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A comparative study of medication use after stroke in four countries

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ABSTRACT

Objectives: The use of medication plays an important role in secondary stroke prevention and treatment of post-stroke comorbidities. The Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) was set up to investigate the inpatient stroke rehabilitation process in four centres, each in a different European country: Belgium, Germany, United Kingdom and Switzerland.
Patients and methods: Patients' medication use 5 years post-stroke was compared between countries. Focus was put on cerebrovascular secondary prevention, including (a) adequate antithrombotic treatment, (b) treatment of cardiovascular comorbidities and diabetes, and (c) the use of lipid-lowering drugs; as well as on the treatment of stroke-related disorders such as depression, anxiety and pain.
Results: Medication data were available for 247 patients. Data about depression and anxiety were available for 233.
Conclusion: There were no significant differences between the four centres in antithrombotic treatment and in the treatment of cardiovascular comorbidities and diabetes. However, significantly more patients from the UK were treated with lipid-lowering drugs compared to Belgian patients. Significant differences were also observed between the centres in the prevalence and treatment of depression. More Belgian patients suffered from depression compared to German patients and significantly more Belgian patients took antidepressants than patients in Germany. This was in contrast to the prevalence and treatment of anxiety and pain, for which no significant differences between the centres were seen. Related to pain treatment, it was observed that almost 40% of all patients suffering from pain, used no specific medication.

1. Introduction

Stroke is an important cause of morbidity and is responsible for 9% of all deaths worldwide [1,2]. After surviving a stroke, the risk of a recurrent stroke is 5–15% [1,3,4]; being responsible for higher mortality, more disability and increased cardiovascular complications [1,4]. Therefore, secondary prevention is of high importance, both in short and in long term, certainly when considering that the total cost for stroke accounts for 2–5% of all healthcare costs [2,5].

When reviewing pharmacological treatment in stroke patients, there are two important aspects e.g. cerebrovascular secondary prevention [1,2] and treatment of stroke-related diseases such as depression, anxiety and pain [5,6]. Cerebrovascular secondary prevention consists of an adequate antithrombotic treatment, treatment of cardiovascular comorbidities and diabetes, and the use of lipid-lowering drugs.

Patients who suffered from an ischemic stroke need to be treated with antithrombotic medication to prevent a second stroke [7].

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Most patients need a treatment with antiplatelet agents. Patients suffering from atrial fibrillation should be treated with anticoagulants, except for patients revealing contraindications [1,7].

The importance of the treatment of comorbidities and their relation to stroke are well-known. Hypertension is responsible for almost half of the strokes, but treatment with antihypertensive medication reduces that risk significantly [2,8]. Atrial fibrillation can cause embolisms of cardiac origin, due to the irregular heart rhythm. It should be treated with antiarrhythmics and antithrombotic medication [4]. Also patients with an earlier myocardial infarct or coronary artery disease need a treatment with beta-blockers, statins and antithrombotics. Diabetes increases the risk of stroke by two-fold, compared to non-diabetic patients [9]. Those patients require a treatment with an appropriate combination of life style modifications, antidiabetic drugs and treatment of comorbidities. Hyperlipidemia is also very common in the elderly. It is well-known that lowering the lipid levels can reduce the stroke risk [2,8]. There is also evidence that statins have plaque-stabilising effects and can therefore have an additional positive effect in the secondary prevention of stroke [2,10].

Patients with a stroke show a higher risk to develop depression, anxiety or pain disorders compared to the general population [11–15]. All these conditions compromise the quality of life [11,13,16]. Different studies show that 11–61% of all stroke patients suffer from post-stroke depression, mostly in the first months after stroke [5,6,11,13,17]. In a previous study of the same investigators, a prevalence of depression of 24–30% was observed in the first six months after stroke [12] and a prevalence of 33% was observed 5 years post-stroke [18]. It is known that the severity of depression can be related to the degree of invalidity and cognitive impairment after stroke [11,13,19]. Finally, it is important to mention that depression may negatively affect the functional recovery of stroke patients [17].

After stroke, different types of pain may occur. Common pain disorders are shoulder pain, headache, painful spasticity, musculoskeletal pain conditions and central post-stroke pain [14,15,20]. The latter is defined as *"a neuropathic pain syndrome that occurs after a cerebrovascular accident"*. Pain and sensory abnormalities arise from body parts, in neuronal connection with the damaged brain area [14,15]. Pain has an important influence on patients' life. It has not only an impact on rehabilitation [21], but interferes with sleep as well [22] and can even lead to suicide [15,23,24]. Despite those observations, pain, both non-stroke-related and stroke-related, still remains undertreated [20,25], an important argument to analyze the use of pain medication.

The initial Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) was carried out in four European countries: Belgium (BE), Germany (DE), United Kingdom (UK), and Switzerland (CH). Five years after the initial data collection, follow-up studies were carried out. Taking into account the importance of pharmacological treatment in long term secondary prevention, the aim of the present study is to document and compare patients' medication use 5 years post-stroke.

2. Patients and methods

2.1. Settings and study design

Data collection for the CERISE project started in 2002 in four European rehabilitation centres: UZ Pellenberg (Pellenberg, BE), City Hospital & Queens Medical Centre (Nottingham, UK), Reha-Clinic (Zurzach, CH) and Fachklinik (Herzogenaurach, DE). Those centres were reference centres for rehabilitation after stroke in each country. To be enrolled in the study, patients needed to fulfill the following inclusion criteria: (a) between 40 and 85 years old, (b) affected by a primary stroke, (c) admission to the rehabilitation centre in the first 6 weeks after stroke, and (d) clear motor impairments (Gross Motor Function of the Rivermead Motor Assessment (RMA-GF) $\leq$ 11 and/or Leg and Trunk Function of the Rivermead Motor Assessment (RMA-LT) $\leq$ 8 and/or Arm Function of the Rivermead Motor Assessment (RMA-A) $\leq$ 12). Exclusion criteria were: (a) suffering from other neurological impairments with permanent damage, (b) stroke-related symptoms due to subdural hematoma, tumor, encephalitis or a trauma, and (c) prestroke Barthel Index (BI) < 50. The latter criterion allows distinguishing between pre-existing disabilities and disabilities due to stroke [12,26–32].

The study project was approved by the Ethic Committees of the participating centres and all patients signed an informed consent [26,30]. Comorbidities at admission from the rehabilitation centre were derived from patients' medical record. After five years, a researcher visited the patient at his/her respective residence and patients were asked about their current medication use.

The medication data was first converted according to the World Health Organization (WHO) – Anatomical Therapeutic Chemical (ATC) classification [33] and allocated into 20 categories, based on their relevance for stroke treatment. This classification was reviewed by a constituted expert committee of stroke rehabilitation specialists, geriatrics and community physicians. Drug categories and corresponding ATC-codes are shown in Table 1.

Five years post-stroke, the prevalence of depression and anxiety were measured, using the Hospital Anxiety and Depression Scale (HADS) [34]. Patients with a score $\geq$ 8 on the HADS-A subscale Anxiety are considered 'anxious'. Patients with a score $\geq$ 8 on the HADS-D subscale Depression are considered 'depressed' [35]. Patients' quality of life was assessed using the validated Euroqol 5 Dimensions Scale (EQ-5D) [36]. The EQ-5D pain scales ranges from 0, defined as no pain, to 3, defined as extremely pain or discomfort. Patients with a score of 2 or 3 were considered as suffering from pain. The degree of independence was measured with the BI and

Table 1
Drug categories and corresponding ATC codes.

Code	Classification	Corresponding ATC-codes
AAG	Antiaggregants	B01AC
ACO	Anticoagulants	B01AA, B01AB
ADE	Antidepressants	N06A
ADI	Antidiabetics	A10
ADM	Antidementia drugs	N06D
AEP	Anti-epileptics	N03
APD	Antiparkinson drugs	N04
ASM	Antispastica and myotonolytica (muscle relaxants)	M03
ATS	Tranquilizers and sedatives	N05B, N05C
CVP	Cardiac therapy and antihypertensives	C01, C02, C03, C07, C08, C09
END	Corticosteroids for systemic use, thyroid therapy and calcium homeostasis	H02, H03, H05
GIP	Drugs used for gastro-intestinal diseases	A02, A03, A04, A06, A07, A09, C05A
GSH	Genito-urinary system and sex hormones	G
LIR	Lipid-lowering drugs	C10
NEO	Antineoplastic and immunomodulating agents	L
NLP	Neuroleptics and antipsychotics	N05A
PAP	Drugs used for the treatment of pain	M01, M02, M04, M05, N02
RES	Respiratory system	R
VAN	Analeptics/nootropica and peripheral vasodilators and antivertigo drugs	C04, N06B, N06C, N07C
VAR	Various products	A01, A11, A12, B03, C05B, C05C, D, J, N07A, N07B, N07X, S, V