

A person in a red dress stands in a bright, ethereal light, possibly a doorway or a large window. The scene is filled with soft, golden light, creating a dreamlike atmosphere. In the foreground, a large, white, multi-petaled flower is visible, partially obscuring the view. The overall mood is serene and contemplative.

Janneke de Man-  
van Ginkel

*Early  
Detection* of  
Post-Stroke  
Depression

# **Early Detection of Post-Stroke Depression**

**Janneke de Man-van Ginkel**

# Early Detection of Post-Stroke Depression

## Vroegsignalering van depressie na een beroerte

(met een samenvatting in het Nederlands)

### Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht  
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,  
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in het openbaar te verdedigen op  
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door

### Jannetje Marijke de Man-van Ginkel

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### Early Detection of Post-Stroke Depression

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Promotoren: Prof.dr. M.J. Schuurmans

Prof.dr. D.E. Grobbee

Prof.dr. E. Lindeman

Co-promotor: Dr. T.B. Hafsteinsdóttir

*The spirit of a man will sustain his infirmity;  
but a wounded spirit who can bear?*

(Proverbs 18:14, King James Version)

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## **Chapter 1**

### **General Introduction**

Stroke is the third leading cause of death in Western societies. Worldwide, an estimated 50 million patients who have survived a stroke currently live with physical, cognitive, or emotional deficits, and 25% to 74% of these survivors require some assistance or are fully dependent on caregivers for activities of daily living.<sup>1</sup> In the Netherlands, approximately 41,000 individuals suffer from a stroke every year<sup>2</sup>, and it is estimated that 190,000 patients cope with the consequences of stroke.<sup>3</sup> Thus, stroke is currently the most important cause of disability and handicaps in the Western world.<sup>4</sup>

One of the most serious complications of stroke that influences rehabilitation outcome and quality of life is depression, also referred to as post-stroke depression (PSD).<sup>5,6</sup> The American Psychiatric Association (APA) defines the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR™).<sup>7</sup> According to these criteria, the diagnosis of major depressive disorder is defined as the consistent presence of five or more of nine symptoms of depression over a two-week period representing a change from previous functioning. At least one of the symptoms should be either depressed mood or loss of interest or pleasure.<sup>7</sup> Although there is no universally accepted definition for PSD diagnosis, the DSM criteria are generally used.<sup>6</sup>

The reported prevalence of post-stroke depression is highly variable, ranging from 5% to 61%.<sup>5,6,8,9</sup> This variation may be due to methodological differences, such as varied study populations; different examination settings; inclusion and exclusion criteria used with respect to aphasia, pre-existing depression, and decreased level of consciousness; variation in depression diagnosis due to the use of diagnostic criteria for only major depression versus minor depression or only using depression rating tools; and different time intervals following stroke.<sup>5,6</sup> Despite this broad range, a pooled estimate of post-stroke depression indicates that depressive symptoms are present in approximately 33% of all stroke survivors at any time during follow-up.<sup>10</sup>

## Consequences of PSD

Post-stroke depression has a huge impact on the ability of a patient to recover. It has been associated with functional dependence and poor functional recovery,<sup>11;12</sup> poor cognitive function,<sup>13;14</sup> poor communicative function,<sup>15;16</sup> longer institutional care,<sup>17</sup> increased disabilities,<sup>18</sup> reduced social activities,<sup>19;20</sup> failure to return to work,<sup>20</sup> and increased mortality.<sup>21;22</sup> Based on these findings, it is evident that post-stroke depression is an important health problem. In addition, PSD negatively impacts patient participation in rehabilitation and associated outcomes.<sup>5;6</sup> This negative impact is of major importance during recovery, when rehabilitation efforts are most critical to the outcome.

There is increasing evidence that effective treatment leads to lower levels of depression and improved functional outcomes.<sup>5;23;24</sup> A systematic review showed some evidence of pharmacotherapy resulting in complete remission or decreased severity of depression.<sup>23</sup> Pharmacological treatment is also associated with improved functional recovery of stroke patients.<sup>24</sup> Several non-pharmacological treatments were also shown to be effective in post-stroke depression. There is evidence that providing information reduces depression severity.<sup>25</sup> Furthermore, psychological interventions had positive effects on the occurrence and severity of post-stroke depression.<sup>5;26</sup> Initiating treatment within the first month after stroke appeared to be more effective than starting treatment later; patients treated early improved more and maintained this improvement over two years, whereas the late treatment group deteriorated over time.<sup>27</sup> Therefore, the timely recognition and diagnosis of post-stroke depression is essential for the optimization of patient recovery from stroke.

However, despite the high prevalence of PSD, its huge impact on long-term outcome, and the current treatment options, depression is not generally recognized in stroke patients.<sup>6;28</sup> Although 75% of hospitalized stroke patients were identified by independent researchers as being depressed, details about depression were not noted in patient medical charts, including physician,

nursing, and therapy notes.<sup>28</sup> This poor recognition, a passive attitude toward therapy, and concerns about adverse drug effects leads to the underdiagnosis and undertreatment of post-stroke depression.<sup>4</sup>

## Symptoms of depression due to PSD or stroke

Another unresolved question concerns depression symptoms. According to the DSM-IV criteria, depression is characterized by the nine following symptoms: anhedonia (loss of interest or pleasure), depressed mood, sleep disturbances, loss of energy, changes in appetite, feelings of inappropriate guilt, concentration difficulties, psychomotor retardation or agitation, and suicidal thoughts.<sup>7</sup> However, symptoms like sleep disturbances, loss of energy, changes in appetite or concentration difficulties can also be considered as direct consequences of stroke. According to the DSM-IV, symptoms that are clearly due to a general medical condition should not be counted toward the diagnosis of major depressive disorder.<sup>7</sup> Despite this, it is often difficult to distinguish whether a symptom is a clinical manifestation of PSD or due to the stroke itself.<sup>29</sup> In the literature, this question has been debated for many years in stroke patients<sup>30-40</sup> and in patient populations suffering from other physical diseases.<sup>41-43</sup> Different strategies are suggested to manage somatic depression symptoms in patients with physical illnesses: 1) the inclusive approach considers all symptoms to diagnose depression irrespective of whether they appear to be related to the physical illness, 2) the exclusive approach does not include symptoms that are associated with the physical illness, 3) the substitutive approach substitutes psychological symptoms for somatic symptoms associated with the physical illness, and 4) the ethological approach requires the clinician to make decisions about whether specific physical symptoms are due to the physical disorder before counting it toward the diagnosis of major depression.<sup>29;44</sup> However to choose the proper strategy, it is essential to determine whether the somatic symptoms should be considered as clinical manifestations of PSD.<sup>45</sup>



## PSD screening in daily care during hospital stay

The structural use of a depression screening instrument in the daily care of stroke patients increases the early recognition of depression.<sup>28</sup> As described in several reviews, many instruments with acceptable to good diagnostic accuracy are available for screening for depression in stroke patients.<sup>46-48</sup> These reviews focused on the validity and reliability of the instruments and showed the diagnostic accuracy of most of the instruments to be acceptable to good in stroke patients.<sup>46-48</sup> However, little attention was given to the instruments' clinical utility, which focuses on aspects such as training requirements for instrument use and the amount of time needed to administer it.<sup>49</sup> For clinical practice, the validity, reliability, and clinical utility of the measurement should be considered<sup>49</sup> in the daily care of stroke patients to save time for the professionals and to limit the burden of structural screening in patients.<sup>50</sup>

In addition to the availability of a well-performing screening instrument, the structural screening of PSD in stroke patients is complicated by the length of their hospital stay. Due to redesigning the in-hospital care pathways of stroke patients, there is a trend toward decreasing hospital stay length, with a mean stay of less than 14 days.<sup>51;52</sup> This short hospital stay hinders proper PSD screening because the DSM criteria indicate that depressive symptoms need to be present for at least two weeks. This stresses the need to identify stroke patients at risk for PSD during their hospital stays.

## Role of nurses in PSD

In the course of intensive and continuous contact with stroke patients, nurses often encounter patients with depressive symptoms. In general, nurses consider observation, assessment, and interpretation of the observed symptoms as important part of their role in the rehabilitation of stroke patients, along with initiating, administering and monitoring therapeutic interventions.<sup>53;54</sup> Related to these roles is the nurse's supportive function, which emphasizes

the importance of establishing a trusting relationship that is fundamental to promote hope and prevent depression.<sup>55</sup> However, it is unknown how nurses define their role in recognizing and treating PSD in stroke patients.

## Outline of the thesis

The main aim of this thesis was to investigate proper strategies to detect PSD or identify PSD risk in stroke patients and to describe the role of nurses in early PSD detection. The first part of the thesis in **chapter 2** provides a review of the literature focusing on the role of nurses in the daily care of stroke patients with a focus on the early detection of post-stroke depression and therapeutic interventions they can use.

The next part focuses on clinical manifestation of post-stroke depression, addressing in **chapter 3** the question whether all nine symptoms of depression, irrespective of their somatic or psychological nature, should or should not be considered as a clinical manifestations of PSD. Therefore, the symptom profile of depressed stroke patients is compared with that of non-depressed stroke patients, the general practice population, and a population with symptomatic atherosclerotic diseases.

The main part of the thesis presents three studies focusing on the early detection of post-stroke depression in the daily care of stroke patients who were able to communicate adequately. In **chapter 4**, the reliability, validity, and clinical utility of the PHQ-9 and PHQ-2 are examined in the clinical practice of nursing care in hospitalized stroke patients. In **chapter 5**, the diagnostic value of the PHQ-9 and PHQ-2, alone or in combination, is determined in acute stroke patients. **Chapter 6** describes the development and performance of a clinical prediction rule to identify hospitalized stroke patients with an increased risk for PSD, the Post-Stroke Depression Prediction Scale (DePreS).

The thesis ends in **chapter 7**, with a general discussion in which the findings of our studies are discussed in relation with the literature and the implications

for clinical practice, education, and further research are described. Summaries in English and Dutch concludes the thesis.

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## **Chapter 2**

### **A Systematic Review of Therapeutic Interventions for Post-Stroke Depression and the Role of Nurses**

**Janneke de Man-van Ginkel, Floor Gooskens, Marieke Schuurmans, Eline Lindeman and Thóra Hafsteinsdóttir on Behalf of the Rehabilitation Guideline Stroke Working Group\***

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**\*See appendix 1**

## Abstract

**Aims and objectives.** This systematic review explores the nursing role in the management of PSD and identifies effective non-pharmacological interventions that nurses can use in the daily care of stroke patients.

**Background.** Depression is a common complication post-stroke and affects one third of stroke patients. It has a negative impact on functional recovery and social activities and is associated with increased morbidity and mortality. Detection and diagnosis of post-stroke depression is inconsistent and many depressed patients are undertreated. Although nurses recognize that observation and assessment are parts of their role in rehabilitation care, little is known about their role in assessing depression or the interventions they can use.

**Design.** A systematic review was conducted using the Cochrane method.

**Methods.** Literature for the period 1993-2008 was searched in the electronic databases of CINAHL, Medline (PubMed), Nursing Journals (PubMed) and PsycINFO using the following key words: cerebrovascular accident, stroke, depression, post-stroke depression, treatment, therapy, treatment outcome, management.

**Results.** Fourteen articles and one systematic review were identified. There was strong evidence that information provision reduces the severity of depression. Other interventions with positive effects on the occurrence or severity of post-stroke depression were: life review therapy, motivational interviewing, a specific nursing support program, and physical exercise.

**Conclusion.** Depression after stroke is an important problem with adverse effects on the patient's ability to participate in rehabilitation and on rehabilitation outcome. The interventions described can be implemented in nursing care of post-stroke depression patients. The variety of such interventions and the diversity of their nature and design are consistent with the practice of rehabilitation nursing.

**Relevance to clinical practice.** The findings of this review enable nurses to intervene effectively to reduce the occurrence and severity of depression in stroke patients.

**Key words.** Depression, Nursing care, Stroke, Systematic review

Stroke is the third leading cause of death in the Western world. In the Netherlands about 41,000 individuals annually suffer from a stroke<sup>1</sup> and it is estimated that 190,000 patients live with the consequences of stroke.<sup>2</sup> Stroke leads to a multitude of disabilities in physical, psychological and social functioning, which often have a huge impact on the patient's capacity in activities of daily living, social functioning and quality of life.<sup>3;4</sup> Therefore, stroke is the most important cause of disabilities and handicaps in the Western world today.<sup>5</sup>

Post-stroke depression (PSD) is one of the most serious complications after stroke.<sup>6-8</sup> The American Psychiatric Association (APA) has defined the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR™).<sup>9</sup> Although there is no universally accepted definition for the diagnosis of PSD, the DSM criteria are generally used.<sup>7</sup> The most important symptoms of depression are either depressed mood or loss of interest.<sup>9</sup> The prevalence of PSD ranges from 5% to 61%.<sup>6-8</sup> This wide variation may be due to methodological differences.<sup>6;7</sup> A pooled estimate of PSD indicates that depressive symptoms are present in 33% of all stroke survivors at some time during follow-up.<sup>10</sup>

PSD has a huge impact on the patient's ability to recover after stroke. It has been associated with functional dependence and poor functional recovery,<sup>11-13</sup> poor cognitive function,<sup>14;15</sup> poor communicative function,<sup>16;17</sup> longer stay in hospital,<sup>12</sup> increased handicaps,<sup>18</sup> reduced social activities,<sup>19;20</sup> failure to return to work,<sup>21</sup> and increased mortality.<sup>22;23</sup> There is increasing evidence that effective treatment leads to lower levels of depression and to improved functional outcome.<sup>6;8;24;25</sup> However, despite the high prevalence of PSD and its huge impact on long-term outcome, depression is generally badly recognized<sup>7;17</sup> and insufficiently treated.<sup>26;27</sup>

Nurses see observation, assessment, and interpretation of the observed symptoms as important part of their role in the rehabilitation of stroke patients, along with initiating, administering, and monitoring therapeutic interventions.<sup>28;29</sup> Related to these roles is the nurse's consoling function

which emphasizes the importance of establishing a trusting relationship with patients which is fundamental to promoting hope and preventing depression.<sup>30</sup> From studies in elderly patients it is known that nurses find it difficult to assess depression accurately.<sup>31;32</sup> Nevertheless, in depressed elderly patients and in depressed adults in the general population nurses provide effective interventions focusing on promotion of nutrition and sleep-rest patterns, enhancement of physical functioning, social support, maximization of the elder's autonomy, self-efficacy and decision making.<sup>33;34</sup> However, it is unknown how nurses define their role in recognizing and intervening in depressed stroke patients and which intervention they can use. Therefore, the aim of this review was to explore the nursing role in the management of PSD and to identify effective non-pharmacological interventions that nurses can use in the daily care of PSD patients.

## Methods

A systematic review of the literature was conducted according to the Cochrane method<sup>35</sup> and following the Quorum standards<sup>36</sup> aiming to identify and summarize articles published during the period from July 1993 to June 2008. This wide interval is chosen to find all relevant studies available concerning effective non-pharmacologic interventions that can be used by nurses. However, studies performed before that period were not considered to be relevant because of the changes that health care has gone through during the last decade.

### Search methods

Searches were conducted in the databases CINAHL, Medline (PubMed), Nursing Journals (PubMed) and PsycINFO, using the following key words (including MeSH terms): cerebrovascular accident, stroke, depression, PSD, treatment, therapy, treatment outcome and management (Table 1). Key words were not truncated to prevent exploding the number of irrelevant hits. Further, reference lists of

**Table 1. Key words used in the different databases**

Database	Key words* (including MeSH terms)
PubMed (Medline en Nursing Journals)	Cerebrovascular accident <sup>†</sup> , stroke <sup>†</sup> , depression <sup>†</sup> , post-stroke depression, anxiety <sup>†</sup> , emotionalism, psychological stress <sup>†</sup> , prevention, therapy, treatment outcome <sup>†</sup> , management.
CINAHL	Cerebral vascular accident, post-stroke depression, emotions, anxiety, affect, affective symptoms, affective disorder, management, treatment outcome.
PsycInfo	Cerebro Vascular Accident, Cerebro Vascular Disorders, depression, post-stroke depression, endogenous depression, major depression, depression-emotions, affection, affection disorder, emotional adjustment, emotional control, emotional instability, anxiety, anxiety disorder, anxiety management, treatment outcome, management, ability level.

\* Key words were not truncated to prevent exploding the number of irrelevant hits  
<sup>†</sup> Key words which were MeSH terms

the selected studies were searched by hand using the snowballing technique.

### Study selection

Inclusion criteria for the studies were:

- type of participants: patients with stroke; nurses or other professionals involved in the care of stroke patients in the acute, rehabilitation and/or chronic phase;
- type of studies: systematic reviews, randomised clinical trials (RCTs), experimental studies, observational studies and qualitative studies;
- outcome measures: occurrence of depression or severity of depression;
- types of interventions: interventions needed to be related to nursing care. No further restrictions were imposed, because it was anticipated that few if any studies would be found to conform too strict criteria. Interventions provided by other professionals but relevant for nursing care were also included.



Excluded were studies focusing on pharmacological treatment. The limits used for selection concerned language; English or Dutch publications were included. The full strategy is available by contacting the first author. Studies fulfilling these criteria were independently assessed by two reviewers and in the case of discrepancies, consensus was reached by discussion.

### Search outcome

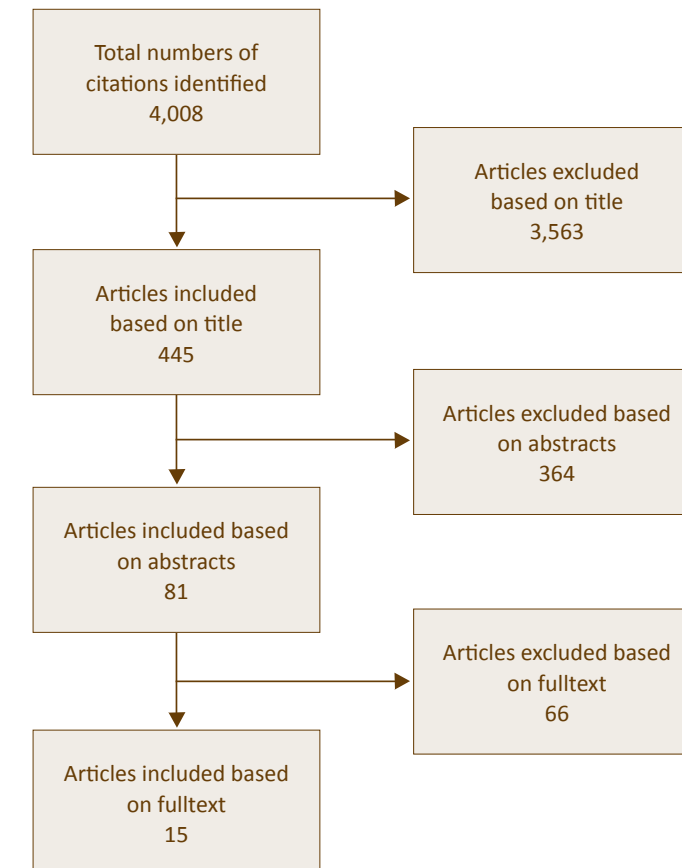
Key word screening led to 4,008 references. Screening of titles resulted in 816 articles. After eliminating the duplicates, 445 abstracts were screened for inclusion resulting in 81 articles. Finally, after reading these 81 articles, 15 were found to be relevant for the daily nursing care of PSD patients (Figure 1).

### Quality appraisal

The methodological quality of the studies was evaluated. Due to the various designs of the included studies, different critical appraisal forms are used for systematic reviews,<sup>36</sup> RCTs and descriptive studies,<sup>37;38</sup> and qualitative studies.<sup>39</sup> The quality was evaluated scoring one point for each of the following six criteria's: well described and adequate design; appropriate patient selection and, if relevant, treatment allocation; valid PSD assessment; clearly described and appropriate analysis; plausible results; clinical relevant results, resulting in a maximum score of six points for the best paper (Table 2).

The level of evidence, ranging from A1 to D, was determined for all the studies. The highest level (A1) was assigned to a systematic review of at least two independent studies of A2-level, level A2 to randomized clinical trials of good quality and sufficient size, B to correlational studies that did not fulfill the criteria for level A2 (e.g. case control and cohort studies), C to descriptive studies, and D to expert opinions.<sup>40;41</sup>

**Figure 1. Flow diagram of the process of data extraction**



### Data abstraction

The following study characteristics were extracted using a data extraction form: study design, setting or phase, sample, intervention or topic, depression scale used, type of outcome, conclusion and level of evidence (Table 3). Only outcomes concerning depression and mood status were described.

## Results

### Description of studies

The 15 studies included differed in methodological quality (Table 2), design, phase

**Table 2. Quality appraisal of the included studies**

Author (year of publication)	Design	Patient selection	PSD assessment	Analysis	Plausible	Clinically relevant	Total Score
Bennett et al (1996) <sup>54</sup>	1	1	-	1	1	1	5
Boter (2004) <sup>42</sup>	1	1	1	1	1	1	6
Claiborne (2006) <sup>43</sup>	1	0	1	0	1	1	4
Davis (2004) <sup>44</sup>	0	0	0	1	1	1	3
Dennis et al (1997) <sup>45</sup>	1	1	1	1	1	1	6
Johnson and Pearson (2000) <sup>46</sup>	1	0	1	0	1	1	4
Kumlien and Axelsson (2000) <sup>55</sup>	1	1	-	1	1	1	5
Lai et al (2006) <sup>48</sup>	1	1	1	1	1	1	6
Lincoln et al (2003) <sup>47</sup>	1	1	1	1	1	1	6
Magee and Davidson (2002) <sup>49</sup>	1	0	0	1	0	1	3
Mant et al (2000) <sup>50</sup>	1	1	1	1	1	1	6
Nayak et al (2000) <sup>51</sup>	1	0	0	1	1	1	4
Smith et al (2008) <sup>56</sup>	1	1	1	1	1	1	6
Watkins et al (2007) <sup>52</sup>	1	1	1	1	1	1	6
Williams et al (2007) <sup>53</sup>	1	1	1	1	1	1	6
<i>Criteria of appraisal:</i>							
Design:	The description of aim, design and methods were well described and appropriate for the design of the study. The sample size was large enough to answer the formulated research question.						
Patient selection:	The patient selection was appropriate for the design of the study and, if relevant in the design, treatment allocation was clearly formulated and sustained. A severe bias could not be detected.						
PSD assessment:	The PSD assessment was able to retrieve all depressive patients. A psychiatric interview or validated assessment tool was used to diagnose PSD.						
Analysis:	The statistical analysis is clearly described and appropriate for the design of the study.						
Plausible:	The statistical analysis made the results plausible.						
Clinically relevant:	The results were clinical relevant.						

after stroke, topic studied relevant to nursing care, and patient characteristics (Table 3). The critical appraisal of 10 publications resulted in a highest quality with a maximum score (score 5 or 6), whereas five were of medium quality (score 3 or 4). Twelve studies were RCTs or quasi-experimental studies,<sup>42-53</sup> two were qualitative studies,<sup>54,55</sup> and one was a systematic review.<sup>56</sup>

Five studies were conducted in the acute and rehabilitation phases,<sup>45;47;50;52;53</sup> five in the rehabilitation phase,<sup>42-44;51;54</sup> one in the rehabilitation and chronic phases,<sup>49</sup> three in the chronic phase,<sup>46;48;55</sup> and one in all phases.<sup>56</sup>

The scope for nursing care differed. Two of the studies focused on the role of nurses in recognizing PSD.<sup>54;55</sup> The others concerned intervention trials. The six following types of interventions were found: information provision,<sup>46;56</sup> life review therapy,<sup>44</sup> motivational interviewing,<sup>52</sup> music therapy,<sup>49;51</sup> physical exercise,<sup>48</sup> and support programs.<sup>42;43;53</sup>

In one intervention trial, only depressed patients were included,<sup>53</sup> whereas in the other studies, depressed and non-depressed patients were included.<sup>42-52;56</sup> The effect of the interventions on different outcomes was studied, although only the results concerning depression are taken into account in this review.

The following depression screening instruments were used: Beck Depression Inventory,<sup>46;56</sup> Bipolar Form of the Profile of Mood States,<sup>51</sup> Faces scale,<sup>49</sup> Geriatric Depression Scale,<sup>43;48;56</sup> General Health Questionnaire,<sup>47;52</sup> Hospital Anxiety and Depression Scale,<sup>42;45;50;56</sup> Hamilton Depression Scale,<sup>53</sup> Patient Health Questionnaire,<sup>53</sup> Yale single question,<sup>56</sup> and Zung Scale of Depression.<sup>44</sup> The Geriatric Depression Scale and the Hospital Anxiety and Depression Scale were used most frequently whereas the other six instruments were only used once or twice. Only one study used a structured clinical interview for DSM-IV for diagnosing depression to confirm the screening outcome.<sup>53</sup> Twelve trials reported depression outcome on a continuous scale indicating the severity of depression.<sup>42-51;53;56</sup> Four trials reported depression as a dichotomous outcome, indicating the number of depressed patients.<sup>48;52;53;56</sup>

Because of these methodological differences, it was not possible to conduct a meta-analysis pooling the results of the various types of therapeutic interventions. Therefore the results are presented in a narrative way.

### Role of nurses in recognition of PSD

The role of nurses in recognizing PSD was investigated in two qualitative studies. The nurses' perception of the care of patients with PSD was explored using structured interviews.<sup>54;55</sup> Bennett<sup>54</sup> focused on rehabilitation nurses ( $n=14$ ) and stroke patients with depression. Kumlien and Axelsson<sup>55</sup> studied nursing care in nursing homes focusing on cognition and mood ( $n=30$ ). The findings of both studies showed that nurses distinguished a screening role from an intervening role. They experienced the assessment of psychological status as difficult because of a lack of knowledge, skills and training and they seldom used measurement instruments.<sup>54;55</sup> In both studies, nurses described PSD as an important problem that needs more attention in the daily nursing care of stroke patients. However, the multidisciplinary focus on physical functioning, lack of time and limited knowledge hindered them from giving these patients adequate care. The interventions given by nurses, such as counseling and listening to the patient were poorly described.<sup>54;55</sup>

### Interventions in daily nursing care

#### Information provision

The effectiveness of information provision was studied in a recent meta-analysis<sup>56</sup> and in an experimental study.<sup>46</sup> In the meta-analysis, 10 trials evaluated the effect of information given to patients on the severity of depression and the number of depressed stroke patients.<sup>56</sup> Information provision was distinguished as active or passive. An intervention was classified as active if, following the provision of information, there was a purposeful attempt to allow the participant to assimilate the information and a subsequent plan for

**Table 3. Overview of included studies concerning therapeutic interventions in PSD.**

Author (year of publication)	Design	Phase/setting	Sample	Intervention/topic	Intervention provided by	Depression scale used	Type of outcome	Conclusion	Level of Evidence*
Bennett et al. (1996) <sup>54</sup>	Qualitative study	Rehabilitation	$n=14$ Qualified nurses at random chosen from a team of 28 nurses	Role of nurses: To understand how nurses experience the problems of depressive patients with stroke, and what their interventions are if it occurs	-	-	-	Nurses: - described depression and mood change in terms of observed behaviour; - explained depression as a reaction to stroke; - found assessment of psychological status difficult, because of a lack of skills and training; - seldom use measurement scales.	C
Boter (2004) <sup>42</sup>	RCT	Rehabilitation	$n=536$	Outreach nursing support program versus care as usual  3 telephone calls and 1 home visit in the 10-14 weeks after discharge by trained stroke nurses	Nurses	Hospital Anxiety and Depression Scale (HADS) - depression subscale	Severity of depression	No significant effect on severity of depression. Difference between median: 1 (95% CI <sup>†</sup> -0.52 to 2.98)	A2
Claiborne (2006) <sup>43</sup>	Randomised pre-post comparison group design	Rehabilitation	$n=28$	Outpatient support program versus care as usual	Social workers	Geriatric Depression Scale (GDS)	Severity of depression	Significant decrease of severity depression after 3 months in the intervention group ( $F^{\ddagger}=18.77, p<.001$ ) and significant difference in severity of depression between in intervention and control group at 3 months ( $p=.03$ )	B
Davis (2004) <sup>44</sup>	Pilot study; post-test only	Rehabilitation	$n=14$	Life review therapy versus alternative treatment (viewing and discussing videos)  3 sessions on 3 consecutive days	Nurse	Zung Scale for Depression (ZSD)	Severity of depression	Significant lower severity of depression in the intervention group compared with the control group ( $F^{\ddagger}=22.46, p<.01$ )	B

\* The different levels of evidence are A1: Systematic review of at least two independent studies of good quality and sufficient size; A2: Randomised clinical trial of good quality and sufficient size; B: Correlational studies but not fulfilling the criteria of level A2 (e.g. case control and cohort studies); C: Descriptive studies; D: Expert opinion  
<sup>†</sup> Confidence Interval  
<sup>‡</sup> Test statistic based on *F*-distribution used in ANOVA

Table 3. Continued

Author (year of publication)	Design	Phase/setting	Sample	Intervention/topic	Intervention provided by	Depression scale used	Type of outcome	Conclusion	Level of Evidence*
Dennis et al. (1997) <sup>45</sup>	RCT	Acute and rehabilitation	n=417	Support program versus care as usual  Home visits by family care worker (with social work background) over 6 months; frequency and nature at direction of family care worker	Social worker	Hospital Anxiety and Depression Scale (HADS)	Severity of depression	No positive effect on severity of depression Controls have less severe depression [Median difference between intervention and control group -1.5 (95% CI <sup>†</sup> -2.0-0.0)]	A2
Johnson and Pearson (2000) <sup>46</sup>	Pretest - post-test design	Chronic	n=41	Education  Structured educational course versus no educational course; eight two hour sessions over a four week period, post-test 1 week after finishing the course	Several health professionals coordinated by a nurse	Beck Depressions Inventory (BDI)	Severity of depression	Significant difference in severity of depression post intervention between matched pairs ( $t^{\ddagger}$ =2.09, $p<.05$ )	A2
Kumlien and Axelsson (2000) <sup>45</sup>	Qualitative study	nursing home	n=30 nurses	Role of nurses: To identify registered nurses description and experiences of stroke patients and their nursing care, focusing on cognition and mood	-	-	-	Nurses: - describe depression en mood change in terms of observed behaviour - found assessment of psychological status difficult, because of a lack of skills and training	C

\* The different levels of evidence are A1: Systematic review of at least two independent studies of A2-level; A2: Randomised clinical trial of good quality and sufficient size; B: Correlational studies but not fulfilling the criteria of level A2 (e.g. case control and cohort studies); C: Descriptive studies; D: Expert opinion

† Confidence Interval

‡ Test statistic based on Student's T-distribution used in t-test

Table 3. Continued

Author (year of publication)	Design	Phase/setting	Sample	Intervention/topic	Intervention provided by	Depression scale used	Type of outcome	Conclusion	Level of Evidence*
Lai et al. (2006) <sup>48</sup>	RCT; secondary analysis	Chronic	n=93 (19 depressed patients)	physical exercise program versus care as usual  Exercise program is progressive structured targeting strength, balance, endurance and upper extremity function  3x per week for 36 sessions supervised by a physical or occupational therapist	Physical and occupational therapists	15-item Geriatric Depression Scale (GDS-15)	Severity of depression	Significant difference in severity of depression between the intervention group and the control group immediately post intervention ( $p<.01$ ) Significantly fewer depressed patients in the intervention group than in the control group Patients who were depressed at baseline showed a significant greater decrease in the severity of depression immediately after the intervention than non-depressed patients ( $p=.03$ )	B
Lincoln et al. (2003) <sup>47</sup>	RCT	Acute and rehabilitation	n=250	Support program versus care as usual  Home visits for up to 9 months; frequency and nature at direction of FSO	Family support organiser (FSO) (background unknown)	12-item General Health Questionnaire (GHQ-12)	Severity of depression	No significant effect on severity of depression	A2
Magee and Davidson (2002) <sup>49</sup>	Pretest -post-test design	Rehabilitation - Chronic	n=14, 4 stroke patients, 10 other neurological diseases	Music therapy  1 session per week in a period of two weeks	Music therapist	Faces scale (self report)	Severity of depression	No significant effect on depression	B
Mant et al. (2000) <sup>50</sup>	RCT	Acute and rehabilitation	n=520	Support program versus care as usual  Home visits over 6 months; frequency and nature at direction of FSO	Family support organiser (FSO) (background unknown)	Hospital Anxiety and Depression Scale (HADS) - depression subscale	Severity of depression	No significant effect on severity of depression: Mean difference between intervention and control group 0.8 ( $p=.12$ )	A2

\* The different levels of evidence are A1: Systematic review of at least two independent studies of A2-level; A2: Randomised clinical trial of good quality and sufficient size; B: Correlational studies but not fulfilling the criteria of level A2 (e.g. case control and cohort studies); C: Descriptive studies; D: Expert opinion

Table 3. Continued

Author (year of publication)	Design	Phase/setting	Sample	Intervention/topic	Intervention provided by	Depression scale used	Type of outcome	Conclusion	Level of Evidence*
Nayak et al. (2000) <sup>51</sup>	Pretest - post-test design	Rehabilitation	n=18	Music therapy + care as usual versus care as usual 10 (group)-sessions, 2-3 sessions per week during admission	Music therapist	Bipolar Form of the Profile of Mood states (POMPS-BI)	Severity of depression	No significant effect on severity of depression	B
Smith et al. (2008) <sup>56</sup>	Review Cochrane Library, Medline, Embase, CINAHL, PsycINFO, SCL and SSCI, Assia, Index to UK theses, Dissertation Abstracts and Journal of Advanced Nursing (hand-searched)  1966-march 2007	All	17 RCTs including 1773 patients  of which in 10 trials depression is an outcome-measure.	Information provision  Divided into – active: if there was a purposeful attempt to allow the participant to assimilate the information and a subsequent agreed plan for clarification and consolidation or reinforcement; – passive: if the information was provided on a single occasion and there was no subsequent systematic follow up or reinforcement procedure	Nurses and other health professionals	Hospital Anxiety and Depression Scale (HADS) (7x)  Geriatric Depression Scale (GDS) (1x)  Beck Depressions Inventory (BDI) (1x)  Yale single question (1x)	Severity of depression  Number of depressed patients (HADS-D $\geq 10/11$ , GDS $\geq 10$ )	Significant effect of the interventions on severity of depression (WMD <sup>†</sup> -0.52, 95% CI <sup>‡</sup> -0.93 to -0.10, $p=.59$ ) Active information had a significantly greater effect than passive information on severity of depression (passive: WMD <sup>†</sup> 0.39, 95% CI <sup>‡</sup> -0.61 to 1.38; active: WMD <sup>†</sup> -0.71, 95% CI <sup>‡</sup> -1.16 to -0.25, $p<.02$ )  Pooled results showed no significant differences in the number of depressed patients between the intervention and control groups (OR <sup>§</sup> 0.90, 95% CI <sup>‡</sup> 0.61-1.32, $p=.59$ ) Active information had a significantly greater effect than passive information on depressed patients (passive: OR <sup>§</sup> 1.57, 95% CI <sup>‡</sup> 0.85 to 2.93; active: OR <sup>§</sup> 0.63, 95% CI <sup>‡</sup> 0.38 to 1.03, $p<.02$ )	A1

\* The different levels of evidence are A1: Systematic review of at least two independent studies of A2-level; A2: Randomised clinical trial of good quality and sufficient size; B: Correlational studies but not fulfilling the criteria of level A2 (e.g. case control and cohort studies); C: Descriptive studies; D: Expert opinion

<sup>†</sup> Weighted Mean Difference

<sup>‡</sup> Confidence Interval

<sup>§</sup> Odds Ratio

Table 3. Continued

Author (year of publication)	Design	Phase/setting	Sample	Intervention/topic	Intervention provided by	Depression scale used	Type of outcome	Conclusion	Level of Evidence*
Watkins et al. (2007) <sup>52</sup>	RCT	Acute and rehabilitation	n=411	Motivational Interviewing (MI) versus care as usual  4 individual sessions in 4 following days. By working with their dilemmas and ambivalence, patients are enabled to identify their own solutions to attain their goals and the perceived blocks in realising these goals	Therapists (back-ground unknown)	28-item General Health Questionnaire (GHQ-28)	Number of depressed patients (GHQ-28 $\geq 5$ )	Significantly more depressed patients ( $p=.03$ , OR <sup>§</sup> [normal mood]: 1.60, 95% CI <sup>‡</sup> 1.04-2.56)	A2
Williams et al. (2007) <sup>53</sup>	RCT	Acute and rehabilitation	n=188  depressive stroke patients	Care management program (Activate-Initiate-Monitor intervention) versus placebo intervention (identical numbers of contact about stroke symptoms but not depression)  A nurse care manager supports depressed patients in 1. activating them to understand and accept depression diagnosis and treatment; 2. initiating antidepressant medication; 3. monitoring treatment effectiveness	Nurses	Hamilton Depression Inventory (Ham-D)  9 item Patient Health Questionnaire (PHQ-9)	Severity of depression  Number of depressed patients (Ham-D $\geq 8$ , PHQ-9 $\geq 5$ )	Significant difference in severity of depression between the intervention group and the control group: – HAM-D Mean (SD) <sup>†</sup> in intervention: 10.6 (6.9) versus control: 13.9 (7.8) ( $p=.004$ ) – PHQ-9 Mean (SD) <sup>†</sup> from in intervention: 6.0 (5.0) versus control: 9.4 (6.3) ( $p<.001$ ) Significantly fewer depressed patients were found in the intervention group than in the control group: – HAM-D 61% versus 77% ( $p=.01$ ) – PHQ-9 52% versus 73% ( $p=.002$ )	A2

\* The different levels of evidence are A1: Systematic review of at least two independent studies of A2-level; A2: Randomised clinical trial of good quality and sufficient size; B: Correlational studies but not fulfilling the criteria of level A2 (e.g. case control and cohort studies); C: Descriptive studies; D: Expert opinion

<sup>†</sup> Standard Deviation

<sup>‡</sup> Confidence Interval

<sup>§</sup> Odds Ratio

clarification and consolidation or reinforcement. It was classified as passive if the information was provided on a single occasion and there was no subsequent systematic follow-up or reinforcement procedure. This meta-analysis showed a significant effect on the severity of depression. The pooled results of these trials showed no significant differences in the number of depressed patients. A subgroup analysis showed that active information had significantly more effect than passive information, both on the severity of depression and on the number of depressed patients.<sup>56</sup>

The trial by Johnson and Pearson<sup>46</sup> was not included in the meta-analysis because it did not provide data suitable for pooling.<sup>56</sup> In this trial, the participants ( $n=41$ ) were matched into pairs based on their pretest scores and then the members of each pair were assigned at random to either the treatment group ( $n=21$ ) or the control group ( $n=20$ ). The treatment group received an education program of eight two-hour sessions over a four week period, aimed at empowering them to develop self-care strategies that promote healthy adaptation to living with stroke-related disabilities. The control group received the program two weeks after the treatment group had completed the course.<sup>46</sup> One week after finishing the intervention, the intervention group showed a significant decrease in severity of depression.<sup>46</sup>

#### *Life review therapy*

In a small RCT ( $n=18$ ), the effect of life review therapy on the severity of depression in stroke patients was studied.<sup>44</sup> In the intervention group a trained nurse discussed in three individual one-hour sessions the patient's experiences of childhood, adolescence, family and home, as well as adulthood.<sup>46</sup> In the control group patients spent the same amount of time individually with the researcher viewing and discussing videos that had no therapeutic intent. The intervention was effective as the intervention group had a significant lower severity of depression.<sup>46</sup>

#### *Motivational Interviewing*

In an RCT, the effect of motivational interviewing on the number of depressed patients was studied in stroke patients ( $n=411$ ).<sup>52</sup> The personal recovery goals and perceived barriers were discussed in individual sessions. Therapists worked with patient's dilemmas and ambivalence and enabled them to identify their own solutions by supporting and reinforcing optimism and self-efficacy.<sup>52</sup> Three months after stroke, motivational interviewing showed a significant effect on the number of depressed patients.<sup>52</sup>

#### *Music Therapy*

The effect of music therapy on the severity of depression in neurological patients, including stroke patients, was investigated in two studies.<sup>49;51</sup> In one of these studies, the intervention consisted of one individual musical session per week for two weeks. The main activities during a session were listening to music and improvising music with the therapist.<sup>49</sup> In the other study, the intervention consisted of group sessions offered two or three times a week with a maximum of 10 sessions.<sup>51</sup> These sessions included various musical activities expressing the emotions experienced.<sup>51</sup> Both studies showed no effect on the severity of depression.<sup>49;51</sup>

#### *Physical Exercise*

In one RCT, the effect of physical exercise on the severity of depression and the number of depressed patients was examined.<sup>48</sup> Physical exercise focused on strength, balance, endurance and upper extremity function. A physiotherapist or an occupational therapist treated the patients in their homes three times a week over nine weeks. The intervention group showed a significant lower severity of depression and significantly fewer patients were depressed immediately and six month after the intervention.<sup>48</sup>

### Support programs

Six studies measured the effects of support programs on PSD.<sup>42;43;45;47;50;53</sup> These programs differed considerably in goal and content and they showed different results. In one RCT, the effects of an outreach nursing support program on severity of depression in stroke patients ( $n=536$ ) was measured after discharge from hospital.<sup>42</sup> The program consisted of three telephone contacts and one home visit in the first half year after the stroke. During these contacts risk factors, consequences and unmet stroke service needs were discussed.<sup>42</sup> No significant effects were found.<sup>42</sup> The effect of coordinated delivery of care for patients at home recovering from stroke on severity of depression was studied by Claiborne.<sup>43</sup> The core elements were ongoing monitoring of the patient's progress related to physical and psychosocial issues, service needs and adherence to self-care activities.<sup>43</sup> Social workers visited the patients ( $n=28$ ) during the first two weeks after discharge from a rehabilitation centre and contacted them weekly by telephone over three months. This program led to a significant decrease in the severity of depression in the intervention group and a significant difference in severity of depression between the intervention and control groups.<sup>43</sup> In another RCT, the effect of a support program on severity of depression was compared with care as usual.<sup>45</sup> In the intervention group a family care worker visited the patients ( $n=417$ ) at home over a six month period. The family care worker decided the nature and frequency of these visits. No significant effect was found and even the control group showed a significantly lower severity of depression.<sup>45</sup> The effect of home visits provided by a family support organiser on the severity of depression was studied in two RCTs.<sup>47;50</sup> In one of these studies, 250 participants were followed for nine months<sup>47</sup> and in the other study 520 participants were followed for six months.<sup>50</sup> The family support organiser decided the nature and frequency of the visits. Both studies showed no effect.<sup>47;50</sup>

The effect of a specific nursing support program on the severity of

depression and the number of depressed patients was studied in an RCT.<sup>53</sup> Only patients with a psychiatric diagnosis of depression ( $n=188$ ) were included.<sup>53</sup> This program was provided for three months and included three main elements: a) activating patients to understand and accept diagnosis and treatment for depression, b) initiating antidepressant medication, and c) monitoring treatment effectiveness. The program resulted in a significantly lower severity of depression.<sup>53</sup>

### Discussion

This review included 15 studies focusing on the role of nurses in the management of PSD and therapeutic interventions that nurses can use in the daily care of PSD patients. Information provision, life review therapy, motivational interviewing, an outpatient support program, a support program concerning activating and monitoring treatment of depression and physical exercise had positive effects on the severity of PSD.<sup>43;44;46;48;53;56</sup> The number of depressed patients was also decreased by motivational interviewing, physical exercise and a support program concerning activating and monitoring treatment of depression.<sup>48;52;53</sup>

To our knowledge, this is the first review focusing on the therapeutic interventions for the daily nursing care of PSD patients. The strong evidence for the positive effect of information provision is based on a meta-analysis including 10 studies.<sup>56</sup> Only few studies have been conducted on the other interventions. However, the results are promising and important for daily nursing care. Furthermore, there is strong evidence that support programs including home visits or telephone calls by health care providers are not effective.

This review has several strengths and limitations. Its internal validity was enhanced by a detailed description of the methodology used.<sup>35</sup> Methodological quality was evaluated using critical appraisal forms. Some of the included interventions which were effective, were provided by nurses, such as information provision, life review therapy, and a specific support program concerning

activating and monitoring treatment of depression.<sup>43;44;46;53;56</sup> However, motivational interviewing and an outpatient support program, were provided by other professionals.<sup>43;44</sup> These interventions may be applied by nurses as the findings of these studies can be extrapolated to the nursing context.

It was expected that few if any studies would be found to conform to rigorous criteria, therefore, no restrictions were imposed on the type of intervention. This decision may be considered a limitation because judging an intervention important to nursing care depends on the subjective opinion of the researchers. In order to overcome this the decision to include a study was taken after independent assessment of two reviewers and discussion of any discrepancies.

Any review focusing on stroke patients needs to consider differences in stroke severity and time elapsed between stroke onset and data collection.<sup>57</sup> Most of the intervention studies did not report information on stroke severity at baseline, and when this was reported, different assessment methods and instruments were used. The time elapsed between stroke onset and data collection was related to the phase after stroke, which differed among the studies included. Most studies focused on patients in the acute and rehabilitation phases. Also, the studies concerning one specific intervention did not differ regarding phase after stroke. Moreover, in the 13 intervention studies included, 10 different depression screening instruments were used measuring the outcome variables. The clinimetric properties of BDI, GDS, GHQ, HADS, HAMD, and PHQ-9 for the detection of depression in stroke patients were acceptable to good.<sup>58-62</sup> All these methodological differences may have influenced the interpretation of the findings and precludes a meaningful comparison of the results of the studies.

The finding that nurses observe and recognize symptoms of depression intuitively and that they find assessment of mood status difficult,<sup>54;55</sup> is supported by studies that have been conducted with elderly patients living in

nursing homes, staying in hospitals or receiving home care which show similar results.<sup>31;32;63</sup> One study, however, showed that screening PSD in patients by a trained nurse leads to a correct identification.<sup>64</sup> Therefore, the structural use of a depression screening instrument in the daily care of stroke patients should increase the early recognition of depression by nurses.<sup>65</sup>

The effect of information provision on depression in patients with stroke has been most extensively studied. A meta-analysis of 10 studies provided strong evidence for positive effects<sup>56</sup> which are also supported by other reviews on education in patients with rheumatoid arthritis and chronic heart failure.<sup>66;67</sup> A meta-analysis showed that structured approaches, reinforcement and multiple strategies in providing information were associated with the greatest effect.<sup>68</sup>

Although life review therapy is shown to be effective, the evidence was weak due to the small sample size and the moderate methodological quality. The evidence for motivational interviewing was stronger because of the high quality and the large sample size of the study. Other studies have shown that motivational interviewing can be applied by nurses.<sup>69;70</sup>

Making music and listening to music in planned sessions had no positive effect on PSD. However, due to the small sample sizes and the moderate quality the evidence for the results was weak. Reviews show that music played via headphones during the daily care of hospitalized patients<sup>71</sup>, and music played to demented elderly people living in a nursing home, have a significant positive effect on depression.<sup>72</sup> Therefore, playing music during daily care may indeed be an effective nursing intervention.

Although the physical exercise in the included study was not provided by a nurse, the results are relevant to nursing care. Patients with depressive symptoms tend to avoid therapeutic and social activities more than non-depressed patients do.<sup>73</sup> Nurses need to integrate activities of daily living and mobility exercises in the daily care and encourage patients to participate actively in physiotherapy and occupational therapy programs. Nurses can thereby play



an important role in creating conditions in the daily patient program that maximize participation in therapy.

In five of the six studies focusing on support programs the interventions were almost identical. Although one study<sup>43</sup> showed a positive effect on severity of depression, the other four found no positive effects. The methodological quality of the study conducted by Claiborne<sup>43</sup> was moderate, whereas of the other four it was good, which could clarify the different results. Therefore, support programs were shown not to be effective on the severity of depression. A support program focusing particularly on activating, initiating, and monitoring the treatment of PSD appears to be effective.<sup>53</sup> It requires a high level of expertise in caring for depressed stroke patients. Therefore, applying these interventions will need the competences of the advanced nursing practice level of a nurse practitioner or clinical nurse specialist.<sup>74</sup>

## Conclusion

Concerning the nurses' contribution to the therapeutic treatment of PSD patients, nurses distinguish between screening and intervening roles. They recognize symptoms of depression, but they find PSD difficult to identify. Measurement scales supporting their observations are seldom used.<sup>54;55</sup> Strong evidence was found for information programs in reducing the severity of PSD.<sup>46;56</sup> Evidence was also found for the positive effects of life review therapy, motivational interviewing, physical exercise, and a support program in reducing the severity of PSD and the number of patients with PSD.<sup>43;44;48;52;53</sup>

## Relevance to clinical practice

The findings of this review enable nurses to intervene effectively to reduce the occurrence and severity of depression in stroke patients. Although most of the interventions described were given by nurses, some were provided by other health care professionals. These findings, however, may be extrapolated

to the nursing context as these interventions relate to the definition of nursing intervention: '...any treatment based upon clinical judgment that a nurse performs to enhance patient outcomes...'.<sup>75</sup> Nurses experience listening to patients and counseling as an important part of nursing care.<sup>54;55</sup> The findings show that listening to patients and counseling play an important role in giving a precise aim and direction to the interventions described. Furthermore, all the interventions studied showed elements of rehabilitation nursing;<sup>28;29</sup> for example, the teaching and coaching role in information provision, life review therapy and support programs and their coordination.

However, prior to implementation in clinical practice, it is important to consider whether the type of intervention fits with the nursing care. For instance motivational interviewing, which needs to be provided in planned sessions, may not fit with the daily nursing practice on clinical wards and may be more appropriate for nursing care in outpatient clinics. Furthermore, it is important to consider basic and post graduate education of nurses concerning management of PSD in patients. For example education and training is needed on which interventions to apply, as well as how and when to apply them. Also concerning the structural screening of depression, it is essential to train nurses in how to use depression screening instruments accurately. Other important issues concern organizational changes needed and optimal collaboration with other professionals. For example, information provision is a multidisciplinary effort, which needs good multidisciplinary collaboration. Before starting such programs it is essential to make a structured plan of the content, the procedure and the participating health care providers. Nurses can initiate this preferably in good collaboration with other health care professionals.

Further research is needed, focusing on the early detection of PSD by nurses using valid and reliable depression screening instruments as well as focusing on testing the interventions identified in this review in preferably randomised studies with larger samples. Research is also needed on developing and testing

nursing interventions that are based on clinical experience, other research or extrapolated evidence from effective interventions by other professionals and that also are tailored to patients' needs. Future studies need to measure the effects of these interventions on depression and other outcomes of patients with stroke. The further development of evidence-based nursing interventions for the early detection of PSD will improve the management of PSD and the outcome of patients with stroke.

### Contributions

Study design: JMG, TBH; data collection and analysis: JMG, TBH and manuscript preparation: JMG, TBH, MJS, EL, FG.

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## Appendix 1

Members of the Rehabilitation Guideline Stroke Working Group: J.M. de Man-van Ginkel, F Gooskens, M.J. Schuurmans, E. Lindeman, T.B. Hafsteinsdóttir.

Other members: D. Bergs, RN, MSc, Department of Rehabilitation, Grensás, Landspítali University Hospital, Reykjavík, Iceland; K. Björgvinsdóttir, RN, MSc, Department of Neurology (at the time of the study), Landspítali University Hospital, Reykjavík, Iceland; M. Klinke, RN, BSc, Department of Neurology, Landspítali University Hospital, Reykjavík, Iceland; I. Poslawsky, RN, MSc, Division Neurosciences, Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, the Netherlands; M. Rensink, MD, Faculty chair Care for Older People, University of Applied Sciences Utrecht, Faculty of Nursing, Utrecht, the Netherlands; S. Sigurjónsdóttir, RN, BSc, Department of Neurology, Landspítali University Hospital, Reykjavík, Iceland; M. Vergunst RN, MSc, Department of Neurology and Neurosurgery, University Medical Center Utrecht, the Netherlands.

## **Chapter 3**

### **Clinical Manifestation of Depression in Stroke Patients, is it Different from Depression in Other Patient Populations?**

**Janneke de Man-van Ginkel, Thóra Hafsteinsdóttir, Eline Lindeman,  
Mirjam Geerlings, Diederick Grobbee, Marieke Schuurmans**

## Abstract

**Objective.** Despite ample research on post-stroke depression (PSD), the debate continues regarding whether symptoms, such as sleep disturbances, loss of energy, changes in appetite, and concentration difficulties should be considered to be consequences of stroke or general symptoms of depression. By comparing symptoms in depressed and non-depressed stroke patients, with depressed patients with other symptomatic atherosclerotic diseases and depressed patients in general practice, we aim to further clarify similarities and distinctions of post-stroke depression and depression in other patient populations.

**Design.** An observational multicenter study.

**Setting.** Three hospitals and seven general practices.

**Participants.** Three hundred eighty-two stroke patients admitted to hospital with a clinical diagnosis of intracerebral hemorrhage or ischemic infarction who were able to communicate adequately, 530 patients with symptomatic atherosclerotic diseases, and 1,160 patients in general practice.

**Main outcome measure.** Prevalence of depressive symptoms.

**Results.** Comparing depressed stroke patients with depressed patients with symptomatic atherosclerotic diseases and depressed general practice patients demonstrated broadly similar symptom profiles in the three cohorts, as well as comparable levels of individual symptom prevalence. However, the stroke patients suffer more severely from these symptoms than patients in general practice and patients with symptomatic atherosclerotic diseases.

**Conclusions.** The findings suggest that PSD is not a different type of depression. This findings indicates that all depressive symptoms should be evaluated in stroke patients, including somatic symptoms.

**Key words.** Depression, Stroke, Symptoms, Major depressive disorder

Post-stroke depression is a frequent complication, that affects approximately one third of all patients in the first two years after stroke.<sup>1,2</sup> In the last decades, post-stroke depression (PSD) has been studied extensively. Despite the frequent occurrence and high impact of PSD, questions persist concerning its nature. There is an on-going debate in the literature regarding whether depression is caused by biological factors provoked by the brain injury or by vascular pathophysiology underlying the stroke, or whether PSD is a secondary psychological response to the physical, cognitive, and social impairments produced by the stroke itself.<sup>3,4</sup> The question remains whether symptoms such as sleep disturbances, loss of energy, changes in appetite, and concentration difficulties should be considered to be clinical manifestation of PSD or secondary consequences of the stroke.<sup>5</sup>

Although many studies have been conducted on various aspects of PSD, such as prevalence, screening measurements, associated factors, treatment, and prevention,<sup>1,2,6-12</sup> only a few studies have investigated the clinical manifestation of depression in stroke patients.<sup>13-23</sup> Moreover, meaningful comparison of the studies is hampered by the diverse in methods and measurement instruments used to diagnose depression, the time elapsed between stroke onset and data collection, the patient groups compared with the stroke patient, and the data analysis.

Hence, the question still remains whether the clinical manifestation of PSD differ from that in other groups of patients. The present study was conducted to determine whether depressive symptom profiles are different in depressed stroke patients compared to non-depressed stroke patients, depressed patients with symptomatic atherosclerotic diseases other than stroke, and depressed patients in general practice.



## Methods

### Study design and participants

A multicenter study was conducted in three hospitals in The Netherlands. Between December 2009 and January 2011, we included 410 consecutive stroke patients who were admitted to the hospitals with a clinical diagnosis of intracerebral hemorrhage or ischemic infarction who did not present with serious cognitive disorders as determined by the Mini Mental State Examination (score  $\geq 18$ )<sup>24</sup> or communicative disorders based on the Frenchay Aphasia Screening Test (scores  $\geq 17$  for patients  $< 60$  years of age,  $\geq 16$  in patients  $\geq 60$ , and  $\geq 15$  in patients  $\geq 71$  years of age).<sup>25</sup>

For comparison, we used data on patients with symptomatic atherosclerotic diseases other than stroke ( $n=592$ ) from the Second Manifestation of Arterial Disease study (SMART) and data on patients with depression in general practice from the PREDICT-NL study. The SMART study is a prospective cohort study aimed at investigating brain changes on MRI in independently living patients with symptomatic coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm.<sup>26;27</sup>

Predict-NL, the Dutch arm of the PredictD study, is a large prospective cohort study that began in 2003. Consecutive general practice patients ( $n=1,338$ ), recruited from seven general practices in the city of Utrecht and the surrounding areas, were approached to participate, irrespective of their reasons for consulting the general practitioner.<sup>28</sup> The design of the PredictD and the Predict NL study have been published previously.<sup>28;29</sup> Depression was measured in the participants, who were invited for follow-up measurements between March 2006 and May 2009. For all studies, ethical approval was obtained from the Medical Ethical Committee of the University Medical Center Utrecht, and written informed consent was obtained from all participants.

### Outcome measures

Major depressive disorder was assessed according to the DSM-IV-TR<sup>TM</sup> criteria<sup>30</sup> using the Composite International Diagnostic Interview (CIDI).<sup>31</sup> The CIDI is a structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders that is designed to meet the need for a short but accurate, structured psychiatric interview for multi-center clinical trials and epidemiological studies.<sup>32</sup> The CIDI shows good diagnostic concordance with the DSM-III-R ( $K=0.84$ ) and the ICD-10 diagnosis ( $K=0.78$ ) for major depression.<sup>32</sup> Its reliability is good, with an inter-rater reliability measured with  $K=0.84$ , and a test-retest reliability of  $K=0.90$ .<sup>32</sup> The depression section of the 2.1 version was administered by trained researchers.

Depressive symptoms were measured with the 9-item Patient Health Questionnaire (PHQ-9).<sup>33</sup> The items include the 9 symptoms of depression according to the DSM-IV-TR<sup>TM</sup>.<sup>30</sup> During the interview, the patients were asked how often they had been bothered by any of the symptoms during the previous two weeks using a 4-point Likert scale ranging from 0 (symptom not at all present) to 3 (symptom present nearly every day).<sup>33</sup> Adding up the item scores yields a sum score ranging from 0 (no depressive symptoms) to 27 (all symptoms occurring nearly every day). The sum score is indicative of depression severity: a score ranging from 0-4 indicates no depression at all, 5-9 suggests mild depression, 10-14 signifies moderate depression, 15-19 indicates moderately severe depression and 20-27 suggests severe depression.<sup>33;34</sup> The PHQ-9 was shown to perform well in medical settings,<sup>34</sup> both in stroke patients<sup>36</sup> and general practice patients.<sup>37</sup>

The stroke patients were visited at home or at the residential health care facility in the 6<sup>th</sup>-8<sup>th</sup> week after stroke onset, and the CIDI and PHQ-9 were administered for the diagnosis of major depressive disorder since stroke onset. In patients with symptomatic atherosclerotic diseases and general practice patients, the CIDI was administered during a general practice visit or hospital

visit to establish whether the patients had suffered from major depressive disorder during the past 6 months or 12 months, respectively.

### Data analysis

Prevalence rates for depression and individual symptoms were analyzed with descriptive statistical methods. Cases with missing data were excluded from the analyses. Of the 410 included patients in the stroke cohort, 382 (93.2%) patients remained after excluding cases with incomplete data regarding depression diagnosis or symptoms. In the symptomatic atherosclerotic diseases and general practice cohorts, data were complete in 530 (89.5%) and 1,160 (86.7%) patients, respectively.

Demographic characteristics were compared between the three cohorts using the percentages and Chi-square tests for dichotomous variables and either the means with standard deviation (SD) and Student's t-test or the median and interquartile range (IQR) with the Mann-Whitney *U*-test for continuous variables, depending on the normality. To analyze differences in sum scores of the PHQ-9 among the cohorts, we assessed the normality of the data using the Kolmogorov Smirnov test and confirmed that the data were positively skewed. Therefore, we used the median scores with their interquartile ranges and employed the Mann-Whitney *U*-test in depressed versus non-depressed patients of the stroke cohort and in depressed patients of the stroke cohort versus the other cohorts separately.

In addition, the answers to the PHQ-9 items were dichotomized at a threshold value of 2 indicating 'symptom present more than half the days' according to previous research.<sup>33</sup> Based on this threshold, the values 0 (not at all) and 1 (several days) were coded as 'symptom present less than half the days', and the answers 2 (more than half the days) and 3 (nearly every day) were coded as 'symptom present at least more than half the days'. Then, the presence of each of the depressive symptoms was compared between the

depressed patients in the stroke cohort and the other patients cohorts using Chi-square tests. Based on recently recommended cut-off scores,<sup>37</sup> we also dichotomized the nine items into 'symptom present on at least several days' (values 1 [several days] to 3 [nearly every day]) or 'symptom absent' (value 0 [not at all]). These analyses were repeated in the non-depressed patients of all the other cohorts.

### Results

The mean age of the 382 stroke patients was 69 years (SD=14.5, range 20-97 years) and 207 (54.2%) of these patients were male. Of the patients with other symptomatic atherosclerotic diseases, the mean age was 61.6 years (SD=9.6, range 31-83 years), and 431 (81.3%) were male; in the patients in general practice, the mean age was 50.5 years (SD=16.3, range 18-88 years), and 438 (37.8%) were male. Table 1a and 1b show the baseline characteristics of patients included in the study.

In the stroke cohort, 54 patients (14.1%, 95% CI 10.9-18.1%) were diagnosed with major depressive disorder according to DSM-IV criteria. In the symptomatic atherosclerotic diseases and the general practice cohorts, 29 (5.4%, 95% CI 3.8-7.9%) and 150 patients (12.9%, 95% CI 11.1-15.0%) were diagnosed with major depressive disorder, respectively. Depression severity, represented by the PHQ sum score, differed between depressed patients in the stroke cohort and the other cohorts. In the stroke cohort, the median PHQ-9 sum score was 15.0 (IQR=10.0-18.0), compared to median sum scores of 7.0 (IQR=4.5-12.5) in the symptomatic atherosclerotic diseases cohort and 9.0 (IQR=6.0-14.0) in the general practice cohort. These results indicate that stroke patients suffered from more severe depressive symptoms than the patients in the symptomatic atherosclerotic diseases cohort and the general practice cohort.

In figure 1 we depicts the symptom profiles of the depressed and non-depressed patients in the three cohorts. Comparing the symptom profiles

of depressed versus non-depressed stroke patients shows that symptom prevalence increased in the depressed stroke patients, including increases in somatic symptoms.

Comparing the symptom profile of depressed stroke patients with that of depressed patients with symptomatic atherosclerotic diseases other than stroke and the depressed patients in general practice reveals a similar pattern. When we used the original threshold value, indicating a symptom to be present if it occurred at least more than half of the days,<sup>33</sup> the symptom profiles differed somewhat with regard to prevalence. This difference disappeared when we employed the recently recommended cut-off value when a symptom was considered to be present if it occurred on several days.<sup>37</sup> This finding indicates that the symptom profiles are quite similar in depressed stroke patients compared to depressed patients with other symptomatic atherosclerotic diseases and depressed patients in general practice. However, depressed stroke patients are more affected by depressive symptoms than depressed patients with other symptomatic atherosclerotic diseases and those in general practice.

The only significant differences in prevalence rates were found between the depressed stroke patients and the depressed patients in general practice. In the former cohort, a higher prevalence rate (87.0%) was found for the symptom 'concentration difficulties' compared to 66.0% of the depressed patients in general practice ( $\chi^2=8.6$ ,  $p=.003$ ). In the general practice depressed patients, the symptoms 'anhedonia' and 'changes in appetite' showed higher prevalence rates. The symptom 'anhedonia' was present in 74.1% of the depressed stroke patients versus 86.0% of the depressed patients in general practice ( $\chi^2=4.0$ ,  $p=.046$ ). The symptom 'changes in appetite' was present in 37.0% of the depressed stroke patients versus 56.0% of the general practice depressed patients ( $\chi^2=5.7$ ,  $p=.017$ ).

**Table 1a. Demographic characteristics of the stroke patients**

	Stroke patients N=382					
	Depressed n=54 (14.1%)			Non Depressed n=328 (85.9%)		
Gender n (%)						
Male	26	(48.1)		181	(55.2)	
Age in years						
Mean (SD) (min-max)	65.8	(17.3)	(20-89)	69.8	(13.9)	(20-97)
Type of stroke n (%)						
Intracerebral hemorrhage	9	(16.7)		39	(11.9)	
Infarction	45	(83.3)		289	(88.1)	
Localization n (%)						
Right	24	(44.4)		122	(37.2)	
Left	21	(38.9)		142	(43.3)	
Other	9	(16.7)		64	(19.5)	
Time since stroke onset in days						
Mean (SD) (min-max)	6.9	(0.9)	(5.6-8.9)	6.9	(1.0)	(1.4-11.6)
Barthel Index						
Median (IQR)(min-max)	19.5	(14.5-20.0)	(0-20)	20.0	(18.0-20.0)	(0-20)
PHQ sum score						
Median (IQR)(min-max)	15.0	(10.0-18.0)	(3-27)	4.0	(2.0-7.0)	(0-23)

IQR = Interquartile range  
SD = Standard deviation

## Discussion

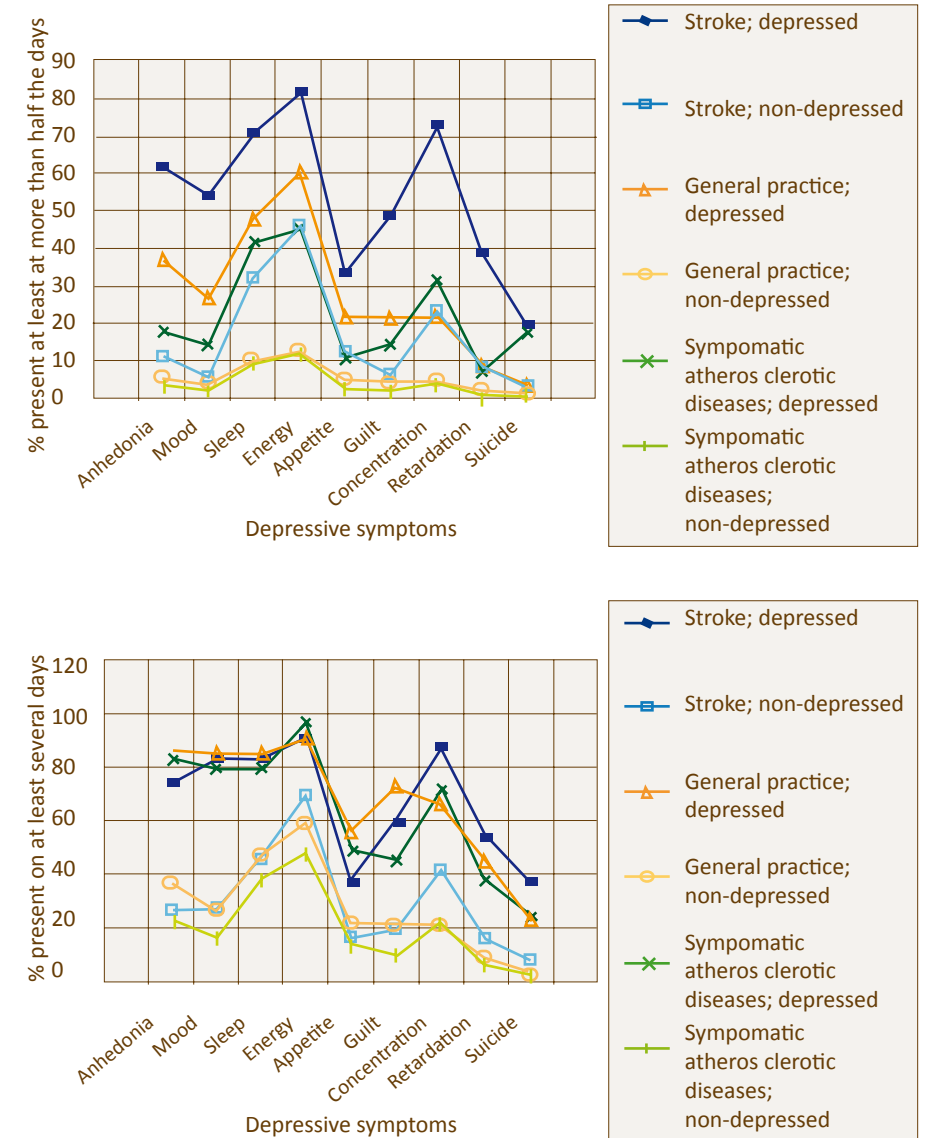
In this study we compare the clinical manifestation of major depressive disorder in stroke patients with that in patients with other symptomatic atherosclerotic diseases and patients in general practice. Our findings suggest that both somatic and non-somatic symptoms in patients with depression are broadly similar, irrespective of whether they occur post-stroke. However, the impact of symptoms seems to be greater in stroke patients.

**Table 1b. Demographic characteristics of depressed stroke patients versus depressed patients with other symptomatic atherosclerotic disease and depressed patients in general practice**

Participants with Major Depressive Disorder based on the CIDI						
	Stroke n=54		Symptomatic atherosclerotic diseases other than stroke n=29		General practice n=150	
Gender n (%)						
Male	26	(48.1)	24	(82.8)	54	(36.0)
Age in years						
Mean (SD)	65.8	(17.3)	55.0	(8.1)	45.9	(14.0)
(min-max)		(20-89)		(39-77)		(20-83)
Marital status n (%)						
Single	4	(7.5)	3	(10.3)	32	(21.3)
Married/ Cohabiting	36	(67.9)	22	(75.9)	93	(62.0)
Widowed/ Divorced	13	(24.5)	4	(13.8)	25	(16.7)
Living situation						
Alone	11	(20.4)	7	(24.1)	39	(26.0)
With partner/ child/other	42	(77.8)	22	(75.9)	111	(74.0)
Nursing home	1	(1.9)	-	-	-	-
Education in years n (%)						
≤ 6	7	(13.5)	5	(17.2)	17	(11.6)
7-10	18	(34.6)	12	(41.4)	45	(30.8)
11-16	18	(34.6)	7	(24.1)	33	(22.6)
≥ 16	9	(17.3)	5	(17.2)	51	(34.9)
PHQ sum score						
Median (IQR)	15.0	(10.0-18.0)	7.00	(4.5-12.5)	9.0	(6.0-14.0)
(min-max)		(3-27)		(0-22)		(0-26)

CIDI = Composite International Diagnostic Interview  
IQR = Interquartile range  
SD = Standard deviation

**Figure 1 and 2. Symptom profiles of stroke patients, patients with other symptomatic atherosclerotic diseases and patients in general practice**



To appreciate these findings, some aspects of the study need to be addressed. To our knowledge, this is the first study in which PSD patient symptom profile is compared with two other patient populations. Prior studies only compared depressed stroke patients with non-depressed stroke patients,<sup>13-16</sup> patients with endogenous depression,<sup>17-20</sup> or other somatic patient populations, such as those with myocardial infarction or geriatric patients.<sup>21-23</sup> Moreover, we used large cohorts, conducted the same diagnostic interviews and used the same depression screening instrument in all of the three cohorts. These instruments were shown to be valid in the different patient populations.<sup>32;35-37</sup>

A limitation of the data is that we only included stroke patients who were able to communicate adequately, because assessing depression with the PHQ-9 and CIDI is highly dependent on verbal and cognitive competence. The difficulty associated with reliably measuring depression in patients with cognitive and communicative disorders<sup>38</sup> limits the generalizability of our results to patients who were able to communicate adequately. In our stroke cohort, the prevalence of PSD was 14.1% (95% CI 10.9-18.1%). Although the literature describes considerable variation in the PSD frequency, a pooled estimate indicates that depressive symptoms are present in one-third of all stroke survivors at any given time during follow-up.<sup>1</sup> The prevalence of depression in our study could have been influenced by the follow-up of eight weeks or the exclusion of patients who were too ill to participate due to stroke severity or severe cognitive or communicative impairments. Previous studies have shown a correlation between PSD and stroke severity, as well as cognitive impairment and depression.<sup>6;38</sup> The stroke patients were generally older than those with other symptomatic atherosclerotic diseases and general practice patients. Additionally, there were more male patients in the symptomatic atherosclerotic diseases cohort, whereas the proportions of male and female participants in the stroke cohort were equal. This factor could have influenced the prevalence rates of major depressive disorder, as age and female sex are

often considered to be risk factors for major depressive disorder in different patient populations.<sup>6;39;40</sup> Finally, we did not register medication use in the stroke cohort and were therefore not able to account for the potential effects of antidepressants. This limitation could have affected our results because medication use influences the degree to which patients experience depressive symptoms, which affects symptom prevalence.

Considering our results in relation to other studies, we identified some remarkable findings. First, all of the symptoms, including the somatic symptoms, were more prevalent in the depressed stroke patients compared with the non-depressed stroke patients. This finding is consistent with previous studies that have concluded that all depressive symptoms are more frequent in depressed stroke patients.<sup>13-16</sup> Second, the symptom profile was not different in the depressed stroke patients compared to that with other symptomatic atherosclerotic diseases and general practice patients. Thus, our study differs from others in that we investigated the symptom profile in more detail. This could explain the differences with previous studies, which is illustrated by the following: using the original threshold value 'symptoms present more than half the days' suggests that there are differences between the stroke patients and the other patient populations, which supports the findings in the literature that symptom profiles differ between patient populations.<sup>19-21</sup> However, using the recently recommended cut-off value 'symptoms present on at least several days' indicates that there is no difference in symptom profile, which corroborates findings in other studies.<sup>18;22</sup> Hence, the comparison of prevalence rates at the different cut-off value allow us to conclude that depressed stroke patients have a similar symptom profile, but they suffer more severe symptoms than depressed patients with other symptomatic atherosclerotic diseases or depressed patients.

## Conclusion

We found that the nature of post-stroke depression does not differ from depression in other patient populations; the symptom profile pattern were similar in depressed stroke patients compared with depressed patients with other symptomatic atherosclerotic diseases as well as with depressed patients in general practice. Our results suggest that the somatic symptoms in the depressed stroke patients should be considered as clinical manifestation of PSD. Furthermore, the high prevalence of depressive symptoms in the early stage after stroke highlights the importance of early PSD detection. Provided that early detection is followed by treatment and follow-up, this early PSD detection may decrease the burden of PSD and the negative impact depression has on stroke patient participation in rehabilitation.

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## **Chapter 4**

### **Screening for Post-Stroke Depression using the Patient Health Questionnaire**

**Janneke de Man-van Ginkel, Floor Gooskens, Vera Schepers,  
Marieke Schuurmans, Eline Lindeman, Thóra Hafsteinsdóttir**

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## Abstract

**Background.** Although post-stroke depression has a significant impact on a patient's ability to recover after stroke, it is generally not recognized. Structured screening can help nurses identify symptoms of depression in stroke patients. In clinical practice, the utility of an instrument is as important as its validity and reliability.

**Objective.** To investigate the reliability, validity, and clinical utility of the 9-item and 2-item Patient Health Questionnaires (PHQ-9 and PHQ-2) in stroke patients in a clinical nursing setting. The results of these questionnaires will be compared against those from the Geriatric Depression Scale.

**Methods.** The PHQ-9 was administered by 43 ward nurses in 55 patients with an intracerebral hemorrhage or ischemic infarction, who were able to communicate adequately. The inter-rater reliability, test-retest reliability and internal consistency, concurrent validity, diagnostic accuracy and clinical utility were evaluated.

**Results.** The inter-rater reliability (ICC=0.98, 95% CI 0.96-0.99), the test-retest reliability ( $\rho_{sp}=0.75$ ,  $p<.001$ ) and the internal consistency (Cronbach's  $\alpha=0.79$ ) of the PHQ-9 were good. The concurrent validity was moderate for the PHQ-9, with a Pearson's correlation of 0.7 ( $p<.001$ ) and acceptable for the PHQ-2 with a Pearson's correlation of 0.8 ( $p<.01$ ). The optimum cut-off point of the PHQ-9 for major depression was 10 (sensitivity, 100%; specificity, 86%; positive predicted value, 50%; negative predicted value, 100%). For the PHQ-2, the optimum cut-off point was 2 (sensitivity, 100%; specificity, 77%; positive predicted value, 38%; and negative predicted value, 100%).

**Discussion.** The PHQ is a brief and easy-to-use instrument for nursing practice. It shows good reliability, validity, and clinical utility when used in stroke patients who are able to communicate adequately.

**Key words.** Depression, Stroke, Screening Instrument

Post-stroke depression is one of the most serious complications following stroke.<sup>1,2</sup> The reported prevalence of post-stroke depression is highly variable, ranging from 5% to 61%. This variation may be due to methodological differences, such as varied study populations; different examination settings; inclusion and exclusion criteria used with respect to aphasia, pre-existing depression and decreased level of consciousness; variation in depression diagnosis due to use of diagnostic criteria for only major depression vs. minor depression or using only depression rating tools; and different time intervals after the stroke.<sup>1,2</sup> Despite this broad range, a pooled estimate of post-stroke depression indicates that depressive symptoms are present in approximately 33% of all stroke survivors at any time during follow-up.<sup>3</sup>

Post-stroke depression has a significant impact on the ability of a patient to recover. It has been associated with functional dependence and poor functional recovery, poor cognitive function, poor communicative function, longer hospital stay, increased handicap, reduced social activities, failure to return to work, and increased mortality.<sup>1,2</sup> Based on these findings, it is evident that post-stroke depression is a significant health problem. There is, however, increasing evidence that effective treatment leads to lower levels of depression and improved functional outcomes.<sup>1,4,5</sup> A systematic review showed some evidence of pharmacotherapy resulting in complete remission of depression or decreased severity of depression.<sup>4</sup> Pharmacological treatment is also associated with improved functional recovery of stroke patients.<sup>5</sup> Several non-pharmacological treatments were also shown to be effective in post-stroke depression. There is strong evidence that providing information reduces depression severity.<sup>6</sup> Furthermore, psychological interventions showed positive effects on the occurrence and severity of post-stroke depression.<sup>1,7</sup> Initiating treatment within the first month after stroke is more effective than starting treatment later than the first month after stroke; patients treated early improved significantly more and maintained this improvement over two years

while the late treatment group deteriorated over time.<sup>8</sup> Therefore, the timely recognition and diagnosis of post-stroke depression is important.

Depression is generally not recognized during the daily care of stroke patients.<sup>9</sup> Although 75% of hospitalized stroke patients were identified by independent researchers as being depressed, details about depression were not noted in patient medical charts, including physician, nursing, and therapy notes.<sup>9</sup> The poor recognition, a passive attitude toward therapy, and concerns about adverse drug effects, means that post-stroke depression is often under diagnosed and under treated.<sup>10</sup> Nurses often encounter patients with depressive symptoms because they have intensive and continuous contact with stroke patients. Our recent review regarding the role of nurses in post-stroke depression revealed that nurses describe it as an important problem that needs more attention in the daily care of stroke patients.<sup>7</sup> However, given their lack of education and training regarding depressive symptoms, they find it difficult to assess patients psychological status and they seldom use measurement instruments.<sup>7</sup> These findings are supported by studies conducted with older patients living in nursing homes, staying in hospitals or receiving home care, which show similar results.<sup>11;12</sup> Therefore, the routine use of a depression screening instrument in the daily care of stroke patients should increase the early recognition of depression by nurses.<sup>9</sup>

As described in several reviews, many instruments with acceptable to good diagnostic accuracy are available for screening for depression in stroke patients (Table 1).<sup>13;14</sup> For clinical practice, the clinical utility of the measurement should be considered, in addition to the validity and reliability. Clinical utility focuses on aspects such as training requirements for use of the instrument and the amount of time needed to administer it.<sup>15</sup> Of the available instruments, the 9-item Patient Health Questionnaire (PHQ-9) and especially the 2-item Patient Health Questionnaire (PHQ-2) are the most promising for four reasons: a) they include the least number of items, b) they take the shortest time to administer,

**Table 1. Descriptions of screening instruments for post-stroke depression**

Screening instruments <small>13;14;18;25;26</small>	No. of items	Response format	Total scores	Cut-off value	Time to administer	Training required	Sensibility	Specificity
Beck Depression Inventory	21	4-points multiple choice	0-63	≥10	10 min	No	80-100%	61-76%
Center for Epidemiology Studies Depression Scale	20	4-point scale	0-60	≥16	20 min	No	60-86%	76-100%
Geriatric Depression Scale	15	Yes/No	0-15	≥6/7	<10 min	No	85-89%	68-73%
Hospital Anxiety and Depression Scale	14	4-point scale	0-42	≥11	2-6 min	No	87%	70%
Hamilton Rating Scale for Depression	21	3/5-point scale	0-52	≥11/12	30 min	Yes	71-78%	81-87%
Patient health Questionnaire-9	9	4-point scale	0-27	≥10	3-5 min	No	91%	89%
Patient health Questionnaire-2	2	4-point scale	0-6	≥3	<2 min	No	83%	84%

c) they do not require training, and d) they have excellent diagnostic accuracy.<sup>16;17</sup>

In a diagnostic meta-analysis, the performance of the PHQ-9 was shown to be good in medical settings.<sup>18</sup> The diagnostic accuracy for stroke patients was investigated in a selected population in a single study.<sup>19</sup> However, neither the PHQ-9 nor the PHQ-2 has been tested by ward nurses caring for stroke patients, and little attention was given to their clinical utility. Therefore, this study was conducted to investigate the reliability, validity, and clinical utility of the PHQ-9 and PHQ-2 in the general clinical practice of nursing care in stroke patients.

## Methods

### Design

A quantitative, observational, longitudinal study design was conducted in two hospitals (a university hospital and a general hospital) and one inpatient rehabilitation center in the Netherlands. Ethical approval was obtained from the Medical Ethical Committee of the University Medical Center Utrecht (07-296/C) and the other participating health care facilities.

### Participants

Stroke patients admitted with intracerebral hemorrhage or ischemic infarction who were able to communicate adequately were recruited for participation. Patients were included if they presented without serious cognitive disorders as measured by the Mini Mental State Examination<sup>20</sup> or communicative disorders based on clinical judgment and the in-hospital subsample with the Frenchay Aphasia Screening Test<sup>21</sup> ( $N=55$ ; in-hospital subsample  $n=30$ , rehabilitation subsample  $n=25$ ). Patients with major psychiatric comorbidity other than affective disorder according to anamnesis or patient chart, presence of depressive disorder at stroke onset according to anamnesis, expected discharge or death within the first 14 days after the stroke, and those that were too ill to participate based on the clinical judgment of the researcher or the nurses caring for the patient were excluded. Nurses working in the participating wards were recruited if they were registered nurses responsible for the care of participating patients at the time of the study ( $N=43$ ; in-hospital subsample  $n=34$ , rehabilitation subsample  $n=9$ ).

### Measures

#### *Index tests – PHQ-2 and PHQ-9*

Depression was measured with PHQ-2 and PHQ-9. The items are used to query symptoms present over the last two weeks by asking how often the patient has

been bothered by any of the following problems: a) little interest or pleasure in doing things, b) feeling down, depressed, or hopeless, c) trouble sleeping, d) feeling tired or having reduced energy, e) poor appetite or overeating, f) feeling bad about himself, g) trouble concentrating, h) moving or speaking slowly or being fidgety or restless, and i) thoughts that they would be better off dead or hurting themselves in some way. The items are rated using a 4-point Likert scale with item scores ranging from 0 (symptom not present) to 3 (symptom present nearly every day). The PHQ-2 concerns only the first and the second item. The individual item scores are summed to produce a value ranging from 0 (no depression symptoms) to 27 (all symptoms occurring nearly every day) for the PHQ-9, and a sum score ranging from 0-6 for the PHQ-2. The sum score of the PHQ-9 can determine depression severity. A score ranging from 0-4 indicates no depression, 5-9 indicates mild depression, 10-14 indicates moderate depression, 15-19 indicates moderately severe depression, and 20-27 indicates severe depression. In a subset of a stroke population the validity of the PHQ-9 and the PHQ-2 showed good results with respective sensitivities of 91% and 83% and respective specificities of 89% and 84% for major depression.<sup>19</sup> The PHQ-9 was shown to be reliable in other populations; internal consistency was 0.89 as measured with Cronbach's  $\alpha$ , and test-retest reliability was 0.84 as measured by the Intra Class Correlation (ICC).<sup>22</sup>

#### *Reference test GDS-15*

Although there is no universally accepted diagnostic definition of post-stroke depression, the DSM criteria are generally used,<sup>14</sup> which requires a standardized psychiatric interview. This study, however, was conducted in the context of clinical nursing care of stroke patients and conducting a psychiatric interview was considered too burdensome for the patients. Therefore, the Geriatric Depression Scale (GDS-15) was used as a reference test and was conducted by clinical nurse specialists (CNSs) in psychiatric nursing. The GDS-15 was chosen

because of its stable and satisfactory clinimetric properties in stroke patients in the acute and rehabilitation phase, as demonstrated by several studies comparing the diagnostic accuracy of different depression measurement scales.<sup>14;23</sup> The GDS-15 is a 15-item questionnaire with dichotomous answer categories and a score ranging from 0-15. It was developed for use in elderly patients and does not contain items involving physical symptoms.<sup>24</sup> In previous studies, a GDS-15 score  $\geq 6$  has been considered as 'major depression'.<sup>25;26</sup> In the stroke patient rehabilitation phase, the sensitivity and specificity of the GDS-15 is 89% and 73%, respectively, and the area under the receiver operating characteristic (ROC) curve was 0.90 at a cut-off point of 6/7 compared to the DSM-IV. The internal consistency was shown by a Cronbach's  $\alpha$  of 0.84, and the Guttman split-half reliability showed a correlation of 0.75.<sup>26</sup> Therefore, we used a cut-off value  $\geq 6$ .

#### *Clinical utility questionnaire*

The clinical utility questionnaire was developed for testing the clinical utility of the depression screening instruments in stroke patients. It focuses on aspects such as training requirements for the use of the instrument and the amount of time needed for its administration.<sup>15</sup> The criteria of Harris and Warren<sup>27</sup> and Salter et al.<sup>28</sup> were used to develop the clinical utility questionnaire. A 2-step procedure based on the method of Lynn<sup>29</sup> was used to construct the clinical utility questionnaire and to determine the content validity with a 5-round Delphi survey by an expert panel of four nursing researchers. After its development, the questionnaire was further reviewed by four expert neuroscience nurses who assessed the clarity of the items and the comparability of item terminology with clinical practice.

The clinical utility questionnaire includes 16 items: one item concerning the time needed to fill in the questionnaire; three items concerning the verbal or non-verbal reaction of patients regarding a) the time required to administer the

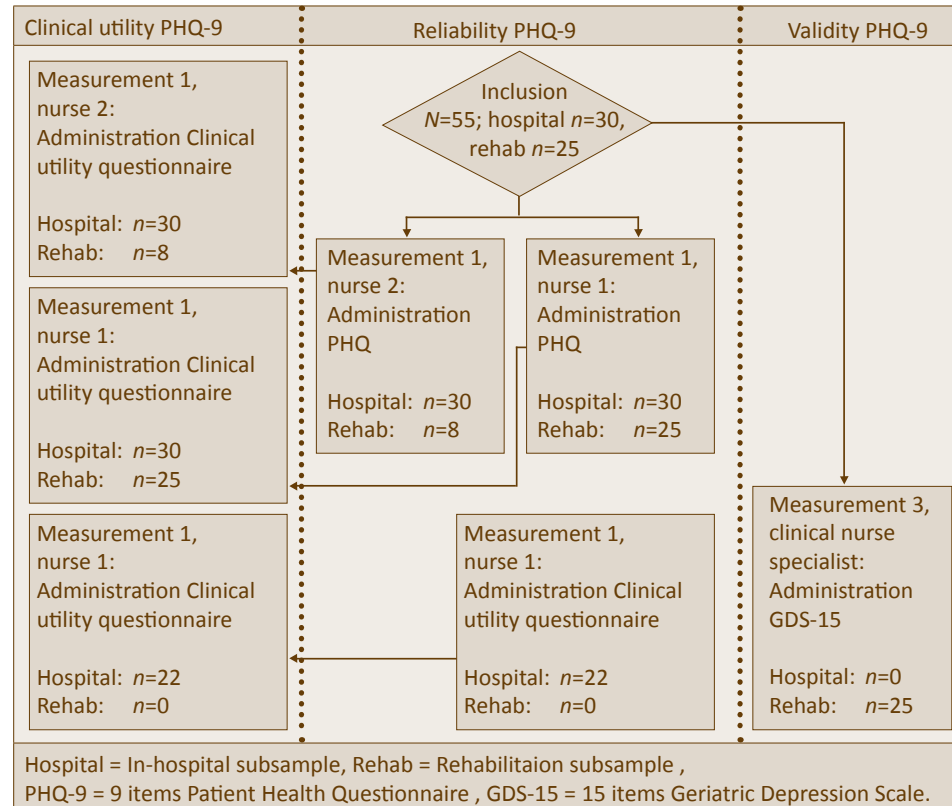
questionnaire, b) the clarity of the items, c) whether the items are acceptable; and 11 items concerning the nurses' view about different aspects of the PHQ-9, such as a) do you think the outcome would be important to the patient, b) is the instrument easy to use in your daily nursing practice, c) do you think the items are clear, d) do you have difficulties in asking some items, e) do the scores clearly indicate patients that require follow-up actions, including further diagnosis, referral, and nursing interventions, and f) does the instrument provide relevant information for the multidisciplinary care plan. Except for the item concerning the time needed to fill in the PHQ-9, all items had a dichotomous answer scale ('Yes' or 'No'), and an explanation could be given for some items. The results are reported at the item level.

#### **Procedure**

Patient recruitment began once ethical approval was obtained. All nurses working in the participating wards were informed about the study procedure, the questionnaires and what to do with the PHQ-9 outcome, and their informed consent was asked before patient recruitment began. The researcher checked whether the patient met the inclusion criteria, and if so, the researcher asked the patient for informed consent and collected baseline data. Then, she asked nurses responsible for the care of that patient to administer the PHQ-9 and fill out the clinical utility questionnaire.

Data from all the patients regarding socio-demographic data, type of stroke, stroke location, consequences of stroke, and time since stroke onset were collected. To establish inter-rater reliability, the PHQ-9 was administered by pairs of ward nurses per patient in the in-hospital subsample ( $n=30$ ) and in eight patients of the inpatient rehabilitation subsample ( $n=25$ ). One of the two nurses read the questions, and both nurses independently recorded the patient's answers. To establish test-retest reliability in the in-hospital subsample ( $n=30$ ), one of those two nurses re-administered the PHQ-9 two

**Figure 1. Flow chart of data collection, including the number of administrations and nurses who administered the questionnaires at different stages of data collection**



days after the first administration in 22 patients (8 patients were discharged between the first and the second administration). The 2 day period was chosen to avoid the risk that depressive symptoms would worsen over a longer time period. To establish concurrent validity in the rehabilitation subsample ( $n=25$ ), the GDS-15 was administered by one of the two participating CNSs. The CNSs had to be scheduled from the hospital, which made it difficult to administer the GDS-15 two days after the first administration of the PHQ-9; therefore, a 5-day period was used. The CNSs were not involved in the care of the patients. The data were collected separately, to ensure that the GDS-15 and PHQ-9 were

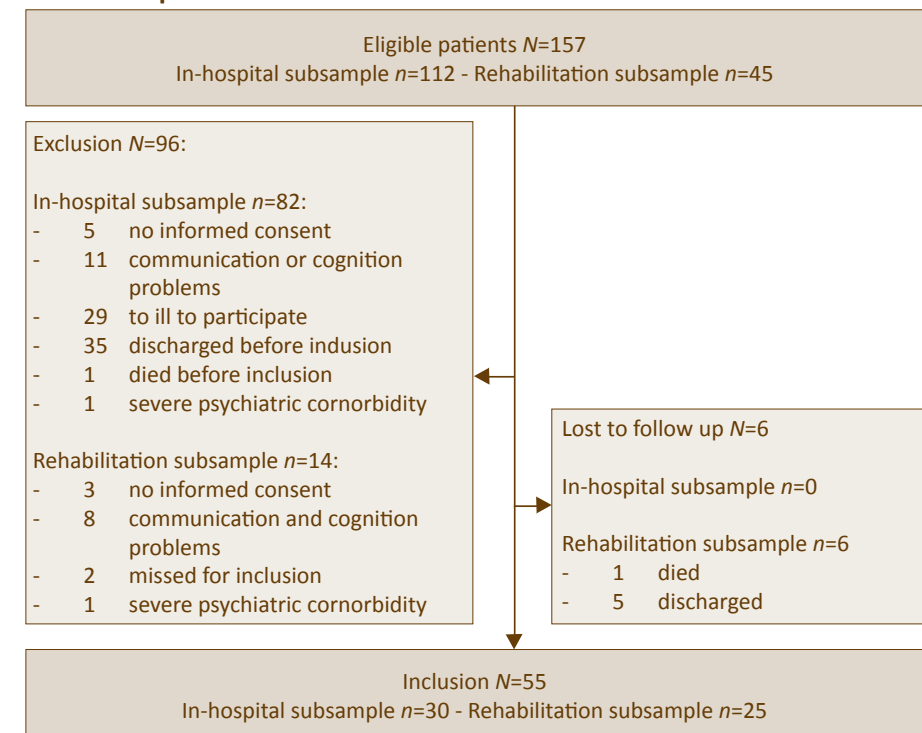
measured independently.

The nurses were asked to provide data regarding their education level and years of experience working with stroke patients. Nursing education included registered nurses with or without a Bachelor degree in Nursing. To study clinical utility, each nurse independently filled out the clinical utility questionnaire after each administration of the PHQ-9. Nurses ( $N=43$ ) completed one to nine clinical utility questionnaires, as some evaluated more than one patient (Figure 1). The data were collected between November 2007 and April 2008.

### Psychometric analysis

Inter-rater reliability was determined by calculating the agreement between the pairs of nurses on the sum score level and was described with the ICC. The

**Figure 2. Flow chart of the number of patients included, excluded, and lost to follow-up**



**Table 2. Demographic characteristics of participants**

	Total sample			Hospital subsample			Rehabilitation subsample		
	Inclusion <i>N</i> =55			Inclusion <i>n</i> =30 (54.5%)			Inclusion <i>n</i> =25 (45.5%)		
<b>Patients</b>									
Gender <i>n</i> (%)									
Male	27	(49)		15	(50)		12	(48)	
Age in years									
Mean (SD) (min-max)	65.1	(15.0)	(22-89)	68.5	(16.3)	(27-89)	61.0	(12.6)	(22-78)
Type of stroke <i>n</i> (%)									
Intracerebral hemorrhage	17	(30.9)		8	(26.7)		9	(36.0)	
Infarction	38	(69.1)		22	(73.3)		16	(64.0)	
Localization <i>n</i> (%)									
Right	30	(54.5)		14	(46.7)		16	(64.0)	
Time since stroke onset in days									
Mean (SD) (min-max)	59.8	(77.4)	(5-350)	17.7	(18.1)	(5-100)	110.3	(90.6)	(42-350)
Barthel Index score									
Mean (SD) (min-max)	-	(-)	(-)	7.2	(6.5)	(0-20) ( <i>n</i> =25*)	-	(-)	(-)
MMSE score $\geq 18$ <i>n</i> (%)	46	(100)	( <i>n</i> =46 <sup>†</sup> )	30	(100)		16	(100)	( <i>n</i> =16 <sup>†</sup> )
FAST score $\geq 25$ c.q. 27 <i>n</i> (%)	-	(-)	(-)	30	(100)		-	(-)	(-)
Major Depression <i>n</i> (%) (PHQ-9 sum score $\geq 10$ )	14	(26.4)	( <i>n</i> =53 <sup>‡</sup> )	8	(28.6)	( <i>n</i> =28 <sup>‡</sup> )	6	(24.0)	
PHQ-9 sum score <i>n</i> (%) (severity of depression)									
None (score 0-4)	24	(45.3)		15	(53.6)	( <i>n</i> =28 <sup>‡</sup> )	9	(36.0)	
Mild (score 5-9)	15	(28.3)		5	(17.9)		10	(40.0)	
Moderate (score 10-14)	9	(17.0)		4	(14.3)		5	(20.0)	
Moderately severe (score 15-19)	4	(7.5)		3	(10.7)		1	(4.0)	
Severe (score 20-27)	1	(1.9)		1	(3.6)		-	-	
Major Depression <i>n</i> (%) (GDS sum score $\geq 6$ )	-	(-)		-	(-)		3	(12.0)	
<b>Nurses</b>	Inclusion <i>N</i> =43			Inclusion <i>n</i> =34 (79.0%)			Inclusion <i>n</i> =9 (20.9%)		
Education level <i>n</i> (%)									
Registered nurse with Bachelor of Nursing degree	17	(38.6)		15	(44.1)		2	(22.2)	
Registered nurse without Bachelor of Nursing degree	27	(61.4)		19	(55.9)		7	(77.8)	
Years of experience									
Mean (SD) (min-max)	6.8	(7.0)	(0-30)	5.5	(6.2)	(0-30)	11.4	(8.6)	(0-28)
MMSE = Mini Mental State Examination, FAST = Frenchay Aphasia Screening Test; cut-off value: age $\leq 60$ : $\geq 27$ , age $\geq 61$ : $\geq 25$ , PHQ-9 = 9 items Patient Health Questionnaire.									
*The Barthel Index was not completed for 5 patients									
† MMSE was not completed for 9 patients									
‡ The PHQ-9 was not completed for 2 patients									

one-way model of the ICC was used because of the different pairs of raters and the broad score range of 0-27.<sup>30</sup> Test retest reliability was determined within the in-hospital subsample by calculating the Spearman's rank correlation. Internal consistency was determined by calculating the 'Cronbach's  $\alpha$  based on standardized items' because all items had the same score range of 0-3.<sup>31</sup>

A scatter plot was generated to determine concurrent validity of the sum scores of the PHQ-9 and the GDS. The Pearson's correlation coefficient was calculated based on the plot's slope.<sup>30</sup> Positive and negative predictive values and likelihood ratios were calculated to determine diagnostic accuracy, sensitivity, and specificity. The optimum cut-off points of the PHQ-9 and PHQ-2 were determined using Youden's index.<sup>32</sup> Clinical utility questionnaires were grouped based on the frequency the nurse rated the questionnaire, which resulted in four groups of questionnaires rated by nurses who administered the PHQ-9 the first time (*n*=43), the second time (*n*=24), the third time (*n*=15), or the fourth time (*n*=8). Some nurses filled in the questionnaire 5-9 times. However, those questionnaires in the latter groups were not taken into account because of the small numbers per group (*n* $\leq 3$ ). Clinical utility was evaluated using descriptive statistics that provided overall results and trends.

## Results

Of the 157 patients admitted with an intracerebral hemorrhage or ischemic infarction during the study period, 96 did not meet the inclusion criteria, and 6 patients were lost before data were collected. Therefore, 55 patients were included: 30 patients from the two hospitals and 25 patients from the rehabilitation center (Figure 2). The demographic characteristics of the participants are summarized in Table 2. The baseline characteristics within the subsamples differed slightly with respect to age, localization and time since stroke onset, whereas all other characteristics were similar.

The PHQ-9 was completed for 53 of the 55 included patients; one item was

missed for two of the hospital subsample patients, resulting in missing sum scores. According to the PHQ-9, 26.4% of these patients had 'major depression'. With respect to severity, most patients in the rehabilitation subsample had mild or moderate depression, whereas patients in the hospital subsample also had moderately severe or severe depression.

### Reliability

To evaluate inter-rater reliability, the ICC was determined based on the sum score level of the PHQ-9 and the PHQ-2, which showed similar results (ICC=0.98, 0.95% CI 0.96-0.99). We used the Spearman's rank correlation calculated at the sum score level to calculate test-retest reliability and obtained a value of 0.75 ( $p<.001$ ). The mean time between these measurements was 2.1 days (SD=0.3). The internal consistency of the PHQ-9 was strong (overall Cronbach's  $\alpha=0.79$ ), and it was adequate for the PHQ-2 (overall Cronbach's  $\alpha=0.68$ ).

### Validity and diagnostic accuracy

To evaluate the concurrent validity and diagnostic accuracy of the PHQ-9 and the PHQ-2, depression was measured with the PHQ-9 and the GDS-15 in the rehabilitation subsample ( $n=25$ ). The mean time between these measurements was 4.7 days (SD=2.6). According to the GDS-15, three patients (12%) were identified with 'major depression' (Table 2). The concurrent validity of the PHQ-9 and PHQ-2 against the GDS-15 showed Pearson's correlations of 0.7 ( $p<.01$ ) and 0.8 ( $p<.01$ ), respectively. In screening for major depression, the optimum cut-off value for the PHQ-9 was 10, which showed a sensitivity of 100%, 95% CI 100-100%, a specificity of 86%, 95% CI 72-100%, a positive predicted value of 50%, 95% CI 9-90%, and a negative predicted value of 100%, 95% CI 100-100%. The optimum cut-off value for the PHQ-2 was 2, with a sensitivity of 100%, 95% CI 100-100%, a specificity of 77%, 95% CI 60-95%, a positive predicted value of 38%, 95% CI 4-71%, and a negative predicted value of 100%, 95% CI 100%-

**Table 3. Diagnostic accuracy of the PHQ-9 and PHQ-2**

Cut-off point	PHQ-9 Major depression			PHQ-2 Major depression			
	≥6	≥10	≥15	≥2	≥3	≥4	≥5
Sensitivity (%)	100	100	33	100	67	67	33
Specificity (%)	64	86	92	77	91	100	100
PPV* (%)	27	50	100	38	50	100	100
NPV† (%)	100	100	100	100	95	96	92
Youden's Index‡	0.64	0.86	0.25	0.77	0.58	0.67	0.33

PHQ-9 = Patient Health Questionnaire.  
 \* Positive Predicted Value  
 † Negative Predicted Value  
 ‡ Youdens index = sensitivity + specificity - 1

100% (Table 3).

### Clinical utility

The clinical utility questionnaire was filled out 90 times by 43 nurses. The mean time required to administer the PHQ-9 was 10.7 minutes (SD=5.8), and almost all nurses thought this was an acceptable amount of time (93%-100%). The majority of nurses also thought the PHQ-9 was easy to use. The more frequently they administered it, the more the nurses found it easy to use (81%-100%). In addition, most nurses (81%-100%) found that the PHQ-9 gave relevant information for the multidisciplinary care of their patients, and the nurses (71%-88%) found that the scores clearly identified patients that would benefit from follow-up actions, including referral for further diagnosis and treatment. Sixty-five percent of nurses thought that the items were clear. However, items that contained two opposite aspects of a symptom were perceived as difficult to interpret. An example of this was the item 'trouble falling or staying asleep or sleeping too much'. After more experience administering the PHQ-9, 88% of nurses were satisfied with the item's clarity. Twenty-five percent of nurses experienced difficulties in asking the items concerning 'feelings of guilt and



worthlessness' and 'thought of death or suicide'. Nevertheless, the nurses recognized the importance of these items. In 80% to 100% of the measurements, nurses did not observe any verbal or non-verbal reactions of patients regarding the time needed to administer the PHQ-9. With respect to the acceptability of the questions, the nurses did not observe verbal or non-verbal reactions from patients in 86% to 91% of the measurements other than their actual responses. The few reactions given concerned the item 'thought of death or suicide'; some patients found this question too strong, but others stated that it gave them an opportunity to speak about their feelings with the nurse. The patients gave verbal and non-verbal reactions about question clarity for 10% to 40% of the measurements. This finding was especially apparent with respect to the items 'sleeping difficulties', 'feelings of guilt and worthlessness', and 'psychomotor agitation or retardation'.

## Discussion

This study presents the clinimetric evaluation of the PHQ-9 and PHQ-2 questionnaires administered by nurses to stroke patients who were able to communicate adequately. The reliability, test-retest reliability, and internal consistency of both the PHQ-9 and the PHQ-2 were good. The concurrent validity with the GDS-15 was acceptable. The diagnostic accuracy of the PHQ-9 and PHQ-2 compared to the GDS-15 was good for 'major depression'. The nurses judged the clinical utility of the PHQ-9 as good.

To our knowledge, this study is the first in which the clinimetric properties of the PHQ-9 were investigated in the context of the clinical care of stroke patients. Nurses consider observation, assessment, and interpretation of symptoms as an important part of their role in stroke patient rehabilitation.<sup>33</sup> Post-stroke depression screening is also considered an important nurse responsibility.<sup>7</sup> A brief and useful instrument is more likely to be used, so the clinical utility of an instrument is especially important. The current study

provides the first impression of the diagnostic accuracies of the PHQ-9 and PHQ-2 is given, which show that they are promising post-stroke depression screening instruments. Their brevity makes them particularly attractive for use in clinical practice, which is often very busy with competing demands.<sup>17</sup> We thoroughly investigated the clinical utility of the PHQ-9. Although administering the PHQ-9 was twice as long as the time reported in another study,<sup>34</sup> the nurses and patients in our study considered the time needed to administer the PHQ-9 to be acceptable. A possible reason for this difference in administration time could be the subtle cognitive problems in stroke patients.<sup>35</sup> Our study did not measure the time needed to administer the PHQ-2, but it might be assumed that administering only two items will save time. The finding that nurses were less positive with regard to the clarity of the PHQ-9 items, especially in items with two opposing aspects of a symptom, corresponds with studies showing that nurses found the accurate assessment of depression in elderly patients to be difficult.<sup>11,12</sup> However, this does not support the suggestion that the PHQ-9 could be conducted without training.<sup>16</sup> We assume that specific training about the items and administration instructions could increase item clarity for nurses. Moreover, one study showed that screening for post-stroke depression in patients by a trained nurse led to correct identification of depression.<sup>36</sup> This finding is supported by the results of Edwards et al.,<sup>9</sup> where the structured use of a depression screening instrument in the daily care of stroke patients increased the early recognition of depression by nurses.

Our study was conducted in both a hospital and a rehabilitation setting. The participating nurses were registered nurses with and without Bachelor of Nursing degrees. Based on these results, it is unknown whether the level of education influences the clinimetric properties of the PHQ-9. Therefore, the question remains whether nurses with higher education levels, such as CNSs or nurses with Master's degrees, are better equipped to conduct depression screenings of depression using the PHQ-9. It is possible that the clinimetric

properties of the PHQ-9 could be different depending on nurses' educational levels.

The reliability of the PHQ-9 in stroke patients was adequate. This result is similar to other studies that investigated the reliability of the PHQ-9, where internal consistency and test-retest reliability was assessed in primary care and obstetrics-gynecology patients.<sup>16;22</sup> Another study conducted in primary care patients showed a high ICC.<sup>16</sup> Our PHQ-9 test-retest reliability was slightly lower than in other studies.<sup>16;22</sup> This could be a result of differences in depression prevalence, which increases early in the acute phase after stroke.<sup>37</sup> Therefore, the prevalence of symptoms could differ across the measurement timepoints, reducing the strength of the correlation, which may underestimate the relationship results of the study.

### Limitations

The main limitations of this study are the small sample and subsample sizes, and the use of the GDS-15 as a reference test. In general, the hospital patient population represents almost the entire stroke patient population range, whereas the rehabilitation center covers a select group of patients. Only 8.4% of Dutch stroke patients are admitted to a rehabilitation center after a hospital stay, whereas other patients return home, move to nursing homes or other hospitals, or die during hospitalization.<sup>38</sup> Given that the validity of the PHQ was only investigated in a rehabilitation subsample of 25 patients, this study only gives an indication of the PHQ diagnostic accuracy in stroke patients. However, the whole sample ( $n=55$ ) was used to evaluate the reliability and clinical utility, which is considered sufficient to test the clinimetric properties of a diagnostic instrument.<sup>39</sup>

With respect to the reference test, the DSM-IV diagnosis of depression is viewed as the gold standard for testing the value of a depression screening instrument.<sup>13;23</sup> In this study, we aimed to give an impression of the validity of

the PHQ in the clinical practice of nursing care in stroke patients. Conducting a psychiatric interview was considered too burdensome for patients. Therefore, the GDS-15 conducted by CNSs is used as the reference test. Although the GDS-15 has been validated in several stroke patient studies, there is no unequivocal optimal cut-off point for determining depression.<sup>14;23</sup> This could explain why we only found a moderate correlation between the PHQ-9 and the GDS-15.

This study only included patients who were able to communicate adequately because the PHQ-9 and GDS-15 are highly dependent on verbal communication. Therefore, it is difficult to reliably measure depression in patients with cognitive or communicative disorders.<sup>40</sup> This limits the generalizability of our results to this subpopulation.

In conclusion, the PHQ-9 was found to be a promising instrument for nurses to screen for post-stroke depression. The PHQ-9 is a brief and easy-to-use instrument, showing good reliability and clinical utility, and promising validity.

### Recommendations for clinical practice and research

The use of a depression screening instrument in the daily care of stroke patients should increase the recognition of depression by nurses.<sup>9</sup> For optimal implementation of a screening instrument in the clinical practice involving stroke patients, training in the nursing care context is important. Therefore, it is important to train nurses in using the PHQ-9. This training should be appropriate to the educational levels of the nurses and linked to their specific clinical practice. In addition, it is important that after screening, patients are appropriately monitored by nurses and referred to psychiatrists or psychologists for further diagnosis and treatment if the screening suggests they are suffering from depression. These aspects need to be discussed within the multidisciplinary team providing care and treatment of the stroke patient.

Post-stroke depression has a significant impact on a patient's rehabilitation.

Depression after stroke has been associated with several consequences, including functional dependence, poor functional, and increased disability.<sup>2</sup> Further research is needed to investigate the effect of screening for post-stroke depression on stroke-related outcome. Above all, it is very important to develop and test an intervention to decrease post-stroke depression.

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## **Chapter 5**

### **An Efficient Way to Detect Post-stroke Depression by Subsequent Administration of a 9-Item and a 2-Item Patient Health Questionnaire**

**Janneke de Man-van Ginkel, Thóra Hafsteinsdóttir, Eline Lindeman, Huibert Burger, Diederick Grobbee, Marieke Schuurmans**

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## Abstract

**Background and Purpose.** The early detection of post-stroke depression (PSD) is essential for optimizing recovery after stroke. A prospective study was conducted to investigate the diagnostic value of the 9-item and the 2-item Patient Health Questionnaire (PHQ-9, PHQ-2).

**Methods.** One hundred seventy-one consecutive stroke patients who could communicate adequately were included. In the 6th-8th weeks after stroke, depression was measured using the PHQ-9 and PHQ-2 and diagnosed using the Composite International Diagnostic Interview.

**Results.** Of the participating patients, 20 (12.2%) were depressed. The PHQ-9 performed best at a score  $\geq 10$ , with a sensitivity of 0.80 (95% CI 0.62-0.98) and a specificity of 0.79 (95% CI 0.73-0.86) and the PHQ-2 at a score  $\geq 2$  with a sensitivity of 0.75 (95% CI 0.56-0.94) and a specificity of 0.76 (95% CI 0.69-0.83). Administering the PHQ-9 only to patients who scored  $\geq 2$  on the PHQ-2 improved the identification of depression (sensitivity: 0.86 95% CI 0.69-1.04).

**Conclusions.** The diagnostic value is acceptable to good for PHQ-9 scores  $\geq 10$  and PHQ-2 scores  $\geq 2$ . Conducting a PHQ-9 only in patients with a PHQ-2 score  $\geq 2$  generates the best results.

Post-stroke depression (PSD) is a frequent complication that worsens rehabilitation outcomes and quality of life.<sup>1,2</sup> Despite this, PSD is underdiagnosed and undertreated.<sup>3</sup> Increasing evidence shows that treatment leads to a decrease in depression and an improved functional status.<sup>4</sup> To enable treatment early detection of PSD is essential.

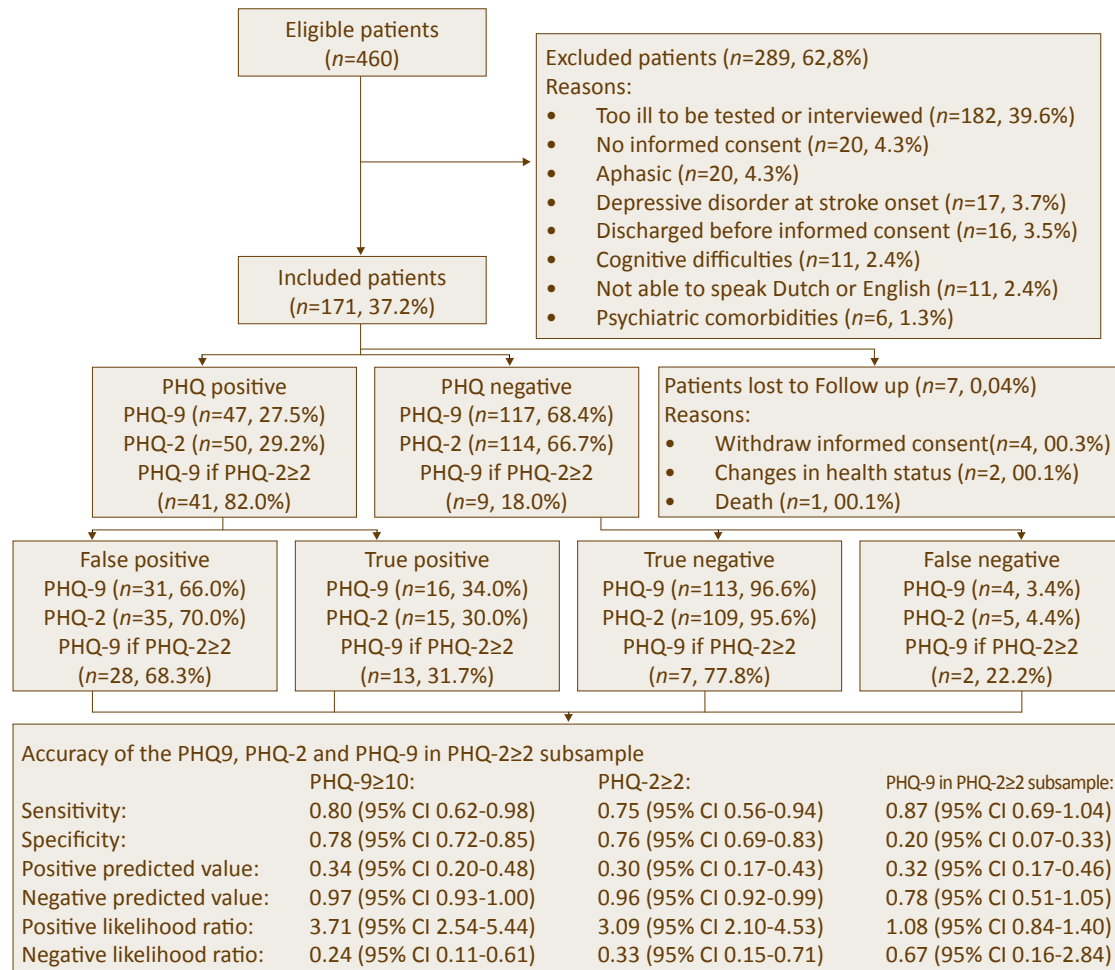
For detecting PSD, the 9-item Patient Health Questionnaire (PHQ-9) and the 2 item Patient Health Questionnaire (PHQ-2) are promising instruments. These instruments are acceptable to patients, brief and easy to use and administration does not require intensive training.<sup>5, 6</sup> In a diagnostic meta-analysis, the performance of the PHQ-9 in different types of patients was good.<sup>7</sup> Although one study investigated the performance of the PHQ 9 and the PHQ-2 in a selected stroke population with depressive symptoms,<sup>8</sup> no study has been conducted in the general stroke population. In the present study we determined the diagnostic value of the PHQ-9 and PHQ-2 alone or in combination in acute stroke patients who are able to communicate adequately.

## Materials and Methods

### Participants

A prospective study was conducted in three hospitals. Ethical approval was obtained from the Medical Ethical Committee of the University Medical Center Utrecht and the other participating hospitals. In 2010, 460 consecutive patients, admitted to hospital with a clinical diagnosis of stroke, were approached for participation. Patients ( $n=171$ , 37.2%) were included if they did not present with serious cognitive disorders, defined as a Mini Mental State Examination score  $\geq 18$ <sup>9</sup> or with communicative disorders based on the Frenchay Aphasia Screening Test with scores of  $\geq 17$  for patients  $< 60$  years of age,  $\geq 16$  in patients  $\geq 60$  and  $\leq 70$  years of age, and  $\geq 15$  in patients  $\geq 71$  years of age.<sup>10</sup> After inclusion, seven patients were lost before follow-up depression data were collected. Therefore, the data were complete for 164 patients (Figure 1).

Figure 1. Flow diagram



### Instruments

Depression was measured using the PHQ-9 and the PHQ-2 (index tests).<sup>5,6</sup> The PHQ-9 includes all 9 symptoms of depression, whereas the PHQ-2 includes ‘anhedonia’ and ‘depressed mood’ only. Items are rated on a 4-point Likert scale, with a total score of 0 to 27 for the PHQ-9 and a total score of 0 to 6 for the PHQ-2.

As a reference test, a diagnosis of depression was made using the Composite

International Diagnostic Interview (CIDI), a structured diagnostic interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and International Classification of Diseases, 10th Revision psychiatric disorders, showing good diagnostic concordance and reliability.<sup>11</sup> The researcher was trained in administering the CIDI-auto 2.1 version.

### Procedure

All patients with stroke admitted to the participating wards were registered. Before discharge (T=0), a research nurse checked whether the patient fitted the inclusion criteria. If that was the case, the nurse asked informed consent and collected the baseline data. After discharge, the research nurse and the researcher visited the patient at 6 to 8 weeks after stroke onset (T=1). The nurse administered the PHQ-9 followed by the researcher who administered the CIDI. To be blinded to the PHQ-9 scores, the researcher left the room at the time the nurse completed the PHQ-9.

### Analysis

Appropriate parameters based on a 2x2 table were calculated to determine the diagnostic accuracy of the PHQ for different cut-off values. As a summary measure of discriminatory power, independent of cut-off value, the area under the curve was determined.

### Results

Out of 164 patients, 20 (12.2%, 95% CI 7.2-17.2) were diagnosed with depression (Table 1). The discriminatory power of the PHQ-9 and PHQ-2 for major depression was good with an area under the curve of 0.87 (95% CI, 0.80-0.93) and 0.82 (95% CI 0.73-0.91), respectively (Figure 2). The accuracy of the PHQ-9 was best at a cut-off score of ≥10 with a sensitivity of 0.80 (95% CI 0.62-0.98) and specificity of 0.78 (95% CI 0.72-0.85). The PHQ-2 showed the best



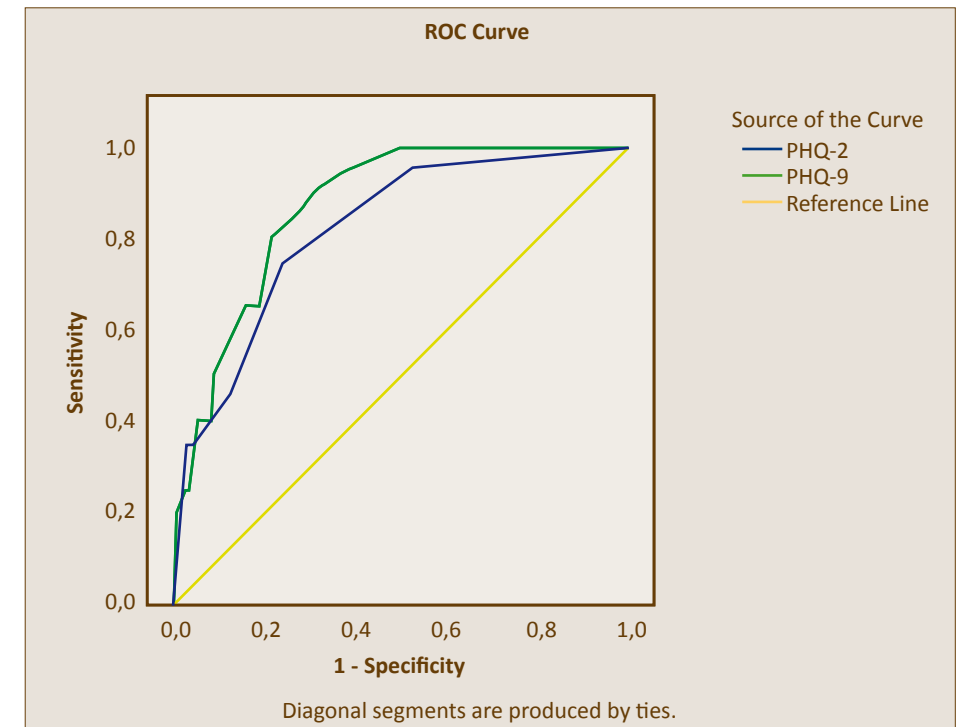
**Table 1. Study Population**

Patients	n=164		
Gender n (%)			
Male	97	(59.1)	
Age in years			
mean (SD) (min-max)	70.6	(13.99)	(20-97)
Type of stroke n (%)			
Intracerebral hemorrhage	22	(13.4)	
Infarction	142	(86.6)	
Localization n (%)			
Left	69	(42.1)	
Right	67	(40.9)	
Others	28	(17.1)	
Barthel Index			
Mean (SD) (min-max)	13.0	(6.2)	(0-20)
MMSE score $\geq 18$ n (%)	164	(100)	
FAST score $\geq 15, 16$ or $17$ n (%)	162	(98.8)	
Diagnosis of Depression (CIDI) n (%)	20	(12.2)	
Time since stroke onset in weeks			
Mean (SD) (min-max)	6.7	(0.9)	(5-9)

MMSE = Mini Mental State Examination, FAST = Frenchay Aphasia Screening Test; cut-off value: age in years  $\leq 60$ :  $\geq 17$ ,  $\geq 60$  and  $\leq 70$ :  $\geq 16$ ,  $\geq 71$ :  $\geq 15$ , CIDI = Composite International Diagnostic Interview, SD = standard deviation

accuracy at a cut-off score of  $\geq 2$  with a sensitivity of 0.75 (95% CI, 0.56-0.94) and specificity of 0.76 (95% CI 0.69-0.83).

The administration of the PHQ-9 only in patients who scored  $\geq 2$  on the PHQ-2 improved the identification of depressed patients, as shown by the sensitivity (0.87; 95% CI 0.69-1.04). The specificity was 0.20 (95% CI 0.07-0.33). The other parameters at the different cut-off values are presented in Figure 1.

**Figure 2. ROC PHQ-9 and PHQ-2 versus CIDI scores**

## Discussion

The findings of this study show that the diagnostic value for PHQ-9 scores  $\geq 10$  and for PHQ-2 scores  $\geq 2$  was acceptable to good. The highest sensitivity was found for the PHQ-9 in patients who had a PHQ-2  $\geq 2$ .

Only patients who were able to communicate adequately were selected because the assessment of depression using the PHQ-9 and the CIDI highly depends on verbal and cognitive competence. This limits the generalizability of our results to this subpopulation.

The diagnostic performance of the PHQ-9 was slightly lower than the performance found by Williams and colleagues.<sup>8</sup> In our study, however, patients were not selected on symptoms of depression which is essential for

assessing diagnostic accuracy of a test. Moreover, the diagnosis of depression was made blind to PHQ scores assessment. Selected patients and unblinded diagnoses may have produced too optimistic results in the study of Williams and colleagues.<sup>12</sup> Compared to the results of a diagnostic meta-analysis of the PHQ-9 within different patient groups, some differences were found in the specificity (0.79 versus 0.92 in the meta-analysis), but the sensitivity was comparable.<sup>7</sup> The lowest specificities were found in cardiology, brain injury and stroke populations. Interestingly, in those studies, it was unclear whether the diagnoses were performed blinded for PHQ-9, possibly leading to overly optimistic results.<sup>12</sup>

Different instruments are available for the screening of depression in patients with stroke.<sup>1</sup> Although their performance in the stroke population is adequate, the PHQ-9 and PHQ-2 are preferable over other instruments, because they are brief and easy to use and are acceptable to patients.<sup>5,6</sup> To save time and limit the burden of patients it is recommended to conduct the PHQ-2 screening in all patients and only the PHQ-9 in case of a positive outcome of the PHQ-2.

In summary, the results of this prospective study among unselected stroke patients suggest that the PHQ-9 and PHQ-2 are preferable instruments for the early detection of PSD in the daily care of stroke patients.

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## **Chapter 6**

### **In-hospital Risk Prediction for Post-Stroke Depression: Development and Validation of the DePreS**

**Janneke de Man-van Ginkel, Thóra Hafsteinsdóttir, Eline Lindeman,  
Roelof Ettema, Diederick Grobbee, Marieke Schuurmans**

**Submitted**

## Abstract

**Objective.** The timely detection of post-stroke depression (PSD) is complicated by the decrease in the length of a hospital stay. Therefore, the Post-Stroke Depression Prediction Scale (DePreS) was developed and validated. The DePreS is a clinical prediction rule for the early identification of stroke patients at increased risk for PSD.

**Methods.** The study included a total of 410 consecutive stroke patients who were able to communicate adequately. Predictors were collected within the first week after stroke. Between the 6th and 8th weeks after stroke, depression was diagnosed using the Composite International Diagnostic Interview (CIDI). Multivariable logistic regression models were fitted. A bootstrap-backward selection process resulted in reduced final models. Performance of the models was expressed by discrimination and calibration.

**Results.** The final model included a medical history of depression or other psychiatric disorders, hypertension, angina pectoris and the Barthel index-item 'Dressing'. The resulting prediction model had acceptable discrimination, based on an area under the receiver operating characteristic curve (AUC) of 0.78 (0.72-0.85), and calibration ( $p$ -value of the  $U$ -Statistics = .96). Transforming the model to an easy-to-use risk assessment table, the lowest risk category (sum score  $\leq$ -10) showed a 2% risk of depression, which increased to 82% in the highest category (sum score  $\geq$ 21).

**Conclusions.** The clinical prediction rule enables clinicians to estimate the degree of the depression risk for an individual patient within the first week after stroke. The prediction could be used as the basis for a simple decision tree to guide a more selective screening process for PSD.

**Key words.** Depression, Stroke, Prediction, Risk factor, Screening

Post-stroke depression (PSD) is a serious and common complication of stroke. Although there is a considerable variation in the frequency of PSD, a pooled estimate indicates that depressive symptoms are present in one-third of all stroke survivors at any time during the follow-up.<sup>1</sup> PSD negatively impacts patient participation in rehabilitation and associated patient outcomes.<sup>2;3</sup> This negative impact is of major importance during patient recovery, when rehabilitation efforts are most critical to the outcome. There is increasing evidence that treatment with antidepressants decreases the severity of depression<sup>3;4</sup> and improves functional status.<sup>5;6</sup> Therefore, the early detection of PSD is essential to optimize the recovery of stroke patients.

Generally, PSD is defined using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR<sup>TM</sup>).<sup>2;3</sup> According to these criteria, depression is characterized as the consistent presence of five or more out of nine depression symptoms over a two-week period.<sup>7</sup> Several instruments with acceptable diagnostic accuracy are available for screening depression in stroke patients.<sup>8-10</sup> However, there is a trend toward a decreasing length of hospital stay with a mean of less than 14 days,<sup>11;12</sup> and this short hospital stay complicates proper PSD screening. Notably, due to the DSM requirement that depression symptoms be present for two or more weeks, these criteria can no longer be applied. To enable the early detection of PSD while acknowledging a limited window of in-hospital opportunity, we developed a clinical prediction rule to identify hospitalized stroke patients at risk for PSD after discharge. The focus was on the predictors available to clinicians in the first week after a stroke.

## Methods

### Study design and participant selection

A prospective multicenter cohort study was conducted in three hospitals in The Netherlands. Ethical approval was obtained from the Medical Ethical Committee of the University Medical Center Utrecht and the other participating hospitals. Between December 2009 and January 2011, 1,033 consecutively admitted stroke patients (admitted with a clinical diagnosis of intracerebral hemorrhage or ischemic infarction to a participating hospital), were approached for participation in the first week after stroke onset but before discharge. Patients ( $n=410$ , 39.7%) were included if they did not present with serious cognitive disorders, as measured by the Mini Mental State Examination (with a score  $\geq 18$ )<sup>13</sup> or with communicative disorders based on the Frenchay Aphasia Screening Test (with scores of  $\geq 17$  for patients  $<60$  years of age;  $\geq 16$  in patients  $\geq 60$  and  $\leq 70$  years of age; and  $\geq 15$  in patients  $\geq 71$  years of age).<sup>14;15</sup> Written consent was obtained from all included patients. Patients ( $n=623$ , 60.3%) who did not meet the inclusion criteria or who met any of the following criteria were excluded: presence of a major psychiatric comorbidity, other than affective disorder (according to patient history or medical records); presence of depressive disorders at stroke onset; antidepressant medication use at stroke onset; or too ill to participate based on the judgment of the clinicians or the researcher. Most of the excluded patients (69.0%) were too ill to participate due to stroke severity, severe aphasia or severe cognitive impairments.

### Primary outcome

A diagnosis of depression was made in the 6th-8th week after stroke onset according to the DSM-IV-TR™<sup>7</sup> criteria, using the Composite International Diagnostic Interview (CIDI).<sup>16</sup> For most patients (99.5%), this was after hospital discharge. The CIDI, a structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders, is designed to meet the need for a short but

accurate structured psychiatric interview for multi-center clinical trials and epidemiology studies.<sup>17</sup> The CIDI shows good diagnostic concordance with the DSM-III-R ( $K=0.84$ ) and the ICD-10 diagnosis ( $K=0.78$ ) for major depression.<sup>17</sup> The reliability is good as well; the inter-rater reliability measured with Cohen's kappa is 0.84, and the Cohen's kappa for the test-retest reliability is 0.90.<sup>17</sup> The CIDI can be administered by trained lay interviewers.<sup>17</sup> In this study, the CIDI-auto 2.1 version was used by a researcher (JMMG) after formal training in the administration of CIDI. She visited the patients at home or at a residential health care facility to administer the CIDI.

### Post-stroke depression risk factors

From all included patients, data were collected regarding potential risk factors for PSD.<sup>18</sup> This included socio-demographic and stroke-related factors such as age, gender, marital status, premorbid living situation, educational level, work, the type of stroke, the stroke location, and the consequences of stroke. The following medical history data were collected: 1) vascular risk factors such as diabetes mellitus, hypertension, dyslipidemia, impaired renal function, smoking and alcohol consumption; 2) vascular diseases such as prior stroke, transient ischaemic attack, angina pectoris, myocardial infarction, atrial fibrillation and peripheral arterial disease; and 3) other diseases such as other brain disorders, depression or other psychiatric disorders; functional status post stroke measured using the Barthel Index (BI)<sup>19</sup> and the Modified Rankin Scale (mRS).<sup>20</sup> The patients perceived lack of or excess of social support was measured with the Social Support List (SSL-6).<sup>21;22</sup> For a variable to be considered a candidate predictor for PSD, it had to be easily collected in a clinical setting with a view to future applicability. Consequently, the data collected were a proportion of the data normally collected in hospital care.

### Data analysis

The total percentage of missing values was 1.8%. Missing values were substituted through multiple imputation to reduce the biases and to increase the statistical power.<sup>23-25</sup> The imputation technique involves creating multiple copies of the data and replacing missing values with imputed values on the basis of a suitable random sample from their predicted distribution.<sup>23-25</sup> We used the 'mice' package (version MICE V2.10) of the statistical packages R (version 2.14.0 [2011-10-31]) to obtain five completed data sets.<sup>26</sup>

We used a two-step procedure to develop the prediction model for PSD. First, we selected the most strongly associated predictors from each subgroup of variables using multivariable logistic regression with backward stepwise selection based on a likelihood-ratio test with a *p*-value of 0.1, resulting in a 'full model'.<sup>27;28</sup> Second, the final prediction model was selected from this set of variables and validated with backward stepwise selection in multivariable logistic regression. One thousand bootstrap samples were drawn from the original sample, estimating the overfitting-corrected regression coefficients from the 'final model' and the overfitting-corrected measures of the model performance.<sup>29;30</sup> These statistics may be considered as an estimate of the performance that is expected in future patients.<sup>30</sup> We used the 'rms' package (version 3.3-2) from the statistical package R (version 2.14.0 [2011-10-31]). In this backward step, selection was based on the Wald Chi-squared test of the individual predictors with a *p*-value of  $\leq 0.1$ .

To quantify the performance of the models, we determined the discrimination and calibration by comparing the actual presence of PSD with the calculated predictions for the presence of PSD. The discrimination indicates the extent to which the model distinguishes between patients with or without PSD. The ability to discriminate was expressed with the concordance-statistic, i.e., the area under the Receiver Operating Characteristic curve (AUC), by calculating the AUC with a 95% confidence interval (CI) where the higher values

indicate better discrimination.<sup>29;31</sup> The calibration of a model describes the extent to which the predicted probabilities of PSD reflect the true probabilities of PSD.<sup>31</sup> The calibration was judged with the *U*-statistics which compares the actual slope and intercept of the calibration plot to the ideal values of 1 and 0, respectively and tested against a  $\chi^2$  distribution with 2 degrees of freedom.<sup>30</sup> We also calculated the following measurements for model accuracy: the Yates slope, a discrimination slope that measures the difference between the mean predicted probabilities for the patients with and without PSD; the Brier score, an expression of the squared differences between the actual presence of PSD and the calculated predictions for presence of PSD; Brier scaled, scaling the Brier score by its maximum score to overcome the influence of PSD incidence on the Brier Score. For the Yates Slope and the Brier Score, lower values indicate better accuracy, whereas higher values of the Brier Scaled represent better accuracy.<sup>30-33</sup> All analyses were conducted in the five completed data sets. The five sets of regression coefficients, the performance estimates and their variances were pooled according to Rubin's rules to produce estimates and confidence intervals that incorporate missing-data uncertainty.<sup>34</sup> To construct an easily used clinical score card, the regression coefficients of the prediction rule predictors from the 'final model' were standardized, dividing all regression coefficients by the smallest coefficient and transforming them into points by multiplying by three and rounding the results. The total scores were linked to the risk of PSD.

To enhance the clinical utility, we converted the regression model into a score table, the Post-Stroke Depression Prediction Scale (DePreS), which can be used as a clinical prediction rule (Figure 1). We calculated the risk score for each of the participants and sorted them in ranges of total scores.

## Results

The mean age of the 410 participating patients was 70 years (SD=14.3, range 20-

**Figure 1. Score table Post-Stroke Depression Prediction Scale (DePreS) derived from the logistic regression model to predict the risk of PSD**

Post-Stroke Depression Prediction Scale (DePreS)		
Does the patient have a medical history of <b>depression or other psychiatric disorders</b> ?	no	<input type="checkbox"/> 0
	yes	<input type="checkbox"/> 13
Does the patient have a medical history of <b>hypertension</b> ?	no	<input type="checkbox"/> 0
	yes	<input type="checkbox"/> -5
Does the patient have a medical history of <b>angina pectoris</b> ?	no	<input type="checkbox"/> 0
	yes	<input type="checkbox"/> 7
To what extent needs the patient <b>help with dressing</b> in the first week after stroke? (Barthel Index item 'Dressing')	Completely independent	<input type="checkbox"/> 0
	Needs help but can do about half unaided	<input type="checkbox"/> -9
	Dependent	<input type="checkbox"/> 3
<b>Sum score</b>	Add the item scores to obtain the sum score.	.....

97 years), and 221 (53.9%) were male. The characteristics of the patients with and without incident PSD are summarized in Table 1, presenting the patients (n=382, 93,2%) in whom the outcome 'incident PSD' was measured. Of these patients, 54 (14.1%, 95% CI 10.9-18.1%) were diagnosed with major depressive disorder in the aftermath of the stroke event, according to the DSM-IV. The patients who developed PSD showed a significant difference in the baseline medical history of impaired renal function, angina pectoris, depression or other psychiatric disorders, perceived lack of social support, and perceived excess of social support.

The selection of the candidate predictors for each subgroup of variables in a 'full model' consisting of the candidate predictors: medical history of hypertension, alcohol consumption, angina pectoris and depression or other psychiatric disorder, Barthel Index item 'Dressing', social support interactions, and perceived lack of support interaction.

A multivariable regression analysis showed that a medical history of depression or other psychiatric disorder was the most important predictor (OR 7.22, 95% CI 3.63-14.35). Other variables remaining in the model were medical

**Table 1. Baseline characteristics of study sample with complete outcome data**

Patients	Depressed n=54 (14.1%)		Non-depressed n=328 (85.9%)	
	n	(%)	n	(%)
Gender n (%)				
Male	26	(48.1)	181	(55.2)
Age in years				
Mean (SD) (min-max)	70.2	(13.95)	66.2	(17.31)
			(20-97)	(20-90)
Marital status n (%)				
Single	4	(7.5)	17	(5.2)
Married/Cohabiting	36	(67.9)	208	(63.4)
Widowed/Divorced	13	(24.5)	103	(31.4)
Discharge direction n (%)				
Home	36	(66.7)	208	(63.4)
Rehabilitation center	5	(9.3)	37	(11.3)
Nursing home	10	(18.6)	72	(21.9)
Other hospital	3	(5.6)	11	(3.4)
Type of stroke n (%)				
Intracerebral hemorrhage	9	(16.7)	39	(11.9)
Infarction	45	(83.3)	289	(88.1)
Localization n (%)				
Left	21	(38.9)	142	(44.7)
Right	24	(44.4)	122	(38.4)
Other	9	(16.7)	54	(17.0)
Symptoms n (%)				
Motor	36	(67.9)	228	(70.2)
Sensory	18	(37.5)	86	(26.2)
Speech	18	(34.0)	77	(24.3)
Language	25	(46.3)	160	(50.3)
Visual	10	(24.4)	82	(29.9)
Medical history concerning:				
Vascular risk factors n (%)				
Diabetes Mellitus	10	(18.5)	40	(12.2)
Hypertension	24	(44.4)	187	(57.0)
Dyslipidemia	20	(37.0)	116	(35.6)
Impaired renal function	8	(14.8)	21	(6.4)
Smoking	11	(20.4)	59	(18.0)
Alcohol consumption	29	(54.7)	196	(59.7)

SD = Standard deviation



Table 1 Continued

Patients	Depressed n = 54 (14.1%)		Non-depressed n = 328 (85.9%)		
	n	(%)	n	(%)	(n/N)
Medical history concerning:					
Vascular diseases n (%)					
Prior stroke	12	(22.3)	59	(18)	
Transient ischaemic attack	14	(25.9)	67	(20.6)	
Angina pectoris	15	(27.8)	37	(11.3)	
Myocardial infarction	8	(14.8)	28	(8.5)	
Atrial fibrillation	17	(32.1)	93	(28.4)	
Peripheral arterial disease	7	(13.0)	36	(11.0)	
Other diseases n (%)					
Other brain disorders	7		51	(15.6)	
Depression or other psychiatric Disorders	23	(42.6)	31	(9.5)	
Barthel Index					
Mean (SD) (min-max)	13.7 (5.6)	(0-20)	13.4 (6.2)	(0-20)	
Modified Rankin Scale					
Mean (SD) (min-max)	2.9 (1.4)	(0-5)	2.9 (1.5)	(0-5)	
Social support Mean (SD) (min-max)					
Interactions	15.7 (3.2)	(9-23)	15.0 (3.0)	(6-24)	
Perceived lack of support	7.1 (2.1)	(6-14)	6.5 (1.3)	(6-14)	
Perceived excess of support	0.3 (0.6)	(0-2)	0.1 (0.3)	(0-3)	
SD = Standard deviation					

history of hypertension, angina pectoris, and Barthel Index item 'Dressing', as shown in Table 2. The model showed a good discriminatory performance; the AUC of the model was 0.78 (95% CI 0.72-0.85). Additionally, the calibration was adequate with non-significant *U*-statistics (*p*-value =.96). The other measures of the predictive performance are shown in Table 3.

Table 4 shows the predicted risks and observed proportions for the ranges of total scores. To use the Post-Stroke Depression Prediction Scale (the risk assessment table) as a decision tool for distinguishing patients with a high PSD risk from low risk, we dichotomized the total score at several thresholds and calculated the screening characteristics of the prediction scale. Table 5

Table 2. Multivariable logistic regression model for the occurrence of PSD

Predictors	Odds Ratio	(95% CI)	Coefficient <sup>†</sup>	SE	<i>p</i> -value <sup>‡</sup>
Depression or other psychiatric disorders	7.22	(3.63-14.35)	1.98	0.28	(<.001)
Hypertension	0.49	(0.26-0.92)	-0.71	0.35	(.08)
Angina Pectoris	2.82	(1.33-6.21)	1.04	0.39	(.01)
Barthel item 'Dressing'					
Completely independent	*	*	*	*	*
Needs help but can do about half unaided	0.26	(0.08-0.82)	-1.34	0.58	(.03)
Dependent	1.57	(0.80-3.09)	0.45	0.35	(.31)

CI = Confidence interval, SE = Standard error  
\* reference category  
<sup>†</sup> Coefficient: logistic regression coefficient, shrunken for future patients and pooled from the five completed data sets according to the Rubin's rules  
<sup>‡</sup> the *p*-values represents the highest value found in the five completed data sets

Table 3. Predictive performance of the logistic regression model for the occurrence of PSD

	Yates Slope*	Brier Score*	Brier Scaled*	AUC* (95% CI)	<i>U</i> -Statistics <i>p</i> -value ( $\chi^2$ )*	Mean Predicted Risk PSD
Final model	0.19	0.11	0.07	0.78 (0.72-0.85)	.96 (0.09)	0.15

\* All statistics are scaled from 0 to 1. Higher Yates slope, as well as lower Brier Score and higher Brier Scaled and higher discrimination AUC and non-significant *p*-values of the calibration *U* statistic, represent better performance

Table 4. Risk Scores based on the Post-Stroke Depression Prediction Scale (DePreS) with corresponding predicted and observed risks for PSD

Total score	Predicted Risk	Observed Risk (n/N) *
≤-10	2%	0% (0/32)
-9 - -5	5%	9% (11/127)
-4 - 0	11%	6% (8/125)
1 - 5	19%	19% (13/67)
6 - 10	31%	33% (8/24)
11 - 15	49%	47% (14/30)
16 - 20	67%	77% (7/9)
≥21	82%	100% (2/2)

\* number of patients diagnosed as depressed out of the total number of patients within a total score range

**Table 5. Performance of the 'Post-Stroke Depression Prediction Scale (DePreS)**

Cut-off score	Sensitivity (95%CI)	Specificity (95%CI)	Negative predicted value (95%CI)	Positive predicted value (95%CI)	Number (%) False Positive Risk Prediction
≥ 2	0.73 (0.60-0.83)	0.75 (0.70-0.80)	0.94 (0.91-0.97)	0.33 (0.25-0.42)	87 (25%)
≥ 3	0.69 (0.57-0.80)	0.80 (0.75-0.84)	0.94 (0.90-0.96)	0.37 (0.28-0.47)	70 (20%)
≥ 6	0.53 (0.39-0.66)	0.90 (0.87-0.94)	0.92 (0.88-0.94)	0.49 (0.37-0.62)	32 (9%)
≥ 11	0.36 (0.24-0.49)	0.95 (0.92-0.97)	0.90 (0.86-0.93)	0.55 (0.38-0.71)	17 (5%)

summarizes the prediction scale screening characteristics at different cut-off values. At a cutoff score of  $\geq 2$ , the best accuracy is achieved with a sensitivity of 0.73 (95% CI 0.60-0.83) and specificity of 0.75 (95% CI 0.70-0.80).

## Discussion

This study presents the development and performance of a clinical prediction rule with its accompanied risk assessment table to identify admitted stroke patients able to communicate adequately, who are at increased risk for PSD. The DePreS showed acceptable discrimination and calibration.

The structural use of a screening instrument in the daily care of stroke patients will promote the early recognition of depression.<sup>10,35</sup> The trend toward decreasing hospital stays,<sup>11,12</sup> complicates proper screening for the occurrence of PSD during hospital stay<sup>7</sup> and emphasizes the need for an easy-to-use prediction rule to identify the risk for PSD after discharge. Our aim was to develop a prediction rule that is useful for clinicians in the daily care of stroke patients and that can be applied in the first week after stroke. Although a systematic review showed that several studies have been conducted on the prediction of PSD,<sup>18</sup> the overall conclusion of the reviewers was that most of the available models lack precision, were not thoroughly developed or validated and were

not clinically useful for predicting the occurrence of depression after stroke. In this study, we rigorously developed and internally validated the prediction model. Additionally, a few study characteristics must be noted to appreciate the findings. We included consecutively admitted stroke patients. This resulted in a sample reflecting the entire target population, as shown by the range of discharge destinations of the patients and by large variation in functional status. We decided to impute missing data to prevent biased estimates of the regression coefficients and their standard errors, which could have resulted in a model with suboptimal performance in future populations. Multiple imputation is the best method available to deal with both random and non-random missing values.<sup>24,25</sup> For the selection of the candidate predictors, we used predictors available to clinicians in the first week after stroke. These predictors will enhance the clinical utility of the prediction rule in daily hospital care. The selection of candidate predictors was performed based on multiple logistic regression using the backward elimination of candidate predictors which is preferable above forward selection.<sup>36</sup> Finally, to correct for optimism and prevent overfitting,<sup>37</sup> we internally validated our model using bootstrap samples derived from the study sample. This resulted in a well-developed prediction rule, which could be used as the basis for a simple decision-tree to guide a more selective screening process for PSD.<sup>10</sup> It is important that patients are structurally monitored and, if scored positively, are eligible for further diagnosis and treatment by specialized professionals such as psychiatrists or psychologists.<sup>35</sup>

Most of the predictors in our PSD prediction rule were previously reported as a predictor, boosting the potential applicability of the prediction rule to other populations. However, there are also studies in which our predictors did not remain in a multivariable logistic regression.<sup>18</sup> The strongest predictor for PSD was a medical history of depression or other psychiatric disorders. Another hospital-based study confirmed previous depressive episodes to be a predictor for PSD in a multivariable analysis, although less strongly.<sup>38</sup> Functional status

as a predictor of PSD has been studied more often than the medical history of depression and has been shown to contribute almost always in a multivariate regression model.<sup>18</sup> None of the studies, however, investigated the association of the individual functional status items with PSD,<sup>39-41</sup> in our prediction rule the item 'Dressing' notably appears to be a stronger predictor than the total Barthel Index score. Moreover the partial need for help in dressing protects from PSD, while the complete dependence in dressing was found to be a risk factor for PSD. This might be explained by the fact that the partial need for help in dressing gives patients the perspective of recovery. The correlation between PSD and vascular risk factors is less clear because in most previous studies these variables were not considered as predictors.<sup>18</sup> In our study, a medical history of hypertension appears to protect from PSD, while angina pectoris is an independent predictor. In the few studies considering vascular risk factors as predictor, angina pectoris has not been reported to be an independent predictor for PSD, whereas hypertension was an independent predictor in most of the studies.<sup>18;42-44</sup> Medication use may be a possible explanation for the protective effect of hypertension in our study. We did not register medication use; therefore, we were not able to verify the effect on the predictors or to add medication use to the regression analysis. Note that a predictive relationship does not equal a causal relationship.<sup>45</sup> The aim of prediction research is to predict, as accurately as possible, the risk of future outcomes based on a minimal set of predictors, using all of the variables that are potentially associated with the outcome. These variables, however, are not necessarily causally related to the outcome.<sup>45</sup>

Our study has certain limitations. First, our target population comprised patients able to communicate adequately because the assessment of depression with the CIDI highly depends on verbal and cognitive competence. Although PSD is associated with communicative and cognitive impairment following stroke,<sup>46;47</sup> it remains difficult to reliably measure depression in patients with

cognitive and communicative disorders.<sup>46</sup> This restricts the application of our model to those patients. Second, the data collection in the first week after stroke resulted in a relatively high proportion of patients (69%) who were too ill to participate. This could also explain the relatively low cumulative incidence of PSD. In our study, depression was defined by a diagnostic interview according to DSM-IV, resulting in a cumulative incidence of 14.1% (95% CI 10.9-18.1%) in the first 8 weeks after the event. A systematic review focusing on the frequencies of PSD showed (for hospital-based studies) a pooled prevalence of 33% (95% CI 23-41%).<sup>1</sup> However, for most of the studies included in the review, PSD was detected using a screening instrument and not a diagnostic interview. This could explain the difference because the use of screening instruments is associated with some misclassification.<sup>10</sup> Internal validation does not directly address the generalizability of the model, although internal validation of the model (using bootstrap samples drawn from the original sample) results in the overfitting-corrected regression coefficients from the prediction model and the overfitting-corrected measures from the model performance.<sup>29;30</sup> Therefore, to use this instrument with confidence new data are needed for confirmation<sup>37</sup> (collected from an appropriate [similar] patient population in a different center). Furthermore, additional research is needed to investigate the proper methods to screen for PSD in patient with cognitive and communicative impairments.

In conclusion, we have identified the most important clinical predictors for PSD in stroke patients who are able to communicate adequately. We have also developed a prediction rule that enables clinicians to estimate the risk of PSD the first week after stroke. The predictive performance of the prediction rule is good. The use of the Post-Stroke Depression Prediction Scale (DePreS) in daily practice may materially improve the clinical evaluation of stroke patients, provided it is followed by adequate treatment and follow-up.

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## **Chapter 7**

### **General Discussion**

After surviving a stroke, the majority of patients must cope with a multitude of disabilities in physical, psychological and social functioning.<sup>1</sup> These disabilities often have a huge impact on patient's activities of daily living, social functioning and quality of life.<sup>1</sup> In approximately 33% of stroke survivors, the burden of stroke is aggravated by post-stroke depression (PSD).<sup>2</sup> PSD has been associated with several impairments, such as functional dependence and poor functional recovery,<sup>3;4</sup> cognitive dysfunction,<sup>5;6</sup> poor communicative function,<sup>7;8</sup> increased disability,<sup>9</sup> reduced social activities,<sup>10;11</sup> failure to return to work,<sup>11</sup> longer institutional care,<sup>12</sup> and increased mortality.<sup>13;14</sup> Moreover, PSD hampers patient participation in rehabilitation.<sup>15</sup> This substantially increases the negative impact of associated impairments on recovery.<sup>15</sup> The first episode of rehabilitation after stroke is thought to be the most critical in defining stroke recovery outcome. Therefore, early recognition and diagnosis of PSD is of major importance for optimizing stroke patient recovery. This is emphasized by growing evidence that effective treatment results in decreased depression severity or complete remission and improves functional recovery after stroke.<sup>16-20</sup> To properly identify PSD in the early stage after stroke, different aspects should be considered. In our systematic review, we showed that nurses distinguish between screening and intervening roles, and we described several therapeutic interventions enabling nurses to intervene effectively (chapter 2). Furthermore, we demonstrated that PSD is not a different type of depression (chapter 3). Moreover, the PHQ-9 and PHQ-2 are effective instruments for PSD screening (chapters 4 and 5). The clinical prediction rule, the DePreS, was developed to identify the risk for PSD during recovery within the first week after stroke and showed good discrimination and calibration (chapter 6). In this chapter, the results are discussed in view of the evidence from the literature. Finally, recommendations for further research and implications for clinical practice and education are described.



## PSD symptoms

In the last decades, many studies have investigated the prevalence, screening and diagnosis of PSD and factors associated with PSD.<sup>2;17;21;22</sup> In these studies, PSD is generally defined using the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR<sup>TM</sup>),<sup>17;22;23</sup> in which depression is characterized by nine symptoms: anhedonia (diminished interest or pleasure), depressed mood, sleep disturbances, loss of energy, changes in appetite, feelings of inappropriate guilt, concentration difficulties, psychomotor retardation or agitation, and suicidal thoughts.<sup>24</sup> Major depressive disorder is defined as the consistent presence of five or more of these symptoms, including depressed mood or anhedonia, over a two-week period and representing a change from previous functioning.<sup>24</sup>

However, symptoms such as sleep disturbances, loss of energy, changes in appetite or concentration difficulties can also be consequences of the stroke itself.<sup>25</sup> According to the DSM-IV, symptoms that are clearly due to a general medical condition should not be counted toward the diagnosis of major depressive disorder.<sup>24</sup> In diagnosing PSD in daily practice, however, it is often difficult to determine whether a symptom is related to the stroke itself or to depression.<sup>26</sup> Therefore, four different approaches are described to address the somatic symptoms of depression in diagnosing depression in patients with physical illness: 1) the inclusive method, which considers all symptoms to diagnose depression irrespective of whether they appear to be related to the physical illness; 2) the exclusive approach, which excludes symptoms shown to be associated with the physical illness; 3) the substitutive approach, which substitutes psychological symptoms for somatic symptoms associated with the physical illness; and 4) the etiologic approach, which requires that the clinician make decisions on whether specific physical symptoms are related to the physical disorder before counting it toward the diagnosis of major depression.<sup>27;28</sup> In our research (chapter 3), we showed that the prevalence of the somatic symptoms

in stroke patients able to communicate adequately, increased in depressed patients compared with non-depressed patients, similar to the psychological symptoms. This emphasizes the fact that somatic symptoms in depressed stroke patients should be considered as clinical manifestations of PSD. The findings enhance the results of the few previously conducted investigations<sup>29-32</sup> and provide stronger evidence for the relevance of somatic symptoms in diagnosing PSD. Therefore, the inclusive method is preferable above the other three.

## Recognition of post-stroke depression in daily practice

In the daily care of stroke patients, PSD is not generally recognized without the routine use of a depression screening instrument.<sup>33</sup> Many instruments with acceptable to good diagnostic accuracy are available for use in stroke patients.<sup>22;34;35</sup> These screening instruments also reflect the various strategies for managing somatic symptoms in the detection of depression. Some include all symptoms irrespective of their nature, representing the inclusive approach, such as the 9-item Patient Health Questionnaire (PHQ-9).<sup>22;36;37</sup> Other instruments only consist of items concerning psychological symptoms, reflecting the exclusive approach, e.g., the Hospital Anxiety and Depression Scale.<sup>22;38</sup> The Post-stroke Depression Rating Scale was developed according to the etiologic approach by asking the clinician to decide whether the symptoms were caused by the stroke.<sup>22;22;39</sup> Finally, the substitutive approach is not reflected in the screening instruments. Our findings concerning the clinical manifestation of PSD (chapter 3), suggest that in detecting PSD, the use of instruments not reflecting the inclusive approach could bias the diagnosis. This may explain why the various measurements used to diagnose PSD contribute to the great variation in the prevalence of post-stroke depression.<sup>17;23</sup>

In our study of stroke patients able to communicate adequately, we focused on the clinimetric properties of the PHQ-9, which is an instrument based on the inclusive approach, as well as the 2-item Patient Health Questionnaire

(PHQ-2), consisting of the first two items of the PHQ-9 (chapters 4 and 5). The results showed that the clinimetric properties of these instruments are good.<sup>40</sup> Compared to other instruments, with respect to diagnostic accuracy, the PHQ-9 and PHQ-2 perform as good as or better than other instruments reflecting the inclusive approach.<sup>22</sup> Furthermore, for the use in daily practice, they are preferable above others because of their good clinical utility; they are brief, easy to use, and acceptable to patients.<sup>36;37</sup> An important benefit of these instruments is the possibility to use a stepped strategy, by using the PHQ-2 for screening all patients and only to administer the PHQ-9 in the case of a positive outcome of the PHQ-2. This will save time for the clinician and limit the burden on patients (chapter 5).

### Prediction of PSD in the early stage of stroke

With respect to hospital stay length, there is a trend toward a decreasing length of stay with a mean less than 14 days due to redesigned in-hospital care pathways of stroke patients.<sup>41;42</sup> This results in a large proportion of patients who are discharged within two weeks after stroke. Therefore, it is complicated to perform a proper PSD screening according to the DSM criteria during the hospital stay because depressive symptoms need to be present for two weeks or longer. This underscores the need to develop another strategy to detect PSD in the early stage after stroke. Therefore, we developed a clinical prediction rule to enable clinicians to estimate the risk of PSD in patients who are able to communicate adequately during their hospital stay (chapter 6). We identified the most important predictors for PSD, which were medical history of depression or other psychiatric disorders, hypertension, angina pectoris, and the level of dependence in dressing within the first week after stroke based on the item 'Dressing' of the Barthel Index.<sup>43</sup> This resulted in a well-developed prediction rule with its accompanied scorecard, the DePreS (chapter 6). The risk score derived from the score chart can be used as the basis for a simple

decision-tree, directed toward individuals at high risk for developing PSD, to guide a more selective screening with the PHQ-2 and PHQ-9 during recovery.<sup>22</sup>

### The nature of PSD

Prediction research does not equal etiological research. The aim of prediction is to predict the risk of future outcomes based on a minimal set of predictors as accurately as possible. All variables that are potentially associated with the outcome can be considered in a prognostic study. However, unlike etiological research, these variables do not necessarily have a causal relationship to the outcome.<sup>44</sup> Nevertheless, a prediction model can be used to provide insight into the pathophysiology of an outcome.<sup>44</sup> With respect to PSD, questions persist regarding the etiological explanation of depression. There is an on-going debate in the literature whether the depression is caused by biological factors provoked by the brain injury or the vascular pathophysiology underlying the stroke. Or alternatively, whether depression after stroke is a secondary psychological response to the physical, cognitive, and social impairments caused by the stroke itself.<sup>14;45</sup> Potential biological factors described in the literature are lesion location,<sup>17;46-48</sup> changes in the serotonergic neurotransmitter responsiveness,<sup>49;50</sup> generalized vascular brain damage in addition to stroke,<sup>45;51-53</sup> and vascular risk factors.<sup>21;54-56</sup> The psychological factors are related to the secondary psychological response to the physical, cognitive, and social impairments resulting from stroke<sup>45</sup> and to the vulnerability for depression due to patient's personality associated with neurocism.<sup>57</sup> Our research suggests that a biological and a psychological component contribute to the pathogenesis of depression; the predictor 'medical history of depression' is related to the psychological component, the predictors concerning the vascular risk factors 'angina pectoris' and 'hypertension' are related to the biological component and the predictor 'level of dependence in dressing within the first week after stroke' based on the item 'Dressing' of the Barthel Index is related to the reactive

component (chapter 6). In addition, in chapter 3, we discussed how the nature of PSD is not different from depression in other patient populations, as the symptom prevalence is broadly similar in depressed stroke patients compared to depressed patients with other symptomatic atherosclerotic diseases and depressed general practice patients. Thus, although we did not investigate the etiological aspects of PSD, the results of our research strengthened the assumption that PSD cannot be explained only by biological factors or by psychological factors. In general, the nature of endogenous depression is considered to be of multifactorial origin.<sup>58</sup> Similarly, the nature of PSD should be considered as an interaction of biological, psychological and social factors.<sup>45</sup>

### Treatment aspects

Although we showed that PSD is similar to depression in other patient populations, stroke patients suffer more severe depressive symptoms than patients with other symptomatic atherosclerotic diseases and general practice patients (chapter 3). This emphasizes the importance of early PSD detection and adequate treatment. According to the literature, there is some evidence of pharmacotherapy resulting in complete remission of depression or decreased severity of depression.<sup>16</sup> Pharmacological treatment is also associated with improved functional recovery of stroke patients.<sup>18</sup> In addition, several non-pharmacologic therapies are shown to be effective in post-stroke depression.<sup>17;19;20</sup> Psychological interventions have been demonstrated to have positive effects on PSD occurrence and severity.<sup>17;20</sup> Furthermore, there is evidence that providing information reduces depression severity.<sup>19</sup> Our systematic review (chapter 2) focusing on PSD therapeutic interventions that nurses can use in their daily care showed that physical exercise, life review therapy and motivational interviewing had positive effects on PSD occurrence and severity.<sup>59</sup> Finally, initiating treatment within the first month after stroke is more effective than starting treatment later; patients treated early improved

more and maintained this improvement over two years, while the late treatment group deteriorated over time.<sup>60</sup>

Despite this growing evidence, a passive attitude toward therapy prevails in daily practice. This is maintained by concerns about adverse drug effects. Although these concerns are not entirely unfounded,<sup>61</sup> they seem to overshadow the positive effects described in recent meta-analyses.<sup>16;62</sup> Recommendations in the different national and international guidelines (such as the Guidelines for Stroke and Traumatic Brain Injury of the Dutch Institute for Healthcare Improvement and the National Clinical Guidelines for Stroke of the Royal College of Physicians) appear to confirm this. They suggest that antidepressant treatment for PSD should start only after a period of ‘watchful waiting’ to determine if the depressive episode is persistent, but they do not specify how long that period should be.

Our findings that stroke patients suffer from more severe symptoms of depression (chapter 3) argue against this passive attitude. Given the severity of symptoms and the increasing evidence in favor of treatment, a reluctant attitude is not justifiable. A change in attitude from ‘watchful waiting’ toward ‘watchful acting’ is required. In line with our conclusions regarding the nature of PSD (chapter 3), treatment should have a multidisciplinary structure, consisting of a combination of pharmaceutical, psychological and social interventions that have been shown to be effective.<sup>16-20</sup> Our systematic review confirms the possibility of a multidisciplinary focus on treatment as it describes several interventions derived from various disciplines, such as psychology, physiotherapy and nursing found to reduce PSD occurrence and severity.<sup>59</sup>

### Role of nurses

Nurses often encounter patients with depressive symptoms because they have intensive and continuous contact with stroke patients. Therefore, one of the core questions underlying our research focused on the role of nurses with respect

to PSD. In general, nurses consider observation, assessment, and interpretation of the observed symptoms as important parts of their role in rehabilitating stroke patients, along with initiating, administering and monitoring therapeutic interventions.<sup>63;64</sup> Our systematic review (chapter 2) revealed that nurses describe PSD as an important problem that needs more attention in stroke patient daily care. However, due to a lack of knowledge and skills, they find it difficult to assess patient's psychological status; they seldom use measurement instruments, and the interventions they apply are rather indistinct, such as counseling and listening to the patient.<sup>59</sup> Our studies regarding the prediction and clinical manifestation of PSD help nurses recognize depressive symptoms and assess PSD during recovery. The results clarify which signs and symptoms, and in particular, what combination of signs and symptoms should alert them. Furthermore, as nurses distinguished a screening role from an intervening role in their nursing care, the results concerning the clinimetric properties of the PHQ-2 and PHQ-9 (chapters 4 and 5) demonstrate that they actually are able to perform their screening role by using these assessment tools during patient recovery.<sup>40</sup> Finally, our review showed how nurses can contribute to PSD treatment of PSD, which goes beyond talking with and listening to the patient, even though this is an undeniably important part of the nursing support function.<sup>65</sup>

### **Further research, implication for clinical practice and education**

Two important constraints limited the inclusion of patients in our studies. The first was the large proportion of patients who were not able to communicate adequately due to cognitive or communicative impairments, and second was the large proportion of patients discharged within two weeks after stroke onset.

Usually, depression assessment depends on verbal and cognitive competence.<sup>7;66</sup> However, 20-40% of all stroke patients have cognitive

problems<sup>67</sup> and/or communicative impairments, such as aphasia.<sup>67;68</sup> Although there are some instruments available that were developed for assessing PSD in patients with communicative impairments,<sup>69-71</sup> the clinimetric properties of these instruments have generally been tested in patients who were able to communicate adequately.<sup>69;72;73</sup> Therefore, it remains difficult to reliably measure depression in patients with cognitive and communicative disorders.<sup>7</sup> The consequences of this is that approximately 30% of all the stroke patients are usually excluded from studies concerning PSD due to communicative or cognitive impairments.<sup>7;22;74</sup> Therefore, the first priority for further research is the need for PSD detection in patients who are unable to communicate adequately.

In our research, we developed a clinical prediction rule, the DePreS, to identify PSD risk. The last step in the development of a prediction rule is external validation to test the generalizability of the prediction model by using new data collected from similar patients in other hospitals. In future study, our prediction rule for risk of PSD should be externally validated in a new dataset.<sup>75</sup> Finally, further research should be performed to develop an intervention focusing on a treatment plan combining the effort of all disciplines involved in the rehabilitation of stroke patients to decrease the negative impact of depression on patient participation in rehabilitation and reduce the burden of PSD on stroke patients.

Despite the research that remains to be done, the results of our studies should influence clinical practice and education. The growing evidence that effective treatment leads to complete remission of depression or decreased severity of depression and improves functional recovery after stroke emphasizes the major importance of early PSD detection in optimizing the recovery of stroke patients.<sup>16-20</sup> Our research highlights several aspects related to early PSD detection and concludes that clinicians, and in particular nurses, are able to identify depressed patients when they use the PHQ-2 and PHQ-9. Moreover,

our findings show that the risk for PSD during recovery can be identified with just four variables, which are already known in the first week after stroke. The implementation of these instruments in daily practice allows clinicians to identify patients at risk for or with PSD. This is of major importance as depression is generally not recognized during the daily care of stroke patients, even though the routine use of a depression screening instrument in the daily care of stroke patients increases early recognition.<sup>33</sup> Based on our results, a care program for early PSD detection can be developed, including risk detection in all patients during the first week after stroke followed by PSD screening and diagnosis during recovery. Those identified to be at risk or to have PSD can be targeted with a specialized set of interventions that can be applied in patients identified to be at risk and in patients screened to be depressed. This care program should have a multidisciplinary focus and encompass the whole pathway of stroke rehabilitation. However, research shows that although there is a positive attitude toward early PSD detection, the compliance of clinicians to structurally screen for mood status is low.<sup>33;76</sup> Reasons for non-compliance include limited time and concerns about screening tests, whereas being knowledgeable about screening, having screening in the job role and belief in the value of screening were identified as facilitating structural screening in daily practice.<sup>77</sup> Therefore, attention should be given to these barriers and facilitators in daily practice. As shown in our systematic review, several of the facilitators were identified by the nurses' descriptions.<sup>59</sup> Therefore, nurses should play a key role in developing care programs for early PSD detection. Furthermore, several aspects can contribute to reducing barriers and strengthening facilitators, such as participation in the development and implementation by clinicians involved in the care of stroke patients, support of the managers, and education of future users with respect to the nature and consequences of PSD, the background and application of screening tools and possible interventions.<sup>78;79</sup>

Solomon said in his Proverbs: The spirit of a man will sustain his infirmity; but a wounded spirit who can bear? (Proverbs 18:14, King James Version). May changing practice and further study regarding depressed stroke patients be our challenge for the future.

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## **Chapter 8**

### **Summary**

Samenvatting  
Dankwoord  
Curriculum Vitae

In the first two years after stroke approximately one-third of the patients suffer from depression, also referred to as post-stroke depression (PSD). Patients with PSD suffer from symptoms, such as a diminished interest or pleasure (anhedonia), depressed mood, sleep disturbances, loss of energy, changes in appetite, feelings of inappropriate guilt, concentration difficulties, psychomotor retardation or agitation, and suicidal thoughts. PSD aggravates the burden of physical, psychological and social disability after a stroke, as it is related to functional dependence and poor functional recovery, cognitive dysfunction, poor communicative function, increased disability, reduced social activities, failure to return to work, longer institutional care, and increased mortality. PSD hinders patient participation in rehabilitation, increasing the negative impact of associated impairments on recovery. Since rehabilitation in the first months after stroke is considered the most critical in defining stroke recovery outcome, early detection and diagnosis of PSD is of major importance for optimizing stroke patient recovery. There is growing evidence that effective pharmacological and non-pharmacological treatment results in decreased depression severity or complete remission and improved functional recovery after stroke, which emphasizes the importance of early detection. However, despite the high prevalence, its impact on rehabilitation outcome and the current treatment options, post-stroke depression is not generally recognized in stroke patients. This poor recognition, along with a passive attitude of health care professionals toward therapy, leads to underdiagnosis and undertreatment of PSD. **Chapter 1** describes how these aspects have led to the various studies in this thesis. The main aim of this thesis is to investigate proper strategies to early recognize patients at risk and to detect PSD in stroke patients, and to describe the role of nurses in PSD.

The first part of the thesis in **chapter 2** provides a review of the literature on the role of nurses in the daily care of depressed stroke patients with a focus on the early detection of PSD and therapeutic interventions that they can use. Using the

Cochrane method literature was reviewed for the period 1993-2008, resulting in fifteen articles. The role of nurses was investigated in two qualitative studies. The findings of both studies showed that nurses distinguished a screening role from an intervening role. They recognized symptoms of depression, however, they experienced the assessment of psychological status as difficult because of a lack of knowledge, skills, and training. Measurement scales supporting their observations were seldom used. Therapeutic interventions reducing the occurrence and severity of depression are information provision, life review therapy, motivational interviewing, an outpatient support program, a support program concerning activating and monitoring treatment of depression, and physical exercise. These interventions enable nurses to intervene effectively in the daily care of PSD patients.

**Chapter 3** focuses on the nature of PSD addressing the question whether all nine symptoms of depression, irrespective of their somatic or psychological nature, should or should not be considered as a clinical manifestations of PSD. Symptoms like sleep disturbances, loss of energy, changes in appetite, or concentration difficulties can also be regarded as direct consequences of stroke. Although according to the DSM-IV, symptoms that are clearly due to a general medical condition are not taken into account in the diagnosis of major depressive disorder, it is often difficult to distinguish whether a symptom is a clinical manifestation of PSD or if it is due to the stroke itself. Therefore, it is essential to determine whether symptom profiles are different in patients with PSD as compared to patients with symptomatic atherosclerotic diseases other than stroke or with patients in general practice. An observational multicenter study was conducted in 382 stroke patients who were able to communicate adequately, 1,160 patients in general practice, and 530 patients with other symptomatic atherosclerotic diseases. Comparing the symptom profile of depressed and non-depressed stroke patients, with depressed and non-depressed patients with other symptomatic atherosclerotic diseases, and

general practice patients demonstrated broadly similar symptom profiles in the three cohorts. However, the stroke patients suffered more severely from these symptoms than the patients with other symptomatic atherosclerotic diseases or the patients in general practice. The findings show that PSD is not a different type of depression. This findings indicate that all depressive symptoms, including somatic symptoms, should taken into account when diagnosing depression in patients after stroke.

The main part of the thesis presents three studies focusing on the early detection of post-stroke depression in the daily care of stroke patients who were able to communicate adequately. In **chapter 4**, the reliability, validity, and clinical utility of the 9-item and the 2-item Patient Health Questionnaire (PHQ-9, PHQ-2) was investigated in daily nursing practice of hospitalized patients with stroke. The PHQ-9 and the PHQ-2 were administered by 43 ward nurses in 55 patients with an intracerebral hemorrhage or ischemic infarction. The resulting scores of the PHQ-9 and 2 were compared with the scores of the Geriatric Depression Scale. The inter-rater reliability (ICC=0.98, 95% CI 0.96-0.99), the test-retest reliability ( $\rho_{sp}=0.75, p<.001$ ) and the internal consistency (Cronbach's  $\alpha=0.79$ ) of the PHQ-9 were good. The concurrent validity was moderate for the PHQ-9, with a Pearson's correlation of 0.7 ( $p<.001$ ) and acceptable for the PHQ-2 with a Pearson's correlation of 0.8 ( $p<.01$ ). The optimum cut-off point of the PHQ-9 for major depression was 10 (sensitivity, 100%; specificity, 86%; positive predicted value, 50%; negative predicted value, 100%). For the PHQ-2, the optimum cut-off point was 2 (sensitivity, 100%; specificity, 77%; positive predicted value, 38%; and negative predicted value, 100%). Nurses judged the PHQ to be a brief and easy-to-use instrument in daily practice of nursing stroke care.

In **chapter 5**, the diagnostic value of the PHQ-9 and PHQ-2, alone or in combination, is determined in 171 acute stroke patients who could communicate adequately. In the 6th-8th weeks after stroke, depression was measured

using the PHQ-9 and PHQ-2 and diagnosed using the Composite International Diagnostic Interview (CIDI) as the gold standard. The PHQ-9 performed best at a score  $\geq 10$  with a sensitivity of 0.80 (95% CI 0.62-0.98) and a specificity of 0.79 (95% CI 0.73-0.86) and the PHQ-2 at a score  $\geq 2$  with a sensitivity of 0.75 (95% CI 0.56-0.94) and a specificity of 0.76 (95% CI 0.69-0.83). Administering the PHQ-9 only to patients who scored  $\geq 2$  on the PHQ-2 improved the identification of depression (sensitivity: 0.86 95% CI 0.69-1.04). These results suggest that the PHQ-9 and PHQ-2 are preferable instruments for the early detection of PSD in the daily care of stroke patients, able to communicate adequately.

The timely detection of post-stroke depression (PSD), however, is complicated by a decrease in the length of hospital stay, resulting in a large proportion of patients who are discharged within two weeks after stroke. This underscores the need to develop another strategy to detect PSD in the early stage after stroke. Therefore, the Post-Stroke Depression Prediction Scale (DePreS), which is a clinical prediction rule for the early identification of stroke patients at increased risk for PSD, was developed and validated. **Chapter 6** describes the development and performance of the DePreS. Within the first week after stroke, predictors were collected from 410 consecutive stroke patients who were able to communicate adequately. Between the 6th and 8th weeks after stroke, depression was diagnosed using the CIDI. Multivariable logistic regression models were fitted and a bootstrap-backward selection procedure resulted in a reduced final model. The resulting prediction model, which includes a medical history of depression or other psychiatric disorders, hypertension, angina pectoris and the Barthel Index-item 'Dressing', had acceptable discrimination, based on an area under the receiver operating characteristic curve (AUC) of 0.78 (95% CI 0.72-0.85), and calibration ( $p$ -value of the  $U$ -Statistics =.96). Transforming the model to an easy-to-use risk assessment table, the lowest risk category (sum score  $\leq 10$ ) showed a 2% risk of depression, which increased to 82% in the highest category (sum score  $\geq 21$ ).

The clinical prediction rule enables clinicians to estimate the degree of the depression risk for an individual patient within the first week after stroke. The prediction could be used as the basis for a simple decision tree to guide a more selective screening process for PSD.

The thesis ends in **chapter 7** discussing the findings of our studies in relation with the literature. This resulted in some overall findings. First, the nature of PSD should be considered as an interaction of biological, psychological and social factors. Second, given the severity of symptoms of PDS and the increasing evidence in favor of treatment, a passive attitude toward therapy no longer is justifiable, requiring a change in attitude from 'watchful waiting' toward 'watchful acting'. Third, the nursing role goes beyond 'listening to and talking with the patient' even though this is an undeniably important part of the nursing care. According to our findings nurses taking care of patients with stroke should use valid and reliable assessment tools in order to detect PSD, which needs to be followed by effective and efficient treatment. The challenge in the future will be to create a continuous process in which further research leads to ongoing development and testing of effective and efficient care for patients with stroke which may eventually decrease the burden of PSD and the negative impact on patient's recovery.

## Chapter 8

Summary  
**Samenvatting**  
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In de eerste twee jaar na een beroerte krijgt ongeveer een derde van alle patiënten te maken met een depressie, ook wel post-stroke depressie (PSD) genoemd. Bij een depressie lijden patiënten aan symptomen, zoals verlies van interesse of plezier, depressieve stemming, slaapstoornissen, vermoeidheid, veranderingen in de eetlust, irreële schuldgevoelens, concentratiestoornissen, psychomotore traagheid of onrust en suïcidale gedachten. Daarnaast verergert PSD de last van de fysieke, psychologische en sociale beperkingen na een beroerte door de relatie met functionele afhankelijkheid en verminderd functioneel herstel, cognitieve beperkingen, communicatieve beperkingen, ernstiger mate van invaliditeit, verminderde sociale activiteiten, falende werkhervatting, langduriger institutionele zorg en verhoogde sterfte. Bovendien belemmert PSD de deelname aan therapie. Dit beïnvloedt het herstel van de gevolgen van de beroerte negatief, want revalidatie in de eerste maanden na een beroerte is bepalend voor de mate van herstel van de gevolgen van de beroerte. Daarom is het vroegtijdig opsporen en diagnosticeren van PSD van essentieel belang voor het optimaliseren van herstel. Er is toenemend bewijs dat bepaalde farmacologische en niet-farmacologische behandelingen leiden tot vermindering van de ernst of volledig herstel van depressie en tot een verbetering van het functioneel herstel na een beroerte. Dit onderstreept het belang van vroegsignalering van PSD. Echter, ondanks de hoge prevalentie, de negatieve invloed op het herstel en de huidige behandelmogelijkheden wordt PSD in het algemeen onvoldoende herkend. Dit, in combinatie met een terughoudende attitude van hulpverleners ten aanzien van behandeling, leidt tot onderdiagnose en onderbehandeling van PSD. In **hoofdstuk 1** is beschreven op welke wijze deze aspecten tot de verschillende onderzoeken in dit proefschrift hebben geleid. De studies hebben tot doel adequate strategieën te onderzoeken om PSD op te sporen, het risico op PSD vast te stellen en de rol van verpleegkundige in het vroegsignaleren van depressie te beschrijven.

In **hoofdstuk 2** is een systematische literatuurstudie beschreven, gericht

op de rol van de verpleegkundige bij het vroegtijdig opsporen van PSD en interventies die zij kunnen toepassen in hun dagelijkse zorg. Aan de hand van de Cochrane methode is literatuur uit de periode 1993-2008 bestudeerd. De rol van verpleegkundigen was onderzocht in twee kwalitatieve studies. Beide studies tonen aan dat verpleegkundigen voor zichzelf een rol zien in het screenen en behandelen van PSD. Ze herkennen de symptomen van depressie, maar ervaren het beoordelen van de psychologische status van patiënten als moeilijk door een tekort aan kennis en vaardigheden en het ontbreken van training daarin. Ook maken ze nauwelijks gebruik van meetinstrumenten om hun observaties te objectiveren. Interventies die verpleegkundigen in staat stellen effectief bij te dragen aan de behandeling van patiënten met PSD, zijn voorlichtingsprogramma's, life review therapie, motiverende gespreksvoering, een nazorgprogramma gericht op behandeling en therapietrouw van depressieve patiënten en bewegingsprogramma's.

In het volgende gedeelte van het proefschrift wordt de aard van depressie na een beroerte belicht, waarbij in **hoofdstuk 3** de vraag wordt beantwoord of de negen symptomen van depressie, ongeacht hun psychologische of somatische aard, beschouwd dienen te worden als een klinische manifestatie van PSD. Symptomen als slaapstoornissen, vermoeidheid, veranderingen in de eetlust en concentratiestoornissen kunnen het directe gevolg van de beroerte zelf zijn. Hoewel op grond van de DSM-IV criteria de symptomen die duidelijk het gevolg zijn van een somatische aandoening niet toegeschreven dienen te worden aan de diagnose 'depressieve episode', is het moeilijk te onderscheiden of een symptoom een uiting is van PSD of het gevolg van de beroerte zelf. Daarom is het van belang om vast te stellen of het symptoomprofiel van PSD verschilt van dat van patiënten met symptomatische atherosclerotische aandoeningen, anders dan een beroerte, en patiënten in de huisartspraktijk. Daarvoor is een observationele multicenter studie verricht met 382 patiënten met een beroerte opgenomen in een ziekenhuis, 1338 patiënten uit de huisartspraktijk en 592

patiënten met symptomatische atherosclerotische aandoeningen anders dan een beroerte. De vergelijking van de symptoomprofielen van depressieve en niet-depressieve patiënten met een beroerte, met depressieve en niet-depressieve patiënten met symptomatische atherosclerotische aandoeningen en met patiënten in de huisartspraktijk toont sterk overeenkomende symptoomprofielen aan. Wel blijken de patiënten met een beroerte in ernstiger mate te lijden aan de symptomen dan de patiënten in de beide andere groepen. Deze bevindingen tonen aan dat alle depressieve symptomen dienen te worden geëvalueerd bij patiënten met een beroerte, met inbegrip van de somatische symptomen.

In het laatste gedeelte van het proefschrift worden drie studies gepresenteerd, gericht op het vroegtijdig opsporen van PSD in de dagelijkse zorg aan patiënten met een beroerte die tot adequate communicatie in staat zijn. In **hoofdstuk 4** is een onderzoek beschreven naar de betrouwbaarheid, validiteit en de klinische bruikbaarheid van de 9-item en de 2-item Patient Health Questionnaire (PHQ-9, PHQ-2). De PHQ-9 en de PHQ-2 zijn afgenomen door 43 verpleegkundigen, werkzaam op de participerende verpleegafdelingen, bij 55 patiënten. De uitkomsten van de PHQ-9 en de PHQ-2 werden vergeleken met de Geriatric Depression Scale. De interbeoordelaarsbetrouwbaarheid (ICC=0.98, 95% BI 0.96-0.99), de test-hertest betrouwbaarheid ( $\rho_{sp}=0.75$ ,  $p<.001$ ) en de interne consistentie (Cronbach's  $\alpha=0.79$ ) van de PHQ-9 waren goed. The concurrente validiteit van de PHQ-9 was redelijk, Pearson's correlatie was 0.7 ( $p<.001$ ). Van de PHQ-2 was de concurrente validiteit goed, Pearson's correlatie was 0.8 ( $p<.01$ ). Het optimale afkappunt van de PHQ-9 voor depressieve episode was 10 (sensitiviteit, 100%; specificiteit, 86%; positief voorspellende waarde, 50%; negatief voorspellende waarde, 100%). Voor de PHQ-2 was het optimale afkappunt 2 (sensitiviteit, 100%; specificiteit, 77%; positief voorspellende waarde, 38% en negatief voorspellende waarde, 100%). Verpleegkundigen beoordelen de PHQ-9 als een kort en makkelijk te gebruiken



instrument.

In **hoofdstuk 5** is de diagnostische waarde vastgesteld van de PHQ-9 en de PHQ-2, afzonderlijk en in combinatie, met het Composite International Diagnostic Interview (CIDI) als gouden standaard. De optimale diagnostische waarde van de PHQ-9 is gevonden bij een score van  $\geq 10$  met een sensitiviteit van 0.80 (95% BI 0.62-0.98) en een specificiteit van 0.79 (95% BI 0.73-0.86) en van de PHQ-2 bij een score  $\geq 2$  met een sensitiviteit van 0.75 (95% BI 0.56-0.94) en een specificiteit van 0.76 (95% BI 0.69-0.83). De diagnostische waarde is het best wanneer gestart wordt met de PHQ-2 en alleen bij een score  $\geq 2$  de PHQ-9 wordt afgenomen (sensitiviteit: 0.86 95% BI 0.69-1.04). Uit deze resultaten blijkt dat de PHQ-9 en de PHQ-2 aan te bevelen zijn voor vroegsignalering van PSD in de dagelijkse zorg aan patiënten met een beroerte die tot adequate communicatie in staat zijn.

Tijdige opsporing van depressie bij een beroerte wordt echter bemoeilijkt door een dalende opnameduur in het ziekenhuis. Daardoor is een groot deel van de patiënten al ontslagen binnen twee weken na het ontstaan van de beroerte. Om toch in staat te zijn zo vroeg mogelijk na een beroerte PSD op te sporen is de Post-Stroke Depressie Predictie Schaal (DePreS) ontwikkeld. Dit is een instrument waarmee voor de individuele patiënt al in de eerste week na de beroerte het risico op het ontstaan van PSD in de tweede maand kan worden voorspeld. In **hoofdstuk 6** zijn de ontwikkeling en de eerste resultaten van de DePreS beschreven. Bij 410 patiënten werden in de 1e week na de beroerte gegevens verzameld die beschouwd werden als voorspellers voor PSD. Tussen de 6e en 8e week na een beroerte werd met behulp van de CIDI vastgesteld of er sprake was van PSD. Met multivariabele logistische regressie en bootstrap procedure met 'backward' selectie is een voorspellende model (predictiemodel) ontwikkeld, waarmee de kans op PSD in de 2e maand na de beroerte kan worden voorspeld met de gegevens 'depressie of een andere psychische ziekte in de voorgeschiedenis', 'hoge bloeddruk', 'pijn op de borst' en 'de mate waarin

hulp nodig is bij het aan- en uitkleden' (item 'Kleden' van de Barthel Index). Dit model blijkt goed in staat onderscheid te maken tussen de patiënten met PSD en de patiënten zonder PSD; de discriminatieve waarde weergegeven met het 'gebied onder de receiver operating characteristic curve' was 0.78 (95% BI 0.72-0.85). Ook toont het model een goede overeenstemming tussen de voorspelde kans op PSD en het daadwerkelijk ontstaan van PSD, de calibratie ( $p$ -waarde van de  $U$ -statistics =.96). Het model is omgezet naar een makkelijk te gebruiken risico score tabel, waarbij de laagste risicocategorie (somscore  $\leq 10$ ) duidt op 2% risico op PSD en de hoogste risicocategorie (somscore  $\geq 21$ ) op een risico van 82%. De risicoscore kan worden gebruikt als uitgangspunt in een beslisboom voor een meer selectief screeningsproces voor PSD.

Het proefschrift eindigt in **hoofdstuk 7** met een discussie van de bevindingen in relatie tot de literatuur wat leidt tot enkele overstijgende bevindingen. Allereerst ondersteunen de verschillende onderzoeken de opvatting dat de aard van PSD beschouwd dient te worden als een interactie tussen biologische, psychologische en sociale factoren. Ten tweede, gegeven de ernst van de symptomen van PSD en het toenemende bewijs in het voordeel van behandeling, is een passieve houding ten aanzien van behandeling niet langer gerechtvaardigd. Het huidige attitude van 'watchful waiting' zou moeten veranderen in de richting van 'watchful acting'. Ten derde, de verpleegkundige rol gaat verder dan 'luisteren naar en praten met' de patiënt, ook al is dit onmiskenbaar een belangrijk aspect van de verpleegkundige zorg. Onze bevindingen stellen verpleegkundigen in staat hun screenende rol meer concreet vorm te geven. Ten slotte, de uitdaging voor de toekomst is om een continue proces te creëren waarin voortschrijdend wetenschappelijk onderzoek leidt tot doorlopende ontwikkeling en toetsing van effectieve en efficiënte zorg aan patiënten met een beroerte om zo de last van PSD en de negatieve gevolgen voor het herstel van de beroerte te verminderen.

## **Chapter 8**

Summary  
Samenvatting  
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Curriculum Vitae

‘Er zou weinig van mij overblijven indien ik alles moest afstaan, wat ik aan anderen te danken heb’. Terugblikkend op de achterliggende jaren, blijken deze woorden van de Duitse schrijver en dichter Johann Wolfgang von Goethe (1749-1832) ook voor mij veel waarheid te bevatten. Allereerst wil ik daarom de patiënten bedanken die bereid waren hun ervaringen met me te delen. In de gesprekken met u bleek mij opnieuw dat het doormaken van een beroerte een gebeurtenis is waarvan de impact op het leven van u en uw naasten nauwelijks overschat kan worden. Dat u dat met mij wilde bespreken, ook als die ervaringen zwaar waren om te dragen of moeilijk om te delen, ervaarde ik als een groot voorrecht. Uw openheid was een sterke stimulans voor mij om van uw ervaringen te leren hoe we de zorg na een beroerte verder kunnen verbeteren en ontwikkelen om de last van een depressie en van een beroerte zoveel als mogelijk is te beperken.

Mijn promotoren prof. dr. Marieke Schuurmans, prof. dr. Rick Grobbee en prof. dr. Eline Lindeman en co-promotor dr. Thóra Hafsteinsdóttir wil ik op deze plaats hartelijk dank zeggen. Nog tijdens mijn studie Verplegingswetenschap kreeg ik, totaal onverwacht, de vraag of ik wilde solliciteren op de vacature voor onderzoeker met de mogelijkheid te promoveren. Maar hoe kon ik daar nu een goed besluit in nemen; ik had zelf nog geen onderzoek gedaan en ik wist nog niet zeker of onderzoek wel bij mij paste. Dat het onderzoek patiënten met een beroerte betrof en dat jullie al tijdens de sollicitatiegesprekken blijf gaven er vertrouwen in te hebben met mij dit onderzoek te kunnen verrichten, deed mij besluiten de uitdaging aan te gaan en zélf te ontdekken of ik tot een goed onderzoeker kon uitgroeien.

Marieke, ik ontdekte in de afgelopen jaren dat ik goed ben in het focussen op kleine dingen. Dat maakte mij tot een neuroverpleegkundige die zich samen met de patiënten kon verheugen op elk klein stapje in het herstel. Maar voor het onderzoek is het vaak juist nodig om door de kleine dingen heen naar het grotere geheel te kijken. Jouw stimulerende en bemoedigende support,

je kritische vragen en de prikkelende gesprekken hebben er belangrijk aan bijgedragen dat ik steeds beter in staat ben me te focussen op dat grotere geheel. Maar nog belangrijker was dat je me stimuleerde ook ten aanzien van mijzelf niet bij de 'kleine dingen' te blijven steken, maar te leren vertrouwen op mijn kwaliteiten om positie te nemen in de wereld van het onderzoek. Ik verheug me op het vervolg van onze samenwerking om met gedegen onderzoek de best mogelijke verpleegkundige zorg na te streven.

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Eline, bij een van onze overleggen over de complexiteit het onderzoek in goede banen te leiden, begroette je me met de woorden: "Je hebt nog steeds lichtjes in je ogen...." Je rustige, bescheiden wijze van begeleiden, je vermogen om met weinig woorden belangrijke punten in te brengen en zo nodig bij te sturen en je altijd supersnelle reacties op welke vraag dan ook, regelmatig onder omstandigheden die maakten dat zo'n snelle reactie helemaal niet vanzelfsprekend was, brachten vaak rust in de hectiek van het moment en het vertrouwen om verder te gaan. Ik beschouw je als een voorbeeld als het gaat om ook in de moeilijkste omstandigheden die dingen vast te houden, die maken dat de lichtjes in mijn ogen blijven schijnen.

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Verschillende mensen hebben elk op hun eigen wijze bijgedragen aan dit onderzoek. De afdelingen die participeerden in het onderzoek; zorglijn Cerebrovasculaire Ziekten van het UMC Utrecht, afdeling Neurologie van Ziekenhuis Gelderse Vallei in Ede en afdeling Neurologie van het Meander Medisch Centrum in Amersfoort dank ik voor hun deelname aan de verschillende studies. In het UMC Utrecht denk ik in het bijzonder aan Maud, dank voor je altijd open deur en je vermogen om overal een kans in te zien, en aan de verpleegkundigen van C3West, jullie maken dat ik me nog steeds thuis voel als ik op C3West kom, ondanks dat ik door de jaren heen steeds verder van de afdeling af verhuisde. Op de afdeling Neurologie in Ziekenhuis Gelderse Vallei ligt mijn bakermat als neuroverpleegkundige. Het was bijzonder om na zoveel jaar terug te komen en met zoveel enthousiasme ontvangen te worden. Bij een van mijn eerste bezoeken aan het Meander Medisch Centrum zei iemand dat het leek alsof ik er al jaren rondliep. Dat kenmerkte ook mijn gevoel als ik bij jullie was. Allen dank voor de heel plezierige en soepele samenwerking!

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Janneke de Man-van Ginkel was born in Amerongen, the Netherlands October 20th 1973. After graduating from the secondary school at the 'Van Lodensteincollege' in Amersfoort, she obtained her nursing education ('A-Inservice' program) at 'Ziekenhuis Gelderse Vallei' Ede in 1995. Her interest in neurosciences nursing was aroused during her work as a nurse student at the department of Neurology. After finishing her nursing education she continued working at this department for seven years, where she was involved in various quality projects concerning transmural multidisciplinary care of stroke patients. She obtained her certificate of Neuroscience Nursing in 1999.

In 2002 she started working at the University Medical Center Utrecht as a nurse practitioner, first at the department of Internal Medicine and three years later at the department of Neurology. In 2003 she finished education for Clinical Nurse Specialist at the University of Applied Science in Utrecht. She continued her studies at the Utrecht University, obtaining her Master of Science degree in Health Science in 2008, having specialized in Nursing Sciences. During this study she was invited by her supervisor to apply for a research position in Nursing Science. This enabled her to combine her graduate study with the doctoral research described in this thesis. She obtained a Master of Science degree in Epidemiology at Utrecht University Graduate School of Life Sciences in July 2010.

From September 2012 Janneke will continue her research at the department of Rehabilitation, Nursing Science and Sports of the University Medical Center in Utrecht. Since 2008 she works as a lecturer in the Master program of Clinical Health Sciences.