from two hours pre-intervention to twp hours post-intervention. All participants Were Confusion Assessment Method for the ICU (CAM-ICU) negative until discharge.

Effectiveness VR for Sleep					
Study	**Study type**	**Number of patients of those who are exposed to VR**	**Attrition rate (number of patients who received full target number of sessions)**	**Interventions**	**Results**
Lee and Kang 2020, Lee et al 2020 (50, 51)	Randomised controlled trial	26	24	VR meditation to improve sleep (30 minutes) Vs standard interventions (ear plugs and mask)	Data was collected in the form of a self-reported sleep questionnaire as well as data from a FitBit Charge 2 activity tracker. The researchers observed significantly higher subjective sleep quality scores in the VRT group when compared to controls (Mean sleep quality score = 2.25 ± 0.19, N= 24 VS 2.06 ± 0.2 1, N=24, p = .002). Although when comparing activity tracker data, no significant difference was seen in the total sleep time and the light sleep time. However, the amount of deep sleep was significantly higher (Minutes = 75.83 ± 17.03, N=24 Vs 63.92 ± 12.09, p = .008), and the wake after sleep onset time significantly shorted in the experimental group (Minutes = 52.50 ± 12.25, N=24 Vs 65.00 ± 15.50 N=24)
Ong et al (2020) (18)	Single arm prospective Pre-and post-test design study	59	46	Relaxing environment with audio (once daily for up to 7 days)	Ong et al. reported the impact of their VR interventions on sleep quality using a subjective questionnaire, the Richards-Campbell Sleep Questionnaire (RCSQ). There

					was no statistical difference in the sleep scores reported by participants
Suvajdzic et al (2019) (66)	Single arm prospective repeated measures design study	37	10	Relaxing environment with audio (5-min family-friendly VR Films + 5-10-Minute beaches, forests, famous locations	Although no statistical analysis was completed for the data, two participants reported some level of improvement according to their RCSQ sleep scores (participant 1: 33.8 to 38.6; participant 2: 20.2 to 68).
VR for early neurocognitive stimulation					
Study	**Study type**	**Number of patients of those who are exposed to VR**	**(number of patients who received full target number of sessions)**	**Interventions**	**Results**
Quah et al (2019) (59)	Randomised controlled trial	11	N/R	Relaxing environment with audio (5-minute sessions of VRT a day) Vs specific details on what the control group received was not reported	Although the primary objective of the study was to assess the tolerability and safety of the intervention, their secondary analysis showed the intervention group were mechanically ventilated for a shorter period of time compared to the control (2.8 ± 1.2 days vs. 5.4 ± 3.6 days), however the statistical significance of this difference was not reported.

VR for Relaxation

Phase of development and Study characteristics

When comparing the five different uses of VR in ICU, the application of VR for relaxation had the largest number of studies [9 studies (42-46, 48, 49, 52, 54, 60, 63, 64)]. The majority of the studies in this area were classified to be at VR2 development [five single arm prospective repeated measures design studies (44-46, 60, 63, 64), one case study (48) and one single arm prospective study (60, 64). The remaining two studies in this area were classified to be at VR1 [one development paper (49)] and VR3 which was a protocol for a randomised controlled trial (RCT) (54). These studies explored and developed the use of VR for relaxation with a wide range of patients ranging from healthy subjects (45), current medically stable patients [fore studies (49, 52, 54, 60, 64)], to critically ill patients [three studies (46, 48, 63)] (defined by the author as patients being on a ventilator). The most common approach was to create relaxing 3D and 2D environments with corresponding environmental sounds, these included landscape, beaches, forests, animals (44-46, 60, 63, 64), Greek sculptures (49), nature walk and a guided relaxation (52). The remaining two studies used either VR gaming (42, 43, 48) or plan to use VR movies (54).

Completion rate of target treatment VR for Relaxation

Six studies were included in a meta-analysis of completion rates (44-46, 48, 60, 63, 64). This resulted in an estimated completion rate of 73.6%, (95% CI: 51.1%; 96.0%) however there was substantial statistically significant heterogeneity for completion rates of target treatment (I^2 = 98.53%, P= < 0.001) (see Supplementary electronic file 1 for forest plot). On visual inspection of the forest plot, only two studies did not have 100% completion rate these were Gerber et al (2019a) (57.9%) (44) and Zheng et al (2020) (15%) (60, 64). Gerber et al (2019a) reports that the 24 ICU patients who did not receive the full intervention were due to external factors such as changing condition and early transfer to another ward (44). Similarly, Zheng et al (2020) reports a similar attrition issue with 51 ICU patients out of 60 who did not receive the full treatment regimen due to similar external factors or medical condition or discharge (60, 64). However, they did report that eight ICU patients refused to use the VR headsets.

Acceptability of VR for Relaxation

Out of the nine studies which explored the use of VR for relaxation in ICU patients, four studies reported acceptability outcomes (44, 46, 60, 63, 64). Gerber et al (2017) and Gerber et al (2019a) both reported that ICU patients felt that the VRT was well accepted, easy to use and appreciated by ICU patients (44, 46). This was reflected in the high scores reported by the ICU patients in usability (Mean score (M) = 4.5/5, 3.57/5) immersion (M= 3.6/5, 2.7/5) and low scores in sickness/nausea (M = 1.16/5, 0.03/5), oculomotor problems (M= 1.35 /5, 0.15/5), disorientation and nausea (M=0.04/5, 1.16/5). Similarly, Zheng et al (2020) reported a high percentage of ICU patients indicating that the headset was easy to use (93%) and comfortable (83%) (60, 64). The study also reported a low percentage of ICU patients reporting dizziness (7%) and difficulty seeing the objects (23%). Wacker and Haley (2020) reported no ICU patients reporting cyber sickness (63).

Effectiveness of VR for Relaxation

All studies which examined the effectiveness of VR for relaxation used a similar approach of a relaxing environment with audio (e.g., beach, forests, waterfalls, and meadow) and were all deemed to be of weak quality. A statistically significant improvement was observed for anxiety levels (60, 64) [one pre-

and post-test study], pain scores (60, 64) [one pre-and post-test study], heart rate (45, 46) [two repeated measures design study], respiratory frequency (45, 46) [two repeated measures design studies] and mean arterial pressure (46) [one repeated measures design study]. No statistically significant improvement was observed for mean blood pressure during the intervention (44, 45) [two repeated measures design studies], respiratory rate and heart rate (45) [one repeated measures design study]. Subjective improvement in anxiety levels were reported in two single arm prospective pre- and post-test design studies (60, 63, 64) and one case report (48). See Table 3 for results.

VR for Delirium

Phase of development and Study characteristics

The second largest group of studies were based around the use of VR for Delirium (18, 47, 56, 66). Out of the four studies, three studies were classified to be in VR2 stage of development [two single arm prospective repeated measures design studies (18, 66), single arm prospective study (47)] and one study of a protocol for a RCT to be at VR3 (56). All four studies had a similar target population of current ICU patients (18, 47, 56, 66). However, Jawed et al (2020) also included healthcare professionals (47). All four studies took a similar approach of using VR to help to relax the patients. Two studies used a nature-based environment with environmental sounds (47, 56) and two studies used nature environments with guided meditation using the RelaxVR software (www.relaxvr.co) (18, 66).

Completion rate of target treatment VR for Delirium

Only two studies in this area reported completion rates of target treatment (18, 66). When combined these two studies resulted in an estimated completion rate of 52.7% (95% CI 52.7 – 102.7%) with substantial statistically significant heterogeneity (I^2 = 96.8%, P= < 0.001) (see Supplementary electronic file 1 for forest plot). Non-completion was reported to be due to emergency or discharge (18) and to referral to another hospital or change in medical condition (66).

Acceptability VR for Delirium

Three out of the four studies reported acceptability outcomes. All three studies reported that ICU patients felt that the VR headset was comfortable (18, 47, 66). With 90.5% (66) and 95.6% (18) of ICU patients agreeing that the VR headset was comfortable and 100% of ICU patients judged the VR headset to be at least moderately comfortable (47). Ong et al (2020) and Suvajdzic et al (2019) reported that 80% and 88.9% of ICU patients respectively liked the experience of using VR (18, 63). Jawed et al (2020) reported that 13.3% were slightly dizzy and 6.7% had nausea (45).

Effectiveness VR for Delirium

All studies which examined the effectiveness of VR for delirium used a similar approach of a relaxing environment with audio. Two of the studies reported that the intervention did not seem to appear to be associated with change in delirium state (18, 66) [two single arm prospective Pre- and post-test design study, weak quality]. A statistically significant reduction was observed for anxiety and depression severity (18) [one single arm prospective Pre-and post-test design study, weak quality] and out of 15 participants six reported an improvement in their anxiety levels (47) [one single arm prospective Pre-and post-test design study, weak quality]. No significant difference was observed for reductions in pain scores (18, 66) [two single arm prospective Pre- and post-test design study, weak

quality], or for systolic and diastolic blood pressure, mean arterial pressure, heart rate and respiratory [one single arm prospective Pre- and post-test design study, weak quality] (47). See Table 3 for results.

VR for Post-traumatic stress disorder (PTSD)

Phase of development and Study characteristics

Three studies were identified which used VR to prevent/treat PTSD (57, 58, 62). One study was deemed to be at VR2 (62) [Retrospective cohort study] and two RCTs protocols were classified to be at VR3 stage of development. All three studies used a target sample of discharged ICU patients (57, 58, 62). Van et al (2017) only describe the intervention as VR exposure therapy (62). Both RCTs protocols proposed a similar approach by basing their VR exposure therapy on creating a specific 3D mock-up of the Franciscus Gasthuis Hospital (57, 58). The 3D environment had given information on specific ward processes such as ward rounds and intubation.

Attrition rates and Acceptability VR for PTSD

Van et al (2017) did not report completion rates (62). However, the study report that 65% of patients with PTSD favoured the VR exposure therapy compared to an information sheet.

Effectiveness VR for PTSD

Van Genderen et al. have recently published a study protocol to assess the effectiveness of VR interventions to improve PTSD in ICU survivors (60). The multicentre, randomised protocol aims to examine the impact of VR interventions in participants who have recovered from severe COVID-19 infections which resulted in admission to the ICU. At the time of publication, no results were available for this study.

VR for early neurocognitive stimulation, sleep, lower limb function and orientation

The remaining five studies explore the potential use of VR for early neurocognitive stimulation, sleep, lower limb function and orientation (51, 53, 55, 59, 65). The areas of application of VR for potential early neurocognitive stimulation [one RCT (59) and one RCT protocol (65)] and sleep were judged to have a study at the VR3 stage of development [one RCT(51)]. For the areas of VR for orientation and lower limb function the studies were judged to be at VR1 [one development paper/commentary (53)] and VR3 [one RCT protocol (55)] respectively. However, this study trial registry has now been withdrawn due to the trial being judged to be too big, with indications that it will be splitting down to smaller steps/studies (January 6, 2021). Unfortunately, there are no current links to the new separate studies linking to this original trial. These studies had a range of different target populations of current ICU patients (51), current and past ICU patients (53), post ICU patients (55) and critically ill ICU patients (59, 65). The approaches taken in these areas of application vary with a VR ICU ward being used for orientation (53) and a similar approach taken for both VR for sleep and VR for early neurocognitive stimulation in the use of a nature environment with relaxing music (51, 59). For the remaining study of VR for early neurocognitive stimulation it was unclear of the exact method of VR which was used (55).

Attrition rates and acceptability VR for early neurocognitive stimulation, sleep, lower limb function and orientation

Only one study reported target treatment completion rates (51). This study assessing the effectiveness for VR for sleep reported a completion rate of 92% in the intervention group. The two patients who did not complete the target intervention reported that the headset was uncomfortable (heavy) and the patients reported that they found it difficult to use the VR headset and did not want to continue.

One small RCT (n=11) for VR for early neurocognitive stimulation identified that there was 50% of patients 3/6 which showed increased agitation compared to the control group of 1/5 (59). None of the studies on VR for early neurocognitive stimulation, sleep, lower limb function and orientation reported any other acceptability outcomes.

Effectiveness VR for sleep and early neurocognitive stimulation

There was a statistically significant improvement for sleep quality scores, deep sleep and wake after sleep onset time when comparing VR meditation to improve sleep compared to standard interventions (ear plugs and mask) (50, 51) [one random controlled trial, weak quality]. There was no statistically significant improvement for sleep time and the light sleep time when comparing VR meditation compared to standard intervention (50, 51) [one random controlled trial, weak quality]. There was also no statistically significant improvement in Richards-Campbell Sleep Questionnaire scores (18) [single arm prospective pre- and post-test design study, weak quality]. See Table 3 for results.

Discussion

With the continued development of VR technology, its use as a therapeutic intervention in health care has grown (23, 24). Despite its potential application within ICUs, the evidence base appears limited. Evaluations have tended to focus on the early stages of development, on specific clinical conditions and different patient groups. Consequently, studies have tended to report early testing of VR in terms of feasibility, acceptability, tolerability and some initial clinical efficacy, with limited consideration of effectiveness. VR appears well tolerated in different patient groups.

When used for relaxation of ICU patients and for treating delirium or PTSD, VR was widely accepted due to its ease of use and comfort. Adverse events were limited. Disorientation/slight dizziness (<15%) and nausea (<7%) were reported, although sickness varied depending on participant age, exposure time, visual stimulation and locomotion (68). Half of patients who received VR therapy for early neurocognitive stimulation showed increased agitation. Treatment completion rates varied, ranging from 53% for treating delirium, 74% for relaxation and 92% for sleep. Non-completion of treatment was rarely due to VR itself, usually reflecting external factors associated with their condition or from referral for other care.

Early efficacy studies have shown some statistically significant benefit. VR appeared to significantly reduce anxiety, pain, heart rate, respiratory frequency and arterial pressure among those receiving VR for relaxation. It had no effect on delirium itself, however it did significantly reduce those patients' anxiety and depression. People with PTSD reported a significant improvement in outcomes associated with sleep. The approach taken to VR has tended to focus on nature-based virtual environments with nature sounds, particularly for relaxation and PTSD, which has been a common approach (69) and preferable to patients (70). There is growing evidence about the benefits of nature-based activities

and their salutogenic effects (71, 72), which can be replicated virtually (73). It is important to recognise that the evidence is immature, both in terms of effectiveness (VR3) and also early published development studies (VR1). RCTs to assess effectiveness of VR are underway, all are focused on treatment with no consideration of the potential for VR as prevention.

Strengths and weaknesses

The main strengths of this review are the systematic methods used to undertake the multi-database search strategy. Alongside this multi-database search, we also screened all included studies' citation lists and did not identify any additional papers through this process suggesting a high recall search strategy. We had a previous ICU patient helping us with each stage of the review, which ensured that we addressed not just clinical questions, but also patient concerns around using VR in ICU. This resulted in the focus around acceptability and tolerability being a key topic of the review and also helped with ensuring that this manuscript was readable from a patient's perspective. We applied an evidence-based structured framework to identify current maturity levels of VR use in ICU to identify areas of future research and development required in this field. We were also able to carry out a meta-analysis on treatment completion rates which have begun to give some very broad estimates of treatment completion rates for these VR applications. Unfortunately, there was substantial statistically significant heterogeneity.

The main limitation of the review is the possible introduction of error caused by single screening, the data extraction and assessment of bias (74, 75). Furthermore, this review was not registered and the search strategy did not include grey literature (76). Additional to these methodological issues of the review, there are also substantial limitations to the evidence-base used within the review. There was widespread methodological weakness within the studies themselves, they were also small and used a wide range of varying outcomes to assess effectiveness and acceptability. Based on this, limited confidence should be given to the estimates of effect identified within the studies. Due to classifying the therapeutic applications of VR by the primary focus of the review, this has led to similar applications such as delirium and anxiety studies to be split, even though they have a similar focus, dividing the evidence base in that particular area.

Future research

All of the uses for VR identified in this review are not currently at the point where any recommendations to clinical practice can be made. Subsequently, current uses of VR should only be considered as part of an ethically approved study. There are currently protocols registered for VR for relaxation, delirium, PTSD, as well as VR for lower limb function and potential early neurocognitive stimulation. However, there are no trials currently registered for VR for sleep and orientation. As orientation is at an early stage of development, future research in this area should focus on assessing acceptability and tolerability. Furthermore, as VR for sleep demonstrated potential efficacy and good acceptability of treatment, further robust RCTs are needed in this area. There are currently a notable lack of preventative uses of VR in ICU, with the majority of studies focusing on curative applications. Therefore, there is a need for future research to explore the use of VR in preventative applications. Due to the clinical environment of an ICU ward there was notable issues in completion rates of target treatment due to external factors which should be considered when designing any future research for VR with ICU patients.

As identified in this review, there were substantial issues in regard to reporting methods used within the studies, thus it is important, wherever possible, that standard reporting guidelines such as CONSORT standards are followed (77). Additionally future research should ensure that there is

adequate and appropriate levels of patient and end user engagement at all stages of development. Wherever possible this should be reported clearly and concisely using such frameworks as GRIPP2 (Guidance for Reporting Involvement of Patients and the Public) (78) and as part of this reporting of any improvement study, the most relevant patient outcome set, such as the core outcome set for critical care ventilation trials, should be used (79).

Conclusion

VR for ICU is a relatively new area of research with the majority of areas of application being in the early stages of assessment of acceptability and tolerability. These areas of application are currently not at a point where any clinical recommendations can be made and should only be used as part of an ethically approved research study. The use of VR in ICU patients seems to be well-tolerated and demonstrates great potential for use in the ICU environment.

What is known about this topic:

- Intensive care patients may be left with long-term physical, cognitive, and quality of life impairments and a psychological legacy.
- Virtual reality has been demonstrated to be effective in treating pain, morbidity, post-traumatic stress, anxiety, and depression in non-intensive care patients.
- No previous review has explored the use of VR in an intensive care unit population.

What this paper adds:

- Virtual reality for ICU patients is at an early stage of development.
- Virtual reality has good acceptability and tolerability in intensive care patients.
- The use of VR for relaxation, delirium and sleep demonstrates potential benefits.

Declaration of interest: *This report is independent research funded by the National Institute for Health Research Applied Research Collaboration North West Coast (ARC NWC). The views expressed in this publication are those of the author(s) and not necessarily those of the National Institute for Health Research, the NHS or the Department of Health and Social Care.*

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