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EPIDEMIOLOGICAL AND RECOVERY FACILITATING STUDIES OF AN URBAN POPULATION OF STROKE PATIENTS IN IRAN

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To my supervisor:

Assoc. Professor Johan Lökk

And my family:

Saeideh, Delaram, and Sadra

Abstract

Introduction

Approximately 15 million people have a stroke annually in the world, of whom one third will die within one year and one third will suffer permanent disability. Over 85% of these deaths happen in people living in low- and middle-income countries. Existing evidence indicates motor impairment as the most common disability caused by stroke. Following stroke, mood disorder and cognitive impairment may either directly or indirectly lead to more significant impairments in daily activities, which require more careful services and sometimes institutionalization of the stroke patients. AMPH-like drugs are reported to enhance motor recovery, Activities of Daily Living (ADL), mood, and cognition in stroke rehabilitation, but results from trials with humans are inconclusive.

Aims

The main objectives of this PhD thesis were to estimate epidemiological aspects of stroke among an urban population in Iran and also to investigate the potential for "rehabilitation pharmacology" of stroke recovery. Our interventional studies are aimed to investigate if levodopa (LD) and /or methylphenidate (MPH) in combination with physiotherapy can improve functional motor recovery, ADL, mood, and cognition in stroke patients.

Material and methods

The epidemiological studies were multihospital-based, cross-sectional and were performed on patients with stroke admitted to the hospitals in Qom-Iran from January 1st, 2001 through January 1st, 2002 (Study I) and between March 2006 and September 2007 (Study II).

In the interventional studies (Study III & IV), a randomized, double-blind, placebo-controlled trial with ischemic stroke patients randomly allocated to one of four treatment groups of either MPH, LD or MPH + LD or placebo combined with physiotherapy was performed. Stroke patients were enrolled within 15 to 180 days after stroke onset. Motor function, ADL, stroke severity, mood, and cognition were assessed by Fugl-Meyer (FM), Barthel Index (BI), National Institute of Health Stroke Scale (NIHSS), Geriatric

Depression Scale (GDS), and Mini Mental State Examination (MMSE) at baseline, 15, 90, and 180 days, after start respectively.

Results

Epidemiological studies: stroke crude rate in Qom city was estimated to be 53/100.000 per year in 2001 and the age-standardized incidence (to the European population) was 384 per 100,000 person-years. In study II the mean age of patients was 68 years. Hypertension was found in 64% of patients, followed by diabetes mellitus in 36%, heart disease in 34%, hypercholesterolemia in 32%, and smoking in 20%.

Interventional studies: Motor function and ADL were recovered for all participants during treatment and at 6-month follow-up. There were slight but significant differences in BI and NIHSS compared to placebo at the 6 month follow-up. Mood and cognitive status demonstrated continuously significant improvement in all four groups across baseline and the three follow-ups but the strongest improvement was found between baseline and first follow-up immediately after the intervention. A significant improvement in mood compared to placebo was found with the combined treatment (MPH+LD) at 90 and 180 days.

Conclusion

Stroke incidence was higher than in Western countries. Hypertension and Diabetes mellitus were more frequent than average global findings. One month case fatality was higher than in European countries but less than in developing countries. We strongly recommend establishing a stroke registry, improved primary and secondary prevention as well as promoting rehabilitation facilities in Iran.

A daily dose of LD 100 mg and /or MPH 20 mg combined with physiotherapy for 15 drug therapy sessions were safe and well tolerated and significantly improved mood status in ischemic stroke patients. It showed a slight ADL and stroke severity improvement over time and future studies should determine the optimal therapeutic window for and dosage of psychostimulants, as well as to identify those stroke patients who may benefit from treatment.

1 LIST OF PUBLICATIONS

I. Delbari A, Salman Roghani R, Tabatabaei S.S, Rahgozar M, Lökk J
Stroke Epidemiology and One-Month Fatality among an urban population in Iran.
International Journal of Stroke (Accepted)

II. Delbari A, Salman Roghani R, Tabatabaei S. S, Rahgozar M, Lökk J
A Stroke Study of an Urban Area of Iran:Risk Factors, Length of Stay, Case Fatality and Discharge Destination.
Journal of Stroke and Cerebrovascular Diseases, 2010;19(2):104-9.

III. Lökk J, Salman Roghani R, Delbari A
Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke: A randomized, double blind, placebo-controlled trial
Acta Neurologica Scandinavica (Accepted)

IV. Delbari A, Salman Roghani R, Lökk J
Effect of methylphenidate and/or levodopa combined with physiotherapy on mood and cognition after stroke: A randomized, double blind, placebo-controlled trial
Manuscript

CONTENTS

2 LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AMPH	Amphetamine
BI	Barthel. Index
BI	Brain Infarction
CI	Confidence Interval
CNS	Central Nervous System
CVA	Cerebrovascular Accidents
DA	Dopamine
DM	Diabetes Mellitus
FM	Fugl-Meyer
GDS	Geriatric Depression Scale
HLP	Hyperlipidemia
HTN	Hypertension
ICD	International Classification of Diseases
ICH	Intracerebral Hemorrhage
IHD	Ischemic Heart Disease
LD	Levodopa
LOS	length Of Hospitalization
MMSE	Mini Mental State Examination
MPH	Methylphenidate
NE	Noradrenalin
NIHSS	National Institute of Health Stroke Scale
P	Placebo
SAH	Subarachnoid
SD	Standard Deviation
UND	Undetermined
WHO	World Health Organization

3 INTRODUCTION

3.1 OVERVIEW

Stroke is a major cause of death (1) and long-term disability (2) in the elderly worldwide. It can have potentially enormous psycho-social and economic effects on patients, their families, caregivers, and also the health care system (3). In high-income countries, stroke is the third most common cause of mortality (1) and is the main cause of acquired adult disability (4). Stroke and coronary-artery disease collectively are expected to be the principal causes of lost healthy life-years by 2020 (5).

The combined impact of increases in life expectancy and advances in medical management in the developed and developing countries, has resulted in a larger number of elderly persons surviving (6). Therefore, identification of stroke prevalence and related risk factors in elderly is very important in planning, primary stroke risk prevention, secondary stroke prevention basis and health care strategies (4).

3.2 EPIDEMIOLOGY OF STROKE

According to World Health Organization (WHO)(2004), approximately 15 million people annually have a stroke in the world, of whom one third will die during the first year and one third will suffer permanent disability (7). Over 85% of these deaths happen in people living in low- and middle-income countries (8). The prevalence of stroke in different developed countries is approximately 500–800 per 100,000 inhabitants (9-10), which is not too different in developing countries ranging from 415/100,000 in South Vietnam to 690/100,000 in Bangkok, Thailand (11).

The incidence rate of first-ever stroke is estimated per 1000 person-years and the mortality rate of stroke is estimated with the same method, with the numerator consisting of all deaths occurring within one month of the stroke new onset. According to demographic changes in the European population, it is expected with an increased first-ever stroke incidence from 1.1 million in 2000 to more than 1.5 million in 2025 annually (12). This leads to a decrease in the projected European population, during the equal period of time, from 728 million to 715 million residents (11). It is shown that mortality rates of stroke have decreased during the last decades in many countries,

developed areas such as; western Europe, Japan, and North America (1-13). Despite the decrease in stroke mortality rate for many decades, incidence trends of stroke have been more contradictory (4).

3.2.1 Stroke in Sweden

The incidence rate of stroke in Sweden demonstrates considerable variations over time with decreasing stroke incidence rate until the early 1980s, a balance or an increase in stroke incidence rate in the late 1980s and early 1990s (3). However, the results of incidence rates since the beginning of the 21st century are conflicting (14-16). According to the WHO MONICA project, stroke incidence rates show high-incidence stroke rate areas in northern and lower incidence stroke rates in the southern area of Scandinavia (17). In Sweden, about 30,000 people have a stroke each year, of whom two thirds for the first time (18).

There is lack of evidence regarding the incidence stroke tendency for Sweden as a whole (18). However, epidemiological regional studies have shown inconsistent, increasing (19-20) and decreasing (17) tendencies for stroke incidence rates in younger people since 20 years. According to a study in Lund city in 2001, the crude total stroke incidence rate during 2000 to 2002 was 194 per 100,000 person-years. When adjusted to the European population, the annual rate of stroke was 144 per 100,000. The median age of stroke patients in Sweden is 80.4 years for female (range 44 to 105 years) and 74.2 years for male (range 17 to 94 years). Among them, 80% had brain infarction (BI) as a cause, 10% intracerebral hemorrhage (ICH), 4% subarachnoid hemorrhage (SAH) and 6% were undetermined (UND). The crude mortality rate of stroke patients in that study was 14.3% at 28 days, 23.7% at 1 year and 35.3% at 3 years after stroke (4).

3.2.2 Stroke in Iran

Stroke is currently a major public health problem in developing countries, and has been highlighted during the last decade (21). In spite of numerous epidemiological studies of stroke in developing countries, there is still limited population-based information (22). This is mainly because of the high expenses, not having enough resources, and the problems of performing such research due to the complex case finding methods.

Regarding stroke incidence and mortality, there are considerable differences between countries.

According to a recent well-designed population-based study in Mashhad, Iran (MSIS), incidence of stroke in Iran is considerably higher than in most Western countries, with stroke occurring at younger ages (23). The crude annual incidence stroke rate of first-ever stroke is 139 per 100,000 inhabitants, and the rates adjusted to the European population aged 45-84 years are higher than in most western countries: 616 for BI, 94 for ICH, and 12 for SAH (23). The results of this study also showed that 71.8% of patients are admitted to a hospital and 28.2% are managed in the community (23).

The results of a study in northern Iran, during 2001 to 2003, indicate a mean age of stroke patients of 68.10 years, ranging from 30 to 90 years. About 50% of hospitalized stroke patients were male, about 70 % of them were older than 65 years, and more than 90% of them were from urban areas (24). Stroke subtypes were BI 67.2%, ICH 28.4%, and SAH 4.4% (24). Based on another study in Isfahan-Iran during 2000 to 2003, 66.2% of stroke patients were hospitalized on the day of the stroke attack and about 5% of them were hospitalized after 72 h of their stroke attack (25). The 28-day case fatality rate among hospitalized stroke patients in this study was about 32% (25). Brain herniation (60%), aspiration pneumonia (20%), myocardial infarction (4%) and pulmonary embolism (4%) constitute causes of death in another study conducted in southern Khorasan-Iran (26).

3.2.2.1 Stroke risk factors in Iran

Hypertension is reported as the leading risk factor with greatest impact on stroke (64%) followed by cardiac disease (43.2%), hypercholesterolemia (26%), diabetes mellitus (24%), smoking (26%) and atrial fibrillation (16%) in a study conducted in northern Iran (24). The results of this study also showed that 32.8% of patients had a history of cerebrovascular disease, which in 24% of them had occurred during the last 4 years (24). Hypertension was the most frequent risk factor for fatality, followed by ischemic heart disease, hypercholesterolemia, and diabetes mellitus in another study conducted in Qom-Iran during 2006 to 2008 (27).

3.3 RECOVERY AFTER STROKE

3.3.1 Motor and ADL recovery

Existing evidence indicates motor impairment as the most common disability caused by stroke; it appears as functional problems in muscle control or movement, or limitation in mobility (28). This impairment affects about 80% of stroke patients and typically weakens lower and upper-limb of one side of the body and the movement control of the face (29). Conservative therapeutic approaches try to improve physical independence through the facilitation of skill achievement and motor control (30). There seems to be a direct relation between function and motor impairment and therapy for motor impairment aims to improve the function and recovery of movement (31). Ischemic or hemorrhagic injury to the motor cortex, premotor cortex, motor tracts, or associated parts in the cerebrum or cerebellum can lead to motor impairment (32). Changes in motor ability may be caused through various mechanisms: restitution, substitution, or compensation (33). Recovery of motor function after stroke is pretty confusing and complicated. Motor recovery happens in the following four main areas: (1) movement and function of the upper-limb (arm and hand); (2) gait (walking ability; as this is a primary function of the lower limbs); (3) balance (as this is a primary function of the trunk); and (4) mobility (combination of upper-limb function, lower-limb function, and balance to enable normal movements)(32).

3.3.1.1 Motor Recovery and enriched environment

The neural plasticity induced by psychostimulants resembles that when being exposed to an enriched environment after ischemic infarction in animals, which is related to promoted functional outcome (34-36). Enriched environment could be defined as “a combination of complex inanimate and social stimulation” (37). In an enriched environment, the level of physical activity deeply influences the efficacy of active drugs in improving motor function and induces axonal growth after stroke (38). An elegant experiment by Papadopoulos et al. has provided further insight into enriched environment in rats. Rats in different experimental groups were provided with different housing conditions (38). Control housing conditions included singly housed rats in a standard plexiglas cage with no additions. Enriched environment contained 3 rats per cage in bigger plexiglas cages and was equipped with hanging

toys, inclined ladders, tunnels, and chewable material. In the enriched environment cages, a subset of rats were also given focused activity sessions. All animals were enrolled in the trial at 2, 5, and 8 days after middle cerebral artery occlusion. They received either D-amphetamine sulfate injection (2 mg/kg subcutaneously) or vehicle (0.9% sterile saline). All animals received different levels of "physical rehabilitation" represented by a control environment, enriched environment, or enriched environment with additional focused activity sessions. Animals that only received Amphetamine (AMPH) treatment in the enriched environment without any additional physical rehabilitation, didn't show any significant motor improvement compared to the vehicle-treated animals in enriched conditions. In this study, both AMPH and various rehabilitation strategies induced a prominent but limited level of improvement over control animals when administered alone. AMPH treatment can encourage motor recovery, and obtaining measurable axonal outgrowth is only feasible when given in combination with focused activity and an enriched environment (38).

3.3.2 Psychological sequelae

The psychological sequelae caused by stroke can be devastating. Post-stroke depression (PSD) is one of the unresolved issues in recovery and rehabilitation of stroke patients (39). It has been considered the most common neuropsychiatric consequence of stroke (40). It is a common consequence of stroke up to 2 to 3 years after stroke onset (41). Cognitive impairment is frequently associated with mood disorder in stroke patients and the nature of the relationship between cognitive impairment and post-stroke depression remains complex (42).

Prevalence rates of PSD vary anywhere from 6% to 79% (43-44). Peak incidence and greatest severity of depression commonly occur between 6 months and 2 years after stroke (45). Depression may either directly or indirectly lead to more significant impairments in Activities of Daily Living (ADL), which require more careful services and institutionalization of stroke patients (46-48). The risk of fatality is higher in stroke patients with depression compared to non-depressed stroke patients (49). Deteriorated cognitive function and increased medical complication rates among patients with PSD adversely influence the speed of recovery and level of residual function following rehabilitation (50-51). Other consequences of PSD include higher health care costs,

diminished social abilities, and an increased risk of vascular-related events and death (52-53).

Several factors have been identified that impact the risk of PSD development. Social isolation, living alone, physical functional impairments, or a history of depression (or other psychiatric disorder) are identified as predictive risk factors for PSD (54-55). Some symptoms associated with PSD are the same as the risk factors, such as reduced social activity, failure to return to work, and poor participation in processes of rehabilitation (45). There is no clear relationship between the severity of stroke and the occurrence of PSD (56). Doubts have arisen in terms of whether the site of infarct can influence the PSD development (57). In a meta-analysis of 35 studies conducted by Carson and colleagues, no data conclusively supported an association between intra-hemispheric location and the risk of depression (58). Early diagnosis of PSD is extremely important in order to make an efficient treatment plan for the patient.

The importance of an early recognition and diagnosis of PSD is widely agreed upon in order to improve functional and psychosocial outcomes (59). All treatments must be modified to individual needs, based on patients' needs including cost, accessibility, and availability of treatments (60). Effective treatment will generally include the participation of the family, and other support networks (60). In all circumstances, it is recommended that the treating clinician supervise a person presenting with depression at least weekly for the first 6 weeks to evaluate mood changes, suicidal thinking, physical safety, the person's social life and adverse effects of any drugs that have been prescribed (60). Major goals of such a treatment include reducing depressive symptoms, improving mood and quality of life, appropriate use of healthcare resources and reducing the risks of medical complications (61).

Antidepressants are generally not indicated in mild forms of PSD because the balance of benefit and risk is not satisfactory in elderly stroke patients (62). For many years, stimulant medications have been employed in stroke rehabilitation and in PSD, but large randomized clinical trials are still lacking (63). The result of stimulant medications suggested a high degree of efficacy (80% improvement of depressive symptom) and a relatively low incidence of side effects (64). In a retrospective study done by Lazarus et al, they reviewed hospital charts of older adults with stroke and major depression. Among studied cases, 30 were treated with Nortriptyline and 28 with

MPH. Symptoms of depression resolved in 53% of MPH-treated and 43% of nortriptyline-treated patients, which showed no significant difference (64). However, a more significant difference was observed in response time. In those received MPH, mean response time to peak effect was 2.4 days versus 27 days for those whom were treated with nortriptyline. Also, side effects were reported in 14% of MPH and 30% of nortriptyline-treated patients, including delirium requiring termination of nortriptyline therapy in two patients (64). They also prospectively studied MPH administration for elderly stroke patients (mean age 73 years)(65).

MPH showed to be a safe and efficient therapy for elderly patients with PSD. Fast onset of action (usually within 3 to 10 days) and relatively few adverse effects of MPH may offer significant benefits over tricyclic antidepressants whose onset of action need 2 to 4 weeks (65). It can be concluded that specifically in conditions where patients' active participation in the recovery process is essential and issues like limitations in insurance coverage and subsequently shorter hospital stays, prescribing MPH would be best option. MPH therapy also has many benefits including mood elevation, better motor functioning, and the ability to conduct regular ADL without any considerable side effects (66).

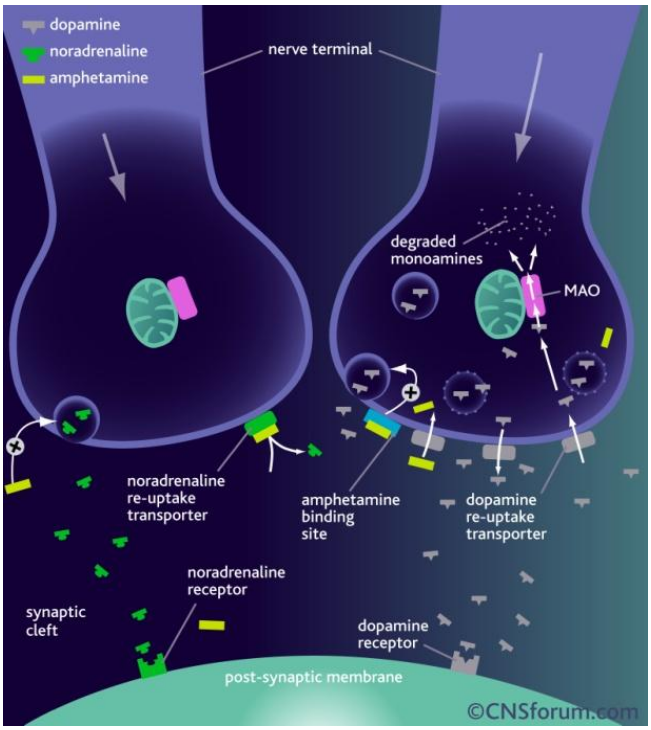
3.4 PHARMACOLOGICAL TREATMENT OF STROKE

Following stroke, 40–67% of patients may have persisting motor deficits without any improvement even with ongoing physical therapy (67). In spite of major advances in prevention and intervention of stroke, rehabilitation has traditionally received little scientific attention (68). Although there are lots of information and new findings regarding neural plasticity, unfortunately there is not enough clinical application of this knowledge for stroke rehabilitation (69). Among new therapeutic options for stroke rehabilitation, the role of "rehabilitation pharmacology" in stroke treatment is very important (70). Animal studies showed that functional recovery after stroke could be improved pharmacologically (71). Rehabilitation pharmacology has been named upon the experimental work over the past two decades showing that pharmacologic intervention to improve recovery might be possible in the subacute stages, days to weeks post-stroke, and even after irreversible injury has occurred (68). The aim of rehabilitation pharmacology is to enhance structural and functional reorganization (plasticity) of the injured brain (72) and to produce a long lasting effect which stays even after termination of treatment (70). It includes treatments that are supposed to

induce natural neuroplasticity and supports the restoration of impaired functions (69). Most evidence shows that AMPH treatment combined with physiotherapy lead to better functional recovery compared to placebo treatment (73). Also augmentation of central catecholaminergic activity has been considered as a central nervous stimulant and a potential treatment strategy for post stroke depression, based on the evidence implicating catecholamine deficits in the etiology of mood disorders in stroke (74).

The catecholamine system can be improved by stimulant medications, and have been administrated in stroke rehabilitation and refractory depression, where cognitive and mood impairments are predominant (63). It has been shown that functional recovery after stroke could be related to changes in catecholaminergic concentration, especially noradrenalin (NE)(75). The significance of noradrenergic theory is also supported by the observation that medications acting as NE antagonists reinstate motor deficits in animal models (76). In that way, improvement in recovery of motor function seems to depend on an increased NE concentration at the synapse, thus stimulating the NE receptors (77)(Figure 1).

Figure 1. Molecular mechanisms of noradrenalin and dopamine action



Many drugs have been tested in order to improve stroke recovery and rehabilitation. AMPH is one of the most studied ones, which seems to works as a psychomotor stimulant by inducing its effects at various levels such as gene expression alteration, protein synthesis, release of monoamines and even structural changes in dendrites (78-79). Many studies have tried to identify the exact mechanism of action of AMPH on functional recovery after stroke. It seems that its main effect is to facilitate the release of excitotoxic amino acids by NE from neurons (80). Therefore, combination of task specific physical therapy and AMPH would be a good therapeutic approach (81).

In this regard, there are many studies demonstrating that AMPH-like drugs such as methylphenidate (MPH)(82) and levodopa (LD)(83), two monoamines as well as catecholaminergic agents, are able to increase the extra cellular levels of NE in the cortex and cerebellum. Interestingly, clinical trials have reported minimal adverse effects following MPH and LD treatments (69-81). Grade and colleagues (1998) suggested MPH as an effective and safe adjunct treatment for the rehabilitation of acute stroke patients. According to them, patients treated by MPH improved in motor functioning, mood, and ability to conduct daily activities (66).

Many similar drugs have been studied and showed various effects; hence, they still need careful consideration in randomized clinical trials. Until now, no drug alone has been proven sufficient to facilitate recovery but some are promising. However, in human clinical trials, there were inconsistent results regarding the effects of D-AMPH (84), selective serotonin reuptake inhibitors (85), Donepezil (86) MPH (66) or LD (81) on post-stroke recovery.

3.4.1 Noradrenergic agents

Among monoamine stimulating treatments, noradrenergic agonists have been extensively investigated. It has been shown in brain injured animals that the noradrenergic system activating drugs enhance responsiveness, attention and other cognitive skills and noradrenergic system inhibitor drugs appear to have a negative influence (69). Animal experiments have shown that application of α2-adrenergic agonists such as clonidine resulted in relapse of symptoms likewise application of

dopamine (DA) and α1-adrenergic receptor antagonists like haloperidol cancel them (87).

The most studied noradrenergic agents include AMPH, MPH, and L-threo-3,4-dihydroxyphenylserine (L-DOPS)(70). Their mechanisms of action are different. Release of NE from nerve terminals is enhanced by AMPH, the reuptake of NE is blocked by MPH, and L-DOPS is a precursor of NE (70)(Figure 1).

Among catecholaminergic agents, MPH is considered as "AMPH-like" and a central nervous stimulant, which is widely and successfully used to treat ADHD, (69) usually at doses of 10 to 60 mg per day. As a noradrenergic agent, MPH amplifies endogenous NA and DA levels in the frontal and prefrontal regions of the brain by inhibiting NE and DA reuptake, stimulating release of and norepinephrine , and is characterized by a short duration of action (88). In contrast to AMPH, MPH is not causing addiction and doses of ≤ 40 mg do not lead to insomnia or loss of appetite in adults but sometimes hypertension and tachycardia are the side effects of this medication (89-90). In an interesting study done by Kline and colleagues, they reported beneficial effects of MPH treatment in rat model of hemiplegia (induced by cortical ablation)(91).

3.4.2 Dopaminergic agents

Dopaminergic agents exist in all parts of central nervous system. However, substantia nigra and hypothalamus have majority of dopaminergic agent fibers. It is a very important neurotransmitter for memory control, arousal, and executive functions (92). Several animal researches have indicated that DA or DA agonists have a positive effect on synaptic plasticity, learning (72-82), and recovery after brain injury (93) while haloperidol, a DA antagonist, and impaired recovery (94). After brain injury, it is common to have reductions of DA level in the frontal lobes, which may last for several weeks (92).

LD, as a dopaminergic agent precursor, is metabolized in the brain to produce DA (95%) and NA (5%)(83). To prevent its elimination before reaching the brain, LD is usually given with a peripheral decarboxylase inhibitor (carbidopa, benserazide)(69). Medication with LD preceding motor training, improved the development of an

elementary motor memory in healthy humans, and in stroke patients it enhances motor improvement (95-96). It seems that there are some plastic changes in the cortex as well (97). Also In chronic stroke patients, it can improve the capacity to encode motor memory (96).

There are two hypotheses for LD´s mechanism of action, supporting the natural self-repair processes locally in the frontal lobe and stimulation of the prefrontal cortex for regulation of executive functions like attention, working memory, planning and organizing, self-monitoring, and motivation (69). In that way it can improve learning abilities, and enhance the acquisition of new skills and behavioral changes during rehabilitation training. New efforts mostly focus on recognizing drugs that could increase the capacity for regeneration of CNS and maximizing the gains of rehabilitating motor and/or cognitive functions. However, this focus needs more investigation to be approved for clinical trials (69).

With the existing evidences, just small number of chemical compounds can induce a minimal improvement in post-stroke function, and others should be considered carefully with regard to their negative effects on recovery. These studies show that DA and DA agonists have positive effects on motor memory recovery not only in the subacute stage, but also in the chronic stage after stroke, when treatment opportunities are less accessible (98). They also carry no serious cardiovascular risks, compared to AMPH (81-99), so their usages as an adjunct are reasonable.

3.5 AIMS

3.5.1 General aims

The main objectives of this PhD thesis were to estimate epidemiological aspects of stroke among an urban population in Iran and also to investigate the potential for "rehabilitation pharmacology" of stroke recovery in patients within 15 to 180 days after stroke onset.

3.5.2 Specific aims

Study I:

To estimate the incidence of stroke and one-month fatality and also to describe stroke subtypes and the occurrence of established risk factors of stroke in a city of Iran in order to have a basis for preventive and rehabilitation interventions.

Study II:

To investigate the demographics, co-morbidities, risk factors, length of hospitalization, hospital discharge destination, and also case-fatality of ischemic stroke patients from a city of Iran as well as analyses of interaction of these factors.

Study III:

To investigate if Levodopa and /or Methylphenidate in combination with physiotherapy can improve functional motor recovery and ADL in stroke patients.

Study IV:

To investigate if Levodopa and /or Methylphenidate in combination with physiotherapy can improve mood and cognition in stroke patients.

4 MATERIAL AND METHODS

4.1 STUDY DESIGN

In order to have a basis of the epidemiological stroke situation in the city of Qom, Iran, study I was a hospital-based, cross-sectional study performed on all 460 patients with diagnosed stroke admitted to the hospitals in Qom from January 1st, 2001 through January 1st, 2002.

Study II was also a cross-sectional, multihospital-based study on risk factors of stroke performed on all 953 discharged and diagnosed ischemic stroke patients in the city of Qom between March 2006 and September 2007.

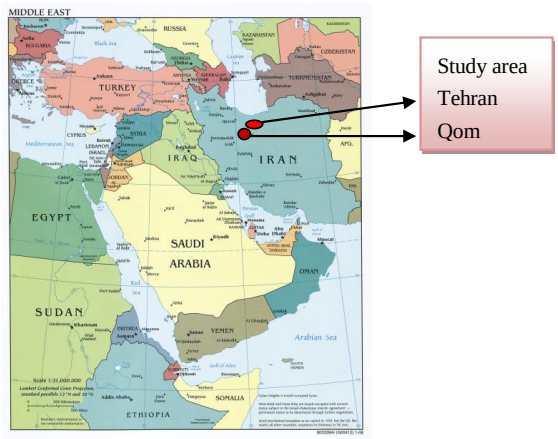
Studies III & IV were interventional, randomized, double-blind; placebo-controlled trials conducted with a 2 × 2 factorial design on all 100 ischemic stroke patients with a limb paresis in the cities of Tehran and Qom between March 2006 and September 2007.

4.2 STUDY AREA AND POPULATION IN EPIDEMIOLOGICAL STUDY (STUDY I & II)

Qom is a city of Iran situated 156 kilometers southwest of Tehran (the capital of Iran) and is the capital of the Qom Province (Figure 2).

There are five hospitals located in and near the urban area of Qom with an average of 872 beds. The area covered about 940,151 inhabitants of which 136,094 (14.47%) persons were >45 years in 2001 (100).

Figure 2. Study area



4.3 CASE-FINDING PROCEDURES IN EPIDEMIOLOGICAL STUDIES (STUDY I & II)

For study I & II all stroke patients were screened by searching all medical documents and the discharge diagnosis at Qom Hospitals by two experienced health care personnel, who were specifically educated before the study start. The diagnosis was based on clinical findings by an experienced neurologist confirmed in each case by computed tomography or magnetic resonance imaging. It was performed through screening of all medical records by searching for the classifications of ICD-10: G45, G81, G83, I60 –I67, and I69 as well as stroke-related terminology (cerebrovascular accident, cerebral infarction and brain infarction). Also a cross-sectional method for case ascertainment consisting of screening of all patients´ discharge lists of the Emergency Unit and Neurology Departments at Qom Hospitals was performed. As complementary information patients were interviewed face to face or by phone (after written or verbal consent to participate in the study), regarding the presence of risk factors prior to stroke, ADL after stroke and discharge destination from the acute care hospital.

Stroke risk factors were recorded, including diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), current or past history of smoking, and hyperlipidemia (HLP). Fatality figures after discharge were received from family members, caregivers or medical records. A standard systematic computer program was used for coding of data, analyzing demographic features, age proportions, sex differences, established cerebrovascular risk factors, history of previous stroke and length of hospitalization (LOS), hospital discharge destination, and fatality rate. Patients were followed-up through ambulatory visits to the hospital. Those who failed to attend the follow-up were contacted and interviewed by phone and, if not possible, their relatives were contacted.

4.4 CASE-FINDING PROCEDURES IN INTERVENTIONAL STUDIES (STUDY III & IV)

For study III & IV the participants were consecutively enrolled from eight acute care hospitals in Tehran and Qom when referred to outpatient rehabilitation treatment at the Neurorehabilitation Clinic of Rofeydeh Hospital affiliated to the University of Social Welfare and Rehabilitation located in Tehran. After screening medical records of 1043 stroke patients, 953 in Qom and 90 in Tehran, a total of 100 ischemic stroke patients were found to be eligible.

At the beginning, a trained general practitioner assessed all referred patients for inclusion and exclusion criteria. Non-eligible patients were offered the standard rehabilitation care. All therapists were trained to provide a standardized rehabilitation program specifically written for this study, to all patients. Another trained physician evaluated the patients completely, at the baseline for medical history and general, neurologic and outcome specific physical examination. He was also following-up patients at all evaluation sessions (15, 90 &180 days after start), ensuring that every patient's evaluation was performed adequately. Each patient's treatment status was kept unavailable from the patients themselves, the caregivers, the study physicians and the physiotherapists. The patients' demographic data including age, gender, established stroke risk factors, paretic side, stroke duration and any history of stroke were collected. The rehabilitation program was usually scheduled to be performed in the morning. Blood pressure and heart rate were monitored immediately before receiving study drugs and 2 hours after intake (Table 1). Full written informed consent was obtained from the patients before randomization or an assent was taken from a relative/caregiver if the participant was incapable of giving his/her consent. A computerized random-number generator was used by a person not involved in the study to generate the random allocation sequence list with four groups.

Table 1. Flow-chart of assessments

	Screening	Baseline	15-day	90-day	180-day
Demographic data	x				
Physical examination	x				
Vital signs	x	x	x	x	x
Risk factors	x				
Inclusion and exclusion criteria	x				
Medical consultation	x				
Informed consent	x				
Fugl-Meyer		x	x	x	x
Barthel Index		x	x	x	x
NIHSS		x	x	x	x
MMSE		x	x	x	x
GDS		x	x	x	x
Adverse events		x	x	x	x

4.5 INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria of the patients included in the studies (Table2)

Table 2. Inclusion and exclusion criteria

	Exclusion criteria	Inclusion criteria
Study I		▪ All patients with stroke from January , 2001 through January, 2002
Study II	▪ Hemorrhagic stroke ▪ Cases with neurological deficits secondary to: Tumor Infection Craniotomy Metabolic causes Traumatic causes	▪ All ischemic stroke patients
Study III & IV	▪ Hemorrhagic stroke ▪ Myocardial infarction or angina pectoris within the last 4 weeks ▪ Decompensated cardiac insufficiency ▪ Unstable metabolic disease ▪ Sequelae of earlier cerebral lesion ▪ Non-controlled hypertension (Systolic blood pressure ≥170mmHG, diastolic blood pressure ≥ 110 mm HG) ▪ Tachycardia (≥ 100 bpm) ▪ Major cognitive deficit (aphasia, apraxia, neglect, concentration and memory deficits) ▪ Glaucoma ▪ Uncontrolled epilepsy ▪ Hypersensitivity to MPH or LD ▪ Prominent agitation ▪ Current antidepressant treatment ▪ Patients receiving Alfa-adrenergic antagonists or agonists Neuroleptics Benzodiazepines MAO-inhibitor	▪ Ischemic stroke ▪ Paretic arm and/or leg ▪ Days since Stroke, 15-180 ▪ Able to follow instructions

4.6 DEFINITION OF VARIABLES (STUDY I & II)

Stroke is defined as an acute neurological dysfunction of vascular origin with rapidly developed clinical signs of focal and global disturbance of cerebral function lasting more than 24 hours (101).

Hypertension was defined as a self-reported history of HTN or the use of antihypertensive medications, or a measured blood pressure consistently >140 mm Hg [Systolic] or 90 mm Hg [Diastolic] (102).

Diabetes mellitus was defined as a fasting blood sugar >126 mg/dl, a non-fasting blood sugar >200 mg/dl (103)(Paper I) and persistent fasting hyperglycemia higher than 110 mg/dl after stroke (104)(Paper II) or a documented history of receiving anti-diabetic drugs.

Hyperlipidemia was defined as previous history of hyperlipidemia, patients taking lipid-lowering drugs or persistent elevation of total cholesterol higher than 200 mg/dl (105).

Ischemic heart disease was defined as reported angina pectoris, myocardial infarction, previous percutaneous transluminal cardiac stenting, coronary bypass graft, or cardiac arrhythmias (106).

Smoking was defined as current daily use of cigarettes, cigars or pipe (107).

Length of stay: The LOS for a single stroke hospitalization was defined as the time spent in hospital from admission until death, discharge to home or other residential institution (108).

Case fatality: At hospital, 30-days, 90-days, and 180-days case fatality was defined as the proportion of strokes where death occurred within these time limits (109).

Discharge destination: Was defined as discharge destination from acute care hospital, to home, nursing home, rehabilitation unit, or other hospitals.

4.7 MEDICATION PROTOCOL (STUDY III AND IV)

The study drugs Methylphenidate/ Levodopa / placebo drugs were randomly distributed in boxes labeled 1–100. The drug protocol developed for study III and IV was based on what was prescribed and suggested in previous studies (110) documenting MPH therapeutic efficacy at a mean dose of 17 mg per day in PSD (111). The reasons for

choosing MPH and LD were the following: they were suggested from animal and human experiments (91, 112-113), they had rare side-effects (114) and they were readily available in Iran. In contrast to AMPH, MPH does not cause addiction and doses of less than 40 mg do not lead to insomnia or loss of appetite in adults (69). In the four-group intervention model, drug treatment was given in the form of identical white tablets of 2 × 10 mg of either MPH or placebo of identical appearance and a tablet with either 100 mg LD or placebo (figure 3). It was administrated at least 60 minutes before the training session to coincide with the timing of peak pharmacological action of drugs (115). Treatments continued for five days a week, for a total of 15 drug therapy sessions, a frequency often used in the above-mentioned studies.

Patients received the boxes in consecutive order. Placebo and drugs were prepared by a hospital pharmacist independent of the investigators to be indiscernible. The potential side-effects of LD, including cardiovascular symptoms, nausea, vomiting, and psychosis were assessed and recorded. Also for MPH, the possible side effects were closely monitored including insomnia, nausea, or nervousness, over the first 24 hours after administration. If any side effects appeared, the patient would be dropped out and would discontinue his or her study plan.

Figure 3. The four-group interventional model

MPH-group MPH 20mg + Physiotherapy LD-placebo	**LD-group** MPH-Placebo + Physiotherapy LD 100 mg
MPH/LD-group MPH 20mg + Physiotherapy LD 100 mg	**Placebo -group** MPH-Placebo + Physiotherapy LD-placebo

4.8 PHYSIOTHERAPY INTERVENTION (STUDY III AND IV)

In study III and IV, the patient received a daily 45-minute physiotherapy session with standard treatment with a goal-oriented approach. Each session included mobilization, selective movements exercise (coordination, strengthening and active relaxation

exercises), sensory-motor, visual, perceptual and cognition training programs related to lying sitting, standing, balance, transfer, ambulatory activities, and other personal and instrumental activities of daily living (116). The theoretical framework of treatment was a neurodevelopmental approach aimed at normal movement facilitation versus abnormal movement inhibition (117). In order to make progressive improvements in trunk and limb muscle control, more complex functional activities were gradually included (117). The content, not the volume of the training, varied from each patient depending of the severity of his or her paresis within the standard written protocol for this study. Individuals received additional rehabilitation such as speech therapy treatment, depending on their neurological impairments. All therapists were trained to provide patients with standardized rehabilitation program. Patients were monitored during all sessions, to ensure that they received standard rehabilitation and that evaluations were performed adequately.

4.9 OUTCOME MEASURES

4.9.1 Motor Function (Study III)

Motor function skills were assessed quantitatively using the Fugl-Meyer (FM) scale which is developed for use in clinical rehabilitation settings (118). In study III it was assessed at baseline, and at follow-ups 15, 90 and 180 days after start, respectively. It is a stroke specific impairment index that is widely used for assessment of motor recovery. Its reliability and validity are well documented (118-120). On this scale, a score of 0 means no motor function (flaccid hemiplegia) and a score of 100 indicates normal motor function (divided into 66 points for normal arm motor function and 34 points for normal leg motor function)(118). Each item is scored on a 3-point ordinal scale (0 cannot perform, 1 performs partially, and 2 performs fully). Motor function was assessed by a physiotherapist at baseline, at the end of the 15th session and at follow-ups (3 months and 6 months after baseline).

4.9.2 Activities of Daily Living (Study III)

Autonomy in ADL was evaluated using the Barthel Index (BI)(121). Autonomy In study III was evaluated at baseline, and 15, 90 and 180 days after the study start. BI was developed as a scoring technique measuring the patient's performance in 10 activities of

daily living. The BI is considered a reliable disability scale for stroke patients (122). The items can be divided into one group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and one group related to mobility (ambulation, transfers, and stair climbing)(110). The maximal score is 100 in five-point increments. The lowest score is 0, representing a totally dependent, bedridden state (123).

4.9.3 Stroke severity (Study III)

The National Institute of Health Stroke Scale (NIHSS) is used to assess stroke severity (124). In study III it was assessed at baseline, and at follow-ups 15, 90 and 180 days after start, respectively. It consists of 11 items and the maximum possible score is 31. A score of 0 indicates no clinically relevant neurological abnormality. The NIHSS is not time-consuming to administer, taking <8 minutes to perform (125). Good overall interrater reliability has been shown in multicenter stroke trials (126) and the NIHSS has shown a very good sensitivity, specificity, and accuracy in predicting clinical results at 3 months (127).

4.9.4 Mood status (Study IV)

There are not many researches and data regarding diagnostic criteria of PSD but two reports suggest that using the Geriatric Depression Scale (GDS) has been reasonable in the elderly patients (128-129). The GDS is most useful in diagnosis of depression among patients who are in higher functioning levels, and have mild cognitive impairment (130). This 15-item short form questionnaire has been studied widely and is validated in a number of patients and requires approximately 5-7 minutes to administer (131). The optimum cutoff score for the Iranian version of GDS-15 is 7.8 with a sensitivity of 0.9 and a specificity of 0.84 (132). In study IV, mood was assessed at baseline, and at follow-ups 15, 90 and 180 days after start respectively. The Farsi version of this test showed acceptable reliability and validity among community-dwelling Iranian older people (132).

4.9.5 Cognitive Function (Study IV)

Cognitive function was assessed by means of the Mini Mental State Examination (MMSE)(133). It is an 11-question measure that tests five areas of cognitive function: orientation in place and time, registration, attention and calculation, recall, and language.

It has 19 items and the maximum score is 30. According to the Iranian version of MMSE, a score of 21 or lower with a sensitivity of 0.9 and a specificity of 0.84 is indicative of cognitive impairment (134).

4.10 ETHICAL CONSIDERATIONS

These studies were conducted in accordance with the ethical principles approved in the Declaration of Helsinki (135). The Ministry of Health in Iran, University of Social Welfare and Rehabilitation, and the local Qom Ethics Committees approved the studies. In study III and IV , full written informed consent was obtained from the patients before randomization or an assent was taken from a relative/caregiver if the participant was incapable of giving his/her consent. These include information about the participants' right to end their participation in the research project at any time if they wish not compromising their hospital stay and rehabilitation.

4.11 STATISTICS

In study I standard descriptive statistics were used to describe the variables, applying means, medians and standard deviations. Categorical variables were summarized as counts and percentages. Rates of strokes were adjusted to standard Iranian and European populations by direct method. To enable comparison with other population-based studies, rate was age-adjusted to 45 years or older based on Iranian and European populations as standards, respectively. We calculated Confidence Interval (CI) for crude rates and for rates specific for age and sex assuming normal distribution. Case fatality was defined as the proportion of events that were fatal within one- month of stroke onset.

In study II comparisons among variables with two levels were analyzed by proc t test. In contingency tables data were analyzed using proc freq and chi-square statistics. Fatality rates were analyzed using "logit regression" by proc catmod through SAS program.

In study III and IV descriptive statistics calculated for these data were means, standard deviations, frequencies, and percentages used to describe age, gender, days since stroke onset, history of previous stroke, paretic side, and risk factors. In paper III data of the four treatment groups and the mean change from baseline to 15, 90, and 180 days of BI, FM, and NIHSS were compared by ANOVA or Kruskal Wallis test, as appropriate.

Significant results were further investigated with post hoc test (Tukey). One-Sample Kolmogorov-Smirnov was used to check normality of distribution of variables. In paper III and IV with an 80 % power to detect a 20 % difference from baseline to 3 and/or 6 months a significance level of 0,05, one hundred patients were needed.

In paper IV cognitive and depression scores were dichotomized to cognitive normality (MMSE>21) versus cognitive impairment (MMSE≤21) and to non-depression (GDS < 8) versus depression (GDS ≥ 8) respectively. In paper IV each assessment occasion (baseline, 15, 90 and 180 days, respectively), data of the four treatment groups (MPH, LD, MPH+LD, and P) were compared by ANOVA or Kruskal Wallis test, as appropriate. In the efficacy analyses, a repeated measure of ANOVA was used with factors for time effect, treatment group, and time points. The non-parametric One-Sample Kolmogorov-Smirnov was used to check for normality of distribution of variables. In this thesis the significance level was established at 0.05 and Statistical analyses were performed using SPSS-11, SPSS-18 and SAS-9.1 software packages (Table 3).

Table 3. Analyses used in the four papers included in this thesis

Analyses	Paper I	Paper II	Paper III	Paper IV
Descriptive Statistics	X	X	X	X
Confidence Interval	X	X		
Age-Standardized Rate	X			
Logit Regression		X		
Proc t Test		X	X	X
Chi-square		X	X	X
Kruskal Wallis test			X	X
Kolmogorov-smirnov Test			X	X
ANOVA			X	X
Post hoc Test (Tukey)			X	X

5 RESULTS

5.1 ANNUAL RATES OF STROKE IN QOM, IRAN IN 2001

During January 1st, 2001 through January 1st, 2002, 460 patients > 45 years and 37 patients < 45 years were admitted and diagnosed as stroke with an equal gender distribution, rendering a crude incidence of 53/100,000 per year. Considering that 136.094 persons of the whole study population of 940.151 were >45 years, the stroke rate in this subpopulation was estimated to 338/100,000 (95% CI, 300-360 (312/100,000 in male and 370/100,000 in female) per year. When adjusted to the Iranian population of 1996, the annual rate of stroke was 344 per 100,000 (95% CI, 340-348) and 384 per 100,000 (95% CI, 381-386) when adjusted to the European population of 2001 (136). Age- and sex-specific annual rates of stroke per 100,000 population of Qom, Iran are summarized in table 4.

Table 4. Age- and sex-specific annual rates of stroke per 100,000 inhabitants of Qom, Iran 2001

Age group years	Male			Female			Both sexes		
	Cases/ at risk	rate	96%CI	Cases/ at risk	rate	96%CI	Cases/ at risk	Rate	96%CI
45-54	18/30650	59	31-85	36/24692	146	117-163	54/55342	98	71-122
55-64	44/20734	212	149-274	45/17329	260	213-287	99/38063	260	234-286
65-74	87/16737	520	403-617	74/15021	493	380-600	161/31758	507	461-539
75-84	70/4529	1546	1150-1850	66/3827	1725	1320-2120	136/8356	1628	1482-1758
85 +	11/1171	939	659-1219	19/1370	1387	1065-1695	30/2541	1181	761-1599
All ages	230/73821	312	280-340	230/62239	370	336-384	460/136060	338	300-360
ASR 1		312	306-314		370	366-374		344	340-348
ASR 2		343	339-340		414	409-411		384	381-386

ASR= Age-Standardized Rate
ASR 1= Adjusted to the 1996 Iranian Population
ASR 2= Adjusted to the 2001 European Population

5.2 PATIENT CHARACTERISTICS (STUDY I)

The mean age for all strokes was 69.6 ± 10.15 and for the subtypes: Thrombotic, Embolic, ICH, and SAH 71.6 ± 9.1, 67.1 ± 11.1, 67.8 ± 10.6, and 62.1 ± 10.2 respectively. Distribution of stroke subtype in age grope and sex of stroke patients are summarized in table 5. The proportions of main types of stroke were BI 75%, ICH 20.7%, SAH 3%, and UND 1.3%. 51.2% of Thrombotic strokes were female and 48.8% were male. Among Embolic and ICH subtypes, 39.6% and 52.6% were female as well as 71.4% among SAH.

Table 5. Distribution of Stroke subtypes in age groups and sex of stroke patients

		Age							Sex	
Stroke Subtype		**45-54**	**55-64**	**65-74**	**75-84**	**≥ 85**	**N**	**Mean(SD)**	**Female**	**Male**
Ischemic Stroke	Thrombotic 55.2%	14 5.5%	35 13.8%	104 40.9%	84 33.1%	17 6.7%	254	71.65(9.1)	130 51.2%	124 48.8%
	Embolic 19.8%	14 15.4%	25 27.5%	22 24.2%	23 25.3%	7 7.7%	91	67.07(11.15)	36 39.6%	55 60.4%
Hemorrhagic Stroke	Subarachnoid 3%	4 28.6%	4 28.6%	4 28.6%	2 14.3%		14	62.07(10.22)	10 71.4%	4 28.6%
	Intracerebral 20.7%	11 11.6%	25 26.3%	29 30.5%	24 25.3%	6 6.3%	95	67.81(10.60)	50 52.6%	45 47.4%
Undetermined	1.3%	1 16.7%		2 33.3%	3 50.0%		6	7 2.00(10.66)	4 66.7%	2 33.3%
Total	100%	44 9.6 %	89 19.3%	161 35%	136 29.6%	30 6.5%	460	69.61(10.15)	230 50%	230 50%

The one-month fatality rate in patients aged over 45 years was 24.6%. Mean LOS in hospital was 7.8 days (1-40 days). Among subtypes, Thrombotic subtype had the lowest LOS with a mean of 7.17 days and SAH subtype had the highest LOS with a mean of 12.3 days. HTN, DM, IHD, HLP, and smoking were found in 74.6%, 55.7%. 40.4%, 15.2%, and 5.4% of patients respectively. HTN was the main risk factor and significantly different between ischemic and hemorrhagic strokes, 69.8% and 89.7%, respectively. Previous CVA status, fatality rate, mean and standard deviation of los in hospital in stroke patients are presented in table 6.

Table 6: Previous CVA status, fatality rate, mean and standard deviation of length of stay in hospital in stroke patients

Stroke Subtype		Previous CVA		Fatality			Length Of Stay		
		CVA—	CVA+	Cure	Death	Others	N	Mean	SD
Ischemic Stroke	Thrombotic	197	57	200	48	6	254	7.17	4.95
		77.6%	22.4%	78.7%	18.9%	2.4%			
	Embolic	69	22	70	19	2	91	7.78	4.87
		75.8%	24.2%	76.9%	20.9%	2.2%			
Hemorrhagic Stroke	Subarachnoid	11	3	9	5		14	12.29	11.62
		78.6%	21.4%	64.3%	35.7				
	Intracerebral	84	11	54	35	6	95	9.08	7.08
		88.4%	11.6%	56.8%	36.8%	6.3%			
Undetermined		5	1		6		6	3.00	2.61
		83.3%	16.7%		100%				
Total		366	94	333	113	14	460	7.78	5.81
		79.6%	20.4%	72.4%	24.6%	3.0%			

Abbreviation: CVA: Cerebrovascular accident

5.3 PATIENT CHARACTERISTICS (STUDY II)

A total of 953 patients, 466 male (48.9%) and 487 female (51.1%), diagnosed with ischemic stroke were discharged from the 5 hospitals from March 2006 to September 2007. The mean age of patients was 68 ± 13.8 years (range 27 to 104 years) (68 ± 14.3 for male and 68± 13.4 for female). Forty seven (4.93%) patients were younger than 45 years and 611(64.1) patients aged >65 years. No risk factors were found in 91 patients (9.5%) and 862 (90.5%) had at least one risk factor. Female patients smoked less than male but had more HTN, DM, IHD and HLP. Through logistic regression analysis we found HTN to be the risk factor with greatest impact on ischemic stroke (64%) followed by DM (36%), IHD (34%), HLP (32%), and smoking (20%). Patient characteristics and demographics are presented in table 7. Median Barthel Index score at 4 months was 85 with an interquartile range from 55 to 100. BI was significantly associated with the number of risk factors (P= 0.046). All patients were discharged with secondary ischemic stroke prevention medication: antiplatelet agents in 96 % and 4 % with warfarin. The antiplatelet regimes were 25 % with aspirin 80mg/day, 28 % with clopidogrel 75 mg/day, a combination therapy with aspirin 80 mg/day + dipyridamole 76 mg x 3 in 27 % and clopidogrel 75 mg/day + aspirin 80 mg/day in 16 %.

Table 7. Characteristics of the 953 ischemic stroke patients included in analysis stratified by sex

Characteristic		Total		Female		Male		P- Value
		N	%	N	%	N	%	
Total patients		953	100	487	51.1	466	48.9	0.5
Age: y, mean± SD		68 ± 13.8		68 ± 13.4		67.9 ± 14.3		
Age group	**< 45**	47	4.9	20	2.1	27	2.8	0.3
	45-64	295	31	156	16.4	139	14.6	0.3
	≥65	611	64.1	311	32.6	300	31.5	0.7
Risk Factors:	**None**	91	10	34	37	57	63	0.016
	All	9	1	2	22	7	78	0.1
	HTN	610	64	347	71	263	56	0.0005
	DM	343	36	198	41	145	32	0.085
	IHD	324	34	174	36	150	31	0.34
	HLP	305	32	187	38	118	24	0.01
	Smoking	190	20	44	9	146	32	0.001

Abbreviations: DM, diabetes mellitus; HLP, hyperlipidemia; HTN, hypertension; IHD, ischemic heart disease.

5.4 LENGTH OF STAY AT HOSPITAL (STUDY II)

The average LOS for all ischemic stroke-related admissions was 7.7 days (95% CI, 7.2- 8.2). Females had a significantly longer LOS compared to male (8.4 vs. 7, P=0.0075) and patients with IHD had a significantly longer LOS [8.9 days, 95% CI=8-10, P=0.004]. No significant association between LOS and age groups, recurrent stroke, HTN, DM, HLP, and smoking was observed. Characteristics of the Stroke patients in study II stratified by LOS are presented in table 8.

5.5 FATALITY CHARACTERISTICS (STUDY II)

The overall proportion of stroke fatality rate was 1.8% (17/953) at hospital, 15.3% (146/953) at one month, 18.8% (180/953) at three months, and 20.5% (196/953) at six months after stroke onset. No statistically significant sex differences were found for fatality rate (24.8% for female and 20% for male, P=0.08). HTN was the most frequent risk factor accompanying fatality, which was followed by IHD, HLP, and DM. The mean number of risk factors per person, who died at hospital, was 2.2, 1.8, 1.8, and 1.5 for one month, three months, and six months after stroke onset, respectively (table 9).

Table 8. Characteristic of the 953 ischemic stroke patients included in analysis stratified by LOS

Characteristic		LOS	P-Value
Male &female		7.71	
Male		7	0.0075
Female		8.4	
Age group	≤ 45	6.2	
	46-64	6.9	0.7
	≥65	8.2	
HTN	yes	7.7	0.88
	no	7.8	
DM	yes	8.4	0.08
	no	7.3	
IHD	yes	8.9	0.005
	no	7.1	
HLP	yes	7.3	0.26
	no	7.9	
Smoking	yes	7.3	0.14
	no	8.3	

Abbreviations: DM, Diabetes Mellitus; HLP, Hyperlipidemia; HTN, Hypertension; IHD, Ischemic Heart Disease; LOS, Length Of Stay.

Table 9. Fatality rate with regard to sex, age, and number of risk factors

Characteristic	All	Hospital Stroke fatality		30-Day Stroke fatality		90-Day Stroke fatality		180-Day Stroke fatality	
	N	N	%	N	%	N	%	N	%
Male &female	196	17	1.8	146	15.3	180	18.8	196	20.5
Male	86	6	0.6	63	6.6	76	8	86	9
Female	110	11	1.1	84	8.8	104	10.9	110	11.5
Age: mean ± SD	73.3±12.9	73.6±10.3		73.2±14.1		75.1±7.9		73.6±13.8	
Age group <45	5	0	0	4	2	5	2.5	0	0
46-64	32	3	1.5	25	12.8	28	14.3	32	16.3
≥65	159	14	7.1	117	59.7	147	75	159	81.1
Mean number of risk factors		2.2		1.8		1.8		1.48	

5.6 DEMOGRAPHIC CHARACTERISTICS AND CLINICAL DATA AT BASELINE (STUDY III & IV)

One hundred patients, diagnosed with ischemic stroke were recruited from March 2006 to September 2008. Baseline characteristics of the patients of the respective group are presented in Table 10. Patients were compared regarding age, gender, risk factors, stroke duration, history of stroke, and paretic side. The participants, ranging in age from 40 to

87 years, had a mean age of 64 ± 9.8 years (61.5% male and 38.5% female) with 2.6% younger than 45 years, 46.1% were 45-64 years of age, and 51.3% above 65 years. The four groups did not significantly differ regarding demographics (age and gender) or clinical characteristics (days since stroke onset, prior stroke, HLP, IHD, smoking and paretic side of stroke).

Table 10. Demographics and clinical characteristics

		All	MPH †	LD†	MPH & LD†	P†	P value
Mean age , (SD*)		64 (9.8)	64.05 (10.8)	66.3 (9.5)	60.2 (9.1)	65.3 (9.6)	0.230
Gender:	**Male**	48	9	14	11	14	0.403
	Female	30	10	6	8	6	
Days since Stroke, mean days (SD*)		65.6 (34.2)	66.26 (40.7)	67.8 (32.1)	73.6 (41.5)	54.9 (18.1)	0.386
Prior stroke, n (%)							
	Yes	6 (7.7)	3 (15.8)	2 (10)	0 (0)	1 (5)	0.297
	No	72 (92.3)	16 (84.2)	18 (90)	19 (100)	19 (95)	
Risk factors, n (%)							
	HTN ‡	57 (73.1)	18 (31.6)	15 (26.3)	11 (19.3)	13 (22.8)	0.059
	DM ‡	44 (65.4)	9 (20.4)	14 (31.8)	6 (13.6)	15 (34.1)	0.021
	HLP ‡	39 (50.0)	12 (30.8)	8 (20.5)	10 (25.6)	9 (23.1)	0.500
	IHD ‡	22 (28.2)	3 (13.6)	7 (31.8)	6 (27.3)	6 (27.3)	0.564
	Smoking	18 (23.1)	5 (27.8)	5 (27.8)	4 (22.2)	4 (22.2)	0.959
Paretic side Right / left, n (%)		45/33 (57.7 /42.3)	10/9 (52.6/ 47.4)	13/7 (65/ 35)	11/8 (57.9/ 42.1)	11/9 (55/ 45)	0.874

†Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo
‡ HTN: Hypertension, DM: Diabetes Mellitus, HLP: Hyperlipidemia, IHD: Ischemic Heart Disease
*****SD: standard deviation

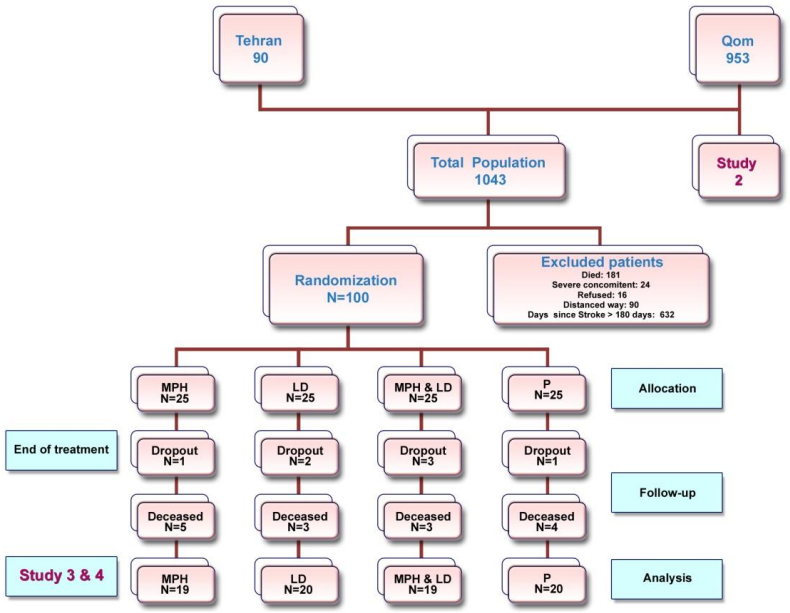
Through logistic regression analysis, HTN was the most common risk factor, 73.1%, followed by DM, 65.4%, HPL, 50%, IHD, 28.2%, and smoking 23.1%. Right-side paresis was found in 57.7% of patients. Groups differed significantly regarding DM (p=0.021) and close to significance regarding HTN (p=0.059) when performing logistic regression analysis.

All side effects during 15 drug therapy sessions were recorded and active drugs were well tolerated and no patients had to discontinue treatment because of cardiovascular symptoms, i.e. HTN and tachycardia, insomnia, nausea, loss of appetite or nervousness.

5.7 PATIENT RECRUITMENT AND DROP-OUTS (STUDY III & IV)

After screening medical records of 1043 stroke patients, 953 in Qom and 90 in Tehran, a total of 100 ischemic stroke patients were found to be eligible. The vast majority of non-eligibility was too long duration (>6 months) since stroke onset (N= 632), followed by death before recruitment to study (N=181), long-distance to hospital (N=90), severe concomitant disease (N=24), and refused (N=16). Twenty-two patients were lost during the follow-up period due to the following reasons: 15 (4.2%) died and 7 patients (11.5%) refused examination or follow-up. Seventy eight patients completed all the questionnaires and scales of the study at all three follow-up assessments. There were not any differences in the intervention arms regarding age, gender, or time since stroke onset. The mortality was not related to the 15 days of intervention, the causes of death were not considered to be related to the intervention per se. Treatment with active dugs, and placebo were started on average 65.6 ± 34.2 days in four groups. A flow-chart for the patients recruitment in study II and patients randomized in study III and IV are shown in Figure 4.

Figure 4. Patients' recruitment flow-chart



5.8 OUTCOME AND MEAN IMPROVEMENT (STUDY III & IV)

Baseline data of motor function (FM), ADL (BI), cognitive function (MMSE), depression (GDS) and stroke severity (NIHSS) were homogeneous and well balanced in all four groups. Separate model for arm and leg motor scores in FM, self care and mobility in BI revealed no significant differences of baseline data (Table 11).

Table 11. Mean and standard deviation of Baseline Barthel Index, Fugl-Meyer, NIHSS, MMSE, and GDS scores of the three actively treated and the placebo-treated group

	MPH † Mean (SD¶)	**LD †** Mean (SD)	**MPH & LD†** Mean (SD)	**P †** Mean (SD)	**P value**
Barthel Index					
Total	51.8 (16.1)	54.5 (20.6)	52.6 (17)	56.7 (17.2)	0.821
Self care	36.84 (36.8)	37.50 (37.5)	36.58 (36.6)	38.25 (38.2)	0.974
Mobility	15.00 (15)	17.00 (17)	16.05 (16)	18.50 (18.5)	0.423
Fugl-Meyer					
Total	38.3 (32.3)	46.4 (32.2)	33.8 (28.5)	41.1 (31.1)	0.639
Arm motor	23.2 (23.3)	29.7 (22.7)	19.1 (20.3)	24.9 (22.3)	0.519
Leg motor	15.1 (10.1)	16.7 (10.4)	14.7 (10.9)	16.2 (9.8)	0.919
NIHSS	5.9 (2.8)	4.3 (2.6)	7.1 (2.7)	5.5 (3.6)	0.065
MMSE	21.1 (3)	22 (5.2)	23.5 (4)	21.1 (6.1)	0.357
GDS	6.7 (3.5)	7.2 (3.6)	6.4 (2.6)	6.5 (3.5)	0.896

†Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo

¶ SD: standard deviation

5.9 MOTOR FUNCTION

Motor function graded on FM improved over the intervention period but the improvements were similar in active groups and the placebo groups. FM improved over the treatment period (baseline to 15-day) but differences in gain of motor function between active groups and the placebo group were not significant ($F\ 3, 74 = 0.610$, $P= 0.611$). Placebo-treated patients showed non-significant lower scores at follow-ups. There were no significant differences in FM scores between the active groups and placebo group at follow-ups (3 & 6 months), as analyzed by post hoc test. Table 12 shows the scores and outcome at end of treatment and follow-ups for FM (total score, arm, and leg).

Table 12: Mean and standard deviation of Baseline Barthel Index, Fugl-Meyer, and NIHSS scores at 15 day, 3 and 6 months and scores of and mean change of the three actively treated and the placebo-treated group

		MPH †	LD †	MPH&LD†	P †	P value
		Mean(SD¶)	Mean (SD)	Mean (SD)	Mean (SD)	
Barthel Index						
15 days	Total	61.84 (18.2)	67.5(19.1)	59.7(20.3)	65.7(16.8)	0.551
3 months	Total	71.58 (16)	76.75 (12.4)	72.37(14.4)	70.50 (14.4)	0.548
	Self care	41.8	46.2	42.4	40.5	0.777
	Mobility	29.7	30.5	30.0	30.0	0.205
6 months	Total	77.4 (14.5)	84.5 (8.5)	83.2 (15.4)	73.25 (14.1)	0.343
	Self care	53.7	57.0	56.84	49.75	0.224
	Mobility	23.7	27.5	26.32	23.50	0.123
Scores of mean change:						
6 months to baseline						
	Total	25.5 (14.2)	30 (18.9)	30.5 (13.3)	16.5 (9.6)	0.011
	Self care	16.8	19.5	20.3	11.5	0.038
	Mobility	8.7	10.5	10.3	5.0	0.021
Fugl-Meyer						
15 days	Total	54.6(34.8)	64.1(31.5)	52.2(34.6)	51.1(34.2)	0.611
3 months	Total	57.0 (35.3)	66.3 (31.7)	57.7 (37.1)	53.4 (34.4)	0.685
	Arm motor	34.0 (26.1)	40.7 (24.6)	34.9 (26.1)	32.4 (24.5)	0.752
	Leg motor	23.0 (9.7)	25.6 (7.7)	22.7 (11.4)	21.0 (10.7)	0.534
6 months	Total	58.0 (35.5)	68.2 (31.4)	56.9 (35.5)	54.4 (34.2)	0.597
	Arm motor	34.7 (26.3)	41.7 (25.1)	33.8 (25)	32.8 (24.3)	0.675
	Leg motor	23.3 (9.6)	26.5 (7.1)	23.1 (11.1)	21.6 (10.7)	0.757
Scores of mean change:						
6 months to baseline						
	Total	19.7 (13.7)	21.8 (12.2)	23.1 (19)	13.3 (12.7)	0.169
	Arm motor	11.5 (9.3)	12 (10.2)	14.7 (17.6)	7.9 (8.9)	0.374
	Leg motor	8.2 (6.1)	9.8 (5.3)	8.4 (5.1)	5.4 (4.4)	0.081
NIHSS						
	15 days	3.5 (2.8)	2 (2)	4.4 (3)	3.8 (3.5)	0.75
	3 months	2.9 (2.6)	1.8 (2)	3.7 (3)	4.0 (3.6)	0.089
	6 months	2.6 (2.5)	1.7 (1.9)	3.5 (3)	3.6 (2.8)	0.104
Scores of mean change:						
6 months to baseline		-3.3 (1.4)	-2.6 (1.2)	-3.6 (1.6)	-1.9 (1.4)	0.001

†Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo

¶ SD: standard deviation

5.9.1 Activities of daily living (ADL)

ADL function graded on BI improved over the treatment period but differences in gain of ADL function between active groups and placebo groups were not significant (F 3, 74 = 0.706, P= 0.551). There were no significant differences in BI scores between the active groups and placebo group at follow-ups (3 & 6 months) but there were significant differences between groups on 6 months to baseline (F 3, 74 = 4.000, P= 0.011). The greater gain was in the combined MPH & LD group. Mean and standard deviation of Baseline Barthel Index score of the four arms are summarized in table 12.

5.9.2 Stroke severity

All four arms had improvement during the intervention period assessed with NIHSS. There were no statistically significant differences in NIHSS scores between the active groups and placebo groups at follow-ups (3 & 6 months), but there were significant between group differences in scores of mean changes of total BI and NIHSS at 6 months to baseline (F 3, 74 = 5.728, P= 0.001) with a greater gain in the combined MPH & LD group (Table 12).

5.9.3 Cognitive Function

A two-way ANOVA on MMSE scores showed that there was no significant difference between groups in general and in time interaction scene too (p-values >0.1). In addition, post-hoc t-test showed that groups did not show any differences at any time of assessment in MMSE scores (p-values > 0.1). Table 13 shows the scores and outcome at baseline and at the three follow-up assessments of cognitive function. Cognitive status measured by the MMSE improved significantly and continuously in all four groups across baseline and the three follow-up assessments (F 3, 74 = 156.914, p= 0.000). The greatest improvement was found between baseline and first follow-up immediately after the intervention. MMSE scores improved significantly between baseline and 15-day assessment ($p<0.05$), 15-day and 90-day assessment ($p<0.05$), 90-day and 180-day assessment: ($p<0.05$). When dividing patients into two groups based on whether depressed or not (GDS < 8 and GDS ≥ 8, respectively), we found depressed patients to have significantly greater improvement in MMSE scores than patients who were not depressed.

Table 13: MMSE scores at baseline and at the three follow-ups for the four groups

	Baseline *	15- Day	90- Day	180- Day
Cognitive impairment				
Mean of MMSE, (SD)	17.9 (3.43)	16.87 (3.7)	17.31 (3.3)	17.47 (3.5)
N (%)	36(46.1%)	15(19.2%)	13(16.7%)	13(16.6%)
Cognitive Normality				
Mean of MMSE, (SD)	25.4 (2.36)	25.7 (2.27)	26.5 (2.33)	26.7 (2.36)
N(%)	42(53.8%)	63(80.7%)	65(83.3%)	65(83.3%)
MPH †				
Mean(SD)	21.1 (3)	23.7 (2.9)	24.7 (3.2)	24.9 (3.3)
LD †				
Mean(SD)	22 (5.2)	24.4 (4.9)	25.3 (4.8)	25.3 (5)
MPH& LD†				
Mean(SD)	23.5 (4)	25.1 (3.7)	26 (3.2)	26.3 (3.4)
P †				
Mean(SD)	21.1 (6.1)	22.8 (5.4)	23.8 (5.3)	24.2 (5.2)
Group Effect				
F	3.231	1.008	2.540	0.859
P	0.357 ¶	0.394 ‡	0.468 ¶	0.466 ‡
Time Effect				
F		156.914		
P		0.000		
Group × Time Effect				
F		0.537		
P		0.659		
Post hoc Comparison P	ns	ns	ns	ns
Post hoc Comparison of time points, t-value, P	a: 9.07, 0.000 b: 11.609, 0.000 c: 12.459, 0.000		d: 6.668, 0.000 e: 8.225 , 0.000 f: 2.377, 0.000	

* Higher scores of MMSE indicate better function
‡ P-value of F-test ¶ P-value of $\chi 2$ ns: non significant
†Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo
a: baseline vs. 15-day b: baseline vs.90-day c: baseline vs. 180-day d: 15-day vs. 90-day e: 15-day vs. 180-day f: 90-day vs. 180-day

5.9.4 Mood status

Mood status measured by the GDS improved significantly and continuously in all four groups across baseline and the three follow-up assessments (F 3, 74= 32.927, p= 0.000). The strongest improvement was found between baseline and first follow-up. Table 14 shows the scores and outcome at baseline and at the three follow-up assessments of Mood status. GDS scores improved significantly between baseline and 15-day assessment ($p<0.05$), 15-day and 90-day assessment ($p<0.05$), 90-day and 180-day assessment ($p<0.05$). GDS scores were significantly different between groups when

performing two-way (group x time of assessment) ANOVA. Post-hoc t-test showed that the combined treatment (MPH and LD) had significantly more improvement compared to placebo at 90 (p=0.018) and 180-day post baseline (p=0.006).

Table 14: GDS scores at baseline and at the three follow-ups for the four groups

	Baseline *	15- Day	90- Day	180- Day
Depressed				
Mean of GDS, (SD)	9.91 (1.46)	8.62 (1.06)	8.42 (0.79)	8.57(0.53)
N(%)	33(42.3%)	8(10.3%)	7(8.9%)	7(8.9%)
Non Depressed				
Mean of GDS, (SD)	4.4 (2)	4.67 (1.4)	4.34 (1.64)	4.14 (1.77)
N(%)	45(57.7)	70(89.7)	71(91.1)	71(91.1)
MPH †				
Mean(SD)	6.7 (3.5)	5.1 (1.7)	4.5 (1.9)	4.3 (2)
LD†				
Mean(SD)	7.2 (3.6)	5.4 (1.9)	4.8 (1.9)	4.8 (2.4)
MPH& LD.G†				
Mean(SD)	6.4 (2.6)	4.1 (0.9)	3.7 (1.3)	3.4 (1.3)
P.G†				
Mean(SD)	6.5 (3.5)	5.7 (2.1)	5.7 (2.2)	5.7 (2.1)
Group Effect				
F	0.199	11.944	3.683	4.694
P	0.896‡	0.008 ¶	0.016‡	0.005‡
Time Effect				
F		32.927		
P		0.000		
Group × Time Effect				
F		1.564		
P		0.205		
Post hoc Comparison			MP&LV>P	MP&LV>P
P	ns	ns	0.018	0.006
Post hoc Comparison of time points, t-value, P	a: 5.447, 0.000 b: 5.537, 0.000 c: 5.714, 0.000		d: 2.850, 0.006 e: 3.414 , 0.01 f: 1.580, 0.118	

* Higher scores of GDS indicate worse function
‡ P-value of F-test
¶ P-value of $\chi 2$ ns: non significant
†Groups: MPH: Methylphenidate, LD: Levodopa, MPH& LD: Methylphenidate & Levodopa, P: Placebo
a: baseline vs. 15-day b: baseline vs.90-day c: baseline vs. 180-day d: 15-day vs. 90-day e: 15-day vs. 180-day, f: 90-day vs. 180-day

6 DISCUSSION

6.1 SUMMARY OF MAIN FINDINGS

During the one year period, 2001-2002, stroke crude rate in Qom city was estimated to be 53/100.000 per year and stroke rate for inhabitants older than 45 years was estimated to be 338 per 100,000. The annual rate of stroke was 384 per 100,000, adjusted to the European population in 2001. The mean age for all stroke subtypes was 69.6 years. Stroke subtypes included were ischemic infarction 75%, intracranial hemorrhage 20.7%, subarachnoid hemorrhage 3%, and undetermined 1.3%. Main risk factors were found to be hypertension responsible for 74.6% and diabetes for 55.7% of stroke cases. Mortality rate was 24.6% within the first month.

Between 2006 and 2007 the mean age of ischemic stroke patients in Qom was 68 years. Hypertension was found in 64% of patients, followed by diabetes mellitus in 36%, heart disease in 34%, hypercholesterolemia in 32%, and smoking in 20%. The average length of stay at hospital was 7.7 days. Female had significantly longer length of stay compared to males (8.4 vs. 7) and also patients with heart disease had a significantly longer length of stay (9 days). Overall, one month fatality rate was 15.3%.

In interventional studies a daily dose of LD 100 mg and /or MPH 20 mg combined with physiotherapy for 15 drug therapy sessions were safe and well tolerated but provided no benefits on total motor score, and cognitive status in chronic ischemic stroke patients. It was revealed that motor function and ADL were recovered for all participants during treatment and at 6-month follow-up. There were slight but significant differences in BI and NIHSS compared to placebo at the 6 month follow-up.

Mood and cognitive status demonstrated continuously significant improvement in all four groups across baseline and the three follow-ups but the strongest improvement was found between baseline and first follow-up immediately after the intervention. A significant improvement in mood compared to placebo was found with the combined treatment (MPH+LD) at 90 and 180 days.

6.2 COMPARISON WITH OTHER STUDIES

6.2.1 Epidemiological studies

The low crude stroke rate in Qom was likely to be attributable to the higher proportion of younger persons in the population of Qom (84.5% < 45 years)(100). Stroke rate, when adjusted to the European population(136), had a high figure which possibly could be due to differences in risk factors e.g. HTN is not aggressively diagnosed and treated in Iran. The mean age of stroke onset in our study in 2001 was 69.6 years, which is in line with the findings of a Japanese study (137) but older than reported in other studies of developing countries, 58 years in Gambia (138) and 60.4 years in Senegal (139). The one-month fatality of stroke in Western Europe has been reported to 22.9 % in a meta-analysis (3) and in Australia has this figure been reported to be between 23.9 and 35.5% with seasonal variation (140). DM had been diagnosed for more than half of the patients, whilst reported in 14% to 38.3% in other studies (141-142). This discrepancy could be explained by the increased risk factor exposure in the whole population with a DM prevalence estimated to 5.7% versus worldwide 2.8% (143).

Our data didn't confirm the general trend of a male-dominant pattern of stroke as the majority of patients were female, in contrast to the results of a recent state wide study (144). Although existing evidence suggests that female are, on average, older than male at stroke onset (144), surprisingly the mean age of male and female in our study was almost similar (68 vs 67.96). It could be that the female were more likely to have a history of HTN (108, 145), and HLP (146), corroborating the findings from other studies (147).

Between 2006 and 2007, the overall fatality of the ischemic stroke patients was 22% during first 6 months, and the 30-day fatality rate was 15.3%. The 30-day fatality rates reported from other major registries range from 5.6 to 8.5% (148). The fatality rate in our study was higher than those reported in Western countries (144) and in Korea but smaller than those reported in a previous Iranian study (26). It may reflect the general trend of declining fatality rate, the inclusion of more patients with smaller lesions detected as a result of the increasing number and use of CT facilities in hospitals, providing Qom emergency staff with guidelines of detection and treatment of stroke patients, and the increase of the number of neurologists in Qom from 3 in 2001 to 7 in 2007. In contrast to

previous studies where female had a higher overall crude stroke mortality rate (149), we did not find sex to be statistically associated with death after stroke. The fatality rate in our study was 20% among male compared to 24.8% in female, which is in line with the reports from other studies. In the Canadian registry, no sex difference in fatality rate was found (150).

6.2.2 Interventional studies

Study III indicates no significant benefit of physiotherapy combined with drugs on total motor scores compared to physiotherapy alone when given for 15 treatments over 15 days. The results of this investigation are in line with those reported by Sonde et al (110), Platz (151) Restemeyer (97) and Sprigg (152) where patients were unable to demonstrate a superiority of LD and /or MPH compared to placebo. Sonde et al used an identical trial design as in our study and also found no benefit in the included 36 patients concerning the FM motor scale or the BI (110). Treig et al studied 24 patients in a nearly identical design and found no significant difference either between AMPH and placebo on the Rivermead Motor Assessment or Barthel Index (153).

The effectiveness of AMPH-like drugs on motor recovery might depend on the stage of disease. Studies that reported a beneficial effect of d-AMPH on motor recovery included patients early after stroke, i.e. 3–30 days post stroke (117,154) while in the present study patients in the LD and /or MPH groups entered the trial on average 9.3 weeks after stroke. Similar studies have failed to address the issue of the most favorable time to recruitment and the optimal therapeutic window remains to be elucidated (152). However, other trials that failed to report a promoting effect of AMPH on motor recovery recruited patients equally early after stroke i.e. < 3–10 days post stroke (155-156). Gladstone showed that duration between stroke onset and treatment session is a critical issue and it differs from the treatment sessions and its frequency (157).

Furthermore, timing between medication and exercise therapy has been similar in positive and negative trials i.e. exercise therapy has been provided within 3 hours of drug administration (84), or 120 minutes (151) or 60 minutes (153), as in this study, after drug administration.

Findings of study IV propose that dopaminergic neuromodulation combined with physical activity may improve mood in ischemic stroke Survivors. The results of this study are in line with those reported by Lazarus and colleagues in 58 MPH-treated chronic stroke patients (64). They demonstrated that in the MPH group, 53% of patients experienced remission of depressive symptoms and speed of response to treatment was significantly faster for the MPH group compared to a Nortriptyline group (2.4 days vs. 27 days). Moreover, Grade et al found that stroke patients receiving MPH 5-30 mg daily for three weeks, showed improvements in mood, however with no difference between the MPH and placebo groups regarding cognitive function assessed by MMSE (66).

6.3 STUDY LIMITATIONS

In study I our results could have been hampered by some issues. With the inclusion process attributable to the hospital-based design of the study, it might be that some stroke patients weren't identified because they weren´t admitted to hospital due to minor symptoms especially from surrounding suburban regions or they died before being admitted to hospital.

Study II had some limitations as well. It was not a population-based but multihospital-based study. Case finding was performed through screening of medical records probably excluding patients with mild stroke, because of not being admitted to hospital. Moreover, we did not have data on the severity of stroke and were not able to discriminate between different ischemic stroke subtypes, thereby not able to differentiate possible differences in risk factors among these subtypes.

We faced some problems with the patients' follow-up either by phone or by inviting them to our clinics. A main problem of not having a stroke registry system in Iran at all contributed to the problems with contacting the patients.

The main shortcoming of the interventional studies III & IV was the small sample size. We had similar difficulties with patient recruitment as other studies have faced due to a wide range of exclusion criteria. Although we chose wide inclusion criteria for stroke patients, more than 90% of screened stroke patients did not meet the initial eligibility criteria and were therefore excluded. The vast majority of non-eligibility reasons were

too long duration, death before recruitment to study, long-distance to hospital, severe concomitant disease, and refusal.

6.4 IMPORTANCE AND FUTURE DIRECTIONS

6.4.1 Implication for epidemiological stroke studies in Iran

The reported stroke morbidity and mortality figures of our studies could have consequences which need to be addressed in future research as well as in healthcare planning. In our study the one-month mortality in 2001 was 24.6 %, which is higher than that reported in developing countries and needs more consideration in future studies in Iran.

Our findings that HTN and DM were considerably more frequent in our study population than in the populations of other developing countries should also be addressed in future research. The findings of our research suggest that a more aggressive stroke prevention regime with low-cost treatments addressing risk factor reduction should be made widely available both on primary stroke risk prevention and secondary stroke prevention basis. Such intervention programs should be sanctioned and financed by local as well as national health care authorities focusing on conceptualization of health and illness so that those involved continue to adhere to ordinations and prescriptions by their medical doctors.

Departing from our results, we also strongly advice a shift from the current non-specified and general care facilities in our general hospitals to the establishment of stroke units and specific stroke rehabilitation centers.

In study II almost all patients were likely to go home after hospital discharge and only 2.2% of them were admitted to a nursing home; this is not surprising due to the lack of inpatient- and day-rehabilitation centers in Qom. Moreover, the Iranian hospital culture, not furnished with stroke units or registers, implies that the vast majority of patients post-discharge are cared for at home by family members with limited support from society or professional caregivers. The medical follow-up is performed by primary care physicians or out-patient visits at the hospitals by internists. Thus, we strongly recommend

establishing and equipping inpatient- and day-rehabilitation centers for stroke patients in the subacute phase of stroke.

We encountered some problems with the patients' follow-up which not having a stroke registry system in Iran was a significant contributor of our difficulties in contacting the patients. Therefore, we highly recommend the establishment of a stroke registry system in Qom and, hopefully, the whole country like in Western countries in order to optimize a well-functioning stroke service to stroke Survivor.

6.4.2 Implication for clinical trials

Despite some significant effects of our intervention study, especially the combination therapy, our findings don't support the routine use of MPH and/or LD in stroke rehabilitation. This "pharmacology rehabilitation" should be further studied with more and eligible stroke patients.

Our findings suggest a significant recovery of the BI for patients who received MPH + LD from baseline to 6 months compared to placebo. However, the interpretation of this result is complicated by the fact that the corresponding mean change of the FM motor score was not significant. It could be that the drug effect has more of a fortifying effect on the ischemic stroke patient resulting in improved functioning rather than a specific motor effect. FM scale is an index for impairment but relating its scores to disability is to be determined more completely. This issue should be considered in future clinical trials to better determine minimal clinical differences in stroke patients with different level of hemiparesis.

Moreover, as patients in this study were recruited on average two months after stroke, and there are large variations in motor abilities of patients, one could assume that the motor function prior to active drug intake was too "good" to show further improvement in some patients. Using a combination of FM and a specific activity measure (Chedoke-Arm and Hand activity Inventory) or a general activity measure (Chedoke-McMaster Disability Inventory) could give more information in future studies.

The potential of achieving further improvement and catching it through the scales could be reduced by a ceiling effect. However, FM seems to be more sensitive than the BI to

identify changes in disability. Because of its ceiling effect, the BI is less useful for assessing minor deficits at a high functional level and more useful for differentiating patients with more severe disabilities (34).

Forty five-minute sessions of physiotherapy may not have been sufficient to induce or support plastic brain changes. In a study by Scheidtmann et al. stroke patients receiving 100 mg LD per day for 3 weeks improved significantly more than the placebo-treated control group(8). Providing further time might contribute in greater recovery, even though, the treatment was well designed to follow the standards through physiotherapy as well.

We suggest that the lack of effect of MPH and/or LD on cognitive impairment might in part be related to the cognitive assessment scale, which is not sensitive enough to catch minor changes. MMSE as a standardized scale for assessment of cognitive function evaluates five areas of cognitive functions. Although it is sensitive to attention, recall and language, it does not encompass all the cognitive deficits and is particularly weak in its ability to measure executive functions such as abstract thinking, judgment, problem solving and perception (158). However, the depressed patients seemed to have cognitive benefits of treatment. This issue must be addressed in future studies with more sensitive cognitive impairment scales to detect minor differences.

In our study population the prevalence of depression was in line with that reported in other studies. Moreover, we had a significantly higher prevalence of depression in females than in males at baseline but gender did not have significant impact on outcome variables. However, further research with psychostimulants is needed to determine whether there are sex-specific differences with regard to response to treatment.
Studies that showed a significant effect of MPH and LD on mood and cognition recruited patients early after stroke i.e. 3– 40 days post-stroke while in our study patients entered the trial on average 65.6 days after stroke onset (66, 159-160).

The studies up to now are limited in a number of ways, and definitive conclusions cannot yet be made. Although MPH and LD affected ADL and mood function significantly in our study, the effect size was not large all the time. Larger and perhaps more consistent effects may be achieved with a higher dose of active drugs; more frequent and longer duration of treatments as well as recruitment of patients earlier after stroke onset,

improved patient selection regarding stroke localization and duration i.e. arteries affected and appropriate time window for intervention. Unfortunately the precise therapeutic dosage and duration of drug therapy is still unclear for stroke patients. Therefore, the best guideline is individual titration and careful monitoring of patients to avoid adverse effects.

Thus, further evaluation with large randomized, placebo controlled, double-blind trials are needed to more clearly assess the role of MPH and LD in neuropsychiatric sequelae after stroke.

Furthermore, to date, no clinical study testing AMPH-like medication in stroke has taken into account ischemic lesion size or localization. Gladstone showed that patients with moderate disability were more responsive to rehabilitation pharmacology than those with severe disability. According to animal studies small cortical lesions are more responsive to additional active drugs and this issue must be addressed in future cerebrovascular studies with a focus on total anterior circulation stroke and partial anterior circulation stroke.

Finally, regarding animal studies, AMPH-like treatments with focused activity and combined with an enriched environment could induce motor recovery and elicit measurable axonal outgrowth. This issue could be interesting and need to be further evaluated in clinical trials.

6.5 CONCLUSIONS

It was revealed that stroke incidence in our study was higher than in Western countries. One month case fatality in ischemic stroke patients was higher than in European countries but less than in developing countries. The discharge destination to home in our study was the most interesting difference compared to developed countries.

Our findings need to be considered in future health education programs in Iran, identifying patients at risk and focusing on more aggressive prevention programs to lower stroke incidence. We strongly recommend the establishing of a stroke registry, stroke units, primary and secondary stroke prevention as well as promoting rehabilitation facilities in Iran.

A daily administration of Methylphenidate +Levodopa combined with physiotherapy for 15 drug therapy sessions was safe and significantly improved mood status in ischemic stroke patients.

Ischemic chronic stroke patients having MPH and/or LD in combination with physiotherapy showed a slight ADL and stroke severity improvement over time.

Future studies should determine the optimal therapeutic window for and dosage of psychostimulants, as well as to identify those stroke patients who may benefit from such a treatment.

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9 APPENDIX

"INFORMATION SHEET"

Patient name: **Patient code: _____**

Age: _____
Sex: Male ☐ Female ☐ (Male=1 Female=0)
Address:

Phone number:

Date:
Admit to:

Primary diagnosis:

Date of onset Stroke symptoms_____

First stroke:	Yes ☐	No ☐	Yes=1	No=0
Paretic side:	Right ☐	Left ☐	Right=0	Left=1
Dominant Hand	Right ☐	Left ☐	Right= 0	Left= 1

***Vital Sign*:**

Blood Pressure: /

Temperature: ——— Heart Rate: ——— Respiratory Rate: ———

Length: …… cm **Weight: ……** kg

Daily estimated intake of coffee/tea, number of cups ……

Smokers Yes ☐ No ☐ (Yes= 1 No= 0)

Number of cigarettes / equivalents a day ……

Addiction Yes ☐ No ☐ (Yes= 1 No= 0)

***Current and earlier disease*:** (Yes= 1 No= 0)

Hypertension:	Yes ☐	No ☐
Diabetes mellitus	Yes ☐	No ☐
Ischemic heart disease (IHD)	Yes ☐	No ☐
Smoking	Yes ☐	No ☐
Lipid profile	Yes ☐	No ☐
History of TIA	Yes ☐	No ☐

Current medication:

……

……

……

……

……

……

Exclusion criteria:

	(Yes= 1	No= 0)
Hemorrhagic stroke	Yes ☐	No ☐
Cardiac failure	Yes ☐	No ☐
Non-controlled hypertension	Yes ☐	No ☐
Tachycardia (≥ 100 bpm)	Yes ☐	No ☐
Major cognitive deficit	Yes ☐	No ☐
Aphasia	Yes ☐	No ☐
Past history of epilepsies	Yes ☐	No ☐
Prominent agitation	Yes ☐	No ☐
Glaucoma	Yes ☐	No ☐
Extra pyramidal diseases	Yes ☐	No ☐
Psychosis	Yes ☐	No ☐
Hypersensitivity to MPH or LD		
Medication:		
Tree cyclic antidepressant	Yes ☐	No ☐
Anti-epileptics	Yes ☐	No ☐
Benzodiazepines	Yes ☐	No ☐
Neuroleptics	Yes ☐	No ☐
α-adrenergic antagonists or agonists	Yes ☐	No ☐

Physical Exam

Aphasia	☐	1. None
	☐	2. Broca
	☐	3. Wernicke
	☐	4. Global
Vision	☐	1. No disturbance
	☐	2. Some disturbance
	☐	3. Almost blind
	☐	4. Blind
Hearing	☐	1. No disturbance
	☐	2. Some disturbance
	☐	3. Deaf
Cardiac Rhythm	☐	1. Regular
	☐	2. Irregular
	☐	3. Extra beat
Pulmonary	☐	1. Normal
	☐	2. Rhonchus
	☐	**3**. Vesicular breathing
Peripheral Pulses	☐	1. Normal
	☐	2. Non palpable
Carotid and	☐	1**.** Normal
Vertebral Bruit	☐	2. Mild
	☐	3. Moderate
	☐	4. Severe

Patient is candidate for the study: **Yes** ☐ **No** ☐ (Yes= 1 No=0)

The patient accepted to participate in the study. All necessary information (oral and written) in this regards were received by the patients.

Name and Signature: _____ **Date: _____**