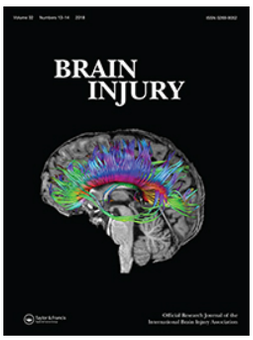

Brain Injury

ISSN: 0269-9052 (Print) 1362-301X (Online) Journal homepage: https://www.tandfonline.com/loi/ibij20

Prevalence of neuropsychiatric symptoms and psychotropic drug use in patients with acquired brain injury in long-term care: a systematic review

Roy F. Kohnen, Debby L. Gerritsen, Odile M. Smals, Jan C.M. Lavrijsen & Raymond T.C.M. Koopmans

To cite this article: Roy F. Kohnen, Debby L. Gerritsen, Odile M. Smals, Jan C.M. Lavrijsen & Raymond T.C.M. Koopmans (2018) Prevalence of neuropsychiatric symptoms and psychotropic drug use in patients with acquired brain injury in long-term care: a systematic review, Brain Injury, 32:13-14, 1591-1600, DOI: 10.1080/02699052.2018.1538537

To link to this article: https://doi.org/10.1080/02699052.2018.1538537

Published online: 29 Oct 2018.

BRAIN INJURY
2018, VOL. 32, NOS. 13–14, 1591–1600
https://doi.org/10.1080/02699052.2018.1538537

Taylor & Francis
Taylor & Francis Group

Prevalence of neuropsychiatric symptoms and psychotropic drug use in patients with acquired brain injury in long-term care: a systematic review

Roy F. Kohnen[a,b], Debby L. Gerritsen[b], Odile M. Smals[a,b], Jan C.M. Lavrijsen[b], and Raymond T.C.M. Koopmans[b,c]

[a]Vivent, Mariaoord, Rosmalen, the Netherlands; [b]Department of Primary and Community Care, Radboud University, Medical Centre, Nijmegen, the Netherlands; [c]De Waalboog, Centre for Specialized Geriatric Care"Joachim en Anna", Nijmegen, the Netherlands

ABSTRACT

Objective: Little is known about the prevalence of neuropsychiatric symptoms (NPS) and psychotropic drug use (PDU) in patients below the age of 65 years with acquired brain injury (ABI) in long-term care. The objective of this study was to review the literature about the prevalence of NPS and PDU.

Methods: A systematic literature search of English, Dutch and German articles in Pubmed, EMBASE, PsycINFO and CINAHL was performed with the use of MeSH and free-text terms.

Results: Six articles met the inclusion criteria. The place of residence was mainly a nursing home and most studies were conducted in a population of patients with traumatic brain injury. Sample sizes varied from 40 to 26,472 residents and NPS were assessed with different assessment instruments. Depressive symptoms were most common with a prevalence ranging from 13.9% to 39.3%. Two studies reported PDU in which tranquillizers (59%) were the most prevalent psychotropic drugs followed by anticonvulsants (35%) and antidepressants (26–34%).

Conclusions: Patients with ABI experience lifelong consequences, regardless the cause of ABI, that have a high impact on them and their surroundings. More insight into the magnitude of NPS and PDU, through prevalence studies, is necessary to achieve suitable provision of care for these patients.

ARTICLE HISTORY
Received 12 December 2017
Revised 13 August 2018
Accepted 17 October 2018

KEYWORDS
Acquired brain injury; prevalence; neuropsychiatric symptoms; psychotropic drug use; long-term care

Introduction

Acquired brain injury (ABI) is an injury to the brain that is not hereditary, congenital, degenerative or induced by a birth trauma, but the result of a sudden event whereby the damage can be focal or diffuse (1). ABI can be traumatic or non-traumatic. The severity can range from a mild temporary concussion to severe damage resulting in a permanent vegetative state, renamed as unresponsive wakefulness syndrome (VS/UWS), or death (1,2).

Brain injury is a major cause of death and disability (3). The mean European incidence of hospitalized and fatal traumatic brain injury (TBI) is about 235 per 100,000 but prevalence data were not reported from any European country (4). Globally, TBI affects approximately 10 million people (5). The most injuries occur in the very young (0–4 years), adolescents (15–24 years), and in people over 65 years of age (6). In a study in the Netherlands (n = 1892), accidents appeared to be the most common cause of TBI as were hypoxic–ischemic events for NTBI in youth aged 1 month to 24 years (7). More than 15% of TBI and NTBI were classified as moderate or severe.

Brain injury can have a direct effect on behavioural control due to injury of frontal, temporal and sub-cortical areas of the brain (8,9). A patient's behaviour may also be the result of frustration with the limitations caused by disability, which put a high burden on the patient and his/her environment (9,10). Behavioural problems occurring after brain injury were reported in a follow-up study of patients with a mean age of 30.4 years during hospital stay (n = 16) and after discharge to home (n = 33) (9). The highest prevalence rates of apathy, irritability, and aggression were found at home, with 73%, 78%, and 55.5%, respectively. In the hospital, the prevalence rates were 25%, 31%, and 6%, respectively.

Patients in the chronic phase of ABI who are unable to live at home are commonly admitted to a long-term care facility (LTCF). Long-term care refers to health, social and residential services provided to chronically disabled persons over an extended period of time (11). ABI was the most common cause of disability in 122 patients and challenging behaviour was found in 207 patients in the general population of people below 60 years of age in an Australian study in residential aged care (n = 330) (12). However, from this study it is not clear how many patients with ABI had challenging behaviour.

Little is known about the population of people up to 65 years of age with ABI that resides in LTCFs. The availability of data about characteristics, neuropsychiatric symptoms (NPS) and psychotropic drug use (PDU) in this group of patients remains unclear. These patients experience lifelong consequences, regardless the cause of ABI that has a high impact on them and their surroundings. Insight into the magnitude of NPS and PDU is necessary to achieve suitable care for these patients. Thereto, the specific question to be answered is: What are the prevalence rates of NPS and PDU for NPS among patients below 65 years of age with ABI in long-term care? Therefore, the aim of this study was to systematically review the literature about the prevalence and

CONTACT Roy F. Kohnen Roy.Kohnen@radboudumc.nl PO Box 9101, PO Box 9101, Nijmegen, the Netherlands
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ibij.

characteristics of NPS and PDU in patients below 65 years of age with ABI in long-term care.

Methods

Search strategy

The approach used for this systematic review was the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (13). The databases Pubmed, EMBASE, PsycINFO (both via Ovid), and CINAHL were searched.

Through the supervision of a librarian from the Radboud University, a list of Medical Subject Headings (MeSH) and free text words, indicating the setting, the wide range of causes of ABI and NPS, and PDU, was used to retrieve relevant articles from Pubmed (Table 1) and was translated for use in EMBASE, PsycINFO and CINAHL. We used an extensive amount of search terms to find as many relevant papers as possible. The Neuropsychiatric Inventory Nursing Home version (NPI-NH) was used as template for the NPS (14). The NPI, a structured interview including 12 NPS, is suitable for assessing NPS in ABI and has been used in severe and moderate TBI (15,16). With regard to PDU, the Anatomical Chemical Classification of the World Health Organization was used as template (17). The search was performed using the following limits: Humans, Adult (19 + years), Adult (19–44 years), Middle Aged (45–64 years), English, Dutch and German. There were no limits concerning the year of publication. The search was performed by two researchers (RFK and DLG) independently and took place in May 2016. The resulting articles were combined in Endnote and duplicates were removed.

Inclusion criteria

Inclusion criteria were (1) patients with a mean/median age below 65 years, and (2) in the chronic phase of nonprogressive ABI. The nonprogressive forms of ABI can be traumatic, haemorrhagic and ischemic stroke, stable situation after brain tumour with residual damage treated with surgery and/or radiotherapy, hypoxia/anoxia, cerebral infections, intoxications and metabolic disorders (1,18).

We chose the age of 65 years as a limit because it was until recently the retirement age in the Netherlands and with this the upper limit for (the possibility of) employment. Instead of using an inclusion criterion regarding a maximum age, the mean/median age was used to include as many relevant studies as possible.

Exclusion criteria

Exclusion criteria were (1) studies in patients with a mean/median age ≥65 years, (2) patients living in the community, (3) patients with disorders of consciousness (DOC) (4) patients in the acute phase (hospital) and rehabilitation phase (rehabilitation centre) of ABI, (5) degenerative forms of ABI, and (6) Korsakoff's Syndrome. The degenerative forms can be dementia, multiple sclerosis, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, mitochondrial disease, cerebellar ataxia, multisystem atrophy,

Table 1. Used search terms in Pubmed.

Setting:
("Long Term Care"[MeSH] OR "Long Term Care"[All Fields] OR "Nursing Homes"[MeSH] OR Nursing Home*[All Fields] OR "Skilled Nursing Facilities"[MeSH] OR Skilled Nursing Facilit*[All Fields])
Causes:
("Brain Abscess"[MeSH] OR Brain Abscess*[All Fields] OR "Brain Anoxia"[All Fields] OR Brain Hemorrhage*[All Fields] OR "Brain Infarction"[MeSH] OR Brain Infarction*[All Fields] OR Brain Inflammation*[All Fields] OR "Brain Injury, Chronic"[MeSH] OR "Brain Injuries"[MeSH] OR Brain Injur*[All Fields] OR "Brain Stem Hemorrhage, Traumatic"[MeSH] or Brain Stem Hemorrhage*[All Fields] OR Brainstem Hemorrhage*[All Fields] OR "Brain Stem Infarctions"[MeSH] OR Brain Stem Infarction*[All Fields] OR Cerebral Abscess*[All Fields] OR "Cerebral Anoxia"[All Fields] OR "Cerebral Hemorrhage"[MeSH] OR "Cerebral Hemorrhage, Traumatic"[MeSH] OR Cerebral Hemorrhage*[All Fields] OR "Cerebrovascular Trauma"[MeSH] OR "Encephalitis"[MeSH] OR Encephalitis[All Fields] OR Encephalopath*[All Fields] OR "Head Injuries, Penetrating"[MeSH] OR Head Injur*[All Fields] OR "Hypoxia, Brain"[MeSH] OR "Intracranial Hemorrhage, Hypertensive"[MeSH] OR "Leukoencephalitis, Acute Hemorrhagic"[MeSH] OR Locked In Syndrome[All Fields] OR Locked-in Syndrome[All Fields] OR "Meningioma"[MeSH] OR Meningioma*[All Fields] OR "Meningitis"[MeSH] OR Meningitis[All Fields] OR "Quadriplegia"[MeSH] OR Quadriplegia[All Fields] OR "Stroke"[MeSH] OR Stroke*[All Fields] OR "Subarachnoid Hemorrhage"[MeSH] OR Subarachnoid Hemorrhage*[All Fields] OR TBI[All Fields])
Neuropsychiatric Symptoms:
("Affect"[MeSH] OR Affect[All Fields] OR "Aggression"[MeSH] OR Aggression[All Fields] OR Agitation[All Fields] OR "Anxiety"[MeSH] OR Anxiety[All Fields] OR "Apathy"[MeSH] OR Apathy[All Fields] OR "Appetite"[MeSH] OR Appetite[All Fields] OR "Behavioral Symptoms"[MeSH] OR Behavioral Symptom*[All Fields] OR Behavioural Symptom*[All Fields] OR "Cooperative Behavior"[MeSH] OR Cooperative Behavior*[All Fields] OR Cooperative Behaviour*[All Fields] OR "Delusions"[MeSH] OR Delusion*[All Fields] OR "Depression"[MeSH] OR Depression[All Fields] OR "Depressive Disorder"[MeSH] OR Depressive Disorder*[All Fields] OR Disinhibition[All Fields] OR Eating Disorder*[All Fields] OR "Euphoria"[MeSH] OR Euphoria[All Fields] OR "Feeding and Eating Disorders"[MeSH] OR "Hallucinations"[MeSH] OR Hallucination*[All Fields] OR "Hearing Loss"[MeSH] OR Hearing[All Fields] OR "Irritable Mood"[MeSH] OR Irritable Mood[All Fields] OR Irritability[All Fields] OR "Mental Health"[MeSH] OR Mental[All Fields] OR "Mood Disorders"[MeSH] OR Mood Disorder*[All Fields] "Neurobehavioral Manifestations"[MeSH] OR Neurobehavioral Manifestation*[All Fields] OR Neurobehavioural Manifestation*[All Fields] OR "Neuropsychiatry"[MeSH] OR Neuropsychiatry[All Fields] OR Neuropsychiatric[All Fields] OR "Neuropsychology"[MeSH] OR Neuropsychology[All Fields] OR "Personality"[MeSH] OR Personality [All Fields] OR "Psychomotor Agitation"[MesH] OR Psychosis[All Fields] OR "Psychotic Disorders"[MeSH] OR Psychotic Disorder*[All Fields] OR "Sexual Behavior"[MeSH] OR Sexual Behavior*[All Fields] OR Sexual Behaviour*[All Fields] OR Sleep Behavior Disorder*[All Fields] OR Sleep Behaviour Disorder*[All Fields] OR "Sleep Wake Disorders"[MeSH] OR Sleep Disorder*[All Fields] OR "Social Behavior Disorders"[MeSH] OR Social behavior Disorder*[All Fields] OR Social Behaviour Disorder*[All Fields] OR "Somnambulism"[MeSH] OR Vision[All Fields] OR "Vision Disorders"[MeSH] OR "Wandering Behavior"[MeSH] OR Wandering Behavior*[All Fields] OR Wandering Behaviour*[All Fields] OR Nocturnal Wandering[All Fields])
Psychotropic Drugs:
("Antidepressive Agents"[MeSH] OR Antidepressive[All Fields] OR "Antipsychotic Agents"[MeSH] OR Antipsychotic[All Fields] OR "Drug Prescriptions"[MeSH] OR "Hallucinogens"[MeSH] OR Hallucinogen*[All Fields] OR Pharmacologic*[All Fields] OR Pill*[All Fields] OR Prescribing[All Fields] OR Prescription*[All Fields] OR "Psychotropic Drugs"[MeSH] OR Psychotropic[All Fields] OR "Tranquilizing Agents"[MeSH] OR Tranquilizing[All Fields] OR Tranquilizer*[All Fields] OR Hypnotic* [All Fields] OR Sedative*[All Fields])

stroke in progressive or degenerative disorder, and brain tumour with progressive deterioration (18).

Eligibility assessment

Original research papers and reviews were considered. Two authors (RFK and DLG) independently screened titles and abstracts on their potential to meet the inclusion criteria. The two reviewers compared the list of selected abstracts and in case of disagreement or when there was insufficient information in the abstract to evaluate the inclusion and exclusion criteria, the full text paper was studied by both reviewers. Disagreements were discussed until consensus was reached.

Data extraction

From the final set of included full text papers, information was extracted on country, year of publication, study design, setting, sample size, mean/median age of patients, methods to assess NPS and PDU, and the prevalence of NPS and PDU using a predefined data extraction form.

Quality assessment

Two authors (RFK and OMS) evaluated the methodological quality of the selected studies independently. Studied were the sample size, what instruments were used to assess NPS and PDU, response rates when questionnaires were used, the construction of estimates, and how the diagnosis was made and by whom.

Also, the methodological quality of the included articles was rated in a structured manner with eight criteria from Boyle's Guidelines for evaluating prevalence studies and adapted by Pitfield et al. (19,20). These criteria represent guidelines to evaluate the basic elements of prevalence studies: sampling, measurement and analysis (20). The objective is to help make informed judgements about the validity of prevalence studies. Boyle's criteria are found in Table 2. Pitfield adapted the Guidelines by adding a rating to these criteria in which a criterion was rated with zero points if the criterion was not met, 0.5 points if it was partially met and 1 point if it was completely met (19).

Each paper was rated using an electronic form with the eight criteria and a total score was calculated. A total score below 3 was considered as poor, 3–6 as moderate, and greater than or equal to 6 as good methodological quality. This grouping was based upon the methodological evaluation of included studies in the systematic review of Van den Brink et al. which used these guidelines for evaluating prevalence studies (27). The individual scores of the raters (RFK and OMS) on the criteria and the total scores of each study were compared and disagreements were discussed until consensus was reached.

Results

Search strategy

The literature search revealed 931 references. A total of 103 duplicates were removed. The remaining 828 references were screened on title and abstract. A total of 750 references were excluded. From 78 records, the full text article was retrieved for assessing eligibility. Six articles appeared to meet the inclusion criteria (Figure 1).

Design and study population

Most studies had a cross-sectional design. The place of residence was mainly a nursing home. Four studies were conducted in the USA and the other two studies were conducted in Scotland and Germany, respectively. The four studies conducted in the USA used the Minimum Data Set (MDS) which included all residents in all Medicare and Medicaid-certified nursing facilities (28). The MDS records behavioural concerns and medications (21,25). Behavioural concerns were items reflecting verbally abusive, physically abusive and socially inappropriate behaviours (24). All behavioural symptoms are rated on two criteria and one of these criteria was the symptom frequency in the last 7 days with four possible ratings ranging from not 'exhibited' to 'daily' (25). Two of the studies obtained data from nursing home patients with TBI throughout the USA (21,24). One study used MDS data of patients with TBI from 215 Medicare- and Medicaid-certified nursing homes in

Table 2. Methodological evaluation of the studies (Boyle, 1998).

	Buchanan et al., 2003 (21)	McMillan et al., 2004 (22)	Gabella et al., 2007 (23)	Karon et al., 2007 (24)	Belanger et al., 2008 (25)	Wolf-Ostermann et al., 2004 (26)
1. Was the target population defined clearly?	1	1	1	1	1	1
2. Was probability sampling used to identify potential respondents, or the whole population approached?	1	1	1	1	1	1
3. Did characteristics of respondents match the target population?	1	1	1	1	1	1
4. Were the data collection methods standardized?	1	1	1	1	1	1
5. Were the survey instruments reliable?	?	0.5	?	0.5	0.5	1
6. Were the survey instruments valid?	0.5	0.5	0.5	0.5	0.5	0.5
7. Were special features of the sampling design accounted for in the analysis, through appropriate weighting of the data, or the whole population approached?	1	1	1	1	1	1
8. Do the reports include confidence intervals for statistical estimates or was the whole population approached?	1	1	1	1	1	1
Quality Score	**6.5**	**7**	**6.5**	**7**	**7**	**7.5**

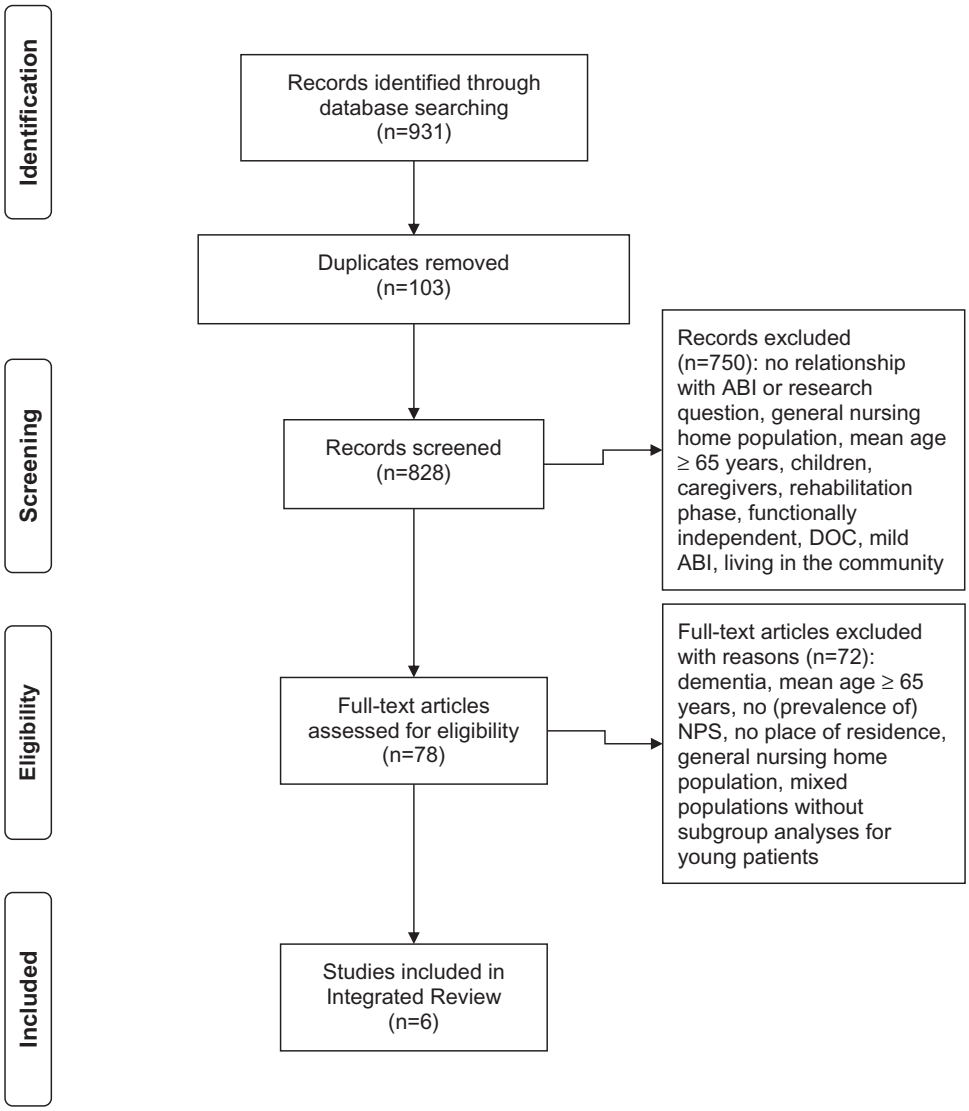

Figure 1. Search and selection procedure of the articles.

Colorado (23). The last study conducted a retrospective review of the MDS in which data were obtained nationally from the Veterans Health Administration which operates nursing homes at 134 medical centres across the USA and Puerto Rico (25).

In the Scottish study, a survey was conducted to describe the characteristics, level of disability and services received by patients with ABI between 16 and 64 years old residing in nursing homes in Greater Glasgow (22). This study used self-developed questionnaires (Form A and B) and the medication cardex, a medication administration record, was reviewed. Form A was used among patients admitted to the nursing home after a brain injury survey in February 1999. Form B was a shorter questionnaire and was sent to nursing homes where patients with brain injury had been identified in the survey of February 1999. One of the items in Form A regarded current and past history of behavioural problems.

In the German study, patients with ABI moved from a residential living facility to two supported living accommodations (SLA) and its aim was to compare the changes of residents' social and health-related outcomes in the SLA group with the group who remained in stationary care (26). The study measured anxiety and depression, which were assessed with the Hospital Anxiety Depression Scale (HADS).

The sample size of the studies varied widely from 40 to 26 472 patients. The mean/median age ranged from 46.2 to 64.6 years. In four studies, two-thirds of the patients were men (21,23,24,26). In one study, only men were included (25). Female residents constituted fewer than 2% of the cases and were excluded. Four studies were performed in a population solely existing of patients with TBI (21,23–25). The other two studies were conducted in a population with different causes of ABI and each reported a group 'other brain injury' without mentioning the types of ABI (22,26). The characteristics of the studies and the types of ABI are displayed in Table 3.

Neuropsychiatric symptoms

The prevalence of depression (four studies) ranged from 13.9% to 39.3%, anxiety (three studies) from 2.8% to 10%, physically abusive behaviours (three studies) from 7.8% to 18% and socially inappropriate behaviour (three studies)

Table 3. Characteristics of the studies.

Reference	Country	Study Design	Setting	N	Age (SD/Range)	Type of ABI	Instruments
Buchanan et al., 2003 (21)	USA	Cross-sectional	Nursing Home	12300	53.1 (21.2)	Traumatic Brain Injury	Minimum Data Set
McMillan et al., 2004 (22)	Scotland	Cross-sectional	Nursing Home	92	50 (10)	Traumatic Brain Injury Stroke Alcohol Related Other Brain Injury	Questionnaire Medication Cardex
Gabella et al., 2007 (23)	USA	Cross-sectional	Nursing Home	239*	53 (18–99) †	Traumatic Brain Injury	Minimum Data Set
Karon et al., 2007 (24)	USA	Cross-sectional	Nursing Home	3912‡ 26472§	54.3 64.6	Traumatic Brain Injury	Minimum Data Set
Belanger et al., 2008 (25)	USA	Cross-sectional	Nursing Home	537‖	61.56 (14.85)	Traumatic Brain Injury	Minimum Data Set
Wolf-Ostermann et al., 2014 (26)	Germany	Longitudinal	RLF/SLA	40	46.2 (12.1)	Traumatic Brain Injury Subarachnoidal Haemorrhage Inflammation/Toxic Stroke Other Brain Injury	Hospital Anxiety Depression Scale

SD = Standard Deviation. NPS = Neuropsychiatric Symptoms. RLF = Residential Living Facility. SLA = Supported Living Accommodations. USA = United States of America. * = Population of patients with only TBI. † = Median. ‡ = Common Definition. § = Expanded Definition. ‖ = TBI Nonwanderers.

from 16% to 25.2%. Two studies reported verbally abusive behaviour with a prevalence rate of 13% and 17.2%. One study reported that 15% was verbally or physically abusive at least once during the observation week. Borderline depression, borderline anxiety, bipolar disease and schizophrenia (each one study) were found in 13.9%, 11.1%, 2.2% and 6.2% of the patients, respectively. One study described NPS overall as challenging behaviour in 35% of the patients (Table 4).

Psychotropic drug use

Only two studies reported prevalence rates of PDU. The prevalence of minor tranquillizers/anxiolytics was 12% in one study and 23% in the other study. The frequency of antidepressants was 26% and 34%, and major tranquillizers/antipsychotics 19% and 36%. Anticonvulsants were studied in one study and the prevalence was 35% (Table 4).

Methodological quality

The sample size varied between studies. Two studies were exceptionally large and included the whole population of interest (21,24). Other strengths of the reviewed studies are a clearly defined target population, characteristics of the respondents, standardized data collection methods, and the reporting of statistical estimates. Furthermore, one study used a validated reliable instrument which was administered by trained persons (26). These strengths were rated with one point according to the Guidelines for evaluating prevalence studies (Table 2). The study using the self-developed questionnaires described above achieved a 100% response rate in which responses were obtained from all 75 nursing homes and all 203 questionnaires were returned (22). There are also limitations. The sample size was low in four studies which could have led to overestimation of the prevalence rates and compromises generalizability (22,23,25,26).

All four studies, using the MDS, used no validated instruments to assess NPS and solely relied on data from the MDS (21,23–25). This is a limitation because the MDS is not a research data set and will, according to Belanger et al., likely have more noise in the data compared to controlled studies (25). Also, the MDS was completed by nursing home staff and there was no guarantee that written guidelines were followed. Furthermore, the reliability and validity of the TBI diagnosis from the MDS had not been established at the time of one of these studies (23). One of these four studies reviewed the identification of TBI among nursing home residents using the common definition (TBI check box item in the MDS) and the expanded definition (check box item and ICD-9-CM codes) (24). Much more patients were identified as having TBI with the expanded definition compared to the common definition and, as consequence, the prevalence rates of NPS were lower in this group of patients with TBI. By using the common definition, patients who actually have TBI are not identified by the MDS. This leads to underreporting of TBI and probably causing an overestimation of the prevalence rates of NPS. Also, the sizes of the validity coefficients were modest, and depression and problem behaviour were less well affirmed than cognition, activities of daily living and time use (29). Although behavioural symptoms were recorded in the MDS, none of these four studies described how these behavioural symptoms were diagnosed and by whom. Because of this, 0.5 points were allocated to the validity and reliability criteria. In two of these studies, the question about reliability could not be answered.

Reliance on questionnaire responses by nursing home staff was the limitation in the study of McMillan et al. (22). According to the same study, 'challenging behaviour' was defined as behaviour that staff found difficult to manage and adversely affected the comfort of other residents. The effects of NPS on the patient himself/herself were not taken into account. It is possible that certain behaviour might not have been perceived as a problem, which could have led to underreporting. Although it was reported that behaviour modification supervised by a clinical psychologist was used in only two cases, it remains unclear how behavioural problems were diagnosed and by whom. We allocated 0.5 points in both the validity and reliability criterion.

Table 4. Neuropsychiatric symptoms and psychotropic drug use.

Reference	Behaviour/NPS	*N*	Psychotropic Use	*N*
Buchanan et al. (21).	Depression	21%	Antidepressant	26%
	Physically Abuse	9%	Antipsychotic	19%
	Others	13%	Anxiolytic	12%
	Verbally Abuse Others	16%		
	Socially Inappropriate Behaviour			
McMillan et al. (22).	Challenging	32	Major	33
	Behaviour	9	Tranquillizer	(36%)
	Physically Violent		Anticonvulsant	*
			Antidepressant	36
			Minor	(35%)
			Tranquillizer	*
				31
				(34%)
				*
				21
				(23%)
				*
Gabella et al. (23).	Depression	39.3%		
	Anxiety	10%		
	Abusive Behaviour	15%		
	Inappropriate Behaviour	18%		
Karon et al. (24).	Verbally Abusive‡	17.2%		
	Physically Abusive	9.8%		
	Socially Inappropriate	25.2%		
	Verbally Abusive§	13.9%		
	Physically Abusive	7.8%		
	Socially Inappropriate	19.8%		
Belanger et al. (25).	Anxiety Disorder	47		
	Depression	(8.75%)		
	Bipolar Disease	152		
	Schizophrenia	(28.31%)		
		12		
		(2.23%)		
		33		
		(6.15%)		
Wolf-Ostermann et al. (26).	Borderline Anxiety	4/36		
	Anxiety	(11.1%)		
	Borderline Depression	1/36		
	Depression	(2.8%)		
		5/36		
		(13.9%)		
		5/36		
		(13.9%)		

NPS = Neuropsychiatric Symptoms. * = Some patients received more than one medication of this type. ‡ = Common Definition. § = Expanded Definition.

One study used the HADS (26). The HADS has been shown to be an effective measure of emotional distress, but is unable to consistently differentiate between the constructs of anxiety and depression, which means that its use needs to be targeted to a more general measurement of distress (30). This was confirmed by a later study (31). Misclassification between anxiety and depression might have occurred. Therefore, we allocated 0.5 points to the validity criterion.

After calculating the total score for each study, all studies had a score greater than six and were considered as having good quality. The lowest score was 6.5 and the highest score was 7.5 out of 8. The individual ratings and total scores are found in Table 2.

Remarkably, one study did not register the indication for PDU and in another study the indication was not clear (21,22). It remains unclear how many patients actually received psychotropic drugs because of NPS.

Discussion

To the best of our knowledge, this is the first review that systematically assessed the prevalence of NPS and PDU in patients below 65 years of age with ABI in long-term care settings. Six studies were found and all studies were of good methodological quality. The place of residence was mainly a nursing home and most studies were conducted in patients with TBI. Depressive symptoms were the most common NPS. Only two studies were published about PDU, in which tranquillizers were the most prevalent psychotropic drugs followed by anticonvulsants and antidepressants.

Comparison with other populations

ABI has also been studied in older patients living in LTCFs, mainly those with TBI and stroke (32–34). They appeared to have higher prevalence rates of aggression and depression than younger patients. Compared to younger patients with similar TBI severity, elderly patients showed worse physical and cognitive outcomes and they were also more often discharged to LTCFs (35). A study performed in geriatric patients with stroke found that 1 year after admission, patients who were still in a LTCF showed significantly more agitation and depression than those who had been discharged (36). The worse outcome and the higher frequency of LTCF admissions may contribute to the higher prevalence rates of aggression and depression in LTCFs in elderly patients with ABI. The prevalence of anxiety in these older populations was, however, lower in TBI and higher in stroke (32,33). A recent study of young, middle-aged and older adults with TBI living in the community found that older adults (60–64 years) experienced less anxiety than young (20–24 years) and middle-aged (40–44 years) adults (37). A possible explanation for this is the inability to maintain established roles in society, such as employment and providing for a family, due to TBI-related disabilities in the younger adults (38,39). For stroke, no comparisons could be made.

In settings other than LTCFs, ABI has been studied as well. The psychosocial and emotional outcomes were studied in a community-based follow-up study of 53 patients with mild to very severe TBI sustained 10 years previously (40). The prevalence rates of clinically significant anxiety and depression were 33% and 42% in patients with severe injuries and 22% and 35%, respectively, in patients with very severe injuries. Aggression scores were significant in 12% of the patients. The reported prevalence rates of anxiety in this study are higher in contrast to the reviewed studies. The prevalence rates of depression are similar in comparison with the study of Gabella et al. (23). Aggression is more prevalent in three of the reviewed studies (21,23,24).

The occurrence of aggressive behaviour was established in a group of 89 patients with closed head injury admitted to the University of Iowa Hospitals and Clinics (n = 58) and the Iowa Methodist Medical Center (n = 31) (41). Aggressive behaviour was found in 33.7% of patients with TBI during the first 6 months after injury and was significantly associated with the presence of major depression. A mood or anxiety disorder was found in 26.4% and 12.6% of the patients,

respectively. The studies in our review found lower prevalence rates for aggression and anxiety. With regard to depression, two reviewed studies found a higher prevalence and two studies a lower prevalence.

The prevalence of aggression has been studied among 57 inpatients with ABI at a specialized post-acute treatment centre in a large general psychiatric hospital in the Netherlands (42). During a period of 17 weeks, 42% of the patients had engaged in aggressive behaviour on one of more occasions, which is much higher than the prevalence rates described in our review.

There are also differences in PDU. Anticonvulsants were the most prescribed type of medication in patients with TBI below 65 years in a retrospective cohort study (n = 306) (43). In patients over 65 years, the prevalence of anticonvulsants was lower. Older patients with stroke also used less anticonvulsants (44). In a sample of 520 patients with TBI, 59 patients had post-traumatic seizures and most seizures occurred in patients between 20 and 50 years of age. The prevalence of antidepressants was higher in older patients with TBI (43). Other studies also found more use of antidepressants in older patients with TBI and stroke (32,44). This can probably be explained by higher prevalence rates of depression in older patients with TBI and stroke (32–34). The use of anxiolytics (20%) in TBI was also different. One study found a higher prevalence rate (20%) and second study a lower prevalence rate (5.9%) (32,43). However, the use of anxiolytics was highest in the age group 45–54 years (43). The reason for this might be the above-described anxiety caused by the inability to maintain established roles in society (38,39). More antipsychotics (41.5%) appear to be prescribed in older patients with TBI and less (8%) in older patients with stroke (32,33).

Remarkable findings

A remarkable finding is that the TBI studies in our review, which reported depression and anxiety, did not report how many patients with anxiety also had depression. Anxiety was found to be highly co-morbid with depression in a study of young, middle-aged and older adults with TBI (37). In their review, Lecrubier concludes that depression and anxiety are often co-morbid which causes greater disability and imposes a greater burden on the patients' daily lives and on healthcare services (45). They recommend that co-morbid anxiety and depression should not be viewed in isolation despite the fact that anxiety and depression are often experienced, diagnosed and treated as independent conditions (37,46).

Furthermore, we noted that anoxia as cause of ABI was not reported. Two studies, however, reported 'other brain injury' which could include anoxia but this is not clear (22,26). Anoxia as a cause of severe ABI has been increasingly found in VS/UWS and has become the major cause after cardiopulmonary resuscitation (47–49). However, little is known about the neuropsychiatry, such as memory impairment and apathy, of ABI caused by hypoxia/anoxia (50,51). If they regain consciousness, these patients may experience severe consequences, such as NPS, which have a high impact on their lives and their environment.

Regarding PDU, the Scottish study stated that a large number of patients had anticonvulsants without the diagnosis of epilepsy, which may be partially explained by continuation as a prophylactic or because of prescription for other reasons, such as reduction in aggression (22). Another indication for anticonvulsants is neuropathic pain and antidepressants are also used for this indication (52). Furthermore, nursing home records did not describe the indication for medication use, but prescription of major or minor tranquillizers tended to be more common in patients with challenging behaviour. The other study which reported prevalence rates of PDU did not register the indication for PDU (21). It remains unclear how many patients actually received psychotropic drugs because of NPS.

Also, medication was not reviewed in 78.8% of the patients with major tranquillizers, 70% with antidepressants, 57.1% with minor tranquillizers, and 72.4% with anticonvulsants (22). Patients with challenging behaviour tended to have had their medication reviewed, but concrete numbers were not reported. It also remains unclear in how many cases psychotropic drugs were discontinued because of the absence of NPS at the time of the medication review. The rate of reappearance of NPS after discontinuation of PDU is not clear as well. Therefore, it is impossible to determine whether NPS had existed without medication or not. It is important to note that in some cases continuation of medication might have been inappropriate if a valid indication was absent. A review concluded that all medication for co-morbid diseases should be critically evaluated and medication that does not benefit the patient in any way should be stopped (53).

Limitations of this review

Concerning this review, there are limitations to acknowledge. We did a combined search of specific headings and keywords in four different databases, but some studies might have been missed, written in a language other than English, Dutch or German. Another limitation is the use of a mean/median age instead of restricting to a population only consisting of people up to 65 years of age. In the latter case, only three studies could have been included. Although the mean/median age indicates that the number of patients below 65 is larger than the number of older patients, inclusion of the three studies that also included some people above 65 would have resulted in reporting slightly higher rates of depression, aggression and the use of antidepressants, and lower rates for anticonvulsants.

Considerations and implications

Despite the fact that the reported studies are of good quality, it is difficult to draw conclusions from the reported prevalence rates and they have to be interpreted with caution. Reasons for this are the different populations, the use of different instruments, the varying sample sizes and the limitations of the included studies, such as a low sample size, and not using validated instruments to assess NPS.

One study was conducted in Veterans Health Administration nursing homes (25). These nursing homes

have a special population and residents are predominantly men contrary to the population of community nursing homes. The findings in this study are not generalizable to a population of patients with ABI other than veterans.

NPS in LTCFs are prevalent and have a high impact on patients with ABI and their surroundings, in the first place family but also other patients and nursing home staff in LTCFs. A recent review found that challenging behaviour hindered the provision of quality care and required the implementation of proactive nursing strategies to maintain safety for both patients with TBI and nurses (54). Nurses had to watch for, and identify, triggers for aggression in patients with TBI and they expressed being fearful for their personal safety. That review also stated that to provide effective care for patients with TBI exhibiting challenging behaviour such as aggression, nurses needed to understand their own perceptions of challenging behaviour and how these perceptions might impact their care choices. Appropriate skills, through a training programme, would better enable nurses to deliver more effective care and avert crisis situations (55). Knowledge about the patient's disease awareness is important to adequately manage consequences of ABI (56). Factors which contribute to a patient's limited disease awareness are an increased psychological defence mechanism due to more changes in life after ABI, having more cognitive disorders and not being informed sufficiently.

Pharmacological treatment may have adverse effects. Antipsychotics, for example, which are used for the treatment of psychoses, agitation and aggression, may have adverse effects on cognition as a study found improvement in cognition after discontinuation of antipsychotics in patients with TBI (57). In long-term therapy, antipsychotics have severe side effects such as stroke and increased mortality (58). A review about cognitive behavioural therapy (CBT), a non-pharmacological anger self-management technique, concluded that CBT appears to be an effective tool to control aggression in a population with ABI (59). The results of that review show promise for CBT as a non-pharmacological, safe, psychotherapy alternative to medication use for treatment of aggression after brain injury. However, their conclusion is that further research with long follow-up times is needed and the effects of CBT in acute and chronic populations with ABI need to be assessed.

Recommendations

Some recommendations for future studies can be made. We propose to assess a wide range of NPS, such as aggression, with the use of a limited number of reliable, validated, standardized instruments. It is advised to report possible co-morbid anxiety and depression. Regarding medication, we recommend to register the indication for PDU so that it is clear whether psychotropics are used for the treatment of NPS or for another indication such as neuropathic pain (52).

Barriers or challenges for performing research in LTCFs and how to bridge the gap between knowledge and practice have been described (60). For example, non-pharmacological studies are more complicated to conduct in nursing homes than pharmacological studies. Other challenges are number and severity of co-morbidities, and the internal organization of nursing homes, such as the presence of special care units. With regard to research ethics, cognitive impairment may be a problem because signed informed consents are impossible to obtain from some patients.

In the Netherlands, we are in the process of bridging this gap. Dutch patients with all type of ABI who are unable to live at home independently live on special ABI wards in LTCFs (61). The benefit of concentrating all types of patients with ABI on specialized wards is obtaining clinical experience in treating a broad range of consequences. The provision of care is facilitated through the use of general care standards that have been developed in the Netherlands for adults and youth (0–24 years) with TBI, to guide the treatment of consequences such as NPS (62,63). The care standard for adults contains a development agenda with four research questions (62). One of these questions is about which care is effective in long-term care and prevents the appearance or deterioration of problems in daily life. With this, expertise in NPS can be developed and training of healthcare professionals can be facilitated. In addition, in 2016 an ABI network of expertise, in which LTCFs are participating with researchers, has been established for specific subcategories of ABI, such as disorders of consciousness and patients with consciousness who experience long-term consequences (64). Also, The Netherlands have developed a roadmap towards academic medicine in long-term care (65). Key elements are a significant contribution in the medical curriculum, a specialty with a 3-year specialist training programme, and academic networks that provide an infrastructure for teaching, research and best practices. Furthermore, the prevalence of specific subcategories of ABI, VS/UWS and the Locked-in Syndrome (LIS), in LTCFs has been studied (47,48,66). The circumstances in the Netherlands provide a good opportunity to conduct this kind of prevalence studies, regarding the high responses between 91% and 100%.

Conclusions

There is a knowledge gap concerning NPS and PDU in patients below 65 years of age in the chronic phase of ABI in LTCFs. These patients experience lifelong consequences, such as NPS, regardless the cause of ABI that have a high impact on them and their environment. Metaphorically, it is mainly a black box. Although there is increasing attention for the survival of patients with severe ABI, it is also necessary to have eyes for (severe) long-term consequences of ABI in a vulnerable group of patients. This review is a first step towards optimal provision of care for these patients.

Author contributions

Roy Kohnen designed the review, evaluated the articles for inclusion, evaluated the methodology of the included articles and wrote the paper. Debby Gerritsen assisted in the design of the review, evaluated the articles for inclusion and co-wrote the paper. Odile Smals evaluated the methodology of the included articles. Jan Lavrijsen assisted in the design of the review and co-wrote the paper. Raymond Koopmans assisted in the design of the review, co-wrote the paper and gave the final approval.

Disclosure Statement

No potential conflict of interest was reported by the author.

Funding

The study is supported and funded by Vivent, a long-term care/nursing home organization in Den Bosch and Rosmalen area, the Netherlands.

References

1. Brain Injury Association of America. About brain injury [Internet]. Available from: http://www.biausa.org
2. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, Sazbon L, Schmutzhard E, von Wild KR, Zeman A, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68. doi:10.1186/1741-7015-8-68.
3. Fakhry SM, Trask AL, Waller MA, Watts DD. Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. J Trauma-Injury Infect Crit Care. 2004;56(3):492–99. doi:10.1097/01.TA.0000115650.07193.66.
4. Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J. A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien). 2006;148(3):255–68. doi:10.1007/s00701-005-0651-y.
5. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: a global perspective. NeuroRehabil. 2007;22(5):341–53.
6. Brown AW, Elovic EP, Kothari S, Flanagan SR, Kwasnica C. Congenital and acquired brain injury. 1. Epidemiology, pathophysiology, prognostication, innovative treatments, and prevention. Arch Phys Med Rehabil. 2008;89(3 Suppl 1):S3–S8. doi:10.1016/j.apmr.2007.12.001.
7. de Kloet AJ, Hilberink SR, Roebroeck ME, Catsman-Berrevoets CE, Peeters E, Lambregts SA, van Markus-Doornbosch F, Vliet Vlieland TP. Youth with acquired brain injury in The Netherlands: a multi-centre study. Brain Inj. 2013;27(7–8):843–49. doi:10.3109/02699052.2013.775496.
8. Eslinger PJ, Grattan LM, Geder L. Impact of frontal lobe lesions on rehabilitation and recovery from acute brain injury. NeuroRehabil. 1995;5(2):161–82. doi:10.3233/NRE-1995-5206.
9. Johnson R, Balleny H. Behaviour problems after brain injury: incidence and need for treatment. Clin Rehabil. 1996;10(2):173–80. doi:10.1177/026921559601000215.
10. Alderman N. Prevalence, characteristics and causes of aggressive behaviour observed within a neurobehavioural rehabilitation service: predictors and implications for management. Brain Inj. 2007;21(9):891–911. doi:10.1080/02699050701543560.
11. Doty P, Liu K, Wiener J. An overview of long-term care. Health Care Financ Rev. 1985;6(3):69–78.
12. Winkler D, Farnworth L, Sloan S. People under 60 living in aged care facilities in Victoria. Aust Health Rev. 2006;30(1):100–08.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006–12. doi:10.1016/j.jclinepi.2009.06.005.
14. Cummings JL. The neuropsychiatric inventory: assessing psychopathology in dementia patients. Neurology. 1997;48(5 Suppl 6):S10–16.
15. Kilmer RP, Demakis GJ, Hammond FM, Grattan KE, Cook JR, Kornev AA. Use of the neuropsychiatric inventory in traumatic brain injury: a pilot investigation. Rehabil Psychol. 2006;51(3):232–38. doi:10.1037/0090-5550.51.3.232.
16. Castano Monsalve B, Laxe S, Bernabeu Guitart M, Vilarrasa AB, Quemada JI. Behavioral scales used in severe and moderate traumatic brain injury. NeuroRehabil. 2014;35(1):67–76. doi:10.3233/NRE-141103.
17. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment [Internet]. Available from: https://www.whocc.no/filearchive/publications/guidelines.pdf
18. Brain Foundation Netherlands. Acquired brain injury (Niet-aangeboren hersenletsel) [Internet]. Available from: http://www.hersenstichting.nl
19. Pitfield C, Shahriyarmolki K, Livingston G. A systematic review of stress in staff caring for people with dementia living in 24-hour care settings. Int Psychogeriatrics. 2011;23(1):4–9. doi:10.1017/S1041610210000542.
20. Boyle MH. Guidelines for evaluating prevalence studies. Evid Based Ment Health. 1998;1(2):37–39. doi:10.1136/ebmh.1.2.37.
21. Buchanan RJ, Wang S, Huang C. Profiles of nursing home residents with traumatic brain injury using the minimum data set. Brain Inj. 2003;17(6):507–23. doi:10.1080/0269905031000070215.
22. McMillan TM, Laurie M. Young adults with acquired brain injury in nursing homes in Glasgow. Clin Rehabil. 2004;18(2):132–38. doi:10.1191/0269215504cr712oa.
23. Gabella BA, Mangione EJ, Hedegaard H, Kelly JP. Comparison of nursing home residents with and without traumatic brain injury: use of the minimum data set. J Head Trauma Rehabil. 2007;22(6):368–76. doi:10.1097/01.HTR.0000300232.98242.ce.
24. Karon SL, Lazarus JC, Holman L. Challenges and approaches to the identification of traumatic brain injury among nursing home residents. J Head Trauma Rehabil. 2007;22(6):350–59. doi:10.1097/01.HTR.0000300230.13490.11.
25. Belanger HG, King-Kallimanis B, Nelson AL, Schonfeld L, Scott SG,Vanderploeg RD. Characterizing wandering behaviors in persons with traumatic brain injury residing in veterans health administration nursing homes. Arch Phys Med Rehabil. 2008;89(2):244–50. doi:10.1016/j.apmr.2007.08.145.
26. Wolf-Ostermann K, Naber S, Gräske J. Housing project 'Living Independently with Intensive Support (WmI)': the scientific evaluation]. Rehabilitation (Stuttg). 2014; 53 Suppl 1:S4–S43.
27. van Den Brink AM, Gerritsen DL, Voshaar RC, Koopmans RT. Residents with mental-physical multimorbidity living in long-term care facilities: prevalence and characteristics. A systematic review. Int Psychogeriatrics. 2013;25(4):531–48. doi:10.1017/S1041610212002025.
28. Morris JN, Hawes C, Fries BE, Phillips CD, Mor V, Katz S, Murphy K, Drugovich ML, Friedlob AS. Designing the national resident assessment instrument for nursing homes. Gerontologist. 1990;30(3):293–307.
29. Lawton MP, Casten R, Parmelee PA, Van Haitsma K, Corn J, Kleban MH. Psychometric characteristics of the minimum data set II: validity. J Am Geriatr Soc. 1998;46(6):736–44.
30. Cosco TD, Doyle F, Ward M, McGee H. Latent structure of the hospital anxiety and depression scale: a 10-year systematic review. J Psychosom Res. 2012;72(3):180–84. doi:10.1016/j.jpsychores.2011.06.008.
31. Norton S, Cosco T, Doyle F, Done J, Sacker A. The hospital anxiety and depression scale: a meta confirmatory factor analysis. J Psychosom Res. 2013;74(1):74–81. doi:10.1016/j.jpsychores.2012.10.010.
32. Colantonio A, Hsueh J, Petgrave J, Hirdes JP, Berg K. A profile of patients with traumatic brain injury within home care, long-term care, complex continuing care, and institutional mental health settings in a publicly insured population. J Head Trauma Rehabil. 2015;30(6):e18–e29. doi:10.1097/HTR.0000000000000112.
33. van Almenkerk S, Depla MF, Smalbrugge M, Eefsting JA, Hertogh CM. Institutionalized stroke patients: status of functioning of an under researched population. J Am Med Dir Assoc. 2012;13(7):634–39. doi:10.1016/j.jamda.2012.05.008.
34. Kowalska J, Bojko E, Szczepańska-Gieracha J, Rymaszewska J, Rożek-Piechura K. Occurrence of depressive symptoms among older adults after a stroke in the nursing home facility. Rehabil Nurs J. 2016;41(2):112–19. doi:10.1002/rnj.2016.41.issue-2.
35. Leblanc J, De Guise E, Gosselin N, Feyz M. Comparison of functional outcome following acute care in young, middle-aged

and elderly patients with traumatic brain injury. Brain Inj. 2006;20(8):779–90. doi:10.1080/02699050600831835.
36. Buijck BI, Zuidema SU, Eijk M, Geurts AC, Koopmans RT. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. Int J Geriatr Psychiatry. 2012;27(7):734–41. doi:10.1002/gps.2781.
37. Osborn AJ, Mathias JL, Fairweather-Schmidt AK, Anstey KJ. Anxiety and comorbid depression following traumatic brain injury in a community-based sample of young, middle-aged and older adults. J Affect Disord. 2017 Apr 15;213:214–21. doi:10.1016/j.jad.2016.09.045.
38. Brzuzy S, Speziale BA. Persons with traumatic brain injuries and their families: living arrangements and well-being post injury. Soc Work Health Care. 1997;26(1):77–88. doi:10.1300/J010v26n01_05.
39. McCabe P, Lippert C, Weiser M, Hilditch M, Hartridge C, Villamere J. Community reintegration following acquired brain injury. Brain Inj. 2007;21(2):231–57. doi:10.1080/02699050701201631.
40. Draper K, Ponsford J, Schonberger M. Psychosocial and emotional outcomes 10 years following traumatic brain injury. J Head Trauma Rehabil. 2007;22(5):278–87. doi:10.1097/01.HTR.0000290972.63753.a7.
41. Tateno A, Jorge RE, Robinson RG. Clinical correlates of aggressive behavior after traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2003;15(2):155–60. doi:10.1176/jnp.15.2.155.
42. Visscher AJ, van Meijel B, Stolker JJ, Wiersma J, Nijman H. Aggressive behaviour of inpatients with acquired brain injury. J Clin Nurs. 2011;20(23–24):3414–22. doi:10.1111/j.1365-2702.2011.03800.x.
43. Yasseen B, Colantonio A, Ratcliff G. Prescription medication use in persons many years following traumatic brain injury. Brain Inj. 2008;22(10):752–57. doi:10.1080/02699050802320132.
44. van Almenkerk S, Depla MF, Smalbrugge M, Eefsting JA, Hertogh CM. Pain among institutionalized stroke patients and its relation to emotional distress and social engagement. Int J Geriatr Psychiatry. 2015;30(10):1023–31. doi:10.1002/gps.4256.
45. Lecrubier Y. The burden of depression and anxiety in general medicine. J Clin Psychiatry. 2001;62(Suppl 8):4–9.
46. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Arlington: American Psychiatric Publishing;2013.
47. Lavrijsen JC, van Den Bosch JS, Koopmans RT, van Weel C. Prevalence and characteristics of patients in a vegetative state in Dutch nursing homes. J Neurol Neurosurg Psychiatry. 2005;76(10):1420–24. doi:10.1136/jnnp.2004.058198.
48. van Erp WS, Lavrijsen JC, Vos PE, Bor H, Laureys S, Koopmans RT. The vegetative state: prevalence, misdiagnosis, and treatment limitations. J Am Med Dir Assoc. 2015;16(1):85.e9-85.e14. doi:10.1016/j.jamda.2014.10.014.
49. Pichler G, Fazekas F. Cardiopulmonary arrest is the most frequent cause of the unresponsive wakefulness syndrome: aprospective population-based cohort study in Austria. Resuscitation. 2016;103:94–98. doi:10.1016/j.resuscitation.2016.02.023.
50. Berlyne N, Strachan M. Neuropsychiatric sequelae of attempted hanging. Br J Psychiatry. 1968;114(509):411–22.
51. Hayhow B, Velakoulis D, Dewhurst R, Gaillard F. Neuropsychiatric presentation following acute hypoxic-ischaemic encephalopathy. Aust N Z J Psychiatry. 2015;49(2):188–89. doi:10.1177/0004867414555418.
52. Kollenburg EGP, Lavrijsen JCM, Verhagen SC, Zuidema SU, Schalkwijk A, Vissers KCP. Prevalence, causes, and treatment of neuropathic pain in Dutch nursing home residents: a retrospective chart review. J Am Geriatr Soc. 2012;60(8):1418–25. doi:10.1111/j.1532-5415.2012.04078.x.
53. van Nordennen RT, Lavrijsen JC, Vissers KC, Koopmans RT. Decision making about change of medication for comorbid disease at the end of life: an integrative review. Drugs Aging. 2014;31(7):501–12. doi:10.1007/s40266-014-0182-4.
54. Kivunja S, River J, Gullick J. Experiences of giving and receiving care in traumatic brain injury: an integrative review. J Clin Nurs. 2018;27(7–8):1304–28. doi:10.1111/jocn.14283.
55. Soreny C. Neuroscience nurses' perceptions of caring for challenging patients. Br J Neurosci Nurs. 2009;5(9):425–31. doi:10.12968/bjnn.2009.5.9.44100.
56. Prinsen A. Go away. The treatment of disease awareness in brain injury (Ga toch weg. De behandeling van ziekte-inzicht bij hersenletsel). Utrecht: Breindok;In press.
57. Stanislav SW. Cognitive effects of antipsychotic agents in persons with traumatic brain injury. Brain Inj. 1997;11(5):335–41.
58. Ballard CG, Gauthier S, Cummings JL, Brodaty H, Grossberg GT, Robert P, Lyketsos CG. Management of agitation and aggression associated with Alzheimer disease. Nat Rev Neurol. 2009;5(5):245–55. doi:10.1038/nrneurol.2009.39.
59. Iruthayarajah J, Alibrahim F, Mehta S, Janzen S, McIntyre A, Teasell R. Cognitive behavioural therapy for aggression among individuals with moderate to severe acquired brain injury: a systematic review and meta-analysis. Brain Inj. 2018;32(12):1443-1449.
60. Rolland Y. de Souto Barreto P. Research can improve care in the nursing home. J Am Med Dir Assoc. 2013;14(4):233–35. doi:10.1016/j.jamda.2013.01.019.
61. Van Sprundel C, Weeder W. Nursing home care for young people with acquired brain injury (Verpleeghuiszorg voor jongeren met niet-aangeboren hersenletsel). Utrecht: Landelijk Coördinatiepunt Niet-aangeboren Hersenletsel, Nederlandse Vereniging voor Verpleeghuiszorg;1995.
62. Brain Foundation Netherlands. Care standard traumatic brain injury (Zorgstandaard Traumatisch Hersenletsel). Zutphen: Tesink;2014.
63. Brain Foundation Netherlands. Care standard traumatic brain injury. Children and youth (Zorgstandaard Traumatisch Hersenletsel. Kinderen en Jongeren). Zutphen: Tesink;2016.
64. Network of Expertise Severe Acquired Brain Injury after Coma (Expertisenetwerk Ernstig Niet-aangeboren hersenletsel na coma). ONEaftercoma (EENnacoma) [Internet]. Available from: https://www.eennacoma.net/
65. Koopmans RT, Lavrijsen JC, Hoek F. Concrete steps toward academic medicine in long term care. J Am Med Dir Assoc. 2013;14(11):781–83. doi:10.1016/j.jamda.2013.08.004.
66. Kohnen RF, Lavrijsen JC, Bor JH, Koopmans RT. The prevalence and characteristics of patients with classic locked-in syndrome in Dutch nursing homes. J Neurol. 2013;260(6):1527–34. doi:10.1007/s00415-012-6821-y.