Randomized controlled clinical trials for the evaluation of efficacy and safety of Chinese medicine in treatment of neurodegenerative diseases

Ka Kit Chua
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Randomized Controlled Clinical Trials for the
Evaluation of Efficacy and Safety of Chinese Medicine
in Treatment of Neurodegenerative Diseases

CHUA Ka Kit

A thesis submitted in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

Principal Supervisor: Prof. LI Min
Hong Kong Baptist University
August 2015
DECLARATION

I hereby declare that this thesis represents my own work which has been done after registration for the degrees of PhD at Hong Kong Baptist University, and has not been previously included in a thesis or dissertation submitted to this or other institution for a degree, diploma or other qualification.

Signature: ____________________

Date: August 2015
ABSTRACT

Background: Neurodegenerative diseases (NDD) are very common in the aging population, of which Parkinson’s disease (PD) and Alzheimer disease (AD) are the two most common. Since the etiology of the neuronal death in these diseases remains unclear, currently no curative therapy is available. Traditional Chinese medicine (TCM) has been used to treat certain diseases, which based on their symptoms we now know that they are included PD and AD, for thousands of years. However, our pervious systematic review reports that the quality of current TCM clinical trials related to this area had limited internal validity due to methodological flaws and insufficient data reporting.

Methods: This study includes two add-on double-blinded randomized controlled trials (RCT), PD full-scale study and AD pilot study. It aims to provide evidence for the efficacy and safety of two specific TCM decoctions, Jia-Wei-Liu-Jun-Zi Tang (JWLJZT) and Di-tan decoction (DTD) in treating PD and AD, respectively. These clinical trials follow the Consolidated Standards of Reporting Trials (CONSORT) as well as the International Conference on Harmonization guidelines on Good Clinical Practice (GCP). Also, this two RCT obtained the approval from the Human and Animal Research Ethics Committee of Hong Kong Baptist University before the study and registered on the Chinese Clinical Trial Registry.

Result: In the PD trial, 111 idiopathic PD patients were randomly assigned to receive either JWLJZT or placebo for 32 weeks. Although there was not significant difference in the primary outcome of Movement Disorder Society – Sponsored Revision of Unified PD Rating Scale (MDS-UPDRS) Part I total score ($p = 0.216$), significant improvements was observed in the secondary outcome of Non-motor symptom assessment scale for Parkinson’s disease (NMSS) total score ($p = 0.019$), subtype of mood/cognition ($p = 0.005$) and hallucinations ($p = 0.024$). In addition, post-hoc analysis showed a significant reduction in constipation ($p < 0.001$). On the other hand, 40 AD patients were randomly assigned to receive either DTD or placebo for 24 weeks in the AD trial. There was an improvement trend in the primary outcome of the cognitive subscale of Alzheimer’s Disease Assessment Scale (ADAS-cog) total score in the DTD group though the difference relative to the placebo group was not statistically significant ($p = 0.315$). No significant difference was found in the secondary outcomes. Adverse events were mild and comparable between treatment and placebo groups in both trials.
**Discussion:** JWLJZT did show some improvement in non-motor symptoms, including mood, cognition, and constipation, in PD patients, while, DTD did show a reducing trend in the cognitive impairment based on rigorous RCT. Further study focusing on the effective dosage, pharmacologic mechanism of JWLJZT and DTD are needed to give a fuller picture as well as better support for using them in human being as a routine treatment. In fact, JWLJZT and DTD are the only two examples of TCM for treating NDD. These two clinical trials are served as examples of how to evaluate efficacy and safety of TCM for the treatment of various diseases using rigorous RCT methods and standard.

**Keywords:** Randomized Controlled Trials, Parkinson’s disease, Alzheimer disease, Traditional Chinese medicine, Jia-Wei-Liu-Jun-Zi Tang, Di-tan decoction, Efficacy, Safety
ACKNOWLEDGEMENTS

Becoming a Chinese Medicine teaching staff in the university has always been my aim and I endeavor to perform my best throughout my postgraduate study. I would like to express my heartfelt thanks for the following persons or groups for their generous support in helping my little dream, although it may not be possible to come true in reality.

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### International Conferences Presentations


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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
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<tr>
<td>AchE</td>
<td>Acetylcholine esterase</td>
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<tr>
<td>AchEI</td>
<td>Acetylcholinesterase inhibitors</td>
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<tr>
<td>AD</td>
<td>Alzheimer disease</td>
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<tr>
<td>ADAS</td>
<td>Alzheimer’s Disease Assessment Scale</td>
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<tr>
<td>ADAS-cog</td>
<td>Alzheimer’s disease assessment scale -cognitive subscale</td>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<td>AE</td>
<td>Adverse events</td>
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<tr>
<td>Akt</td>
<td>Akt murine thymoma viral oncogene homolog 1</td>
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<td>ALT</td>
<td>Alanine transaminase</td>
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<td>APOE</td>
<td>Apolipoprotein</td>
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<td>APP</td>
<td>Amyloid precursor protein</td>
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<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
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<td>A(\beta)</td>
<td>Beta-amyloid peptide</td>
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<tr>
<td>BBB</td>
<td>Blood brain barrier</td>
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<tr>
<td>C-DAD</td>
<td>Chinese version of Disability assessment for dementia</td>
</tr>
<tr>
<td>CDR</td>
<td>Clinical Dementia Rating Scale</td>
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<tr>
<td>ChAT</td>
<td>Acetylcholine transferase</td>
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<td>CMD</td>
<td>Chinese Medicine Decoctions</td>
</tr>
<tr>
<td>C-MMSE</td>
<td>Chinese version of Mini-Mental State Examination</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>COMT</td>
<td>Catechol-O-methyltransferase</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>COMT-I</td>
<td>COMT inhibitors</td>
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<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
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<td>Cory</td>
<td>Corynoxine</td>
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<tr>
<td>Cory B</td>
<td>Corynoxine B</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>DA</td>
<td>Dopamine</td>
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<td>DAD</td>
<td>Disability assessment for dementia</td>
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<td>DAT</td>
<td>Dopamine transporter</td>
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<td>DBS</td>
<td>Deep-brain stimulation</td>
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<td>DDC</td>
<td>Dopa decarboxylase</td>
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<tr>
<td>DDC-I</td>
<td>Dopa decarboxylase-inhibitor</td>
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<tr>
<td>DLB</td>
<td>Dementia with Lewy bodies</td>
</tr>
<tr>
<td>DOPAC</td>
<td>Dihydroxyphenylacetic acid</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>DSQ</td>
<td>Deficiency of spleen qi</td>
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<tr>
<td>DTD</td>
<td>Di-tan decoction</td>
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<td>FTLD</td>
<td>Frontotemporal lobar degeneration</td>
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<td>GI</td>
<td>Gastrointestinal</td>
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<td>H&amp;Y</td>
<td>Hoehn and Yahr</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>HMGB 1</td>
<td>High mobility group box 1</td>
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<td>iNOS</td>
<td>Inducible nitric oxide synthase</td>
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<td>JWLJZT</td>
<td>Jia-Wei-Liu-Jun-Zi Tang</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>LB</td>
<td>Lewy bodies</td>
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<tr>
<td>L-dopa</td>
<td>Levodopa</td>
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<tr>
<td>LOFC</td>
<td>Last-observation-carried-forward</td>
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<td>LRRK2</td>
<td>Leucine-rich repeat kinase 2</td>
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<tr>
<td>MAO-B</td>
<td>Monoamine oxidase-B</td>
</tr>
<tr>
<td>MAO-B-I</td>
<td>MAO-B inhibitors</td>
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<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
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<td>MDS</td>
<td>Movement Disorder Society</td>
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<td>MDS-UPDRS</td>
<td>Movement Disorder Society – Sponsored Revision of Unified PD Rating Scale</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<tr>
<td>MPTP</td>
<td>1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Motor symptoms</td>
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<tr>
<td>MSA</td>
<td>Multiple system atrophy</td>
</tr>
<tr>
<td>mTOR</td>
<td>Mammalian target of rapamycin</td>
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<tr>
<td>NDD</td>
<td>Neurodegenerative diseases</td>
</tr>
<tr>
<td>NFT</td>
<td>Neurofibrillary tangle</td>
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<td>NINCDS-ADRDA</td>
<td>National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate antagonist</td>
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<tr>
<td>NMS</td>
<td>Non-motor symptoms</td>
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<tr>
<td>NMSS</td>
<td>Non-motor symptom assessment scale for Parkinson’s</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>NO</td>
<td>Nitric oxide</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PGC-1α</td>
<td>Peroxisome proliferator-activated receptor-gamma coactivator - 1alpha</td>
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<tr>
<td>PINK1</td>
<td>PTEN-induced putative kinase 1</td>
</tr>
<tr>
<td>PS1</td>
<td>Presenilin 1</td>
</tr>
<tr>
<td>PS2</td>
<td>Persenilin 2</td>
</tr>
<tr>
<td>PSP</td>
<td>Progressive supranuclear palsy</td>
</tr>
<tr>
<td>PTOO</td>
<td>Phlegm turbidity obstructing the orifices</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>ROS</td>
<td>Reactive oxygen species</td>
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<tr>
<td>SFOT</td>
<td>Serum glutamic oxaloacetic transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum glutamic pyruvic transaminase</td>
</tr>
<tr>
<td>SNpc</td>
<td>Substantia nigra pars compacta</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>TCM</td>
<td>Traditional Chinese Medicine</td>
</tr>
<tr>
<td>UKPDSBB</td>
<td>United Kingdom Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria</td>
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<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
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<tr>
<td>VD</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER I: General Introduction

1.1 Background

Neurodegenerative diseases (NDD) are one of the most common diseases [1]. They are debilitating disorders of the nervous system affecting about 30 million people around the world [2]. It is defined as deterioration in the intellectual and cognitive faculties [3] and characterized by progressive nervous system dysfunction due to deposition of abnormal proteins and degeneration of the neural cells [4]. Although imaging techniques may provide useful adjunctive information, diagnosis of NDD are largely based on careful clinical assessment [5]. There is a spreading process hypothesis of the abnormal proteins within the brain [6]. However, the causes of most NDD remain unknown [3], and no effective treatments or cures are available for most of the NDD [7].

Generally speaking, aging is the biggest risk factor for most NDD [8]. Aging not only makes people more prone to NDD, but also impairs their ability of self-repair [9]. Accordingly, more people may suffer from NDD due to increase in lifetime expectancy. It may cause a great economic stress to the world [10]. It is predicted by the World Health Organization (WHO) that NDD will overtake cancer to become the second leading cause of death in 2040 [11].
Parkinson’s disease (PD) and Alzheimer disease (AD) are the two most common NDD in humans [12]. Since the etiology of the neuronal death in these diseases still remains unclear, currently no cure is available [2]. Traditional Chinese Medicine (TCM) has been used for thousands of years to treat some symptoms that are now known to be associated with PD and AD [13]. A number of Chinese medicine decoctions (CMD), which may be useful in relieving these symptoms, is listed in the Chinese Medicine textbook [14]. However, our previous systematic reviews report that the quality of current TCM clinical trials related to this area had limited internal validity due to methodological flaws and insufficient data reporting [15-18]. Therefore, a rigid randomization in controlled trials with adequate blinding is needed to prove beyond doubt the value of TCM for NDD.

1.2 Purpose of the Research

This study will provide clinical evidence for the use of TCM in treating PD and AD by RCT. The efficacy and safety of TCM in treating NDD will be evaluated. Also, it may overcome the limitations of current conventional medication.
1.3 Outline of the Thesis

This thesis is divided into two parts: Part 1 (chapter II) for PD and Part 2 (chapter III) for AD. Both of them were Randomized Controlled Trial (RCT), and also for both, the standard of Consolidated Standards of Reporting Trials (CONSORT) was followed. In addition, these studies were done in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice, and had applied for the approval from the Ethics Committee of Hong Kong Baptist University’s Institutional Review Board (code: HASC/09-10/09 for PD and HASC/11-12/24 for AD). Written informed consent was obtained from every patient before they participated in any study-related activity, and all consent documents were approved by the relevant review boards for each participating institution. A general flowchart of the patient recruitment is shown as follows (Figure 1):
Randomization

Patients fulfilled the inclusion and did not fulfill exclusion criteria

Patients did not fulfill the inclusion or fulfill the exclusion criteria

Agreed to participate

Disagreed to participate

Randomization

CMD group

Placebo group

Exclusion

Figure 1: Flowchart of patient recruitment for PD and AD clinical trials
CHAPTER II: A Randomized Controlled Trial (RCT) of JiaWeiLiuJunZiTang (JWLJZT) on treating Non-motor Symptoms in idiopathic Parkinson’s disease

2.1 Literature Review of Parkinson’s disease (PD)

2.1.1 Introduction

PD was first reported by James Parkinson in the classic “Essay on the Shaking Palsy” in 1817. It is an insidious and the second most common NDD with slowly progressive and intense loss of neuro-melanin containing dopaminergic neurons in the substantia nigra pars compacta (SNpc). Lewy bodies (LB) and dystrophic Lewy neurites may be found in the neuron of PD brain [19]. Clinically, it contains motor and non-motor impairments. For motor symptoms (MS), resting tremor, rigidity, bradykinesia and loss of postural reflexes are the four major symptoms. For the non-motor symptoms (NMS), it mainly include cognitive, autonomic and psychiatric problem.

2.1.2 Epidemiology

The prevalence of PD is around 0.3% of the whole population [12] and incidence is around 20 per 100,000 per year [20]. Both prevalence and incidence may
increase with age. Around 0.2-5.7% of people who were aged from 60 to 65 in the world suffered from PD in 2011 [21]. A study of the Chinese population in Hong Kong reported that prevalence among aged $\geq 55$ years was about 0.5% [22]. It is estimated that the number of people suffering from PD over age 50 was between 4.1 and 4.6 million in 2005 and will become double to between 8.7 and 9.3 million in 2030 [23]. Normally, it is rare to get onset before 50. However, it is increased sharply once elder than 60. Generally speaking, PD male patients are more than PD female patients. Incidence studies showed a male to female ratio of about 1.46 to 1.49 [24, 25]. Also, prevalence of PD may increase with distance from equator. This may or may not relate to the ethnic difference as there is no evidence for it.

2.1.3 Etiology

Aging always being a risk factor of developing PD, however, the actual reason is still unknown. Only losing of dopamine (DA) neuron more than 50% as well as losing of DA more than 80% may lead to appearance of PD symptoms [26]. Although a subject who has first degree relatives suffering from PD may has 2 to 3 times risk developing PD than normal, more than 90% are sporadic [27]. Only PD patient who has onset with age 50 or before is more likely to have significant
genetic component. It is hypothesized that the etiology of PD should be multi-factorial. Possibly, PD subjects may have genetic deface predisposition and becoming sensitive to environmental factors like toxins. This may increase the oxidative stress and causing mitochondrial derangement as well as neurotransmitter distribution imbalance. It results in apoptosis of neural cell and manifestation of symptoms of PD [21].

2.1.3.1. Genetic factors

As only a small proportion of PD patients may have family history of PD, the exact causative gene is still uncertain. To date, 18 genes already were reported to be related to PD, and only five of them are defined relatively clearly. Generally speaking, most of them are associated with autosomal dominant or recessive PD. These phenotypes may share some common underlying mechanisms for both sporadic and familial cases [28]. However, there is still lack of data and research to indicate the penetrant genes of all PD, especially the sporadic PD.
I) Gene associated with autosomal dominant PD

i) PARK1 (α-synuclein)

α-synuclein is a natively unfolded presynaptic protein. It may be response to the synaptic vesicle recycling, storage and compartmentalization of neurotransmitters. It is the major component of LB [29]. Mutations in PARK 1 gene were associated with typical loss in α-synuclein and aggregate of LB. It may present in some family cases or even sporadic cases.

ii) PARK8 (leucine-rich repeat kinase 2, LRRK2)

LRRK2 gene is the most common PD gene known and accounting for more than 10% of dominant cases as well as about 4% of sporadic cases [30]. The most common mutation point of LRRK2 is G2019S, while the penetrance of it is age-dependent [21]. LRRK2 gene may be response to the synaptic vesicle recycling, neurite outgrowth and function inherent to Gogli body, lysosomes and mitochondria [31]. Dysfunction of LRRK2 may have a negative impact on the dopaminergic neuron survival.
II) Gene associated with autosomal recessive PD

i) PARK2 (Parkin)

Mutation of Parkin gene present in about half of autosomal recessive early-onset cases, while it also been detected in some late-onset cases [32]. Parkin gene is an E3 ubiquitin protein in the ubiquitin proteasome pathway for degradation. One of the substrates of Parkin is the glycosylated form of α-synuclein [33]. Some report suggested that Parkin gene may be responsible for the neuro-protecting effect. Mutation in it may result in losing of neuro-protecting ability as it may hamper the normal turnover of damaged mitochondria [34].

ii) PARK6 (PTEN-induced putative kinase 1, PINK1)

PINK1 is related to early-onset family PD cases [35]. Point mutations were reported in the PINK1 gene of family cases, but rare in sporadic cases. About 0.5 to 9% early-onset cases were detected with PINK1 mutations [21]. It is relatively less common than Parkin gene mutations. PINK protein may be responded for protecting neurons from mitochondrial dysfunction caused by proteases inhibitors [35]. Mutations in PINK1 may lose the protecting function.
iii) PARK7 (DJ-1)

Mutations in DJ-1 gene were found in early-onset PD [36]. Point mutations and large deletions were also been reported. It is relatively lesser proportion of cases than Parkin and PINK1. The function of DJ-1 gene is not known completely. It is suggested that it may be involved in the oxidative stress response pathway as an antioxidant protein [37] or a scavenger [38].

2.1.3.2. Environmental factors

Long team exposure to the heavy metals may be a risk factor for PD as metals may interact with the α-synuclein to cause fibrillation. Nevertheless, the evidence was insufficient [21]. On the other hand, some report suggested that smoking, physical activity, consumption of alcohol, tea or coffee may be protective against PD. However, the mechanism is not confirmed yet [39].

It is much commonly accepted that herbicides and pesticides may be a possible risk factor for PD. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a neurotoxin which had been used in agriculture. It was proved that MPTP can cause irreversible Parkinsonism, in human being by selective damage the
nigrostriatal dopaminergic [40]. The toxins form MPP+ is generated by the action of monoamine oxidase-B (MAO-B) and then accumulate in the mitochondria. This may result in the breakdown of DA to generate excessive \( \text{H}_2\text{O}_2 \), which may form hydroxyl radicals leading to cell damage [41]. Nevertheless, apart from MPTP, no other herbicides or pesticides are confirmed to be a risk factor for PD.

### 2.1.4 Pathogenesis

The mechanism in the pathogenesis of PD is still unknown. It is suggested that PD is a mixture of deleterious mechanisms taking place both inside the degeneration neurons (cell-autonomous mechanisms) and outside the degeneration neurons (non-cell-autonomous mechanisms) [28].

#### 2.1.4.1 Cell-autonomous mechanisms

It is the mechanisms take place inside dying neurons. Traditionally, it includes oxidative stress, protein aggregation, defects in the ubiquitin-proteasome pathway and autophagy, these majorly related to the mitochondria including alterations in mitochondrial bioenergetics, dysregulation of calcium homeostasis and impaired turnover of mitochondria [28].
I) Alterations in mitochondrial bioenergetics

PD has strong association with a lot of bioenergetics including glucose metabolism and mitochondrial oxidative phosphorylation [42]. Peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) is a transcriptional coactivator modulates the gene governing mitochondrial bioenergetics and oxidative metabolism [43]. Deregulation of PGC-1α may result in a defect of bioenergetics and ultimately neuronal degeneration. Mutation of Parkin may lead to down regulation of PGC-1α [28].

II) Dysregulation of calcium homeostasis

It was reported that great calcium conductance in dopaminergic neurons was associated with increased intra-mitochondrial production of reactive oxygen species (ROS) [44]. ROS may further induce the mutation of Parkin and result in dysfunction of mitochondria.

III) Impaired turnover of mitochondria

Damaged mitochondria may be disposed by macro-autophagy, which is important to maintain the health of mitochondria and the energy demand of
neurons. Mutation of Parkin might prevent damaged mitochondria being effectively eliminated and lead to neuronal dysfunction or even death [45].

2.1.4.2 Non-cell-autonomous mechanisms

These are the mechanisms including the spread of pathology, especially the \( \alpha \)-synuclein, and neuro-inflammatory processes [28].

**I) Spread of pathology**

LB and Lewy neurites, which are misfolded and aggregated proteins mainly formed by \( \alpha \)-synuclein, are found in SNpc and even in non-DA brain nuclei as well as the periphery [46]. The accumulation of \( \alpha \)-synuclein may lead to decreases in synaptic proteins, progressive impairments in neuronal excitability and connectivity or even neuron death. Cell death of dopaminergic neurons in the SNpc and appearance of LB in the surviving neurons is the pathological hallmark of PD. There are 3 possible pathways that \( \alpha \)-synuclein may spread from the affected neuron to a health neuron by a “prion-like” process. Firstly, it may secrete from neurons vesicles and biological fluids by exocytosis [47]. Secondly, it may transport by the neuro-blastoma cell lines [48]. Thirdly, the preformed fibrils
generated from full-length and truncated recombinant α-synuclein may enter primary neurons and promote recruitment of soluble endogenous α-synuclein into insoluble inclusions reminiscent of LB [49]. Nevertheless, the distribution of the α-synuclein does not correlate with the disease duration and does not explain the progression of clinical severity of the disease [50].

II) Neuro-inflammatory processes

The levels of pro-inflammatory cytokines are increased in the substantia, striatum and cerebrospinal fluid in the PD brain [51]. However, the actual reason, mechanism and stage of the inflammation causing DA neurons deaths are still unknown. Synthesis of high level nitric oxide (NO), which is toxic to neurons, is controlled by inducible nitric oxide synthase (iNOS) [52]. It is suggested that the density of glial cells was increased by expressing iNOS [53], which iNOS is activated by the pro-inflammatory cytokines in the SNpc of PD brain.

2.1.5 Clinical Manifestations

PD is an insidious onset paradigmatic movement disorder; however, it not only affects the areas of dopaminergic nigrostriatal system but also the whole brain. It
has asymmetrical presentation. It was reported that slightly more PD patients in Hong Kong have symptoms on the right side initially [39]. Symptoms wise, PD can be divided into MS and NMS.

2.1.5.1. Motor symptoms (MS)

MS are the most common features that are well-recognized by people. There are four major symptoms of MS:

**I) Resting tremor**

It is the most commonly recognized feature which 75% of PD patients may present this as the first motor symptom [54]. Usually it begins in the distal upper extremity and most prominent when sitting or relaxed with “Pill-rolling” action. It is relatively slow when compare to other kinds of movement disorder with frequency of 4-6 Hz, while, younger patient may have a little bit higher frequency.

**II) Rigidity**

PD patients may resistance to passive movement for both extensors & flexors throughout whole range of motion. It may also call as lead pipe rigidity. When it
combined with tremor, “ratchet” sensation (cogwheel rigidity) can be detected by examiner during passive movement examination of the limbs.

III) Bradykinesia

It is the key diagnostic feature of PD in the United Kingdom Parkinson’s Disease Society Brain Bank Clinical Diagnostic Criteria (UKPDSBB), which all PD patients must contain this symptom. Bradykinesia means the decrease ability to move quickly or even motor freezing. They may be difficult or inability to initiate movement or continue the movement once stopped. When it combines with rigidity, it may result in much more MS like hypohonia, drooling, facial masking and micrographia.

IV) Impaired postural reflex

It is consider as a conclusive result of the late feature of MS in PD. PD patients may reduce the arm swing, foot stride and height during walking. Festination is a specific term and condition describing the walking feature of PD patient.
2.1.5.2 Non-motor symptoms (NMS)

Although medical therapy of MS may result in NMS, some NMS, including olfactory dysfunction, depression and constipation, can be present at the early stage or even before the MS [55]. Generally speaking, NMS are present in all stages of PD, while, patients may have much more NMS when the disease progresses. Fatigue, constipation and pain may be more common and severe in women, but daytime sleepiness and problems in having sex may be more prevalent and severe in men [56]. On the other hand, some NMS, including fatigue, difficulty falling sleep, hallucination, gastrointestinal impairment and urogenital dysfunction, may become worse with the disease duration [57]. These cause major complaints and treatment challenges in advanced stages of PD.

I) Disturbance of autonomic nerve

i) Orthostatic hypotension

Patients may feel dizzy when getting up from a chair or bed due to reduced ability in blood pressure regulation. It is an important symptom of PD but could be worsened by most dopaminergic treatment [58].
ii) Gastrointestinal (GI) impairments

Nausea and constipation are the common GI impairments in PD. Nausea is a common side effect of dopaminergic treatment which may be the result of stimulating the area postrema [59]. Constipation is very common in PD as the intestinal transit time of most PD patients may be prolonged. It is nearly universal and may be worsened by the medical therapy. Some research suggests that constipation may even earlier than MS in some PD patient [60]. It always causes a great negative impact on the PD patient quality of life (QoL) [61].

iii) Urogenital dysfunction

It is a common problem particularly in males [62]. PD patients may have frequency, irritating symptoms, urge incontinence and urgency of urination. For the male PD patients, they may also have the obstructive symptoms with hesitancy and weak urine stream. Some may also have sexual dysfunction such as erectile failure and premature ejaculation [63].

II) Cognitive impairment

Although it is rare in the early stage of PD, about 30% of PD patients may
suffer from dementia [64]. They have 2 to 6-fold higher probability than normal to have dementia [65]. It is related to the frontal lobe functioning, with slow information processing, executive dysfunction, attention dysfunction, visual-spatial dysfunction, memory retrieval and verbal fluency dysfunction [55]. This is not directly related to the DA deficiency but related to the degeneration of ascending cholinergic pathways. Hippocampus, thalamus and anterior cingulate are most affected in the PD with dementia.

III) Psychiatric impairments

i) Psychosis

Psychosis is rare to occur in the early stage of PD, but may begin 10 years after diagnosis [55]. As LB is the major pathology of PD, symptom of psychosis is commonly in form of visual hallucination. It is well formed, rich in detail and colorful. It could be presented in the late stage of PD or as an adverse event (AE) of the medical treatment but may not associate to the level of Levodopa (L-dopa) in the serum [58]. Acoustic and tactile hallucination is less common.
ii) Depression

About 40% PD patients may have the symptoms of depression [66]. It may even earlier than MS. Mostly they may only have mild to moderate depression, but about 25% may suffer from major depression [67]. They are losing the ability to feel joy and pleasure more commonly during the off-state, while lesser during the on-state. Suicide thoughts are common but the attempts to suicide are uncommon [68]. This may relate to serotonergic deficits and loss of mesolimbic dopaminergic innervation.

iii) Apathy

It is common in PD characterized by lack of motivation and hopelessness. It may be related to the prefrontal lobe dysfunction [58].

iv) Fatigue

PD patients may common have over-whelming sense of tiredness, lack of energy or exhaustion feeling. These symptoms may be secondary to other NMS (i.e. sleep disorders), drug effect (i.e. DA agonists), or other medical illness [58].
IV) Sleep disorders

It is one of the most prevalent NMS occurring in 60 to 98% of PD patients [69]. PD patients may be frequency awakenings or difficulties falling asleep. This could be a result of painful dystonia or nocturnal cramping. However, they may have excessive daytime sleepiness, which is also linked to the dopaminergic treatment. Sleep disorder is a known AE of most anti-parkinsonism medication, except the MAO-B inhibitors [58].

V) Sensory symptoms

i) Olfactory dysfunction

It is an early clinical NMS of PD which about 90% of early-stage PD cases may suffer from it [70]. However, it may not a characteristic in young-onset patients [71]. It may relate to hyposmia and LB disorder or synucleinopathies. The exact pathophysiology causing is unclear.

ii) Pain

It is a common complaint in PD. It could be dystonic pain, which is the
complication of L-dopa treatment, or non-dystonic pain, which may be related to the degeneration of brain caused by LB [58]. For dystonic pain, it may occur in the later stage of PD with extremely rigid, cramping and painful muscles. For non-dystonic pain, it may be associated with younger onset PD with abnormal feeling of numbness, burning, coldness, tingling, aching, heat and pain.

2.1.6 Diagnosis

PD is an irreversible, slowly progressive worsening movement disorder. Currently, there is no biological marker for diagnosis of PD. It is still mainly relay on the clinical signs and symptoms. UKPDSBB or also called The Queen Square Brain Bank Criteria is commonly used to diagnosis PD clinically with up to 90% accuracy [39, 72]. It contains three parts, i) diagnosis of parkinsonism, ii) exclusion criteria for PD and iii) supportive prospective positive criteria for PD. Here are the diagnostic criteria:
2.1.6.1 The UK PD Society Brain Bank clinical diagnostic criteria [73, 74]

**Step 1: Diagnosis of parkinsonian syndrome**

Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)

And at least one of the following:

- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

**Step 2: Exclusion criteria for Parkinson's disease**

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of a cerebral tumor or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

**Step 3: Supportive positive criteria of Parkinson's disease**

Three or more required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side onset most
- Excellent response (70%–100%) to L-dopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more
- Hyposmia
- Visual hallucinations
2.1.6.2 Ancillary investigations

The diagnosis of PD is still mainly focus on clinical signs and symptoms. The use of ancillary investigations is mainly used to rule out other diseases. Blood test is used to eliminate the possibility of metabolic disease like thyroidism. Magnetic resonance imaging (MRI) or computed tomography (CT) is used to rule out brain tumors or any other brain diseases. Single photon emission computed tomography (SPECT) scan or positron emission tomography (PET) scan can be used to diagnosis PD, but it is not commonly used as it is too expensive. There is decrease efficiency of dopamine transporter (DAT) and decrease synthesis of DA. Biomarkers for PD in the cerebrospinal fluid (CSF) still need further clarify [75].

2.1.7 Differential diagnosis

Although the overall diagnostic accuracy of PD is pretty high, the rate of misdiagnosing some atypical neuro-degenerative parkinsonian disorders as PD is as high as 20-30% in the early stages [76]. Generally, these atypical neuro-degenerative parkinsonian disorders are characterized by more rapidly progressive parkinsonism associated with early postural instability, poor reaction to L-dopa treatment and some clinical features that are not common in PD.
2.1.7.1. Secondary Parkinsonism

The cause of PD is still unclear, while there should be a clear cause of parkinsonism in the secondary parkinsonism. The MS could be induced by some medication or caused by brain injury whatever due to infection, toxic or trauma. In some cases, like drug-induced parkinsonism, symptoms could be cured by removing the causing drug. However, in most cases like the boxing champion Muhammad Ali is suffering from Parkinsonism due to head trauma, symptoms could not be cured as the brain was injured permanently.

2.1.7.2. Parkinson plus syndrome

These kinds of diseases may share some similar features in the early stage, but mostly are ineffective to L-dopa treatment.

I) Multiple system atrophy (MSA)

It is a degenerative disorder of the central and autonomic nervous systems characterized by abnormal α-synuclein aggregation in oligodendroglia and neurons [76]. Parkinsonian features predominate in 80% of patients (MSA-P subtype) associated with striatonigral degeneration while cerebellar ataxia is the
major motor feature in 20% of patients (MSA-C subtype) associated with olivopontocerebellar atrophy [77]. Progressive akinesia and rigidity is the dominated parkinsonism feature of MSA. Resting tremor is less commonly in MSA, but postural stability is compromised early on.

II) Progressive supranuclear palsy (PSP)

It is a sporadic NDD defined neuro-pathologically as tauopathy with prominent subcortical neurofibrillary degeneration [76]. Besides responds poorly to L-dopa, the clinical hallmarks also included ophthalmoplegia, recurrent falls and dementia. Rigidity is uncommon in the limbs but serious in the body trunk (axial rigidity).

III) Dementia with Lewy bodies (DLB)

Dementia could be present in PD, but relatively uncommon in the early stage. DLB patient may have both dementia and parkinsonism in the early stage. Tremor is not common in DLB but hallucinations are common.
2.1.8 Management

Currently, there is no cure method of PD. Management is mainly aim at improving the motor condition to maintain the QoL.

2.1.8.1. Physical treatments

This includes physiotherapy, hydrotherapy or physical exercises. PD patients are suggested to keep their normal daily life as much as possible. Physical training is applicable in most stage of PD, especially in the early stage as early use of pharmacological or neurosurgical treatments are usually not highly recommended [39]. Physical treatments can enhance the active movement.

2.1.8.2. Pharmacological treatments

I) Levodopa (L-dopa)

Although there are many new drugs developed, L-dopa is still the most efficacious drug and still being the gold standard [78]. It can replace the endogenous deficient neurotransmitter in PD as it is an amine precursor of DA. However, it is being metabolism by the dopa decarboxylase (DDC) and catechol-O-methyltransferase
(COMT) [39]. DDC is not only present in central nervous system (CNS), but also in other organs and blood vessels. If the drugs reacted at peripheral, it not only cannot pass through the blood brain barrier (BBB) to act in the brain, but also may induce a lot of unwanted effect. By blocking the enzyme (aromatic acid decarboxylase) catalyses conversion L-dopa to dopamine peripherally, it may increase the efficacy and safety of L-dopa. Hence, L-dopa is now used as combined with dopa decarboxylase-inhibitor (DDC-I) to reduce systemic side effects. Madopar and Sinemet are the two commonly used L-dopa drugs. Nevertheless, the improvement by L-dopa may only continue for about 5 to 10 years. Exogenous DA source can generate a storage in the remaining nigral neurons that is sufficient to maintain a steady supply to the striatal receptor. It is called the “L-dopa honeymoon period” [79]. Also, the effect may much reduce and the patients may suffer from disabling motor complications in the long-term administration of L-dopa. Food rich in protein is not recommended to intake with L-dopa as protein may compete for carrier system with L-dopa [79]. The common side effect of using L-dopa includes orthostatic hypotension, psychiatric symptoms and gastrointestinal impairment.
Complication

Although L-dopa is golden standard of treating PD, it may induce serious AE during long-term consumption. The presence of motor fluctuations and dyskinesia is about 40% after using the L-dopa for 5 years [80] and 70% for 15 years [81]. The positive effect of L-dopa is largely reduced and even gives a great negative impact on the QoL of PD patients. These AE may affect by several variables like the onset age of PD, initiation time of L-dopa therapy, duration of L-dopa treatment and the total daily dose of L-dopa.

i) Motor fluctuation

The exact mechanism of motor fluctuation is not known completely yet. Some suggested that it may be related to the DA storage in the brain [82]. Since the presynaptic dopaminergic neurons loss continually, the capability of synthesis, storage and reuptake of DA in striatum become much diminish. It reduces the buffering capacity to compensate the fluctuations of L-dopa levels in the plasma. The synaptic DA concentration is directly dependent on the availability of L-dopa. As a result, motor fluctuation may appear if there is any concentration change in the intake L-dopa [79]. It is called “on” when the patient with good effect of
L-dopa, while it is called “off” when the patient without the effect of L-dopa.

There are several subtypes of motor fluctuation:

a) Wearing off / end of dose deterioration

The effect duration of L-dopa becomes much shorter than before. Symptoms and signs of parkinsonism are re-emergence before the next dosage of L-dopa.

b) Random on-off phenomenon

The symptoms and signs of parkinsonism may be worse and improved suddenly. Parkinsonism may re-emergence suddenly during the effective period of L-dopa (off). The parkinsonism may then be suppressed suddenly without further intake of L-dopa.

c) Delayed on

L-dopa takes longer time than usual to give beneficial effect.

ii) Dyskinesia

It is an involuntary movement including chorea, dystonia, ballism, stereotypies, tics and myoclonus. The mechanism is not fully understood yet. Some suggested that it is due to a complex interaction between the fluctuating striatal DA level and its differential stimulation on the subtypes of receptors,
which including agonistic and antagonistic, distributes abnormally in the degenerating striatal pathways [79]. It may be related to the disease duration and the dosage of L-dopa [83]. There are few subtypes of dyskinesia:

a) Peak dose dyskinesia

Dyskinesia occurs during the peaks concentration of L-dopa in plasma. It may even present at the whole “on” time when therapeutic window becomes narrow. Patients may often present as chorea and ballistic [79].

b) Low dose dyskinesia

Dyskinesia occurs during the low concentration of L-dopa in plasma. Patients may often present as typically painful dystonia [79]. The muscles are extremely rigid and cramping. It is commonly occur in the lower limbs in the morning.

c) Diphasic dyskinesia

It is also called as “DID” phenomenon (dystonia-improvement-dystonia). It is linked to a critical L-dopa plasma level and emerges at the transition between rising and falling phase of drug concentration. Patients may often present as missed pattern of chorea, ballism and dystonia [79].
II) Dopamine agonists (DA agonists)

It used to be an adjuvant therapy of L-dopa in treating PD after the present of motor complications, it become much commonly use or even become the main monotherapy drug in treating PD during the early and moderate stage now [79]. It is a mimic of the natural action of DA in the brain which may stimulate the DA receptors directly without the need of metabolic conversion. Hence, it may have lesser unwanted side-effect than L-dopa theoretically [39]. Also, generally speaking, it has long half-life and result in longer duration of action than L-dopa. It may divide into ergot derivatives and non-ergot derivatives, while non-ergot derivatives, like Pramipexole and Ropinirole, are much commonly used in the market. Common side effects may due to stimulate the medulla like nausea, vomiting, postural hypotension, dizziness, bradycardia, leg edema, and other signs of autonomic peripheral stimulation.

III) L-dopa augmentative drugs

i) COMT inhibitors (COMT-I)

As L-dopa mainly metabolized by DDC and COMT, the use of COMT-I is to prolong the L-dopa half-life in plasma and increase the available amount of
L-dopa in the brain by reducing the metabolism of L-dopa in peripheral [84]. Although it does not reduce the time of L-dopa to get to the peak dose or increase the concentration of L-dopa, it does reduce the dosage of L-dopa. Hence, COMT-I is used as an adjuvant therapy of L-dopa and commonly used for patients suffering from motor fluctuation. Entacapone is the only used COMT-I in the market now. It could prolong the “on” time when it is used with L-dopa [39]. It is now commonly used as a combined drug (Stalevo) with L-dopa in treating PD. The main side effect of COMT-I are nausea and orange discoloration of urine. Patients may also has sleep disturbance and worsening in dyskinesias.

ii) MAO-B inhibitors (MAO-B-I)

It selectively & irreversibly inhibits the intra-cellular and extracellular MAO-B function. It may diminish the breakdown of DA to H₂O₂ and dihydroxyphenylacetic acid (DOPAC). It can use as an adjunctive therapy of L-dopa to reduce the L-dopa dose. Nowadays, it is much commonly used as a monotherapy in the early PD to delay the development of disabilities requiring L-dopa [85]. Side effect may include nausea, orthostatic hypotension, dyskinesia and psychiatric problem. Selegiline and Rasagiline are the two commonly used MAO-B-I in the market.
iii) Anticholinergics

It is commonly used in controlling the tremor condition of PD by reversing the process of cholinesterase inhibitors penetrate the brain [39]. It can inhibit the DA reuptake in the striatum. It is relatively suitable for younger patient with tremor as main symptom, but should not be used in PD patient with dementia [86]. Common side effects may include dry mouth, urinary retention, glaucoma, blurred vision and constipation. Artane is the most commonly used anticholinergics in Hong Kong.

iv) Amantadine

It is an antiviral agent with the effect of anticholinergic and possibly dopaminergic and anti-glutaminergic [39]. Mostly, it may use to control the symptom of akinesia, rigidity and resting tremor. However, the precise mechanism still remains unknown. Some report suggested that it may be neuro-protective with long-term use. Another report suggested that it may have anti-dyskinetic effect at high dose [87]. Side effects mainly relate to neuropsychiatric symptoms like insomnia, hallucinations and nightmares.
2.1.8.3. Neurosurgical treatments

Surgery aims at restoring the balance in neurophysiological circuit. It tries to control the activity of subthalamic nucleus and globus pallidus interna. By correcting the imbalance of the basal ganglia circuitry, it may improve the movement of PD patients. In the past, surgery includes the use of destructive agents, like thermal or chemical, to damage the target side. It had been suspended due to permanent and serious side effect.

Deep-brain stimulation (DBS) is now the primary method using in the PD surgery [88]. It is established in the treatment of advanced PD patients who are having good response to L-dopa but with serve motor complication. The most common target is subthalamic nucleus. It may reduce most MS significantly, especially increasing the percentage of “on” time without involuntary movement. Also, it may enhance the QoL of PD patient and reduce the use of L-dopa [89]. Nevertheless, it does not affect the disease progression. Some patient may develop mood or cognitive disorder after the surgery [90]. PD patients with dementia or emotional instability are not recommended to do DBS. Also, the cost for DBS is expensive and the battery has to be replaced in about 5 years.
2.1.9 Prognosis

Although PD is a slow progress NDD, some report showed that women PD patients may have slightly faster progression than men [91]. The duration for development of wearing off and dyskinesia were shorter in women. On the other hand, young-onset PD patients showed longer duration to reach more advanced stages (III, IV and V) but shorter duration to have wearing off and dyskinesia [91].

Normally, PD may not cause death directly. However, it does have negative impact on the patient health. Some report suggested that there was two-fold increased risk of death due to pneumonia or cachexia in PD patients comparing to people without NDD [92]. Consistent with the about report that women PD patients had faster progression than men, women PD patients also had slightly increased risk of death than men [92]. However, the disease duration of PD did not affect the survival rate of PD patients [92].

2.1.10 Understanding of PD in TCM

There is no corresponding semiologic name used for PD in TCM ancient books, it was consider as a “syndrome” [93]. The symptoms similar to PD was first
described in the “Huangdi’s Internal Classic” in TCM. PD was further to be described as “trembling” or “convulsive disease” in terms of TCM. “Senile shaking syndrome” was validated to be the term of PD used in TCM by a conference organized in Chongqing of China in 1991 [94]. The key pathological features of PD in TCM were suggested to include: stagnancy of Qi and blood stasis, deficiency of Qi and blood, stagnancy of phlegm, deficiency of kidney-Yang, deficiency of liver-Yin and kidney-Yin. In fact, PD is a complex disease which is combination of “deficiency of origin” and “excess of superficiality”. Hence, PD patients are not possible to diagnosis as only one subtype in TCM but a mixed condition [95].

2.1.10.1 Treatment of PD in TCM

In general, the principles for treating PD are supplementing the Qi, activating blood circulation, nourishing Yin, suppressing excessive Yang, calming the liver to stop wind as well as clearing and activating the channels and collaterals [93]. TCM were useful in treating PD patients by improving the QoL and diminishing the NMS [93]. Although much more TCM herbs were reported that may be effective in treating PD, treating the patient by a specific TCM herbal formula holistically and individually according to the syndrome differential treatment
principle based on TCM is still the main idea of TCM. Nevertheless, there is still lack of scientific evidence to support the use of TCM as a conventional therapy for PD clinically due to quality of TCM clinical trials are limited and insufficient [15]. High quality RCT is needed to support the usage of TCM in treating PD.
2.2 The RCT of JWLJZT on Treating PD

2.2.1 Introduction

PD is the second most common NDD with a prevalence rate of 1% in the population over age 60 [96]. In recent years, increasing attention has been paid to non-motor aspects of PD which might precede MS [97]. Common NMS of PD includes fatigue, mood disorder, hallucinations, constipation and sleep disorders [98]. Though not fatal, NMS reduce QoL for both patients and their caregivers [99]. The most common treatment for PD is L-dopa. However, L-dopa primarily treats MS and it typically generates AE after long-term use [100]. As a result of both the failure of L-dopa on improving NMS and its side effects, patients often seek alternative treatments [101].

TCM is one of the most investigated streams of alternative medicine [102, 103] and commonly used by PD patients as an adjunct to their routine Western medicine. In TCM theory, patients are divided into categories according to the signs and symptoms presented [104]. The concept is similar to using factor analysis and cluster analysis in modern statistics to classify patients with different clinical patterns [105]. According to TCM theory, PD patients who present with
fatigue, constipation, and/or mood disorder are classified in the subgroup of “Spleen Qi Deficiency”, which 91.91% of PD patients were suffering from it based on our previous survey (data no published yet). Treatment typically involves different herbal formulas to “Replenish Spleen Qi”. RCTs have been conducted to examine the efficacy and safety of using various TCM formulas to treat PD. However, these RCTs were seldom focusing on the “Spleen Qi Deficiency” but mainly focusing on the “Kidney Yin Deficiency”, for example BuShen-Pingchan decoction and ZhiYin-XiFeng granules, the quality of most of them is compromised by methodological defects including poor randomization, insufficient masking, lack of proper sample size calculation, and/or improper data analysis [15].

Our research group previously reported that a Chinese herbal medicine formula, Jia-Wei-Liu-Jun-Zi Tang (JWLJZT), relieved a number of non-motor complications by replenishing the “Spleen Qi” after 24 weeks of treatment [106]. Recently, our group demonstrated that Corynoxine B (Cory B), an active compound isolated from the Chinese medicine Uncaria rhynchophylla (Miq.) Jacks. (Gouteng in Chinese), which is one of the principal herbs in the JWLJZT, efficiently promotes the clearance of α-synuclein aggresomes in vitro and in vivo
via inducing autophagy which protects neurons in PD [107]. Cory B rescues α-synuclein-induced impairment of autophagy, possibly through blocking α-synuclein-HMGB1 (high mobility group box 1, HMGB 1) interaction [108]. Moreover, our group found that Corynoxine (Cory), another active compound isolated from Gouteng, can also promote the clearance of α-synuclein via Akt/mTOR (akt murine thymoma viral oncogene homolog 1, Akt; mammalian target of rapamycin, mTOR) pathway [109].

In this double-blind, randomized, placebo-controlled, add-on trial (ChiCTR-TRC-13003085, data of releasing registration number: 2013/03/03), we aimed to study the efficacy and safety of JWLJZT in treating NMS in idiopathic PD patients by replenishing the “Spleen Qi” with a sample size large enough to provide rigorous clinical evidence.

2.2.2 Objectives

1. To evaluate the efficacy of JWLJZT for the treatment of NMS of PD, especially focusing on constipation;

2. To evaluate the safety of JWLJZT in subjects with idiopathic PD.
2.2.3 Hypothesis

Deficiencies of spleen and kidney, stagnation of phlegm, and the activities of the wind evil are the contributing factors of PD; among them the deficiency of “Spleen Qi” is the major contributing factor of NMS of PD. We hypothesize that JWLJZT, a TCM prescription used to treat deficiency of spleen qi (DSQ), is effective and safe for the treatment of NMS in idiopathic PD patients who have the syndrome of DSQ according to TCM theory.

2.2.4 Research Methodology

2.2.4.1 Study design

This study was a double-blinded, randomized, placebo-controlled, add-on trial. PD patients were randomly assigned to receive 32 weeks of either active herbal treatment or placebo (in a 1:1 ratio); they were followed for a further 6 weeks’ observation period without treatment.
I) Participants

i) Inclusion criteria

Adults between 18-80 who (1) had been diagnosed with idiopathic PD based on UK Brain Bank criteria with Hoehn and Yahr (H&Y) stages 1–4 by conventional medicine physicians [73], and (2) presented symptoms classified as DSQ (Appendix 1) Guidance for Clinical Research of New Chinese Herbal Medicine published by China [110] during a screening visit, were eligible. The diagnostic criteria of DSQ included presentation of dyspepsia, fatigue and abdominal distention. Other inclusion criteria included stable daily administration of L-dopa and permitted anti-parkinsonian drugs (DA agonists, Selegiline, Rasagiline, Entacapone, Amantadine, and anticholinergic drugs) for at least 4 weeks before the start of treatment, and normal liver and renal function.

ii) Exclusion criteria

Patients who had atypical or drug-induced parkinsonism, a score of <24 on the Mini-Mental State Examination (MMSE), history of psychosis, history of Chinese herbal medicine allergy, concurrent intake of anti-depressants, a history of suicide attempts, or unstable medical disorders were excluded. Those who had
participated in other trials within 30 days of the start of this trial as well as women who were pregnant or breastfeeding were also excluded.

iii) Informed consent form

Written informed consent (Appendix 2) was obtained from every patient before they participated in any study-related activity. Detail of the trial and form was explained to every patient and caregivers (if applicable) face to face before they signed any document.

II) Settings and locations

This clinical study was carried out at the Hong Kong Baptist University Chinese Medicine Specialty Centre, which is a Chinese medicine clinic under the School of Chinese Medicine of Hong Kong Baptist University. Insurance was bought for every patient under the study in this clinic.

III) Registration and standard

It had been approved by the Ethics Committee of the Hong Kong Baptist University’s Institutional Review Board (code: HASC/09-10/09) and registered on
the Chinese Clinical Trial Registry (ChiCTR-TRC-13003085). This study report followed the guidelines of CONSORT.

IV) Recruitment procedures

Three methods were used to recruit participants with PD. The first source of candidates was referral from a public Western medicine hospital in Hong Kong (Prince of Wales Hospital) from our co-investigator Prof. Vincent Mok. The second sources were referral from the Chinese medicine clinic of Hong Kong Baptist University. Third sources of candidates were those who respond to advertisements published in local newspapers.

All patients diagnosed with PD were referred to an assessor (Ka-Kit Chua), a registered Chinese Medicine practitioner in Hong Kong, for further assessment and recruitment. The aim, procedures, nature of study and possible side effects of JWLJZT were explained by the assessor; then each subject was asked to sign a written consent to take part in the study. Patients were informed that they were free to withdraw at any time during the study.
All patients had undergone a 4-week run-in period, in which they have to keep their Western medicine and supplement dosages fixed. Their blood was tested to check liver function (alanine transaminase (ALT) / serum glutamic pyruvic transaminase (SGPT), aspartate transaminase (AST)/ serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, gamma glutamyltransferase, total bilirubin, total protein, albumin) and renal function (urea, creatinine, sodium, potassium, chloride, bicarbonate) in a lab test center designated for the project.

V) Sample size calculation

According to our previous pilot study [106], we estimated an effect size of 0.626 and a standard deviation of 1.99 with G-Power version 3.1. At least 105 patients (1:1) were required to provide an 80% power of detecting a difference with a 2-sided $\alpha$-level of 0.05 with a maximum of 20% attrition rate. No covariates or center effects were used in power calculation.

VI) Randomization and masking

This study was a double-blind, randomized, placebo-controlled, add-on trial.
Recruited patients were randomly assigned to receive 32 weeks of either active herbal treatment (Group A) or placebo (Group B) and followed for a further 6 weeks observation period without treatment.

Group A: JWLJZT + routine western medications;
Group B: Placebo + routine western medications.

i) Sequence generation and allocation concealment

The randomization sequence was generated by “Random Allocation Software”. The sequence was password protected and kept in a computer by Lei-Lei Chen. Group allocation was a stratified block randomization according to their H&Y stages at the screening. The sequential number was contained in a sealed opaque envelop and distributed to assessors.

ii) Blinding

Patients, investigators and all sponsoring parties were masked to treatment allocation until the end of this clinical trial.
VII) Study medication

The active herbal medicine under study was JWLJZT (Appendix 3). It was composed of 13.39% Codonopsis Radix (DangShen in Chinese), 13.39% Rehmanniae Radix (DiHuang in Chinese), 10.71% Poria (FuLing in Chinese), 10.71% Uncariae Ramulus Cum Uncis (GouTeng in Chinese), 8.93% Atractylodis Macrocephalae Rhizoma (BaiZhu in Chinese), 8.93% Angelicae Sinensis Radix (DangGui in Chinese), 8.04% Pinelliae Rhizoma Praeparatum (BanXia in Chinese), 8.04% Chuanxiong Rhizoma (ChuanXiong in Chinese), 8.04% Achyranthis Bidentatae Radix (HuaiNiuXi in Chinese), 5.36% Citri Reticulatae Pericarpium (ChenPi in Chinese) and 4.46% Glycyrrhizae Radix Et Rhizoma (GanCao in Chinese).

The granules were produced in a single batch (JWLJZT batch no.: A120065; Placebo batch no.: A120153), mixed and packed to ensure the stability and homogeneity of the composition by PuraPharm Pharmaceuticals Company Limited, a GMP plant, as previously reported [106]. The placebo was made of caramel, gardenia yellow pigment, sunset yellow, permicol egg yellow, cocoa brown, citric acid, sodium cyclamate, dextrin and broadleaf holly leaf [111] following the guideline of China Food and Drug Administration. The herbal
granules and the placebo granules had identical appearance and smell, and both were sealed in plastic bags. All herbal and placebo granules were distributed by Kim-Pong Tse with both written and verbal instructions for each participant. Patients were instructed to take the granules orally by dissolving a bag of granules in 150ml hot water stirring well, then drinking, twice per day, 11g each time (a dosage equivalent to 55g herbs), at least two hours in addition to taking any routine Western medication.

Patients were allowed to discontinue the study granules temporarily if any AE occur. Patients were instructed to report such events to a special e-mail account (bucmpd@hkbu.edu.hk) or by a direct telephone line (+852 6700-8538). Additional treatments for a newly occurring illness, e.g., flu or diarrhea, or AE during the study were allowed but must be reported to the assessors.

VIII) Primary outcome, secondary outcomes and its assessment

The primary outcome of this clinical trial was Part I total score of Movement Disorder Society – Sponsored Revision of Unified PD Rating Scale (MDS-UPDRS) [112]. MDS-UPDRS Part I subscores, total score of non-motor symptom assessment scale for Parkinson’s disease (NMSS) [113] and total scores
of each domain of NMSS, as well as the total score of Part II-IV of MDS-UPDRS were used as secondary outcomes.

Unified Parkinson’s Disease Rating Scale (UPDRS) was the most widely used clinical rating scale for PD [114]. However, it is relatively insufficient in assessing the non-motor part. In 2001, the Movement Disorder Society (MDS) sponsored a critique of the UPDRS to retain the strengths of the original scale, but resolve identified problems in the original version [112]. The assessment of NMS is much completed in this new version and named MDS-UPDRS (Appendix 4). It divided into four parts, including: 1) Non-motor Experiences of Daily Living; 2) Motor Experiences of Daily Living; 3) Motor Examination; and 4) Motor Complications.

NMSS (Appendix 5) is a validated 30-item scale questionnaire specific designed for the assessment of the frequency and severity of NMS in PD patients across all stages in conjunction developed by MDS [115]. It contains nine domains: 1) cardiovascular; 2) sleep/fatigue; 3) mood/cognition; 4) perceptual problems; 5) attention/memory; 6) gastrointestinal; 7) urinary; 8) sexual function; and 9) miscellany. Although both MDS-UPDRS Part I and NMSS are used to
assess NMS in PD and showed a strong convergent validity, however, they may still not concordant in some condition especially for PD patients with severe NMS [116]. It may provide a better and clearer picture to use both MDS-UPDRS and NMSS to assess the NMS of PD patients.

Outcome measurements were carried out during the study visits at weeks 0, 16 (half of treatment), 32 (end of treatment) and 38 (end of observation period) Assessments were carried out in the “on” state. Safety assessment, which included reporting of AE, measurement of vital signs and physical examination, was carried out throughout the study. In addition, laboratory safety screening of liver and renal function was performed at week 32. Both bilingual assessors, i.e. Ka-Kit Chua and Yin-Kei Lau, were blind to the allocation, trained by the same neurology specialist Prof. Vincent Mok, and qualified by the online training program of the MDS.

Clinical assessment was rescheduled within 7 days after the scheduled clinical visit in case of any unexpected condition such as severe weather conditions. Phone call reminders were given to the caregivers one day before the days of assessment.
A home diary was given to each study participant or caregiver to record treatment and changes in the participant’s medical condition. Formal instruction for the home diary was given during the first visit. Revision and checking of the diary was carried out with the patient and caregiver during each formal visit by the assessors. Compliance in taking the treatments was determined by the record of the diary and the number of the returned medicine / placebo packages.

IX) Data management and monitoring

All the data was entered and stored in a password-protected computer. Hardcopy was kept in a locker. No interim analysis was carried out. To ensure high quality of the data, double data entry method was used. All documents and collected data are kept for 7 years after the finish of study and then will be destroyed. The protocol and statistical results will be published in a scientific journal where the public can access to all the results.

X) Statistical analysis

Demographic and clinical data were compared between the JWLJZT and placebo groups using independent sample t test or Chi-Squared test as appropriate.
Changes in primary and secondary outcomes, between baseline and week 32, were compared between the JWLJZT and placebo groups using independent sample t-tests.

Missing data were input in the last-observation-carried-forward (LOFC) manner. All patients randomized with at least one post-randomization measurement were included in the primary analysis to follow the intention-to-treat principle. Analyses were done with SPSS 19.0 package (SPSS, Chicago, IL).

To avoid inflation of type-1 errors due to multiple-endpoint testing, analyses of the primary outcome was performed with a hierarchical approach. To begin, the scores of MDS-UPDRS Part I at week 32 for the JWLJZT and placebo groups were compared. If the difference was deemed statistically significant at a 2-sided $\alpha$-level of 0.05, the scores of MDS-UPDRS Part I at week 16 and 38 were compared between groups. The hierarchical order was: 1) MDS-UPDRS Part I total score at week 32; 2) MDS-UPDRS Part I total score at week 16 and 38. Secondary outcomes were analyzed in the same manner as the primary outcome.
A post-hoc analysis was performed to test any possible effect of JWLJZT by analyzing all the subscores of each domain of NMSS in the same manner as the primary outcome.

**XI) Compliance strategy**

This was a 38-week clinical trial, in which subjects were needed to take study medication for 32 weeks with 7 regular visits (week 0, 4, 8, 16, 24, 32 and 38). In order to maximize subjects’ compliance, first, we had a thorough consent process for all participants; we had explained in detail the study schedule, potential side effects of treatment, and the responsibilities of the subjects. Second, we had screened the potential subjects carefully during a 2-week run-in period in order to exclude ineligible patients or patients who were unlikely to comply with treatment regimen before randomization. Third, we had tried to prevent dropouts by providing ongoing support to patients. A special e-mail account and a direct telephone line were set up for this clinical trial which could enable the study team to personally communicate with the patients. An information sheet was given to each patient providing them and their caregivers with means of urgent contact. Extra visits and free medical care were arranged for any participant who feels harmed by the trial protocol. Fourth, this was an add-on design [117] which means
that the study treatment was added to their existing treatment. It is highly likely that those participants receiving the placebo should not experience any difference in their condition, while those receiving the JWLJZT should improve or at least remain the same.

XII) Early termination

The trial would be terminated for a specific participant if she/he: (1) develops severe adverse side effect(s); (2) shows hypersensitivity towards DTD; (3) develops some other life-threatening condition or disease; or (4) chooses to participate in another Chinese herbal medicine research project. In addition, any participant may voluntarily withdraw.

The whole research plan would be terminated under the following circumstances: (1) presence of serious adverse effect(s) related to Chinese herbal medicine with supportive evidence; (2) completion of all follow-up assessments.

2.2.5 Results

Figure 2 is a flow chart depicting the participant screening and recruitment in this
study. Demographic data and baseline scores are summarized in Table 1. A total of 234 patients were screened for eligibility, and 116 participants were enrolled. Five patients withdrew from the study due to personal reasons after randomization and before the start of treatment. Among the remaining 111 patients (73 male; 38 female; mean ages 62.69 ± 9.11 years; mean duration of PD 5.95 ± 3.97 years), 56 were assigned to the JWLJZT group, 55 to the placebo group. 20 participants dropped out during the study due to reasons listed in Figure 2. Forty-five participants in the JWLJZT group and 46 in the placebo group completed the study.
Figure 2: Flowchart on participant screening and recruitment of PD trial

*Participation in the study could be discontinued because of non-compliance with dosing or visits.

†Patient’s choice to discontinue for reasons unrelated to the study drug.
Table 1. Baseline characteristics of PD patients in the JWLJZT trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JWLJZT group</th>
<th>Control group</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n= 56)</td>
<td>(n= 55)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.48 ± 9.72</td>
<td>63.31 ± 8.20</td>
<td>0.919&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>35/21</td>
<td>38/17</td>
<td>0.464&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>6.42 ± 4.15</td>
<td>5.42 ± 3.77</td>
<td>0.096&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of L-dopa treatment (years)</td>
<td>5.17 ± 4.42</td>
<td>3.94 ± 3.13</td>
<td>0.187&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>L-dopa dosage (mg/day)</td>
<td>459.82 ± 350.90</td>
<td>374.55 ± 257.46</td>
<td>0.148&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-dopa, n (%)</td>
<td>53 (94.6)</td>
<td>50 (90.9)</td>
<td>0.447&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>DA agonist, n (%)</td>
<td>23 (41.1)</td>
<td>17 (30.9)</td>
<td>0.265&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anticholinergic, n (%)</td>
<td>18 (32.1)</td>
<td>21 (38.2)</td>
<td>0.505&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>COMT inhibitor, n (%)</td>
<td>14 (25.0)</td>
<td>4 (7.3)</td>
<td>0.011&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAO-B inhibitor, n (%)</td>
<td>17 (30.4)</td>
<td>12 (21.8)</td>
<td>0.306&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amantadine, n (%)</td>
<td>5 (8.9)</td>
<td>4 (7.3)</td>
<td>0.749&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Senna, n (%)</td>
<td>5 (8.9)</td>
<td>6 (10.9)</td>
<td>0.727&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lactulose, n (%)</td>
<td>4 (7.1)</td>
<td>3 (5.5)</td>
<td>0.714&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Baseline scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;Y score</td>
<td>2.07 ± 0.60</td>
<td>2.02 ± 0.59</td>
<td>0.639&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>NMSS total</td>
<td>65.52 ± 49.77</td>
<td>47.42 ± 35.70</td>
<td>0.030&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-UPDRS part I</td>
<td>10.21 ± 7.06</td>
<td>8.76 ± 6.63</td>
<td>0.267&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-UPDRS part II</td>
<td>14.71 ± 7.95</td>
<td>11.58 ± 7.51</td>
<td>0.035&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-UPDRS part III</td>
<td>33.21 ± 15.39</td>
<td>33.27 ± 14.27</td>
<td>0.983&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDS-UPDRS part IV</td>
<td>4.00 ± 4.45</td>
<td>2.78 ± 3.70</td>
<td>0.120&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D.
a$p$-value was comparing the difference between two groups in baseline

b treatment group compared with placebo group by independent t-test

c treatment group compared with placebo group by Chi-square test with continuity correction

2.2.5.1 Analysis of MDS-UPDRS

In the primary analysis, we observed a trend of improvement, a decreased score was obtained at week 32 in JWLJZT group that suggested an improvement in NMS, in the total score of MDS-UPDRS Part I in the JWLJZT group relative to the placebo group though the difference was not statistically significant ($p = 0.216$). In comparison, an increased score was obtained at week 32 in the placebo group, which suggested worsening. Further analyses performed on the subscores of MDS-UPDRS Part I between the two groups revealed that the JWLJZT group showed non-significant trends of reduction in constipation (mean diff. = -1.09, 95% CI: -2.30 to 0.13, $p = 0.079$) and in hallucination (mean diff. = -0.18, 95% CI: -0.38 to 0.19, $p = 0.075$) compared to the placebo group (Table 2). No statistically significant differences were found in other parts (II-IV) of MDS-UPDRS in week 32. Although certain improvements have been observed in NMS in JWLJZT group, no obvious improvements in MS were observed in both the JWLJZT group and the placebo group.
Table 2. Efficacy result of JWLJZT on PD patients at Week 32

<table>
<thead>
<tr>
<th>Movement Disorder Society – Sponsored Revision of Unified PD Rating Scale (MDS-UPDRS)</th>
<th>JWLJZT</th>
<th>Placebo</th>
<th>p-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part I Total Score (Non-motor Symptom)</td>
<td>-0.46 ± 6.61</td>
<td>0.84 ± 4.09</td>
<td>0.216</td>
</tr>
<tr>
<td>Q.1 Cognitive</td>
<td>-0.07 ± 0.97</td>
<td>0.00 ± 0.69</td>
<td>0.657</td>
</tr>
<tr>
<td>Q.2 Hallucinations</td>
<td>-0.04 ± 0.54</td>
<td>0.15 ± 0.52</td>
<td>0.075</td>
</tr>
<tr>
<td>Q.3 Depress</td>
<td>-0.07 ± 1.03</td>
<td>0.07 ± 0.72</td>
<td>0.393</td>
</tr>
<tr>
<td>Q.4 Anxious</td>
<td>-0.14 ± 0.82</td>
<td>-0.02 ± 0.71</td>
<td>0.393</td>
</tr>
<tr>
<td>Q.5 Apathy</td>
<td>-0.23 ± 1.36</td>
<td>-0.02 ± 0.87</td>
<td>0.327</td>
</tr>
<tr>
<td>Q.6 DA dysregulation</td>
<td>-0.13 ± 0.63</td>
<td>-0.15 ± 0.52</td>
<td>0.854</td>
</tr>
<tr>
<td>Q.7 Sleep</td>
<td>0.23 ± 1.03</td>
<td>0.13 ± 1.06</td>
<td>0.597</td>
</tr>
<tr>
<td>Q.8 Daytime sleep</td>
<td>0.16 ± 0.91</td>
<td>0.11 ± 0.85</td>
<td>0.759</td>
</tr>
<tr>
<td>Q.9 Pain</td>
<td>-0.02 ± 1.30</td>
<td>0.24 ± 1.05</td>
<td>0.261</td>
</tr>
<tr>
<td>Q.10 Urinary</td>
<td>-0.02 ± 0.73</td>
<td>0.02 ± 0.87</td>
<td>0.813</td>
</tr>
<tr>
<td>Q.11 Constipation</td>
<td>-0.13 ± 1.45</td>
<td>0.96 ± 4.35</td>
<td>0.079</td>
</tr>
<tr>
<td>Q12 Light headedness</td>
<td>0.04 ± 1.08</td>
<td>-0.04 ± 0.38</td>
<td>0.641</td>
</tr>
<tr>
<td>Q13 Fatigue</td>
<td>-0.04 ± 1.21</td>
<td>-0.02 ± 0.97</td>
<td>0.796</td>
</tr>
<tr>
<td>Part II Total Score (Motor Symptom)</td>
<td>0.45 ± 4.13</td>
<td>1.05 ± 4.58</td>
<td>0.464</td>
</tr>
<tr>
<td>Part III Total Score (Motor Examination)</td>
<td>-0.52 ± 10.13</td>
<td>1.38 ± 8.27</td>
<td>0.282</td>
</tr>
<tr>
<td>Part IV Total Score (Motor Complications)</td>
<td>0.21 ± 3.56</td>
<td>0.65 ± 3.42</td>
<td>0.508</td>
</tr>
<tr>
<td>Non-motor Symptom Assessment Scale for Parkinson’s Disease (NMSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td>-2.27 ± 32.90</td>
<td>11.78 ± 28.93</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>D1 total Cardiovascular</strong></td>
<td>-0.89 ± 3.38</td>
<td>-0.15 ± 2.31</td>
<td>0.178</td>
</tr>
<tr>
<td><strong>D2 total Sleep/fatigue</strong></td>
<td>3.63 ± 7.98</td>
<td>4.62 ± 7.08</td>
<td>0.490</td>
</tr>
<tr>
<td><strong>D3 total Mood/Cognition</strong></td>
<td>-3.54 ± 14.38</td>
<td>3.13 ± 9.36</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>D4 total Perceptual/hallucinations</strong></td>
<td>-0.88 ± 4.17</td>
<td>0.71 ± 3.04</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>D5 total Attention/memory</strong></td>
<td>-1.86 ± 6.07</td>
<td>-0.15 ± 7.08</td>
<td>0.174</td>
</tr>
<tr>
<td><strong>D6 total Gastrointestinal tract</strong></td>
<td>-0.86 ± 5.15</td>
<td>0.98 ± 5.66</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>D7 total Urinary</strong></td>
<td>1.71 ± 7.57</td>
<td>1.47 ± 7.12</td>
<td>0.863</td>
</tr>
<tr>
<td><strong>D8 total Sexual function</strong></td>
<td>-0.71 ± 4.20</td>
<td>0.16 ± 3.81</td>
<td>0.251</td>
</tr>
<tr>
<td><strong>D9 total Miscellaneous</strong></td>
<td>1.13 ± 6.41</td>
<td>1.00 ± 5.46</td>
<td>0.912</td>
</tr>
</tbody>
</table>

*p-value was comparing the score changes at week-32 between JWLJZT group and placebo group by independent sample t-tests

Values are given as mean ± S.D. Values in JWLJZT group and placebo group are the score changed in the same group between week-32 and baseline (score at week-32 minus score at the baseline)
2.2.5.2 Analysis of NMSS

In the secondary analysis, the data indicate a significant difference in NMSS total score between JWLJZT group and placebo group (mean diff. = -14.05, 95% CI: -25.71 to -2.39, \( p = 0.019 \)) after 32 weeks of treatment. A trend of improvement in the JWLJZT group was also noted by the hierarchical approach in week 16 (mean diff. = -8.87, 95% CI: -18.78 to 1.04, \( p = 0.079 \)). Improvement persisted at 38 weeks (mean diff. = -11.70, 95% CI: -23.12 to -0.28, \( p = 0.045 \)). Further analyses of the NMSS subscores showed that the PD patients in the JWLJZT group experienced greater improvement in mood/cognition (mean diff. = -6.66, 95% CI: -11.24 to -2.09, \( p = 0.005 \)) and reduction in hallucinations (mean diff. = -1.58, 95% CI: -2.96 to -0.21, \( p = 0.024 \)) than those in the placebo group at weeks 32. Although there was no significant different at week-16 and week-38, these improvement were consistent throughout the trial. Relative to the control group, the JWLJZT group showed a trend of improvement in the gastrointestinal tract (mean diff. = -1.84, 95% CI: -3.87 to -0.20, \( p = 0.076 \)) as well as a significant reduction in constipation that persisted through from week 16 (\( p <0.001 \)) to week 38 (\( p = 0.002 \)) (Table 3). There were no significant differences in other subscores between the two groups at week 16 and the end of treatment in other domains.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 16</th>
<th>Week 32</th>
<th>Week 38</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JWLJZT</td>
<td>Placebo</td>
<td>JWLJZT</td>
</tr>
<tr>
<td>Total score of NMSS</td>
<td>-3.13 ± 29.49</td>
<td>5.75 ± 22.67</td>
<td>-2.27 ± 32.90</td>
</tr>
<tr>
<td>p-value</td>
<td>0.079</td>
<td>0.019</td>
<td>0.045</td>
</tr>
<tr>
<td>NMSS D3 total</td>
<td>-1.68 ± 12.12</td>
<td>0.93 ± 7.76</td>
<td>-3.54 ± 14.38</td>
</tr>
<tr>
<td>p-value</td>
<td>0.181</td>
<td>0.005</td>
<td>0.120</td>
</tr>
<tr>
<td>Mood/Cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSS D4 total</td>
<td>-0.64 ± 3.28</td>
<td>0.09 ± 0.59</td>
<td>-0.88 ± 4.17</td>
</tr>
<tr>
<td>p-value</td>
<td>0.105</td>
<td>0.024</td>
<td>0.103</td>
</tr>
<tr>
<td>Perceptual/hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSS D6 Q21 constipation</td>
<td>-1.02 ± 3.89</td>
<td>1.47 ± 2.71</td>
<td>-1.25 ± 3.46</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*p-value was comparing the score changes at different time point between JWLJZT group and placebo group by independent sample t-tests.

Values are given as mean ± S.D. Values in JWLJZT group and placebo group are the score changed in the same group between different time point and baseline (score at different time point minus score at the baseline).
2.2.5.3 Withdrawal and AE

Twenty patients (11 (19.6%) [JWLJZT] vs 9 (16.4%) [Placebo], \( p = 0.65 \)) discontinued treatment after randomization. Among these 12 patients, 4 in each group withdrew because of AE. During the treatment phase, two patients (3.57%) in the JWLJZT groups and four patients (7.27%) in the placebo group had serious AE: one patient had hypoglycaemia (placebo), one had sepsis (placebo), one had finger sarcoma (placebo), two had coronary heart disease (one in placebo & one in JWLJZT), and one had breast cancer (JWLJZT). No deaths were recorded during the trial. AE were reported by at least 5% of patients in each group (Table 4).

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of patients (%)</th>
<th>JWLJZT (N=56)</th>
<th>Placebo (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>3 (5.4)</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5 (8.9)</td>
<td>1 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.8)</td>
<td>3 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (5.4)</td>
<td>7 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (1.8)</td>
<td>5 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td>2 (3.6)</td>
<td>4 (7.3)</td>
<td></td>
</tr>
</tbody>
</table>
2.2.6 Discussion

In this RCT study, there was no strong evidence supporting the hypothesis that JWLJZT reduces overall NMS as represented by the overall MDS-UPDRS Part I score (the NMS of PD). However, reduction of NMS was noted by the NMSS total score in the secondary outcomes. Also, improvement in the form of reduction in hallucinations and constipation was suggested by secondary outcomes analysis of UPDRS Part I subscore. Improvement in mood disorder, hallucinations and constipation, without effect on the motor features of PD, was revealed by post-hoc analysis of the NMSS subscore. JWLJZT was well tolerated. Discontinuation due to AE occurred with the same frequency in the JWLJZT group (4 patients) as in the placebo group (4 patients). Further targeted studies on the effect of JWLJZT on mood disorder and gastrointestinal condition need to be performed to confirm these observations.

TCM has a long history being used to treat symptoms similar to PD in China [118]. According to TCM theory, JWLJZT replenishes and facilitates circulation of “spleen and stomach Qi”, which is related to PD NMS. Depletion and stagnation of “spleen and stomach Qi” would lead to NMS such as constipation, nausea, sleep disruption and mood disorder. In this trial, the improvement of NMS
assessed by the NMSS showed continual effect even after the patients had stopped the medication for 6 weeks. It suggested that the effect of JWLJZT may not just be symptomatic; instead it may alter some pathophysiological processes underlying NMS. Although the improvement of mood and hallucination become lesser after the patients had stopped the JWLJZT, there was still an improvement trend in the treatment group compared to the placebo group. It suggested that these improvements should be related to the use of JWLJZT but not just a false positive due to disease fluctuation.

JWLJZT is an herbal formula composed mainly of Codonopsis Radix (Dangshen), Poria (Fuling) and Uncariae Ramulus Cum Uncis (Gouteng) [106]. Ji et al. found that Gouteng extract is an effective anxiolytic agent and acts via the serotonergic nervous system [119]. Jun et al. showed that triterpenoids in Fuling may regulate the expressed 5-hydroxy-typtamine 3A (5-HT_{3A}) receptors which are implicated in gastric system and nervous system [120]. These suggest that the effect of JWLJZT, which includes improvement in mood disorder and reduction of constipation, may be due to the increased levels or stimulation of serotonin receptors. In TCM clinical practice, JWLJZT is given in combination with other herbs and the dosage and combinations are continuously adjusted based on patients’ symptoms and
conditions. Therefore, the effects observed in our trial may only partially explain clinical results as JWLJZT is taken in isolation during our study with the standard dosage dictated by the Chinese Pharmacopoeia [121].

Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter with a significant role in mood and appetite regulation [122]. It is synthesized in both serotonergic neurons of the central nervous system (CNS) to regulate mood and appetite, and in the alimentary canal to regulate intestinal movements [123]. Neurotransmitters in general, 5-HT in particular, may be involved in the NMS of PD, including mood disorder, psychosis, and constipation [124].

For the limitations, constipation was improved by JWLJZT as suggested by the post-hoc analyses. We are aware that the change in constipation condition is limited by our study’s sample size. Therefore, future studies with larger sample size are needed to test whether there are changes in constipation frequency due to JWLJZT treatment. The evidence suggesting improvements in constipation (p=0.079) and hallucination (p=0.075) among patients taking JWLJZT was noted to be weak. This may be due to inadequate power of the study. The current data suggests that a scaled-up study would be able to confirm the difference [125]. The
scale of NMSS is much more sophisticated in testing the NMS than the UPDRS (score 0-4). It measures the severity as well as the frequency of each NMS independently and then multiplies them to get an overall result (score 0-12). This may result in a slight difference between the two measurements.

An attrition rate of 20% (20 patients) was high for PD patients at a relatively early stage of the disease. This was due to the long treatment period (32-week) when compared to other PD clinical trials [126]. As the main motivation of some PD patients to participate in a clinical trial was to obtain benefit [127], 6 patients withdrawn when they believed the medication was ineffective.

Another limitation is that there was a significantly difference at baseline in the number of patients using COMT-I, and the total score of NMSS and MDS-UPDRS part II even after randomization. Larger sample size may be a possible way to minimize such problem in future. Besides, the randomization method used in this trial was stratified block randomization according to the H&Y stages of patients at screening. Although H&Y staging is a commonly used method, it does not concern the condition of NMS. Patients in the same stage of H&Y may still have different severity of NMS. This may be the reason of
significantly difference at the baseline of NMSS total score.

In conclusion, our data showed that JWLJZT could alleviate gastrointestinal problems and mood disorder in PD patients over 32 weeks with minimal side effects. The effect of JWLJZT on constipation persists 6 weeks after treatment. It appears to be both safe and effective for long-term use to treat NMS of PD. Further clinical studies focusing on the mood disorder and gastrointestinal function improvement of PD patients by JWLJZT are warranted.
CHAPTER III: A Pilot Randomized Controlled Trial of Di-Tan decoction (DTD) on treating Alzheimer’s disease

3.1 Literature Review of Alzheimer’s disease (AD)

3.1.1 Introduction

AD is first described by a German psychiatrist and neuropathologist Alois Alzheimer in 1905. It is an irreversible, progressive and fatal NND with accumulation of beta-amyloid-peptide (Aβ) in the brain and manifested by cognitive and memory deterioration, progressive impairment of activities of daily living as well as a variety of neuropsychiatric symptoms and behavioral disturbances [128]. It is the most common type of dementia in the elderly and imposes a great economic stress to the society [129]. In the fifth Edition of “Diagnostic and Statistical Manual of Mental Disorders” (DSM) criteria, dementia is now renamed as “Major Neurocognitive Disorder” [130].

3.1.2 Epidemiology

The prevalence of dementia, which AD is the most prevalent cause, in people aged over 60 was estimated to be as high as 24 million in 2001 over the world [131]. It was predicted that it will be doubled for every 20 years and may affect
more than 80 million people worldwide in 2040 [132]. This sharply increasing trend is mainly related to the global aging. In fact, as the prevalence rate may also be doubled for every five years of age above 65 [133]. Prevalence is about 2% for people aged 65–69 and up to more than 25% for people aged over 90 [134]. The global AD population may increase to 114 million by 2050 if there is no new preventive intervention [133]. In Hong Kong, the prevalence rate of AD is approximately 6.1% for people over the age of 70 [135].

3.1.3 Etiology

It is true that, most AD patients are diagnosed at age 65 or older. Aging is the biggest risk factor for developing AD, however, the exact reasons and mechanism is still unknown. Besides, females seem to have higher risk than males to develop AD. In general, it is believe that there are many factors contributed to develop AD with a complex interaction [136].

3.1.3.1 Family history

It was reported that people may have higher risk to develop AD if their first-degree relative, like parent, brother or sister, was suffering from AD [137].
The more individuals in a family have the illness, the greater the risk [138]. However, this increased chance of having AD is not entirely explained by the genetic factor. Family lives together may share some common risk factor like environmental and lifestyle. Heredity could be a possible reason but not the only.

3.1.3.2 Genetic

Apolipoprotein (APOE) gene is responded for the production of protein that carries cholesterol in the bloodstream. $\varepsilon2$, $\varepsilon3$ and $\varepsilon4$ are three forms of APOE gene, which $\varepsilon3$ is the most common form. For the form of APOE $\varepsilon4$ gene, it may increase the chance to develop AD at a younger age. It leads to accelerated deposition of amyloid, which may be central to the pathogenesis of AD [139]. The risk may even be higher if an individual has inherited two $\varepsilon4$ genes [136]. It is estimated that 40% to 65% of AD patients have one or two copies of the APOE $\varepsilon4$ gene [140]. Nevertheless, the presence of $\varepsilon4$ gene does not guarantee that person must be suffering from AD [136].

On the other hand, for the early onset AD (before age 65), there are three dominantly inherited genetic mutations reported which are including genes for amyloid precursor protein (APP), genes for presenilin 1 (PS1) and persenilin 2
However, they only account for about 1% of the whole AD population [136].

3.1.3.3 Education and cognitive engagement

There is a hypothesis of cognitive reserve, education or social activities may increase the connections between neurons in the brain [141, 142]. These enable the brain to compensate for the early changes of AD by using an alternate routes of neuron-to-neuron communication to finish a cognitive mission [136]. People with more years of formal education or frequent social activities may support the health of brain and reduce the risk to develop AD or other kind of dementia.

3.1.3.4 Primary diseases

Mild cognitive impairment (MCI) is an early stage of AD or other kind of dementia in the 2011 proposed criteria and guidelines [143]. People with MCI have mild but measurable changes in thinking abilities. Although it may not affect their normal daily activities, it does have some negative impact on their close relatives. MCI may have chance to become AD but not a must. They are recommended to have regular monitoring of their cognitive functions.
On the other hand, people with cardiovascular disease (CVD) may have higher risk to develop AD or other kind of dementia as most of the risk factors of CVD which include smoking [144], obesity [145], diabetes mellitus [146], high cholesterol and hypertension [147], are associated with dementia. In contrast, factors reduce the chance of CVD including physical activities, low saturated fats and rich vegetables diet may also reduce the risk to developing dementia [131].

3.1.4 Pathogenesis

As the reasons and mechanisms developing AD is still unknown, it is a result of multiple factors possibly. The exact pathogenesis is still under research. It is commonly believed that the pathology of Aβ (it is also called senile plaque) protein accumulated outside the brain neurons as well as tau protein (it is also called neurofibrillary tangle, NFT) accumulated inside the brain neurons are contributed to the cell death in AD brain and result in AD [136]. These pathologies are usually found in the hippocampus, temporal cortex and nucleus basalis. Although normal aging may also develop some similar plaques and tangles, the brains of AD patients have a greater number of them. The accumulated Aβ may interfere the communication of neuron by synapses resulting in inflammation, excitotoxicity and activation of apoptotic pathway; while, the
accumulated NFT may block the transport of nutrients and other essential molecules in the neurons resulting in axonal transport disruption [148]. These may finally lead to neuronal cell death. Information transfer may failure through synapses due to the deficits in neurotransmitters (especially the acetylcholine, Ach, which are responsible for the clinical manifestations of AD [149]) with the declines of synapses number.

3.1.5 Clinical Manifestations

AD patients may have progressive patterns of both cognitive and non-cognitive impairments, while cognitive part may be much typical. The classic clinical features of cognitive impairments include memory loss [150], deterioration of language [151] and visuospatial deficits [152]. Functional and behavioral disturbances are also the characteristic of AD [128]. Mood changes and apathy are commonly developed at the early stage. When the disease gets into the moderate stage, psychosis and agitation may become dominant [153]. AD patient may further loss their ability in the higher-level activities of daily living, like writing and taking transport, and even basic activities of daily living, like eating and toilet using at the advanced stage [154]. Non-cognitive impairment such as motor and sensory abnormalities, gait disturbances, and seizures are uncommon until the
advanced stage [155].

3.1.5.1. Mild stage

Learning and memory impairments are the most typical feature in this stage. Old declarative memory and implicit memory are less affected than the recent declarative memory [156]. AD patients are difficulty in remembering recently learned facts and inability to acquire new information. They may start to loss ability in planning, judging and organizing some complex tasks. Communication may also become more difficult due to shrinking vocabulary, decreasing word fluency as well as less precise expressive language [156]. For example, patients may feel difficult to name an object but easy to describe its function instead. On the other hand, depression is one of the most frequent psychiatric complications of AD, affecting about 50% of AD patients [157]. AD Patients may look worse if they have the symptoms of depression. Generally speaking, AD patients can still take care themselves completely in the mild stage.

3.1.5.2. Moderate stage

Continuing to the mild stage, patients may become much more difficult in
planning, organizing, communication as well as logical reasoning. Reading and writing ability may much decline or lose completely. Disorientation is common not only outside, but also present in the home like getting into the wrong room. Agnosia is often in this stage, which including failure to recognize familiar face, and may become mind blind finally. On the other hand, psychiatric impairments are usual to occur. About to 36.5% and 23% of AD patients may have delusions and hallucinations respectively [158]. Patients associated with older age, depression, poor general health and use of anti-hypertensive may have higher chance to develop delusions, while, patients associated with lesser education and longer duration of disease may have higher chance to develop hallucinations [159]. Generally speaking, AD patients cannot survive in the community without close monitoring at this stage [156].

3.1.5.3. Advanced stage

Almost all the cognitive functions are totally loss, even the early biographical memories [156]. Patients can only speak in simple phase or even single words and unable to express what they need. Apraxia is common, even chewing and swallowing may become impair in the extreme case. Incontinence of both urine and stool are also common [160]. Some patients may have yelling or wandering
behavior, while, most of them show extreme apathy and exhaustion [156]. Some proportion of AD patients may have myoclonus and epileptic seizures [161]. At this stage, AD patients depend on caregiver completely.

3.1.6 Diagnosis

The diagnosis of AD is mostly by an elimination method based on the presence of characteristic neurological and neuropsychological features with absence of alternative conditions. All the relative history, clinical observations, physical examinations and ancillary investigations should also be considered. Advanced medical imaging may be used to exclude other cerebral pathology or other types of dementia.

Although diagnosis of dementia is using the criteria of DSM commonly, diagnosis of AD is most commonly based on the criteria developed by the “National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association” (NINCDS–ADRDA) [155]. NINCDS–ADRDA cover eight cognitive impair domains which are memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities. The diagnosis of it can be classified as 3 types: 1)
definite (clinical diagnosis with histologic confirmation); 2) probable (typical clinical syndrome without histologic confirmation); 3) possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation). The sensitivity and specificity of NINCDS–ADRDA for diagnosing AD are 0.65 and 0.75, respectively [128]. Here are the criteria of NINCDS–ADRDA:

3.1.6.1 Criteria of NINCDS–ADRDA

<table>
<thead>
<tr>
<th><strong>Definite AD</strong></th>
<th>Clinical criteria for probable AD</th>
<th>Tissue diagnosis by autopsy or biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probable AD</strong></td>
<td>Deficits in two or more domains of cognition</td>
<td>Progressive decline of memory and other cognitive functions</td>
</tr>
<tr>
<td></td>
<td>Preserved consciousness</td>
<td>Onset between ages 40 and 90</td>
</tr>
<tr>
<td></td>
<td>Absence of systemic or other brain disease that could account for symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Possible AD</strong></td>
<td>Atypical onset, presentation, or clinical course of dementia</td>
<td>Presence of another illness capable of producing dementia</td>
</tr>
</tbody>
</table>

I. Clinical Diagnosis of Probable Alzheimer's Disease

Dementia established by clinical examination and mental status testing and confirmed by neuropsychological testing
Deficits in at least two cognitive domains
Progressive cognitive decline, including memory
Normal level of consciousness
Onset between ages 40 and 90 (most common after 65) years
No other possible medical or neurological explanation

II. Probable Alzheimer's Disease Diagnosis Supported by

Progressive aphasia, apraxia, and agnosia
Impaired activities of daily living

85
### III. Other Clinical Features Consistent with Probable Alzheimer's Disease

Plateau in course
- Associated symptoms: depression; insomnia; incontinence; illusions; hallucinations; catastrophic verbal, emotional, or physical outbursts; sexual disorders; weight loss; during more advanced stages increased muscle tone, myoclonus, and abnormal gait
- Seizures in advanced disease
- CT normal for age

### IV. Features That Make Alzheimer's Disease Uncertain or Unlikely

- Acute onset
- Focal sensorimotor signs
- Seizures or gait disorder early in course

### V. Clinical Diagnosis of Possible Alzheimer's Disease

- Dementia with atypical onset or course in the absence of another medical/neuropsychiatric explanation
- Dementia with another disease not felt otherwise to be the cause of dementia
- For research purposes, a progressive focal cognitive deficit

### VI. Definite Alzheimer's Disease

- Meets clinical criteria for probable Alzheimer's disease
- Tissue confirmation (autopsy or brain biopsy)

### VII. Research Classification of Alzheimer's Disease should specify

- Familial?
- Early onset (before age 65)?
- Down's syndrome (trisomy 21)?
- Coexistent other neurodegenerative disease (e.g., Parkinson's disease)?

### 3.1.6.2 Ancillary investigations

Ancillary investigations, such as blood test and imaging, are mainly used to exclude other type of dementia. The diagnosis of AD must combine the result from clinical features and ancillary investigations.
I) Laboratory test

To date, there is no biomarker of AD, however, laboratory test is still important in identify the causes of dementia other than AD. Abnormal in the thyroid-function and serum vitamin B12 level may also affect the cognitive function. Test for syphilis, human immunodeficiency virus (HIV) antibody or screening for heavy metals may also need to rule out secondary dementia. Although AD patients may have abnormal accumulation of protein in the brain, CSF test is rarely used as it is relatively invasive.

II) Imaging

Although neuroimaging may act as an important role in the diagnosis of AD, it is still mainly used in differential diagnosis of disorders associated with dementia. There may be not apparent structural changes at the early stage based on CT or MRI, while, it may exclude other causes of cognitive impairment like vascular dementia or brain tumor. Atrophy of cortex in temporal lobe, parietal lobe, frontal lobe and hippocampus can be detected at the later stage of AD. Functional brain imaging such as PET scan or SPECT scan may also be helpful in the diagnosis of dementia by finding out the reduced activities area in the brain.
However, it is relatively expensive.

### 3.1.7 Differential diagnosis

#### 3.1.7.1. Vascular dementia (VD)

VD is the second most common type of dementia, following AD. It commonly develops after stroke due to the brain injuries associated with intracerebral bleeding and blood vessel blockage. Symptoms and signs of VD are closely related to the location of the brain injury. It can be of acute onset with impaired judgment or ability to make planning when comparing to AD. VD and AD used to be two different cognitive disorders, while much more evidences show that both VD and AD pathologies can exist simultaneously together.

#### 3.1.7.2. Dementia with Lewy bodies (DLB)

DLB patients may have both dementia and parkinsonism in the early stage, while AD patients are rare to have MS until the advanced stage. Also, DLB patients are more likely to have sleep disturbances and well-formed visual hallucinations at the early stage. The abnormal aggregation of protein pathology in DLB is LB but not Aβ.
3.1.7.3. Frontotemporal lobar degeneration (FTLD)

It is a less common form of dementia characterized by progressive decline in behavior or language associated with degeneration of the frontal and anterior temporal lobes [162]. Personality and behavior changes are typical in the early stage of FTLD. Also, it is much commonly occur in people younger than 65.

3.1.8 Management

There is abnormal amyloid plaque aggregated in the AD brain causing oxidative stress, inflammation and result in neuronal death. However, no evidence to support the use of any anti-amyloid therapy, antioxidant therapy, anti-inflammatory therapy or neuro-protective therapy for the treatment of AD [128]. None of the treatments, whatever pharmacological treatment or non-pharmacological treatment, used today can stop or even slow the progress of neural death and malfunction in AD brain [136]. Pharmacological treatment aimed at improving the symptoms of AD by increasing the amount of neurotransmitters (Ach) in the brain, while, non-pharmacological treatment aim at maintaining the cognitive function or helping the brain compensate for impairments [136]. Both of them can improve the QoL of AD patients.
3.1.8.1 Pharmacological treatment

I) Acetylcholinesterase inhibitors (AchEI)

It is a symptomatic treatment commonly used in mild to moderate AD but do not alter the natural course [163]. It is considered as a standard of care for AD patients [164]. No sufficient evidence for their use in the advanced stage. Reduction in the cholinergic neurons activity and loss of the neurotransmitter Ach in the cerebral cortex is a well-known feature of AD. AchEI can inhibit the broke down rate of Ach. It may increase the availability of Ach in the brain and combating the loss of Ach caused by the death of cholinergic neurons [165]. The effectiveness of AchEI is related to the dosage. Similar efficacy of the three commonly used AchEI, which are donepezil, rivastigmine and galantamine, in the market by evaluation of the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) [128]. Common side effects are gastrointestinal disorders like nausea, vomiting and diarrhea. Muscle cramps, bradycardia, insomnia and fatigue were also reported in some clinical trials.

II) Memantine (N-methyl-D-aspartate antagonist, NMDA)

Memantine is a noncompetitive NMDA receptor antagonist first used as an
anti-influenza agent. It is now used for the treatment of moderate to advanced AD as glutamate-related excitotoxicity was reported to be involved in the formation of abnormal protein aggregation in AD [166]. It may regulate the activity of glutamate by blocking the receptor partially and inhibiting their overstimulation. It was reported that AD patients were having cognitive improvement, reduced decline in daily activities and reduced frequency of new behavioral symptoms with not markedly AE [167].

**III) Practical issues in pharmacological management**

Some reports suggested that there were four clinical issues that have to be considered when using pharmacological treatment for AD.

i) Treatment expectations

Patients were expected to get great improvements when taking medication. In fact, mild to moderate AD patients may reach their peak improvement on cognitive measure at 3 to 6 months; however, it may also drop back to baseline 3 months later. Some patients may even do not experience any typical improvement after taking the medication [163].
ii) Side effects

All the three AchEI used in market are having cholinergic side effects and clearly dose-dependent [163]. Although there is a new formulation of Rivastigmine which is transdermal and is associated with lesser gastrointestinal side effects, it may be associated with skin intolerance in some patients. Start of AchEI needs to begin at low dose.

iii) Switching agents

Although all the AchEI are in the same class, patients may have different response to different AchEI clinically [168]. If there was intolerance or lack of response, patients are suggested not to change the medication immediately. They have to wait for complete resolution of side effects. If there is no response, patients will be recommended to observe for the effect for at least six months.

iv) Discontinuation of therapy

If there was no response to the medication therapy after a reasonable trial period or presence of intolerable side effects, therapy should be discontinued.
3.1.8.2 Non-pharmacological treatment

As pharmacological treatments are just symptomatic but with some side effects, some AD patients may try another approaches other than medication, such as cognitive training and behavioral interventions [136]. Non-pharmacological treatment can neither alter the natural course, some report showed that it may improve or stabilize the cognitive function, performance of daily activities, behavior and mood with no side effect [169]. In general, non-pharmacological treatments are much focus on the QoL and behavioral symptoms like depression, apathy, wandering, sleep disturbances, agitation and aggression [136]. There are four commonly used oriented approaches therapy including: 1) behavior-oriented approaches focus on reducing the previous and consequences of problem behaviors; 2) emotion-oriented approaches focus on controlling mood and emotion; 3) cognition-oriented approaches focus on reducing the cognitive deficits; and 4) stimulation-oriented approaches focus on improving behavior, mood and daily function.

3.1.9 Prognosis

Life expectancy of AD patients is reduced. Some studies reported that the mean
life expectancy of AD patients diagnosed after 65 was approximately 4 to 8 years.

Only a few numbers of them could live with AD for 20 years [170]. AD is the top ten leading cause of death not only in the elderly, but also for the whole population in the developed countries [136]. In fact, the actual causing of death related to AD maybe underestimated as most of the death were mainly related to complications, like pneumonia, but not caused by AD directly. Regardless the death cause in the age group of 70, 61% of AD patients are expected to die before 80 compared to only 30% for non-AD people [171]. The death rate of AD increases with the age dramatically [136]. Even for the surviving AD patients, some research reported that 75% of them have to admitted into a nursing home by age 80 but only 4% for the general population [171]. The long duration of illness before death may also has great negative impact for patients, caregiver and the society [136].

3.1.10 Understanding of AD in TCM

In TCM, the semiologic name “Chidai” (which means dementia) was first used by a famous TCM doctor Zhang Jing-Yue in 1624. Although there was no corresponding semiologic name used for AD specifically in TCM ancient books, AD was covered in the disease of “Chidai” described in terms of TCM. There is
no distinction between AD and VD based on TCM theory [172]. “Geriatric dementia” was validated to be the term of dementia in elderly used in TCM by a conference organized in Lanzhou of China in 1988 [173]. The key pathological features of dementia in TCM were suggested to include: (1) deficiency of vital energy of the kidney, heart and spleen; (2) stagnation of blood and/or phlegm [172]. Dementia was further classified into six subtypes based on the TCM theory: 1) the Bone Marrow deficiency syndrome; 2) the Liver and Kidney Yin deficiency syndrome; 3) the Spleen and Kidney Yang deficiency syndrome; 4) the Qi stagnation and Blood stasis syndrome; 5) the Phlegm Turbid blocking Orifice syndrome; and 6) the Heart and Liver Fire syndrome. In fact, dementia is a complex disease which is combination of “deficiency of origin” and “excess of superficiality” in TCM. Hence, dementia patients are not possible to diagnosis as only one subtype in TCM but a mixed condition.

3.1.10.1 Treatment of AD in TCM

In general, the principles for treating dementia are supplementing the Qi, activating blood circulation, clearing phlegm and opening orifices, nourishing liver, kidney and spleen as well as clearing and activating the channels and collaterals. TCM were useful in treating dementia patients with relatively less AE.
Although much more TCM herbs extract, like Ginkgo biloba, were reported to be effective in treating dementia [174], treating the patient by a specific TCM herbal formula holistically and individually according to the syndrome differential treatment principle based on TCM is still the main idea of TCM. Nevertheless, there is still lack of scientific evidence to support the use of TCM as a conventional therapy for AD clinically due to quality of TCM clinical trials are limited and insufficient. High quality RCT is needed to support the usage of TCM in treating AD.
3.2 The Pilot RCT of DTD on Treating AD

3.2.1 Introduction

AD is the most common type of dementia in the elderly [175]. It is an irreversible, progressive NDD characterized by loss of cognitive functions, disturbing behavioral, and daily living difficulties [176]. Atrophy is progressing in all parts of the brain, especially in the hippocampus region, due to nerve cell death and tissue loss [177]. The number of people suffering from dementia over the world is predicted to be raised from 24.3 million in 2005 to 81.1 million in 2040 [132]. In America, a new case of AD is estimated to be diagnosed for every 33 seconds in 2050 [178].

The devastating impact of AD not only on patients, but also on their caregivers, the communities, and even the health care system in general [129]. Although there are many existing studies on various aspects of AD, including its basic biology, no treatment method has been found to alter the course of the disease [179]. Current pharmacological treatment for AD such as AchEI and Memantine are just symptomatic and commonly associated with some side effects, such as nausea, vomiting, dizziness, and anorexia [163]. Given that the efficacy is mild but with
some side effects, patients often seek for alternative treatments [174].

In TCM, AD is described in terms of TCM principles; it could be caused by (1) deficiency of vital energy of the kidney, heart and spleen; (2) stagnation of blood and/or phlegm [172]. The guideline for classified dementia into different sub-types according to the TCM theory was published in 1990, which symptoms of “phlegm turbidity obstructing the orifices” (PTOO) is considered to be one of the major contributing factors to AD [173]. Thus, the primary TCM strategy for treating AD is to “resolve phlegm in order to open the orifices” [180].

“Di-tan decoction” (DTD) was a classic Chinese medicine formula developed by Dong Su, a famous TCM doctor, in 1449 with the specific function of “resolving phlegm to open the orifices” [181]. It has been frequently used to treat the symptoms that are now defined as AD clinically [182, 183]. Several studies have attempted to verify the clinical effects of DTD in biochemical terms in the recent years. Laboratory studies have shown that the memory impairment of AD model mice was significantly reduced by DTD [184, 185]. In the brain tissue of AD mice which were treated by DTD, Ach and acetylcholine transferase (ChAT) were significantly increased, while acetylcholine esterase (AchE) was decreased [186].
Another study indicate that DTD may inhibit the decline of DA content in brain tissue of model mice as well [187].

There was no clinical trial using DTD as the main intervention for treating AD in our previous systemic review [18]. While, for the AD clinical trials that had involved DTD as an adjunct intervention, we found that most of them support the efficacy of DTD in treating AD. However, the evidence for recommending DTD in clinical practice derives from studies that were methodologically flawed. None of them was a RCT. They not only lacked of randomization, blinding, and the use of control groups, but also failed to define inclusion and exclusion criteria and the quality of the intervention medicine [18]. Because of the methodological problems in previous studies, evidence to suggest that DTD is effective in treating AD is not strong. There is a lack of conclusive recommendation for clinical trial.

As there is no basic information of DTD to conduct a comprehensive AD clinical trial, a rigorous pilot study focusing on efficacy and safety of DTD for treating AD will be needed before conducting a full-scale clinical trial. In this study, we will evaluate the efficacy and safety of DTD in AD patients by a RCT. This study is a randomized, double-blinded, placebo-controlled study, with a restrict
inclusion and exclusion criteria and a clearly defined quality control intervention medicine. The results from this study can provide critical information on sample size and treatment regimen for conducting a full-scale clinical trial later.

3.2.2 Objectives

1. To observe and assess the clinical AD treatment efficacy and safety of DTD, in particular, to observe and assess the effects of DTD on alleviating AD symptoms;

2. To observe and assess the effects of DTD based on the cognitive function, and activities of daily living (ADL) of AD patients.

3.2.3 Hypothesis

AD could be caused by deficiency of vital energy of the kidney, heart and spleen, and stagnation of blood and/or phlegm, while, PTOO is one of the major contributing factors to AD. We hypothesize that DTD with the specific function of “resolving phlegm to open the orifices” can is effective and safe for the treatment of AD patients who have the syndrome of PTOO according to TCM theory.
3.2.4 Research Methodology

3.2.4.1 Study design

This study is a double-blinded, randomized, placebo-controlled, add-on trial. Patients with mild to moderate AD were randomly assigned to receive 24 weeks of either active herbal treatment or placebo (in a 1:1 ratio); they were followed for a further 6 weeks’ observation period without treatment.

I) Participants

i) Inclusion criteria

Adults between 60-90 who (1) had been clinically diagnosed with AD based on the criteria of NINCDS/ADARA [155], and (2) presented symptoms classified as PTOO (Appendix 6) as defined by the Guidance for Clinical Research of New Chinese Herbal Medicine [110] during the screening visit, were eligible. The diagnostic criteria of PTOO include dementia, heavy-headedness and spitting phlegm. Additional inclusion criteria were (1) mild to moderate dementia with ≥2 on Clinical Dementia Rating Scale (CDR) [188]; (2) receiving a stable dose of anti-dementia medication (i.e. Donepezil, Rivastigmine and Memantine) for at
least 4 weeks before the start of treatment; and (3) normal liver and renal function.

ii) Exclusion criteria

Patients who had mixed dementia which means also had any other type of dementia (i.e. VD), and/or other NDD (i.e. PD), depression (defined by a score of ≥8 on the 15-item Chinese version of the Geriatric Depression Scale [189]), or who were unwilling to cooperate with treatment procedures were excluded. For those who had participated in other trials within 30 days of the start of this trial as well as women who were pregnant or breastfeeding were also be excluded.

iii) Informed consent form

Written informed consent (Appendix 7) was obtained from every patient before they participated in any study-related activity. Detail of the trial and form was explained to every patient and their caregivers face to face before they signed any document.
II) Settings and Locations

This clinical study was carried out at the Hong Kong Baptist University Chinese Medicine Specialty Centre, which is a Chinese medicine clinic under the School of Chinese Medicine of Hong Kong Baptist University. Insurance was bought for every patient under the study in this clinic.

III) Registration and standard

It had been approved by the Ethics Committee of the Hong Kong Baptist University’s Institutional Review Board (code: HASC/11-12/24) and registered on the Chinese Clinical Trial Registry (ChiCTR-TRC-12004548). This study report followed the guidelines of CONSORT.

IV) Recruitment procedures

Three methods were used to recruit participants with AD. The first source of candidates was referral from two public Western medicine hospitals in Hong Kong (Prince of Wales Hospital and Queen Elizabeth Hospital) from our co-investigator, Prof. Vincent Mok, and our research teammate, Dr. Andrew Chan. The second source was referral from the Chinese medicine clinic of Hong Kong
Baptist University. A third source of candidates was those who respond to advertisements published in local newspapers and newsletters of local AD societies.

We plan to recruit at least 40 patients, of which 20 for the DTD group and 20 for the placebo group, in this study. All patients diagnosed with AD were referred to an assessor (Ka-Kit Chua), a registered Chinese Medicine practitioner in Hong Kong, for further assessment and recruitment. The aim, procedures, nature of study and possible side effects of DTD were explained by the assessor; then each patients and their caregivers was asked to sign a written consent to take part in the study. Patients were informed that they were free to withdraw at any time during the study.

All patients were undergo a 2-week run-in period, in which they had to keep their Western medicine and supplement dosages fixed. Their blood were tested to check liver function (ALT / SGPT, AST/ sSGOT, alkaline phosphatase, gamma glutamyltransferase, total bilirubin, total protein, albumin) and renal function (urea, creatinine, sodium, potassium, chloride, bicarbonate) in a lab test center designated for the project.
V) Sample size calculation

It is noted that the sample size calculation does not apply to this study. Normally, 10-20 patients in each group would be sufficient to implement the method of a pilot study [190]. Hence, totally 40 patients were required to recruit in this trial to provide sufficient data for simple size calculation in the future comprehensive RCT of treating of AD by DTD.

VI) Randomization and masking

This study was a double-blind, randomized, placebo-controlled, add-on trial. Recruited patients were randomly assigned to receive 24 weeks of either active herbal treatment (Group A) or placebo (Group B) and followed for a further 6 weeks observation period without treatment.

Group A: DTD + routine western medications;

Group B: Placebo + routine western medications.

i) Sequence generation and allocation concealment

The randomization sequence was generated by SPSS 19.0 package (SPSS,
Chicago, IL). The sequence was password-protected and kept in a computer by Lei-Lei Chen. Group allocation was simple randomization in a ratio of 1:1 to either active treatment group or placebo group. The sequential number was contained in a sealed opaque envelop and distributed to assessors.

ii) Blinding

Patients, investigators and all sponsoring parties were masked to treatment allocation until the end of this clinical trial. When there is a serious AE, the event will be discussed between the principal investigator Chinese medicine expert Prof. Min Li, and the co-investigator neurology specialist Prof. Vincent Mok to consider unblinding.

VII) Study medication

The herbal medicine under study is DTD (Appendix 8). It is composed of Arisaema Cum Bile (DanNanXing in Chinese), Pinelliae Rhizoma Praeparatum (FaBanXia in Chinese), Aurantii Fructus Immaturus (ZhiShi in Chinese), Poria (FuLing in Chinese), Citri Reticulatae Pericarpium (ChenPi in Chinese), Acori Tatarinowii Rhizoma (ShiChangPu in Chinese), Ginseng Radix Et Rhizoma
(RenShen in Chinese), Bambusae Caulis In Taenias (ZhuRu in Chinese), Glycyrrhizae Radix Et Rhizoma (GanCao in Chinese), Zingiberis Rhizoma Recens (ShengJiang in Chinese) and dextin [181]. The placebo is made of caramel (2%), gardenia yellow pigment (0.05%), sunset yellow (0.02%), tartrazine (0.02%), dextrin (95%) and broadleaf holly leaf (2.91%) [111] following the guideline of China Food and Drug Administration. The granules were produced in a single batch (DTD batch no.: A12074 Placebo batch no.: A120817) strictly in compliance with standards of Good Manufactory Practice (GMP) and Chinese Pharmacopoeia 2010 to ensure the stability and homogeneity of the composition as produced by PuraPharm Pharmaceuticals Company Limited.

The chemical compositions of the final products were analyzed for contamination with heavy metals, toxic elements, microbe and pesticide residues; both final products were analyzed for stability and adherence to quality standards. The active treatment granules and the placebo granules had identical appearance and smell, and both had been packed in sealed opaque aluminum sachets and put in zip lock bags (10 sachets each). Only the treatment code was printed on the package to ensure successful blinding of patients [42]. One sachet contains 13.5 g, a dosage equivalent to 67.5g herbs. All herbal and placebo granules were
distributed by Lei-Lei Chen with both written and verbal instructions for each participant. Patients were instructed to take the granules orally by dissolving a sachet of granules in 150ml hot water stirring well, then drinking, two times per day, at least two hours apart from taking any routine Western medication.

Patients were allowed to discontinue the study granules temporarily if any AE occur. They were instructed to report such events to a special e-mail account (bucmad@hkbu.edu.hk) or by a direct telephone line (+852 6700-8538). Additional treatments for a newly occurring illness, e.g. flu or diarrhea, or AE during the study were allowed but must be reported to the assessors.

VIII) Primary outcome, secondary outcomes and its assessment

A positive primary outcome of this study were an increase of at least 4 points in the ADAS-cog [191] total score; this is considered to be a clinically meaningful increase [192]. Total scores of the ADAD-cog, Chinese version of Mini-Mental State Examination (C-MMSE) [193, 194] and Chinese version of Disability assessment for dementia (C-DAD) score [195] were used as secondary outcomes.
ADAS-cog (Appendix 9 for the Chinese version provided by co-investigator Prof. Vincent Mok) is the subscale of Alzheimer’s Disease Assessment Scale (ADAS), which was designed to measure the severity of AD [196], focusing on the cognitive assessment. Normally, it contains eleven tasks measuring memory, praxis, and language: 1) word record; 2) naming objects and fingers; 3) following commands; 4) constructional praxis; 5) ideational praxis; 6) orientation; 7) word recognition; 8) remembering test directions; 9) spoken language; 10) comprehension; and 11) word-finding difficulty. It is commonly used in clinical trial assessment and most adequate for patients with moderate AD [197].

Mini-Mental State Examination (MMSE) (Appendix 10 for the Chinese version) is the most commonly used short cognitive assessment scale developed in 1975 [198]. It contains eight categories: 1) orientation to time; 2) orientation to place; 3) registration; 4) attention and calculation; 5) recall; 6) language; 7) repetition; and 8) complex commands. It is used to be a great assessment scale, it may be retired as it has a number of shortcomings such as limited effectiveness for detecting cognitive impairment [199].
The disability assessment for dementia (DAD) (Appendix 11 for the Chinese version) is a commonly used structured interview assessing the basic and instrumental ADL of dementia patients. It contains 40 items under ten domains: 1) hygiene; 2) dressing; 3) continence; 4) eating; 5) meal preparation; 6) telephoning; 7) going on an outing; 8) finance and correspondence; 9) medications; and 10) leisure and housework. This scale is focusing on the actual functional ability of the patients which may give a better overview treatment effectiveness with the cognitive assessment [200].

Outcome measurements were carried out during the study visits at weeks 0, 12 (half of treatment), 24 (end of treatment) and 30 (end of observation period). Safety assessment, which includes reporting of AE, measurement of vital signs and physical examination, were carried out throughout the study. In addition, laboratory safety screening of liver and renal function was performed at week 24. Bilingual assessors, i.e. Ka-Kit Chua, Kim-Pong Tse, and Pauline Kwan, trained by the same neurology specialist Prof. Vincent Mok and clinical psychologist Dr. Adrian Wong, were blind to the treatment allocation.
Clinical assessment was rescheduled within 7 days after the scheduled clinical visit in case of any unexpected condition such as severe weather conditions. Phone call reminders were given to the caregivers one day before the days of assessment.

A home diary was given to each study participant’s caregiver to record treatment and changes in the participant’s medical condition. Formal instruction for the home diary was given during the first visit. Revision and checking of the diary was carried out with the caregiver during each formal visit by the assessors. Compliance in taking the treatments was determined by the record of the diary and the number of the returned medicine / placebo packages.

**IX) Data management and monitoring**

All the data were entered and stored in a password-protected computer. Hardcopy were kept in a locker. To ensure high quality of the data, double data entry method was used. All documents and collected data were kept for 7 years after the finish of study and then will be destroyed.
X) Statistical analysis

The proportion of patients with at least a 4-point change in ADAS-cog and MMSE and the scores on C-DAD were compared between the active treatment and placebo groups using the Chi-Squared test and independent sample t test, respectively. Missing data was input using the LOFC approach. All patients randomized with at least one post-randomization measurement were included in the primary analysis to follow the intention-to-treat principle. Analyses were done with SPSS 19.0 package (SPSS, Chicago, IL).

To get a more comprehensive picture of the efficacy of DTD, a post-hoc analysis of the differences in the change of ADAS-cog and C-DAD sub-scores of the active treatment group were compared between the active and placebo groups. To reduce the number of statistical comparisons, analyses were performed with a hierarchical approach. To begin, the scores of ADAS-cog at week 24 (end of treatment) for the active treatment and placebo groups were compared. If the difference was deemed statistically significant at a 2-sided $\alpha$-level of 0.05, the scores of ADAS-cog at week 12 (half of treatment) and week 30 (end of observation period, i.e. without treatment) were compared between groups. C-DAD was analyzed in the same manner as ADAS-cog.
XI) Compliance strategy

This was a 30-week clinical trial, in which subjects were needed to take study medication for 24 weeks with 8 regular visits (week 0, 4, 8, 12, 16, 20, 24 and 30). In order to maximize subjects’ compliance, first, we had a thorough consent process for all participants; we had explained in detail the study schedule, potential side effects of treatment, and the responsibilities of the subjects. Second, we had screened the potential subjects carefully during a 2-week run-in period in order to exclude ineligible patients or patients who were unlikely to comply with treatment regimen before randomization. Third, we had tried to prevent dropouts by providing ongoing support to patients. A special e-mail account and a direct telephone line were set up for this clinical trial which could enable the study team to personally communicate with the patients. An information sheet was given to each patient providing them and their caregivers with means of urgent contact. Extra visits and free medical care were arranged for any participant who feels harmed by the trial protocol. Fourth, this was an add-on design [117] which means that the study treatment was added to their existing treatment. Certainly those participants receiving the placebo should not experience any difference in their condition, while those receiving the DTD should improve or at least remain the same.
XII) Early termination

The trial would be terminated for a specific participant if she/he: (1) develops severe adverse side effect(s); (2) shows hypersensitivity towards DTD; (3) develops some other life-threatening condition or disease; or (4) chooses to participate in another Chinese herbal medicine research project. In addition, any participant may voluntarily withdraw.

The whole research plan would be terminated under the following circumstances: (1) presence of serious adverse effect(s) related to Chinese herbal medicine with supportive evidence; (2) completion of all follow-up assessments.

3.2.5 Results

Figure 3 is a flow chart depicting the participant screening and recruitment in this study. Demographic data and baseline scores are summarized in Table 5. A total of 66 patients were screened for eligibility, and 40 participants were enrolled. Two patients withdrew from the study due to personal reasons after randomization and before the start of treatment. Among the remaining 38 patients (14 male; 24 female; mean ages 74.45 ± 9.01 years; mean duration of AD 2.32 ± 1.70 years),
21 were assigned to the DTD group, 17 to the placebo group. Six participants dropped out during the study due to reasons listed in Figure 3. Nineteen participants in the DTD group and 13 in the placebo group completed the study.

*Participation in the study could be discontinued because of non-compliance with dosing or visits.

†Patient’s choice to discontinue for reasons unrelated to the study drug.
Table 5. Baseline characteristics of AD patients in the DTD trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TCM group (n= 21)</th>
<th>Control group (n= 17)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76.57 ± 8.16</td>
<td>71.82 ± 9.55</td>
<td>0.107&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/13</td>
<td>6/11</td>
<td>0.859</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>2.58 ± 1.81</td>
<td>1.99 ± 1.54</td>
<td>0.290&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AchEI, n (%)</td>
<td>16 (76.2)</td>
<td>15 (88.2)</td>
<td>0.341&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>NMDA, n (%)</td>
<td>2 (9.5)</td>
<td>1 (5.9)</td>
<td>0.679&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Baseline scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR</td>
<td>1.05 ± 0.67</td>
<td>0.77 ± 0.40</td>
<td>0.134&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MMSE</td>
<td>17.43 ± 5.61</td>
<td>16.82 ± 4.88</td>
<td>0.728&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>140.88 ± 18.35</td>
<td>145.68 ± 22.17</td>
<td>0.470&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>72.79 ± 9.73</td>
<td>74.27 ± 10.50</td>
<td>0.656&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>65.02 ± 8.48</td>
<td>68.06 ± 11.72</td>
<td>0.361&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± S.D.

<sup>a</sup>p-value was comparing the difference between two groups in baseline

<sup>b</sup>treatment group compared with placebo group by independent t-test

<sup>c</sup>treatment group compared with placebo group by Chi-square test with continuity correction
3.2.5.1 Analysis of ADAS-cog

In the primary analysis, we observed a trend of improvement, a decreased score was obtained at week-24 in DTD group that suggested an improvement in cognitive, in the total score of ADAS-cog in the DTD group though the difference was not statistically significant \( (p = 0.315, \text{Table 6}) \) relative to the placebo group. In comparison, the decreased score obtained at week-24 in the placebo group was lesser than the DTD group. In the post-hoc analyses, we observed a continue trend of improvement, a decreased score, throughout the trial from week-16 to week-30 in DTD group (Table 7 & Figure 4) in the total score of ADAS-cog in the DTD group relative to the placebo group. Further analyses performed on the subscores of ADAS-cog between the two groups revealed that the DTD group showed non-significant trends of improvement in ideational praxis (mean diff. = -0.54, 95% CI: -1.20 to 0.11, \( p = 0.100 \)) and in comprehension (mean diff. = -0.26, 95% CI: -0.58 to 0.06, \( p = 0.106 \)) compared to the placebo group (Table 6).
Table 6. Efficacy result of DTD on AD patients at Week 24

<table>
<thead>
<tr>
<th>Cognitive subscale of Alzheimer’s Disease Assessment Scale (ADAS-cog)</th>
<th>DTD</th>
<th>Placebo</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Score</strong></td>
<td>-2.05 ± 5.26</td>
<td>-0.59 ± 2.98</td>
<td>0.315</td>
</tr>
<tr>
<td><strong>D1 Word recall task</strong></td>
<td>-0.10 ± 0.94</td>
<td>-0.18 ± 1.24</td>
<td>0.820</td>
</tr>
<tr>
<td><strong>D2 Naming objects and fingers</strong></td>
<td>0.00 ± 0.71</td>
<td>0.24 ± 0.66</td>
<td>0.302</td>
</tr>
<tr>
<td><strong>D3 Commands</strong></td>
<td>-0.14 ± 0.79</td>
<td>-0.12 ± 0.60</td>
<td>0.914</td>
</tr>
<tr>
<td><strong>D4 Constructional praxis: figures</strong></td>
<td>-0.14 ± 0.66</td>
<td>-0.12 ± 0.78</td>
<td>0.914</td>
</tr>
<tr>
<td><strong>D5 Ideational praxis</strong></td>
<td>-0.19 ± 0.87</td>
<td>0.35 ± 1.12</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>D6 Orientation</strong></td>
<td>-0.14 ± 1.24</td>
<td>-0.53 ± 1.13</td>
<td>0.325</td>
</tr>
<tr>
<td><strong>D7 Word recognition test</strong></td>
<td>-0.76 ± 3.03</td>
<td>-0.06 ± 1.25</td>
<td>0.377</td>
</tr>
<tr>
<td><strong>D8 Remembering test instructions</strong></td>
<td>-0.48 ± 1.47</td>
<td>-0.24 ± 0.83</td>
<td>0.551</td>
</tr>
<tr>
<td><strong>D9 Spoken language ability</strong></td>
<td>0.00 ± 0.32</td>
<td>0.00 ± 0.00</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>D10 Word finding difficulty</strong></td>
<td>0.05 ± 0.38</td>
<td>-0.06 ± 4.3</td>
<td>0.425</td>
</tr>
<tr>
<td><strong>D11 Comprehension</strong></td>
<td>-0.14 ± 0.57</td>
<td>0.12 ± 0.33</td>
<td>0.106</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability assessment for dementia score (DAD)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Score</strong></td>
<td>3.35 ± 7.95</td>
<td>4.42 ± 12.91</td>
<td>0.755</td>
</tr>
<tr>
<td><strong>D1 Hygiene</strong></td>
<td>2.89 ± 9.76</td>
<td>3.78 ± 15.23</td>
<td>0.828</td>
</tr>
<tr>
<td><strong>D2 Dressing</strong></td>
<td>2.04 ± 10.39</td>
<td>4.20 ± 8.40</td>
<td>0.493</td>
</tr>
<tr>
<td><strong>D3 Continence</strong></td>
<td>1.59 ± 7.27</td>
<td>1.96 ± 8.08</td>
<td>0.882</td>
</tr>
<tr>
<td><strong>D4 Eating</strong></td>
<td>2.38 ± 10.91</td>
<td>1.47 ± 6.06</td>
<td>0.760</td>
</tr>
<tr>
<td><strong>D5 Meal preparation</strong></td>
<td>7.29 ± 20.17</td>
<td>-5.13 ± 32.90</td>
<td>0.222</td>
</tr>
<tr>
<td><strong>D6 Telephoning</strong></td>
<td>10.71 ± 29.95</td>
<td>6.25 ± 19.36</td>
<td>0.607</td>
</tr>
<tr>
<td><strong>D7 Going on an outing</strong></td>
<td>-2.58 ± 26.46</td>
<td>2.06 ± 17.24</td>
<td>0.540</td>
</tr>
<tr>
<td><strong>D8 Finance and correspondence</strong></td>
<td>1.75 ± 28.27</td>
<td>2.94 ± 34.48</td>
<td>0.910</td>
</tr>
</tbody>
</table>
D9 Medications 3.17 ± 17.97 11.11 ± 37.09 0.399
D10 Housework -3.57 ± 17.79 8.33 ± 25.17 0.097
D11 Leisure 0.00 ± 55.28 4.76 ± 17.82 0.760

<table>
<thead>
<tr>
<th>Mini-Mental State Examination (MMSE)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Score</td>
<td>0.86 ± 2.85</td>
<td>1.94 ± 3.09</td>
<td>0.269</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Dementia Rating Scale (CDR)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>-0.24 ± 0.33</td>
<td>0.09 ± 0.26</td>
<td>0.268</td>
</tr>
</tbody>
</table>

*p-value was comparing the score changes at week-24 between DTD group and placebo group by independent sample t-tests.
Values are given as mean ± S.D. Values in DTD group and placebo group are the score changed in the same group between week-24 and baseline (score at week-24 minus score at the baseline)

Figure 4: ADAS-cog total score throughout the whole AD trial

**ADAS-cog**

**Total score**

![Graph showing ADAS-cog total score throughout the whole AD trial.](image)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Week 12 DTD</th>
<th>Week 12 Placebo</th>
<th>Week 24 DTD</th>
<th>Week 24 Placebo</th>
<th>Week 30 DTD</th>
<th>Week 30 Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog</td>
<td>-0.81 ± 4.30</td>
<td>-1.00 ± 3.14</td>
<td>-2.05 ± 5.26</td>
<td>-0.59 ± 2.98</td>
<td>-1.90 ± 5.31</td>
<td>-0.12 ± 3.31</td>
</tr>
<tr>
<td>Total score</td>
<td>p-value = 0.880</td>
<td>p-value = 0.315</td>
<td>p-value = 0.235</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAD</td>
<td>2.68 ± 9.38</td>
<td>2.20 ± 12.99</td>
<td>3.35 ± 7.95</td>
<td>4.42 ± 12.91</td>
<td>1.85 ± 7.31</td>
<td>2.18 ± 11.08</td>
</tr>
<tr>
<td>Total score</td>
<td>p-value = 0.918</td>
<td>p-value = 0.755</td>
<td>p-value = 0.913</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAD D10</td>
<td>-1.98 ± 24.14</td>
<td>-1.47 ± 25.72</td>
<td>-3.57 ± 17.79</td>
<td>8.33 ± 25.17</td>
<td>1.59 ± 1.59</td>
<td>0.98 ± 24.63</td>
</tr>
<tr>
<td>p-value = 0.950</td>
<td>p-value = 0.097</td>
<td>p-value = 0.938</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>1.00 ± 2.88</td>
<td>1.71 ± 2.62</td>
<td>0.86 ± 2.85</td>
<td>1.94 ± 3.09</td>
<td>1.43 ± 2.06</td>
<td>1.35 ± 3.08</td>
</tr>
<tr>
<td>Total score</td>
<td>p-value = 0.439</td>
<td>p-value = 0.269</td>
<td>p-value = 0.929</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR stage</td>
<td>0.00 ± 0.03</td>
<td>-0.24 ± 0.09</td>
<td>-0.24 ± 0.09</td>
<td>0.09 ± 0.48</td>
<td>-0.48 ± 0.06</td>
<td>0.06 ± 0.06</td>
</tr>
<tr>
<td>p-value = 0.532</td>
<td>p-value = 0.268</td>
<td>p-value = 0.214</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-value was comparing the score changes at different time point between DTD group and placebo group by independent sample t-tests.

Values are given as mean ± S.D. Values in DTD group and placebo group are the score changed in the same group between different time point and baseline (score at different time point minus score at the baseline).
3.2.5.2 Analysis of DAD, MMSE and CDR

In the secondary analysis, there were no significant differences in the total score of DAD or MMSE. Although there was a trend of improvement in the meal preparation of DAD subscore in the DTD group at week-24, no statistically significant differences were found in it ($p = 0.222$) and other subscore of DAD (Table 6) in the further analyses. On the other hand, there was a worsen trend in the housework of DAD subscore in the DTD group. Post-hoc analysis was done on the housework park of DAD, however, there was not continuous trend of worsen in the DTD group throughout the trial (Table 7).

**Figure 5: CDR stage throughout the whole AD trial**

![CDR stage throughout the whole AD trial](image_url)
Post-hoc analyses were also done on the total score of all secondary outcomes and CDR. Improvement trend was observed in the DTD group throughout the trial in the CDR stage, though it was not significant (Table 7 & Figure 5). No specific trend was found in the total score of DAD or MMSE (Table 7).

**Table 8. AE reported by > 5% of AD patients in each group**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. of patients (%)</th>
<th>DTD (N=21)</th>
<th>Placebo (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint pain</td>
<td>1 (4.8)</td>
<td>4 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>0 (0.0)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Skin rashes</td>
<td>2 (9.5)</td>
<td>2 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (4.8)</td>
<td>2 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>3 (14.3)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (4.8)</td>
<td>2 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>1 (4.8)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4.8)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Numbness</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Cramp</td>
<td>1 (4.8)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0 (0.0)</td>
<td>1 (5.9)</td>
<td></td>
</tr>
</tbody>
</table>
3.2.5.3 Withdrawal and AE

For the withdrawal and adverse events, six patients (2 (9.5%) [DTD] vs 4 (23.5%) [Placebo], $p = 0.239$) discontinued treatment after randomization. Among these 6 patients, 2 withdrew because of AEs (1 in each group). During the treatment phase, two patients (9.5%) in the DTD groups and two patients (11.8%) in the placebo group had serious AEs: one patient had hyperglycaemia (placebo), one had skin rashes (placebo), one had cramp (DTD), and one had fall (DTD). No deaths were recorded during the trial. AEs were reported by at least 5% of patients in each group; these are presented in Table 8.

3.2.6 Discussion

In this RCT study, there was no strong evidence supporting the hypothesis that DTD improve the cognitive condition and daily activity represented by the total score of ADAS-cog and total score of DAD. However, a continuous reduction trend in the cognitive impairment was noted by the ADAS-cog total score and supported by the CDR stage in the post-hoc analyses. Also, improvement trend in ideational praxis and comprehension were suggested by further analysis of ADAS-cog subscore, without affecting other features of AD. Although there was a
worsen trend of housework in DTD group at week-24, it may be just a false negative as it was not consistent throughout the study. DTD was well tolerated. Discontinuation due to AE occurred with the same frequency in the DTD group (1 patient) as in the placebo group (1 patient). Further targeted studies on the effect of DTD on ideational praxis and comprehension need to be performed to confirm these observations.

AD, as a progressive neurodegenerative disorder, has devastating impacts not only on patients but also on family members, friends, and caregivers; a cure would bring immeasurable relief and hope to countless people. Unfortunately, western pharmacological research has been unsuccessful in finding effective treatment without serious side effects [163]. In this case, Chinese herbal medicine may have something to offer. Chinese medicine has been used to treat neurological diseases for thousands years with efficacy, safety, and relatively few side effects—albeit without rigorous and objective testing [201]. In this trial, the improvement trend of cognitive condition assessed by the ADAS-cog and CDR showed continual effect even after the patients had stopped the medication for 6 weeks. It suggested that the effect of DTD may not just symptomatic; instead it may alter the pathophysiological processes underlying cognitive impairment.
In TCM, AD is a complex condition which is combination of “deficiency of origin” and “excess of superficiality”. AD patients are not possible to diagnosis as only one subtype in TCM but a mixed condition in reality. Hence, in TCM clinical practice, DTD is given in combination with other herbs and the dosage and combinations are continuously adjusted based on patients’ symptoms and conditions. The effects observed in our trial may only partially explain clinical results as DTD is taken in isolation during our study with the standard dosage dictated by the Chinese Pharmacopoeia [121], which the dosage may not be enough for AD patients clinically.

For the limitation, we aimed to recruit mild to moderate AD patients, but most of the recruited subjects were only in mild condition. In fact, it is quite difficult to recruit AD patients in Hong Kong. AD patients must get the support and approval from their caregivers when participant in our clinical trial. As a number of moderate AD patients in Hong Kong have been sent to nursing home already, their caregivers often refuse to support them participating in an out-patient clinical trial. Future clinical trials carrying in the nursing home or hospital could be a possible way to recruit more moderate or even advanced AD patients.
On the other hand, although improvement trend had been observed in ADAS-cog and CDR, it is strange that there was no different in the total score of MMSE. In fact, MMSE is one of the most commonly used assessment tool for dementia; it has been a standard measurement in most discipline. It is highly doubted that AD patients may had already developed learning effect on MMSE even before they participated in our trial. This may reduce the assessing accuracy of MMSE. It is suggested that other high sensitivity, lesser used but validated cognitive assessment scale, like the Montreal Cognitive Assessment (MoCA) [202], could be used to replace MMSE in the future study.

In conclusion, this randomized trial was the first rigorous testing of DTD for the treatment of AD patients. Although there was no significant different in the primary and secondary outcomes, a continuous improvement trend was observed throughout the trial in the ADAS-cog total score and CDR stage. This result can provide sufficient data, notable in simple size calculation and possible effective domain, for a further large-scale and comprehensive RCT of DTD in treating AD.
CHAPTER IV: General Conclusion and Future

Considerations

NDD are very common in the aging population, of which PD and AD are the two most common. Since the etiology of the neuronal death in these diseases remains unclear, currently no curative therapy is available. As the patients may lose their self-care ability at the advanced stage, a significant manpower and resource is required for taking care of them. The elderly population is becoming larger and larger; NDDs are therefore a significant burden on the society.

Chinese medicine is the most commonly used alternative medicine, it have been used to treat certain diseases, which based on their symptoms we now know that they are PD and AD, for thousands of years. Although our pervious systematic review reports that the quality of current Chinese medicine clinical trials related to this area had limited internal validity due to methodological flaws and insufficient data reporting, patients did show some improvement in our RCTs which were reported in chapter 2 and 3. These studies follow the standard of CONSORT and registered on the WHO international clinical trials registered organization
registered platform. They do provide evidence for the efficacy and safety of the two specific Chinese medicine decoctions (CMD) in treating PD and AD.

In the PD trial, JWLJZT did show some effects in relieving the NMS, specifically in gastrointestinal problems and mood disorder, of PD patients who were having the DSQ condition over 32 weeks with minimal side effects. This result suggested a possible treatment for the NMS of PD as there is lack of effective therapy currently. Also, this result suggested a possible and commonly treating direction of TCM, replenishing the “Spleen Qi”, in PD other than replenishing the “kidney yin”. As most PD patients may have the DSQ condition based on our previous survey (data not publish yet), JWLJZT could become a routine treatment on NMS of PD in the future. Further clinical studies focusing on the mood disorder and gastrointestinal function improvement of PD patients by JWLJZT are warranted.

In the AD trial, DTD did show a trend in relieving or controlling the cognitive impairments, although it is not significant, of AD patients who were having the PTOO condition over 24 weeks with minimal side effects. This result provided the basic information for conducting a full-scale and comprehensive clinical trial of DTD as the main intervention for treating AD in the future. Also, further study
focusing on the prevalence rate of PTOO in AD patients is highly suggested.

In fact, JWLJZT and DTD are just 2 examples of TCM. There are still many possible CMD that may be of use for treating NDD. These two RCT are served as references for the future RCT on CMD. On the other hand, further study focusing on the effective dosage, pharmacologic mechanism of JWLJZT and DTD are needed to give a fuller picture as well as better support for using them in human being as a routine treatment.

Since there is no in-patient service of TCM in Hong Kong currently, it is impossible to conduct a TCM RCT focusing on advanced disease patients in an out-patient setting clinical trial. Co-operation with the western medicine hospital could be a better way to face this limitation. It will be great advantage if there is a Chinese medicine hospital in Hong Kong, which may be the best solution for TCM RCT in future.

In conclusion, in this thesis:

1. Some NDD, PD and AD, symptoms or condition could be relieved or controlled by Chinese medicine, JWLJZT and DTD; further study focusing on the specific symptoms of a NDD is suggested;
2. Using of Chinese medicine, JWLJZT and DTD, in treating NDD, PD and AD, were safe, further pharmacological studies on the CMD are needed to show a full picture;

3. There were no clear AE using Chinese medicine, JWLJZY and DTD, with Western medicine in treating NDD, PD and AD, with two hours interval, further studies focusing on the interaction between them are suggested;

4. The setting and design of the above RCT for Chinese medicine could serve as an example for future clinical study on CMD, more rigid RCT of Chinese medicine are needed to enhance the evidence of TCM in treating NDD.
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APPENDIX

Appendix 1: Criteria of deficiency of Spleen Qi (DSQ)

1. 证候（参照1986年全国中西医结合虚证与老年病研究学术会议修订“中医虚证辨证参考标准”）
   (1) 主症 食少纳呆，体倦乏力，食后或午后腹胀，大便异常（溏、烂、先硬后溏、时溏时硬）。
   (2) 次症 神疲懒言，口淡不渴，腹痛绵绵，恶心呕吐，脘闷，肠鸣，面色萎黄，浮肿，排便无力，舌质淡，舌体胖或有齿印，苔薄白，脉细弱。
   具备主症2项；或主症1项加次症2项，即可诊断。

2. 症状分级量化（使用时应根据各症状在证候积分中的权重，赋予不同分值） 详见表18-1。

<table>
<thead>
<tr>
<th>症状</th>
<th>轻</th>
<th>中</th>
<th>重</th>
</tr>
</thead>
<tbody>
<tr>
<td>食少纳呆</td>
<td>无食欲，但保持原食量</td>
<td>无食欲，饭量比病前减少1/3</td>
<td>饭量减少2/3以上</td>
</tr>
<tr>
<td>体倦乏力</td>
<td>稍倦，不耐劳动，可坚持轻体力劳动</td>
<td>稍倦，勉强支持日常生活</td>
<td>四肢无力，不能坚持日常生活</td>
</tr>
<tr>
<td>食后腹胀</td>
<td>腹胀轻，2小时内可减轻</td>
<td>腹胀不明显，2小时内至1小时内</td>
<td>腹胀更甚，2小时内仍不能缓解</td>
</tr>
<tr>
<td>大便异常</td>
<td>稀便或腹泻，成形不规则，2～3次/日</td>
<td>稀便，4～5次/日，或粘液便，1～2次/日</td>
<td>稀便，3次/日以上</td>
</tr>
<tr>
<td>神疲懒言</td>
<td>精神不振，不喜多言，不语</td>
<td>精神疲乏，思睡，懒于言语，多语少言</td>
<td>精神极度疲乏，语速慢</td>
</tr>
<tr>
<td>口渴不渴</td>
<td>口干口渴乏味</td>
<td>口干口渴乏味，饮水较平时减少</td>
<td>口干口渴无味，整日无口渴感</td>
</tr>
<tr>
<td>饮食情况</td>
<td>常常有胃胀</td>
<td>有时隐痛腹胀，持续时间不超过2小时</td>
<td>腹胀较明显，持续时间超过2小时，或绵绵不休</td>
</tr>
<tr>
<td>恶心呕吐</td>
<td>偶有恶心</td>
<td>时有恶心，偶有呕吐</td>
<td>频频恶心，有时欲呕或呕吐</td>
</tr>
<tr>
<td>烦闷</td>
<td>食后腹闷，半小时内自行缓解</td>
<td>食后腹闷，2小时内自行缓解</td>
<td>持续腹闷腹胀</td>
</tr>
<tr>
<td>口苦</td>
<td>偶有口苦</td>
<td>时有口苦</td>
<td>时有口苦无汗无热</td>
</tr>
<tr>
<td>面色萎黄</td>
<td>面色萎黄</td>
<td>面色萎黄</td>
<td>面色萎黄不泽</td>
</tr>
<tr>
<td>浮肿</td>
<td>面色浮肿</td>
<td>面色浮肿</td>
<td>面色浮肿不泽</td>
</tr>
<tr>
<td>排便无力</td>
<td>排便无力</td>
<td>排便无力</td>
<td>排便次数异常增加</td>
</tr>
</tbody>
</table>

Appendix 2: Informed consent form for PD trial

香港浸會大學
知情同意書

中新「加味六君子湯」對原發性帕金遜症運動性症狀的療效：
隨機對照雙盲臨床試驗研究

您將被邀請參與一項臨床研究，本研究目的旨在評估中藥「加味六君子湯」對治療原發性帕金遜症運動性症狀之有效性與安全性，以及對生存質量的影響。在您決定參與前，務必清楚了解本研究的目的和所涉及的事項，並請你仔細考慮後才決定是否願意參加本研究。

資料背景
帕金遜症乃目前一種常見的腦部神經系統進行性病變，除了常見的肌肉運動障礙外，非運動性症狀也是病人最常見的病徵。根據本研究小組早前進行的一項先導性臨床研究結果顯示，中藥方劑「加味六君子湯」對改善原發性帕金遜症患者非運動性症狀有較好的療效。因此，本研究目的為藉較大樣本的雙盲隨機對照研究方法進一步觀察「加味六君子湯」對原發性帕金遜症非運動性症狀之臨床療效及安全性。

是次研究將以原發性帕金遜症的診斷標準、研究的納入標準及排除標準進行篩選，最終將會篩選出122位符合中醫辨證邏輯的原發性帕金遜症患者進行一期42週的臨床試驗研究，其中包括4週的篩選期，32週的治療期及6週的觀察期。在正式的臨床研究開始及終結時，合資格參與者將到大學以外的訓練所做肝及腎功能測試以確保參與者達該功能正常及研究的安全性。在研究期間，參與者需同時服用西藥，並按隨機獲分派的中藥箋藥數或安慰劑之指定劑量服用。參與者需於研究過程中第0、4、8、16、24、32及36週（合共七次）到訪浸會大學中醫診所，進行每次約1～2小時的跟進評估，並在第0、16及32週作尿液及睡眠代謝評估。若參與者在研究期間退出，則最後一次評估將被安排於退出日期加減一星期以內進行。

研究期間可能會進行拍攝或錄影以記錄病情或作教學用途，拍攝後您有權要求預覽，而其他情況下，除非事先獲得您的同意，否則一律禁止使用。請注意，在研究期間，參與者不得參加其他臨床研究；如閣下為女性，期間亦不可懷孕。此外，參與者尚須填写日記以記錄日常生活的狀態。本臨床研究以雙盲、隨機、對照的方式進行，治療過程中參加者及負責的註冊中醫師並不知道參加者所屬的治療組別，而安慰劑當中並沒有活性成份，主要作臨床研究的對照比較用途。

風險評估
服用本研究中使用的中藥箋藥是比較安全可靠的，但仍不能保證個別人士可能在服藥後出現身體不適，例如皮膚過敏，腹瀉、嘔吐等症狀。若有關情況發生，臨床試驗將會終止，而有關參與者將獲得相應治療或被轉介予其它治療。

緊急醫療措施
在一般的情況下，臨床研究並不會對參與者身體造成損害。但是，若參與者出現因研究而導致的身體嚴重不適，本臨床研究將承擔治療此嚴重不適而花費的費用。如果參與者在研究過程中出現任何不適，請盡快通知研究人員，除了相關醫藥費用之外，其它開支將不會補償。此為臨床研究的一部分。

研究效益
參與此項臨床研究是完全免費的。參與者有可能從研究中獲益帕金遜症的非運動性症狀，然而此療效並不能被保證。本研究計劃將會協助找出最安全和有效的方案治療帕金遜症非運動性症狀。故此，您的參與將有助於帕金遜症的治療研究及中醫藥的現代化研究和發展。

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私隱保障
在研究開始時，每位參與者將獲隨機分配一個號碼記錄他們的分組編排，有關資料將會分別存放在密封文件夾及加密的電腦檔案內。整個研究過程中除了研究人員外，其他人士皆不可接觸有關資料，所有問卷、病人日記及其他相關文件亦只限研究人員查閱。記錄病程進展的文件將會以代號標示病人的個人資料。所有參與本臨床研究者的姓名、身份等個人資料均獲保密，並在研究結果發表兩年後予以銷毀。

補償
若您在參與此次研究時發生其他疾病，本研究小組並不會作補償安排。但若您在參與是次研究時發生與試驗藥物直接相關的損害，在有充分理由下您可提出索償。此外，若在本研究過程中您認為研究者沒有按照上述的協定進行研究，或您認為您的個人權利受到侵犯，可電郵至hasc@hkbu.edu.hk與大學的人體及動物研究委員會作出投訴。

聯絡資料
若您在參與研究過程中有任何疑問，可與蔡嘉傑醫師聯絡。
地址：香港九龍塘香港浸會大學中醫藥學院教學部
電話：6700-8338
電郵：bucmpd@hkbu.edu.hk

參與條款
您明白參與此次研究乃是出於自己的意願，您可以在研究過程中退出而無需作出賠償。您的個人資料將在您退出後予以銷毀。

同意聲明
本人已閱讀並明白以上條文，並有機會發問。本人願意變易參與本研究，並會獲得本同意書的副本。

參閱者/代理人姓名 ___________________ 參閱者/代理人簽署 ___________________ 日期 ________________

見證人姓名 ___________________ 見證人簽署 ___________________ 日期 ________________

研究員姓名 ___________________ 研究員簽署 ___________________ 日期 ________________

－知情同意書完－
## Appendix 3: Composition table of JWLJZT

<table>
<thead>
<tr>
<th>Chinese</th>
<th>Latin</th>
<th>Medical Properties</th>
<th>Functions</th>
<th>Gram/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>黨參</td>
<td>Codonopsis pilosula (Franch.) Nannf.</td>
<td>Sweet in flavor, warm in nature; Attributive to the spleen and lung meridians</td>
<td>Invigorate stomach and spleen; Benefit Qi; Promote production of body fluids and nourish the blood</td>
<td>15</td>
</tr>
<tr>
<td>白朮</td>
<td>Atractylodes macrocephala Koidz.</td>
<td>Bitter and sweet in flavor; Warm in nature; Attributive to the spleen and stomach meridians</td>
<td>Invigorate the spleen and benefit Qi; Eliminate dampness and promote diuresis; Stop sweating</td>
<td>10</td>
</tr>
<tr>
<td>茯苓</td>
<td>Poria cocos (Schw.) Wolf</td>
<td>Sweet and bland in flavour; Mild in nature; Attributive to the heart, spleen and kidney meridians</td>
<td>Promote diuresis to resolve dampness from the lower energizer; Invigorate the spleen and tranquilize the mind</td>
<td>12</td>
</tr>
<tr>
<td>生甘草</td>
<td>Glycyrrhiza uralensis Fisch.</td>
<td>Sweet in flavor; Mild in nature; Attributive to the heart, lung, spleen and stomach meridians</td>
<td>Co-ordinate herbs; Reduce seizures</td>
<td>4</td>
</tr>
<tr>
<td>當歸</td>
<td>Angelica sinensis (Oliv.) Diels</td>
<td>Sweet and pungent in flavor; Warm in nature; Attributive to the liver, heart and spleen meridians</td>
<td>Stimulate blood circulation; Nourish intestine</td>
<td>10</td>
</tr>
<tr>
<td>陳皮</td>
<td>Citrus reticulate Blanco</td>
<td>Pungent and bitter in flavor; Warm in nature; Attributive to</td>
<td>Regulate Qi; Harmonize spleen and stomach; Eliminate dampness;</td>
<td>6</td>
</tr>
<tr>
<td>西醫</td>
<td>中醫名稱</td>
<td>細胞</td>
<td>功效</td>
<td>每日用量</td>
</tr>
<tr>
<td>------</td>
<td>----------</td>
<td>------</td>
<td>------</td>
<td>----------</td>
</tr>
<tr>
<td>Pinellia ternate (Thunb.) Briet.</td>
<td>法半夏</td>
<td>Pungent in flavor; Warm in nature; Attributive to spleen, stomach and lung meridians</td>
<td>Dry dampness and eliminate phlegm; Lower and adverse rising Qi to stop vomiting; Disperse stagnation and lumps and externally disperse swelling and relieve pains</td>
<td>10</td>
</tr>
<tr>
<td>Ligusticum chuanxiong Hort.</td>
<td>川芎</td>
<td>Pungent in flavor; Warm in nature and attributive to liver, gallbladder and pericardium meridians</td>
<td>Promote Qi circulation; Remove blood stasis; Relieve plan</td>
<td>10</td>
</tr>
<tr>
<td>Uncaria rhynchophylla (Miq.) Jacks.</td>
<td>鈎藤</td>
<td>Sweet in flavor; Slightly cold in nature; Attribute to liver, heart and pericardium meridians</td>
<td>Remove liver heat and wind; Stop seizures</td>
<td>15</td>
</tr>
<tr>
<td>Rehmannia glutinosa Libosch.</td>
<td>生地</td>
<td>Sweet and bitter in flavor; Cold in nature; Attributive to the heart, liver and kidney meridians</td>
<td>Clear away heat and coot the blood; Nourish yin and promote production of body fluids</td>
<td>9</td>
</tr>
<tr>
<td>Achyranthes bidentata Bl.</td>
<td>懷牛膝</td>
<td>Bitter and sour in flavor; Mild in nature; Attributive to liver and kidney meridians</td>
<td>Promote blood circulation to remove blood stasis; Nourish liver and kidney; Strengthen bones and muscles; Induce diuresis to treat stranguria and ensure proper downward flow of blood</td>
<td>9</td>
</tr>
</tbody>
</table>
Appendix 4: Movement Disorder Society – Sponsored Revision of Unified PD Rating Scale (MDS-UPDRS)

<table>
<thead>
<tr>
<th>Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview: This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on patients’ experiences of daily living. There are 13 questions. Part 1A is administered by the rater (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Patient Questionnaire that covers seven questions on non-motor experiences of daily living.</td>
</tr>
<tr>
<td>Part 1A: In administering Part 1A, the examiner should use the following guidelines:</td>
</tr>
<tr>
<td>1. Mark at the top of the form the primary data source as patient, caregiver, or patient and caregiver in equal proportion.</td>
</tr>
<tr>
<td>2. The response to each item should refer to a period encompassing the prior week including the day on which the information is solicited.</td>
</tr>
<tr>
<td>3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.</td>
</tr>
<tr>
<td>4. The answers should reflect the usual level of function and words such as “usually,” “generally,” “most of the time” can be used with patients.</td>
</tr>
<tr>
<td>5. Each question has a text for you to read (Instructions to patients/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the instructions to examiner. You should NOT READ THE RATING OPTIONS to the patient/caregiver, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.</td>
</tr>
<tr>
<td>6. Patients may have comorbidities and other medical conditions that can affect their function. You and the patient must rate the problem as it exists and do not attempt to separate elements due to Parkinson’s disease from other conditions.</td>
</tr>
</tbody>
</table>

**EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A**

Suggested strategies for obtaining the most accurate answer:

After reading the instructions to the patient, you will need to probe the entire domain under discussion to determine Normal vs. problematic. If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the patient functions at this level, better or worse. You will not be reading the choices of responses to the patient as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the patient to identify the most accurate response, giving a final check by excluding the options above and below the selected response.

![Diagram of response options](image-url)
MDS UPDRS
Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)

Part 1A: Complex behaviors: [completed by rater]

Primary source of information:

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

To be read to the patient: I am going to ask you six questions about behaviors that you may or may not experience. Some questions concern common problems and some concern uncommon ones. If you have a problem in one of the areas, please choose the best response that describes how you have felt MOST OF THE TIME during the PAST WEEK. If you are not bothered by a problem, you can simply respond NO. I am trying to be thorough, so I may ask questions that have nothing to do with you.

1.1 COGNITIVE IMPAIRMENT

Instructions to examiner: Consider all types of altered level of cognitive function including cognitive slowing, impaired reasoning, memory loss, deficits in attention and orientation. Rate their impact on activities of daily living as perceived by the patient and/or caregiver.

Instructions to patients (and caregiver): Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town? [If yes, examiner asks patient or caregiver to elaborate and pause for information]

0: Normal: No cognitive impairment.
1: Slight: Impairment appreciated by patient or caregiver with no concrete interference with the patient’s ability to carry out normal activities and social interactions.
2: Mild: Clinically evident cognitive dysfunction, but only minimal interference with the patient’s ability to carry out normal activities and social interactions.
3: Moderate: Cognitive deficits interfere with but do not preclude the patient’s ability to carry out normal activities and social interactions.
4: Severe: Cognitive dysfunction precludes the patient’s ability to carry out normal activities and social interactions.
### 1.2 HALLUCINATIONS AND PSYCHOSIS

**Instructions to examiner:** Consider both illusions (misinterpretations of real stimuli) and hallucinations (spontaneous false sensations). Consider all major sensory domains (visual, auditory, tactile, olfactory and gustatory). Determine presence of unformed (for example sense of presence or fleeting false impressions) as well as formed (fully developed and detailed) sensations. Rate the patient's insight into hallucinations and identify delusions and psychotic thinking.

**Instructions to patients (and caregiver):** Over the past week have you seen, heard, smelled or felt things that were not really there? [If yes, examiner asks patient or caregiver to elaborate and probes for information]

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No hallucinations or psychotic behaviour.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Illusions or non-formed hallucinations, but patient recognizes them without loss of insight.</td>
</tr>
<tr>
<td>2: Mid</td>
<td>Formed hallucinations independent of environmental stimuli. No loss of insight.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Formed hallucinations with loss of insight.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Patient has delusions or paranoia.</td>
</tr>
</tbody>
</table>

### 1.3 DEPRESSED MOOD

**Instructions to examiner:** Consider low mood, sadness, hopelessness, feelings of emptiness or loss of enjoyment. Determine their presence and duration over the past week and rate their interference with the patient's ability to carry out daily routines and engage in social interactions.

**Instruction to the patient (and caregiver):** Over the past week have you felt low, sad, hopeless or unable to enjoy things? [If yes, was the feeling for longer than one day at a time? Did it make it difficult for you to carry out your usual activities or to be with people? If yes, examiner asks patient or caregiver to elaborate and probes for information]

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No depressed mood.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Episodes of depressed mood that are not sustained for more than one day at a time. No interference with patient's ability to carry out normal activities and social interactions.</td>
</tr>
<tr>
<td>2: Mid</td>
<td>Depressed mood that is sustained over days, but without interference with normal activities and social interactions.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Depressed mood that interferes with, but does not preclude, the patient's ability to carry out normal activities and social interactions.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Depressed mood precludes patient's ability to carry out normal activities and social interactions.</td>
</tr>
</tbody>
</table>
### 1.4 ANXIOUS MOOD

**Instructions to examiner:** Determine nervous, tense, worried or anxious feelings (including panic attacks) over the past week and rate their duration and interference with the patient’s ability to carry out daily routines and engage in social interactions.

**Instructions to patients and caregivers:** Over the past week have you felt nervous, worried or tense? If yes, was it for longer than one day at a time? Did it make it difficult for you to follow your usual activities or to be with other people? [If yes, examiner asks patient or caregiver to elaborate and probe for information.]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No anxious feelings.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Anxious feelings present but not sustained for more than one day at a time. No interference with patient’s ability to carry out normal activities and social interactions.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Anxious feelings are sustained over more than one day at a time, but without interference with patient’s ability to carry out normal activities and social interactions.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Anxious feelings interfere with, but do not preclude, the patient’s ability to carry out normal activities and social interactions.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Anxious feelings preclude patient’s ability to carry out normal activities and social interactions.</td>
</tr>
</tbody>
</table>

### 1.5 APATHY

**Instructions to examiner:** Consider level of spontaneous activity, assertiveness, motivation and initiative and rate the impact of reduced levels on performance of daily routines and social interactions. Here the examiner should attempt to distinguish between apathy and similar symptoms that are best explained by depression.

**Instructions to patients and caregivers:** Over the past week, have you felt indifferent to doing activities or being with people? If yes, examiner asks patient or caregiver to elaborate and probe for information.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No apathy.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Apathy appreciated by patient and/or caregiver, but no interference with daily activities and social interactions.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Apathy interferes with isolated activities and social interactions.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Apathy interferes with most activities and social interactions.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Passive and withdrawn, complete loss of initiative.</td>
</tr>
</tbody>
</table>
1.6 FEATURES OF DOPAMINE DYSREGULATION SYNDROME

Instructions to examiner: Consider involvement in a variety of activities including atypical or excessive gambling (e.g., casinos or lottery tickets), atypical or excessive sexual drive or interests (e.g., unusual interest in pornography, masturbation, sexual demands on partner), other repetitive activities (e.g., hobbies, dismantling objects, sorting or organizing), or taking extra non-prescribed medication for non-physical reasons (i.e., addictive behavior). Rate the impact of such abnormal activities/behaviors on the patient’s personal life and on his family and social relations (including need to borrow money or other financial difficulties like withdrawal of credit cards, major family conflicts, lost time from work, or missed meals or sleep because of the activity).

Instructions to patient/caregiver: Over the past week, have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop? (Give patient examples such as gambling, cleaning, using the computer, taking extra medicine, obsessing about food or sex, all depending on the patient).

- Normal: No problems present.
- Slight: Problems are present but usually do not cause any difficulties for the patient or family/caregiver.
- Mild: Problems are present and usually cause a few difficulties in the patient’s personal and family life.
- Moderate: Problems are present and usually cause a lot of difficulties in the patient’s personal and family life.
- Severe: Problems are present and preclude the patient’s ability to carry out normal activities or social interactions or to maintain previous standards in personal and family life.

The remaining questions in Part I (Non-motor Experiences of Daily Living) (Sleep, Daytime Sleepiness, Pain and Other Sensation, Urinary Problems, Constipation Problems, Lightheadedness on Standing, and Fatigue) are in the Patient Questionnaire along with all questions in Part II (Motor Experiences of Daily Living).
Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient  ☐ Caregiver  ☐ Patient and Caregiver in Equal Proportion
### 1.7 SLEEP PROBLEMS

Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Sleep problems are present but usually do not cause trouble getting a full night of sleep.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Sleep problems usually cause some difficulties getting a full night of sleep.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>I usually do not sleep for most of the night.</td>
</tr>
</tbody>
</table>

### 1.8 DAYTIME SLEEPINESS

Over the past week, have you had trouble staying awake during the daytime?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No daytime sleepiness.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Daytime sleepiness occurs but I can resist and I stay awake.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>I sometimes fall asleep when I should not. For example, while eating or talking with other people.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>I often fall asleep when I should not. For example, while eating or talking with other people.</td>
</tr>
</tbody>
</table>
### 1.9 PAIN AND OTHER SENSATIONS

Over the past week, have you had uncomfortable feelings in your body like pain, aches, tingling or cramps?

0. Normal: No uncomfortable feelings.

1. Slight: I have these feelings. However, I can do things and be with other people without difficulty.

2. Mild: These feelings cause some problems when I do things or am with other people.

3. Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people.

4. Severe: These feelings stop me from doing things or being with other people.

### 1.10 URINARY PROBLEMS

Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents?

0. Normal: No urine control problems.

1. Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities.

2. Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents.

3. Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents.

4. Severe: I cannot control my urine and use a protective garment or have a bladder tube.
## 1.11 Constipation Problems

Over the past week have you had constipation troubles that cause you difficulty moving your bowels?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No constipation.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Constipation causes me to have some troubles doing things or being comfortable.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>I usually need physical help from someone else to empty my bowels.</td>
</tr>
</tbody>
</table>

## 1.12 Light Headedness on Standing

Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No dizzy or foggy feelings.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Dizzy or foggy feelings cause me to fall or faint.</td>
</tr>
</tbody>
</table>
1.13 FATIGUE

Over the past week, have you usually felt fatigued? This feeling is not part of being sleepy or sad.

0: Normal: No fatigue.
1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people.
2: Mild: Fatigue causes me some troubles doing things or being with people.
3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything.
4: Severe: Fatigue stops me from doing things or being with people.

Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

2.1 SPEECH

Over the past week, have you had problems with your speech?

0: Normal: Not at all (no problems).
1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself.
2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday.
3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood.
4: Severe: Most or all of my speech cannot be understood.
### 2.2 Saliva & Drooling

Over the past week, have you usually had too much saliva during when you are awake or when you sleep?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: Not at all (no problems).</td>
</tr>
<tr>
<td>1</td>
<td>Slight: I have too much saliva, but do not drool.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: I have some drooling during sleep, but none when I am awake.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.</td>
</tr>
</tbody>
</table>

### 2.3 Chewing and Swallowing

Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: I choked at least once in the past week.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Because of chewing and swallowing problems, I need a feeding tube.</td>
</tr>
</tbody>
</table>
### 2.4 EATING TASKS

Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>Not at all (No problems).</td>
</tr>
<tr>
<td>1: Slight</td>
<td>I am slow, but I do not need any help handling my food and have not had food spills while eating.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>I need help with many eating tasks but can manage some alone.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>I need help for most or all eating tasks.</td>
</tr>
</tbody>
</table>

### 2.5 DRESSING

Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>Not at all (no problems).</td>
</tr>
<tr>
<td>1: Slight</td>
<td>I am slow but I do not need help.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>I am slow and need help for a few dressing tasks (buttons, bracelets).</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>I need help for many dressing tasks.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>I need help for most or all dressing tasks.</td>
</tr>
</tbody>
</table>
### 2.6 HYGIENE

Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene?

- **0**: Normal: Not at all (no problems).
- **1**: Slight: I am slow but I do not need any help.
- **2**: Mild: I need someone else to help me with some hygiene tasks.
- **3**: Moderate: I need help for many hygiene tasks.
- **4**: Severe: I need help for most or all of my hygiene tasks.

### 2.7 HANDWRITING

Over the past week, have people usually had trouble reading your handwriting?

- **0**: Normal: Not at all (no problems).
- **1**: Slight: My writing is slow, clumsy or uneven, but all words are clear.
- **2**: Mild: Some words are unclear and difficult to read.
- **3**: Moderate: Many words are unclear and difficult to read.
- **4**: Severe: Most or all words cannot be read.

### 2.8 DOING HOBBIES AND OTHER ACTIVITIES

Over the past week, have you usually had trouble doing your hobbies or other things that you like to do?

- **0**: Normal: Not at all (no problems).
- **1**: Slight: I am a bit slow but do these activities easily.
- **2**: Mild: I have some difficulty doing these activities.
- **3**: Moderate: I have major problems doing these activities, but still do most.
- **4**: Severe: I am unable to do most or all of these activities.
### 2.9 TURNING IN BED

Over the past week, do you usually have trouble turning over in bed?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: Not at all (no problems).</td>
</tr>
<tr>
<td>1</td>
<td>Slight: I have a bit of trouble turning, but I do not need any help.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: I have a lot of trouble turning and need occasional help from someone else.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: To turn over I often need help from someone else.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: I am unable to turn over without help from someone else.</td>
</tr>
</tbody>
</table>

### 2.10 TREMOR

Over the past week, have you usually had shaking or tremor?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: Not at all. I have no shaking or tremor.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Shaking or tremor occurs but does not cause problems with any activities.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Shaking or tremor causes problems with only a few activities.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Shaking or tremor causes problems with many of my daily activities.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Shaking or tremor causes problems with most or all activities.</td>
</tr>
</tbody>
</table>

### 2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR

Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair?

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: Not at all (no problems).</td>
</tr>
<tr>
<td>1</td>
<td>Slight: I am slow or awkward, but I usually can do it on my first try.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: I need more than one try to get up or need occasional help.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: I sometimes need help to get up, but most times I can still do it on my own.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: I need help most or all of the time.</td>
</tr>
</tbody>
</table>
2.12 WALKING AND BALANCE

Over the past week, have you usually had problems with balance and walking?

0: Normal: Not at all (no problems).
1: Slight: I am slightly slow or may drag a leg. I never use a walking aid.
2: Mild: I occasionally use a walking aid, but I do not need any help from another person.
3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person.
4: Severe: I usually use the support of another persons to walk safely without falling.

SCORE

2.13 FREEZING

Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor.

0: Normal: Not at all (no problems).
1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing.
2: Mild: I freeze and have trouble starting to walk again, but I do not need someone’s help or a walking aid (cane or walker) because of freezing.
3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else’s help.
4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone’s help.

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.
Part III: Motor Examination

Overview: This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS, the examiner should comply with the following guidelines:

At the top of the form, mark whether the patient is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.

Also, if the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

- ON is the typical functional state when patients are receiving medication and have a good response.
- OFF is the typical functional state when patients have a poor response in spite of taking medications.

The investigator should "rate what you see." Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation "UR" for Unable to Rate. Otherwise, rate the performance of each task as the patient performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the patient is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

3a. Is the patient on medication for treating the symptoms of Parkinson's Disease? □ No □ Yes

3b. If the patient is receiving medication for treating the symptoms of Parkinson's Disease, mark the patient's clinical state using the following definitions:

□ ON: On is the typical functional state when patients are receiving medication and have a good response.

□ OFF: Off is the typical functional state when patients have a poor response in spite of taking medications.

3c. Is the patient on Levodopa? □ No □ Yes

3c1. If yes, minutes since last levodopa dose: __________
### 3.1 SPEECH

**Instructions to examiner**: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, paucity (repetition of syllables) and tachypnea (rapid speech, running syllables together).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No speech problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Loss of modulation, diction or volume, but still all words easy to understand.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Loss of modulation, diction, or volume, with a few words unclear, but the overall sentence easy to follow.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Speech is difficult to understand to the point that some, but not most, sentences are poorly understood.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Most speech is difficult to understand or unintelligible.</td>
</tr>
</tbody>
</table>

### 3.2 FACIAL EXPRESSION

**Instructions to examiner**: Observe the patient sitting at rest for 10 seconds, without talking and also while talking. Observe eye-blink frequency, masked facies or loss of facial expression, spontaneous smiling and parting of lips.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>Normal facial expression.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Minimal masked facies manifested only by decreased frequency of blinking.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>In addition to decreased eye-blink frequency, Masked facies present in the lower face as well, namely fewer movements around the mouth, such as less spontaneous smiling, but lips not parted.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Masked facies with lips parted some of the time when the mouth is at rest.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Masked facies with lips parted most of the time when the mouth is at rest.</td>
</tr>
</tbody>
</table>
### 3.3 RIGIDITY

**Instructions to examiner**: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joint simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, flat opening/closing, or brisk tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No rigidity.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Rigidity only detected with activation maneuver.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Rigidity detected without the activation maneuver; full range of motion is easily achieved.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.</td>
</tr>
</tbody>
</table>

### 3.4 FINGER TAPPING

**Instructions to examiner**: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly and as hard as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>
### 3.6 HAND MOVEMENTS

**Instructions to examiner:** Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to make a tight fist with the arm bent at the elbow so that the palm faces the examiner. Have the patient open the hand 10 times as fully AND as quickly as possible. If the patient fails to make a tight fist or to open the hand fully, remind him/her to do so. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problem.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the task.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st open-and-close sequence.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>

### 3.6 PRONATION-SUPINATION MOVEMENTS OF HANDS

**Instructions to examiner:** Test each hand separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to extend the arm out in front of his/her body with the palm down, then to turn the palm up and down alternately 10 times as fast and as fully as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) the amplitude decrements near the end of the sequence.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowing; c) the amplitude decrements midway in the sequence.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st supination-pronation sequence.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>

July 1, 2008
### 3.7 Toe Tapping

**Instructions to examiner:** Have the patient sit in a straight-backed chair with arms, both feet on the floor. Test each foot separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the heel on the ground in a comfortable position and then tap the toes 10 times as big and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problem.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) amplitude decrements near the end of the ten taps.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during the tapping movements; b) mild slowing; c) amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during the tapping movements or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) amplitude decrements after the first tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>

### 3.8 Leg Agility

**Instructions to examiner:** Have the patient sit in a straight-backed chair with arms. The patient should have both feet comfortably on the floor. Test each leg separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to place the foot on the ground in a comfortable position and then raise and stamp the foot on the ground 10 times as high and as fast as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No problems.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the movement; b) slight slowing; c) amplitude decrements near the end of the task.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Any of the following: a) 3 to 5 interruptions during the movements; b) mild slowness; c) amplitude decrements midway in the task.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Any of the following: a) more than 5 interruptions during the movement or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing in speed; c) amplitude decrements after the first tap.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.</td>
</tr>
</tbody>
</table>
### 3.0 ARISE FROM CHAIR

**Instructions to examiner**: Have the patient sit in a straight-backed chair with arms, with both feet on the floor and sitting back in the chair (if the patient is not too short). Ask the patient to cross his/her arms across the chest and then to stand up. If the patient is not successful, repeat this attempt a maximum of two more times. If still unsuccessful, allow the patient to move forward in the chair to arise with arms folded across the chest. Allow only one attempt in this situation. If unsuccessful, allow the patient to push off using his/her hands on the arms of the chair. Allow a maximum of three trials of pushing off. If still not successful, assist the patient to arise. After the patient stands up, observe the posture for item 3.13.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems. Able to arise quickly without hesitation.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Arising is slower than normal; or may need more than one attempt; or may need to move forward in the chair to arise. No need to use the arms of the chair.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Pushes self up from arms of chair without difficulty.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Needs to push off, but tends to fall back, or may have to try more than one time using arms of chair, but can get up without help.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Unable to arise without help.</td>
</tr>
</tbody>
</table>

### 3.40 GAIT

**Instructions to examiner**: Testing gait is best performed by having the patient walking away from and towards the examiner so that both right and left sides of the body can be easily observed simultaneously. The patient should walk at least 10 metres (30 feet), then turn around and return to the examiner. This item measures multiple behaviors: stride amplitude, stride speed, height of foot lift, heel strike during walking, turning, and arm swing, but not freezing. Assess also for “freezing of gait” (next item 3.11) while patient is walking. Observe posture for item 3.13.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td>No problems.</td>
</tr>
<tr>
<td>1: Slight</td>
<td>Independent walking with minor gait impairment.</td>
</tr>
<tr>
<td>2: Mild</td>
<td>Independent walking but with substantial gait impairment.</td>
</tr>
<tr>
<td>3: Moderate</td>
<td>Requires an assistance device for safe walking (walking stick, walker) but not a person.</td>
</tr>
<tr>
<td>4: Severe</td>
<td>Cannot walk at all or only with another person’s assistance.</td>
</tr>
</tbody>
</table>
3.11 FREEZING OF GAIT

Instructions to examiner: While assessing gait, also assess for the presence of any gait freezing episodes. Observe for start hesitation and stuttering movements especially when turning and reaching the end of the task. To the extent that safety permits, patients may NOT use sensory tools during the assessment.

0: Normal: No freezing.
1: Slight: Freezes on starting, turning or walking through doorway with a single halt during any of these events, but then continues smoothly without freezing during straight walking.
2: Mid: Freezes on starting, turning or walking through doorway with more than one halt during any of these activities, but continues smoothly without freezing during straight walking.
3: Moderate: Freezes once during straight walking.
4: Severe: Freezes multiple times during straight walking.

3.12 POSTURAL STABILITY

Instructions to examiner: The test examines the response to sudden body displacement produced by a quick, forceful pull on the shoulders while the patient is standing erect with eyes open and feet comfortably apart and parallel to each other. The examiner stands behind the patient and instruct the patient on what is about to happen. Explain that she is allowed to take a step backwards to avoid falling. There should be a solid wall behind the examiner, at least 1-2 meters away so as to allow enough room for the patient to take several steps to recover independently. Do not allow the patient to flex the body abnormally forward in anticipation of the pull. Observe for the number of steps backwards or falling. Up to and including two steps for recovery is considered normal, so abnormal ratings begin with three steps. If the patient fails to understand the test, the examiner can repeat the test so that the rating is based on an assessment that the examiner feels reflects the patient’s limitations rather than misunderstanding or lack of preparedness. Observe standing posture for item 3.13.

0: Normal: No problems. Recover with one or two steps.
1: Slight: 3-5 steps, but subject recovers unaided.
2: Mild: More than 5 steps, but subject recovers unaided.
3: Moderate: Stands safely, but with absence of postural response, falls if not caught by examiner.
4: Severe: Very unstable, tends to lose balance spontaneously or with just a gentle pull on the shoulders.
3.13 POSTURE

Instructions to examiner: Posture is assessed with the patient standing erect after arising from a chair during walking, and while being tested for postural reflexes. If you notice poor posture, tell the patient to stand up straight and see if the posture improves (see option 2 below). Rate the worst posture seen in these three observation points. Observe for flexion and side-to-side leaning.

0: Normal: No problems.
1: Slight: Not quite erect, but posture could be normal for older person.
2: Mild: Definite flexion, scoliosis or leaning to one side, but patient can correct posture to normal posture when asked to do so.
3: Moderate: Stooped posture, scoliosis or leaning to one side that cannot be corrected voluntarily to a normal posture by the patient.
4: Severe: Flexion, scoliosis or leaning with extreme abnormality of posture.

3.14 GLOBAL SPONTANEITY OF MOVEMENT (BODY BRADYKINESIA)

Instructions to examiner: This global rating combines all observations on slowness, hesitancy, and small amplitude and poverty of movement in general, including a reduction of gesturing and of crossing the legs. The assessment is based on the examiner's global impression after observing for spontaneous gestures while sitting, and the nature of arising and walking.

0: Normal: No problems.
1: Slight: Slight global slowness and poverty of spontaneous movements.
2: Mild: Mild global slowness and poverty of spontaneous movements.
3: Moderate: Moderate global slowness and poverty of spontaneous movements.
4: Severe: Severe global slowness and poverty of spontaneous movements.

3.15 POSTURAL TREMOR OF THE HANDS

Instructions to examiner: All tremor including re-emergent rest tremor, that is present in this posture is to be included in this rating. Rate each hand separately. Rate the highest amplitude seen. Instruct the patient to stretch the arms out in front of the body with palms down. The wrist should be straight and the fingers comfortably separated so that they do not touch each other. Observe this posture for 10 seconds.

0: Normal: No tremor.
1: Slight: Tremor is present but less than 1 cm in amplitude.
2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe: Tremor is at least 10 cm in amplitude.
### 3.16 KINETIC TREMOR OF THE HANDS

**Instructions to examiner:** This is tested by the finger-to-nose maneuver. With the arm starting from the outstretched position, have the patient perform at least three finger-to-nose maneuvers with each hand reaching as far as possible to touch the examiner's finger. The finger-to-nose maneuver should be performed slowly enough not to hide any tremor that could occur with very fast arm movements. Repeat with the other hand, rating each hand separately. The tremor can be present throughout the movement or as the tremor reaches either target (nose or finger). Rate the highest amplitude seen.

0: Normal: No tremor.
1: Slight: Tremor is present but less than 1 cm in amplitude.
2: Mild: Tremor is at least 1 but less than 3 cm in amplitude.
3: Moderate: Tremor is at least 3 but less than 10 cm in amplitude.
4: Severe: Tremor is at least 10 cm in amplitude.

### 3.17 REST TREMOR AMPLITUDE

**Instructions to examiner:** This and the next item have been placed purposefully at the end of the examination to allow the rater to gather observations on rest tremor that may appear at any time during the exam, including when quietly sitting, during walking and during activities when some body parts are moving but others are at rest. Score the maximum amplitude that is seen at any time as the final score. Rate only the amplitude and not the persistence or the intermittency of the tremor. As part of this rating, the patient should sit quietly in a chair with the hands placed on the arms of the chair (not on the lap) and the feet comfortably supported on the floor for 10 seconds with no other directives. Rest tremor is assessed separately for all four limbs and also for the lip/Jaw. Rate only the maximum amplitude that is seen at any time as the final rating.

**Extremity ratings**

0: Normal: No tremor.
1: Slight: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 3 cm in maximal amplitude.
3: Moderate: 3 - 10 cm in maximal amplitude.
4: Severe: > 10 cm in maximal amplitude.

**Lip/Jaw ratings**

0: Normal: No tremor.
1: Slight: < 1 cm in maximal amplitude.
2: Mild: > 1 cm but < 2 cm in maximal amplitude.
3: Moderate: > 2 cm but < 3 cm in maximal amplitude.
4: Severe: > 3 cm in maximal amplitude.
### 3.18 Constancy of Rest Tremor

**Instructions to examiner:** This item receives one rating for all rest tremor and focuses on the constancy of rest tremor during the examination period when different body parts are variously at rest. It is rated purposefully at the end of the examination so that several minutes of information can be coalesced into the rating.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: No tremor.</td>
</tr>
<tr>
<td>1</td>
<td>Slight: Tremor at rest is present &lt; 25% of the entire examination period.</td>
</tr>
<tr>
<td>2</td>
<td>Mild: Tremor at rest is present 26-50% of the entire examination period.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate: Tremor at rest is present 51-75% of the entire examination period.</td>
</tr>
<tr>
<td>4</td>
<td>Severe: Tremor at rest is present &gt; 75% of the entire examination period.</td>
</tr>
</tbody>
</table>

### Dyskinesia Impact on Part III Ratings

A. Were dyskinesias (chorea or dystonia) present during examination?  □ No  □ Yes

B. If yes, did those movements interfere with your ratings?  □ No  □ Yes

### Hoehn and Yahr Stage

0: Asymptomatic.

1: Unilateral involvement only.

2: Bilateral involvement without impairment of balance.

3: Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from fall test.

4: Severe disability; still able to walk or stand unassisted.

5: Wheelchair bound or bedridden unless aided.
Part IV: Motor Complications

Overview and instructions: In this section, the roter uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from patient, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place URF for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for "OFF" time and Dyskinesias. For "OFF dystonia", the total "OFF" time will be the denominator. Operational definitions for examiner’s use.

**Dyskinesias:** Involuntary random movements
Words that patients often recognize for dyskinesias include “irregular jerking”, “wriggling”, “twitching”. It is essential to stress to the patient the difference between dyskinesias and tremor, a common error when patients are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component;
Words that patients often recognize for dystonia include “spasms”, “cramps”, “posture”.

Motor fluctuation: Variable response to medication:
Words that patients often recognize for motor fluctuation include “wearing out”, “wearing off”, “rotor-coaster effect”, “on-off”, “uneven medication effects”.

**OFF:** Typical functional state when patients have a poor response in spite of taking medication or the typical functional response when patients are on NO treatment for parkinsonism. Words that patients often recognize include “low time”, “bad time”, “shaking time”, “slow time”, “time when my medications don’t work.”

**ON:** Typical functional state when patients are receiving medication and have a good response:
Words that patients often recognize include “good time”, “walking time”, “time when my medications work.”

---

### A. DYSKINESIAS [exclusive of OFF-state dystonia]

<table>
<thead>
<tr>
<th>Time Spent with Dyskinesias</th>
<th>Score</th>
</tr>
</thead>
</table>

**Instructions to examiner:** Determine the hours in the usual waking day and then the hours of dyskinesias. Calculate the percentage. If the patient has dyskinesias in the office, you can point them out as a reference to ensure that patients and caregivers understand what they are rating. You may also use your own acting skills to enact the dyskinetic movements you have seen in the patient before or show them dyskinetic movements typical of other patients. Exclude from this question early morning and nighttime painful dystonia.

**Instructions to patient [and caregiver]:** Over the past week, how many hours do you usually sleep on a daily basis, including nighttime sleep and daytime napping? Alright, if you sleep ___ hrs, you are awake ___ hrs. Out of those awake hours, how many hours in total do you have wiggling, twitching or jerking movements? Do not count the times when you have tremor, which is a regular back and forth shaking or time when you have painful feet cramps or spasms in the early morning or at nighttime. I will ask about those later. Concentrate only on these types of wiggling, jerking and irregular movements. Add up all the time during the waking day when these usually occur. How many hours ____ (use this number for your calculation).

0: Normal: No dyskinesias
1: Slight: ≤ 25% of waking day.
2: Mild: 26 - 50% of waking day.
3: Moderate: 51 - 75% of waking day.
4: Severe: > 75% of waking day.

1. Total Hours Awake: ___
2. Total Hours with Dyskinesia: ___
3. % Dyskinesia = (2/4*100): ___
4.2 FUNCTIONAL IMPACT OF DYSKINESIAS

Instructions to examiner: Determine the degree to which dyskinesias impact on the patient’s daily function in terms of activities and social interactions. Use the patient’s and caregiver’s response to your questions and your own observations during the office visit to arrive at the best answer.

Instructions to patient (and caregiver): Over the past week, did you usually have trouble doing things or being with people when these jerking movements occurred? Did they stop you from doing things or from being with people?

0: Normal: No dyskinesias or no impact by dyskinesias on activities or social interactions.
1: Slight: Dyskinesias impact on a few activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
2: Mild: Dyskinesias impact on many activities, but the patient usually performs all activities and participates in all social interactions during dyskinetic periods.
3: Moderate: Dyskinesias impact on activities to the point that the patient usually does not perform some activities or does not usually participate in some social activities during dyskinetic episodes.
4: Severe: Dyskinesias impact on function to the point that the patient usually does not perform most activities or participate in most social interactions during dyskinetic episodes.

B. MOTOR FLUCTUATIONS

4.3 TIME SPENT IN THE OFF STATE

Instructions to examiner: Use the number of waking hours derived from 4.1 and determine the hours spent in the “OFF” state. Calculate the percentage. If the patient has an OFF period in the office, you can point to this state as a reference. You may also use your knowledge of the patient to describe a typical OFF period. Additionally, you may use your own acting skills to enact an OFF period you have seen in the patient before or show them OFF function typical of other patients. Mark down the total number of OFF hours, because you will need this number for completing 4.2.

Instructions to patient (and caregiver): Some patients with Parkinson’s disease have a good effect from their medications throughout their awake hours and we call that “On” time. Other patients take their medications but still have some hours of low time, bad time, slow time or shaking time. Doctors call these periods OFF time. Over the past week, you told me before that you are generally awake hours each day. Out of these awake hours, how many hours in total do you usually have this type of low level of OFF function (Use this number for your calculations).

0: Normal: No OFF time.
1: Slight: 1 – 25% of waking day.
2: Mild: 25 – 50% of waking day.
3: Moderate: 51 – 75% of waking day.
4: Severe: > 75% of waking day.

| 1. Total Hours Awake: | 
| 2. Total Hours OFF: |
| 3. % OFF = (2/1)^100: |

July 1, 2008
4.4 FUNCTIONAL IMPACT OF FLUCTUATIONS

Instructions to examiner: Determine the degree to which motor fluctuations impact on the patient's daily function in terms of activities and social interactions. This question concentrates on the difference between the ON state and the OFF state. If the patient has no OFF time, the rating must be 0, but if patients have very mild fluctuations, it is still possible to be rated 0 on this item if no impact on activities occurs. Use the patient's and caregiver's response to your question and your own observations during the office visit to arrive at the best answer.

Instructions to patient (and caregiver): Think about when those low or "OFF" periods have occurred over the past week. Do you usually have more problems doing things or being with people than compared to the rest of the day when you feel your medications working? Are there some things you usually do during a good period that you have trouble with or stop doing during a low period?

0: Normal: No fluctuations or No impact by fluctuations on performance of activities or social interactions.

1: Slight: Fluctuations impact on a few activities, but during OFF, the patient usually performs all activities and participates in all social interactions that typically occur during the ON state.

2: Mild: Fluctuations impact many activities, but during OFF, the patient still usually performs all activities and participates in all social interactions that typically occur during the ON state.

3: Moderate: Fluctuations impact on the performance of activities during OFF to the point that the patient usually does not perform some activities or participate in some social interactions that are performed during ON periods.

4: Severe: Fluctuations impact on function to the point that, during OFF, the patient usually does not perform most activities or participate in most social interactions that are performed during ON periods.

4.5 COMPLEXITY OF MOTOR FLUCTUATIONS

Instructions to examiner: Determine the usual predictability of OFF function whether due to dose, time of day, food intake or other factors. Use the information provided by the patients and caregiver and supplement with your own observations. You will ask if the patient can count on them always occurring at a special time, mostly occurring at a special time (in which case you will probe further to separate slight from mild), only sometimes occurring at a special time, or are they totally unpredictable? Narrowing down the percentage will allow you to find the correct answer.

Instructions to patient (and caregiver): For some patients, the low or "OFF" periods happen at certain times during day or when they do activities like eating or exercising. Over the past week, do you usually know when your low periods will occur? In other words, do your low periods always occur at a certain time? Do they mostly come at a certain time? Do they only sometimes come at a certain time? Are your low periods totally unpredictable?

0: Normal: No motor fluctuations.

1: Slight: OFF times are predictable all or almost all of the time (> 75%).

2: Mild: OFF times are predictable most of the time (51-75%).

3: Moderate: OFF times are predictable some of the time (26-50%).

4: Severe: OFF episodes are rarely predictable (< 25%).
C. "OFF" DYSTONIA

4.6 PAINFUL OFF-STATE DYSTONIA

Instructions to examiner: For patients who have motor fluctuations, determine what proportion of the OFF episodes usually includes painful dystonia? You have already determined the number of hours of "OFF" time (4.3). Of these hours, determine how many are associated with dystonia and calculate the percentage. If there is no OFF time, mark 0.

Instructions to patient (and caregiver): In one of the questions I asked earlier, you said you generally have ___ hours of low or "OFF" time when your Parkinson's disease is under poor control. During these low or "OFF" periods, do you usually have painful cramps or spasms? Out of the total ___ hrs of this low time, if you add up all the time in a day when these painful cramps come, how many hours would this make?

0. Normal: No dystonia OR NO OFF TIME.
1. Slight: < 25% of time in OFF state.
2. Mild: 26-50% of time in OFF state.
3. Moderate: 51-75% of time in OFF state.
4. Severe: > 75% of time in OFF state.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Total Hours Off:</td>
</tr>
<tr>
<td>2.</td>
<td>Total Off Hours w/Dystonia:</td>
</tr>
<tr>
<td>3.</td>
<td>% Off Dystonia = (2/1)*100:</td>
</tr>
</tbody>
</table>

Summary statement to patient: READ TO PATIENT

This completes my rating of your Parkinson's disease. I know the questions and tasks have taken several minutes, but I wanted to be complete and cover all possibilities. In doing so, I may have asked about problems you do not even have, and I may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this scale with me.

July 1, 2005
MDS UPDRS Score Sheet

**Part I**

1. Source of information
   - Patient
   - Caregiver
   - Patient + Caregiver

2. Cognitive impairment

3. Hallucinations and psychosis

4. Depressed mood

5. Anxiety

6. Apathy

7. Features of DSG

8. Sleep problems

9. Daytime sleepiness

10. Pain and other sensations

11. Urinary problems

12. Constipation problems

13. Light-headedness on standing

14. Fatigue

**Part II**

15. Speech

16. Saliva and drooling

17. Swallowing

18. Eating tasks

19. Dressing

20. Hygiene

21. Handwriting

22. Doing hobbies and other activities

23. Turning in bed

24. Trend

25. Getting out of bed

26. Walking and balance

27. Freezing

28. Is the patient on medication?  No  Yes

29. Patient's clinical state

**Part IV**

30. Is the patient on Levodopa?  No  Yes

31. If yes, minutes since last dose

32. Spontaneous movements

33. Functional impact of dyskinesias

34. Time spent in the OFF state

35. Functional impact of fluctuations

36. Complexity of motor fluctuations

37. Rigidity - Neck

38. Painful OFF-state dystonia

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May 5, 2023
Appendix 5: Non-motor Symptom Assessment Scale for Parkinson’s Disease

(NMSS)

Non-Motor Symptom assessment scale for Parkinson’s Disease

<table>
<thead>
<tr>
<th>Patient ID No:</th>
<th>Initials:</th>
<th>Age:</th>
</tr>
</thead>
</table>

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but cause little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk); 2 = Often (1-2/wk); 3 = Frequent (several times per week); 4 = Very frequent (daily or all the time).

Domains will be weighted differentially. Yes/No answers are not included in final frequency x severity calculation.

Unboxed text in questions within the scale is included as an explanatory aid.

Domain 1: Cardiovascular including falls

1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

2. Does the patient fall because of fainting or blacking out?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

Domain 2: Sleep/Fatigue

3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during meals, or while watching television or reading).  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient’s daytime activities?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

5. Does the patient have difficulties falling or staying asleep?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

6. Does the patient experience an urge to move the legs or restless legs that improves with movement when he/she is sitting or lying down inactive?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

Domain 3: Mood/Cognition

7. Has the patient lost interest in his/her surroundings?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

8. Has the patient lost interest in doing things or lack motivation to start new activities?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

9. Does the patient feel nervous, worried or frightened for no apparent reason?  
   - Severity: [ ]  
   - Frequency: [ ]  
   - Score: [ ]

10. Does the patient seem sad or depressed or has he/she reported such feelings?  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]

11. Does the patient have flat moods without the normal “highs” and “lows”?  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]

12. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]

Domain 4: Perceptual problems/hallucinations

13. Does the patient indicate that he/she sees things that are not there?  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]

14. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]

15. Does the patient experience double vision? (2 separate real objects and not blurred vision)  
    - Severity: [ ]  
    - Frequency: [ ]  
    - Score: [ ]
### Domain 5. Attention/Memory

16. Does the patient have problems sustaining concentration during activities? (For example, reading or having a conversation)
17. Does the patient forget things that he/she has been told a short time ago or events that happened in the last few days?
18. Does the patient forget to do things? (For example, take tablets or turn off domestic appliances?)

**SCORE:**

### Domain 6. Gastrointestinal tract

19. Does the patient dribble saliva during the day?
20. Does the patient have difficulty swallowing?
31. Does the patient suffer from constipation? (Bowel action less than three times weekly)

**SCORE:**

### Domain 7. Urinary

22. Does the patient have difficulty holding urine? (Urgency)
23. Does the patient have to void within 2 hours of last voiding? (Frequency)
24. Does the patient have to get up regularly at night to pass urine? (Nocturia)

**SCORE:**

### Domain 8. Sexual function

25. Does the patient have altered interest in sex? (Very much increased or decreased, please underline)
36. Does the patient have problems having sex?

**SCORE:**

### Domain 9. Miscellaneous

27. Does the patient suffer from pain not explained by other known conditions? (Is it related to intake of drugs and is it relieved by anti-parkinson drugs?)
28. Does the patient report a change in ability to taste or smell?
29. Does the patient report a recent change in weight (not related to dieting?)
30. Does the patient experience excessive sweating? (not related to hot weather)

**SCORE:**

**TOTAL SCORE:**

---

Developed by the International Parkinson’s Disease Non-Motor Group. 
Contacts: ray.chaudhari@uhldh.nhs.uk or alison.forbes@uhldh.nhs.uk

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Appendix 6: Criteria of phlegm turbidity obstructing the orifices (PTOO)

③痰浊阻窍证

主症：智能减退，头重如裹，纳呆食少，痰多口涎。

次症：神情呆板，沉默少言，形体肥胖，动作迟缓，肢体困重，脉闷不欲呼。痰浊化热者，或见昏睡，或见狂躁不安，行为不轨，舌体胖大，舌质淡，苔白腻，脉滑。痰热者舌质红，苔黄腻，脉滑数。

表 3-5 老年期痰浊阻窍症状分度量表

<table>
<thead>
<tr>
<th>症状</th>
<th>轻</th>
<th>中</th>
<th>重</th>
</tr>
</thead>
<tbody>
<tr>
<td>智能减退</td>
<td>MMSE20～23 分为轻度认知障碍</td>
<td>MMSE11～19 分为中度认知障碍</td>
<td>MMSE&lt;10 分为重度认知障碍</td>
</tr>
<tr>
<td>头重如裹</td>
<td>头重如蒙</td>
<td>头重如覆而眠</td>
<td></td>
</tr>
<tr>
<td>纳呆食少</td>
<td>进食量明显减少，活动则明显减少</td>
<td>进食量 2/3 时倦懒不欲，活动少食即倦懒不欲，活动不减，持续 3 小时左右</td>
<td></td>
</tr>
<tr>
<td>形体肥胖</td>
<td>脉浮而数</td>
<td>脉弦而数</td>
<td></td>
</tr>
<tr>
<td>神志呆滞</td>
<td>偶有沉默</td>
<td>偶有意识障碍</td>
<td></td>
</tr>
<tr>
<td>神志模糊</td>
<td>时而清醒</td>
<td>时而昏迷</td>
<td></td>
</tr>
<tr>
<td>睡眠障碍</td>
<td>睡眠多于每日 10 小时，呼之能醒</td>
<td>睡眠多于每日 15 小时，呼之能醒</td>
<td></td>
</tr>
<tr>
<td>或见昏睡</td>
<td>无故昏睡，无故昏迷</td>
<td>无故昏睡，无故昏迷</td>
<td></td>
</tr>
<tr>
<td>舌象</td>
<td>舌苔白</td>
<td>舌体胖大，苔白腻</td>
<td></td>
</tr>
<tr>
<td>体象</td>
<td>体倦乏力，肢体麻木</td>
<td>体倦乏力，肢体麻木</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 7: Informed consent form for AD trial

香港浸會大學
知情同意書

中藥複方治療老年癡症
隨機對照雙盲臨床試驗研究

您將被邀請參與一項臨床研究。本研究目的旨在評估中藥複方對治療老年癡症之有效性與安全性，以及對生活質量的影響。在您決定參與前，請務必清楚了解本研究的目的和所涉及的事項，並請你仔細考慮後才決定是否願意參加本研究。

資料背景
老年癡症乃目前一種常見的中樞神經系統原發性退行性疾病，主要包括有阿爾茨海默病（AD）及血管性癡呆（VD），其中又以前者較為常見，現時統稱之老年癡症基本屬此。中藥治療癡症具有悠久的歷史及豐富的經驗，根據本研究機構最近進行的一項文獻分析顯示，中藥方劑「DID」對改善阿爾茨海默病的認知功能有較好的療效，且在 2007 年被收入國家統一中醫藥標準治療癡呆之用。然而此仍缺乏充分的臨床研究證明其功效，因此，本研究目的規範之雙盲隨機對照研究方法覈實「DID」對阿爾茨海默病之臨床療效與安全性，以及對生活質量的改善。

是次研究將按納入標準及排除標準進行篩選，最終將會篩選出 60 位符合中醫辨證療效阻隔癡症的阿爾茨海默病患者進行為期 32 週的臨床試驗研究，其中包括 2 週的篩選期，24 週的治療期及 4 週的觀察期。在正式的臨床研究開始及結束時，合資格參與者將到大學以外之化驗所作肝及腎功能測試以確保參與者身體功能正常及研究的安全性。治療期間，若參與者有嚴重不適，可能會安排額外之抽血檢查以確保健康情況。在研究期間，參與者需同時服用原有西藥，並遵照醫生分派的中藥顆粒劑或安慰劑之指定劑量服用。參與者需於研究過程中的第 0，4，8，12，16，20，24 及 30 週接受八次到訪浸會大學中醫診所，進行每次為時約一至兩小時的跟進評估，並在第 0，12 及 24 週作尿液及唾液代謝分析。此外，參與者需按規定填寫問卷以記錄日常生活。本臨床研究以雙盲、隨機、對照的方式進行，治療過程中參加者及負責的中醫師並不知道參加者所屬的治療組別。而安慰劑當中並沒有活性成份，主要作為臨床研究的對照比較用途。

風險評估
服用本研究中使用的中藥製劑是比較安全可靠的，但仍不能保證個別人仕可能在服藥後出現身體不適，例如皮膚過敏、腹瀉、嘔吐等症狀。若有不良反應發生，臨床試驗將會終止，而有關參與者將獲得相應治療或被轉介予其它治療。

緊急醫療措施
在一般的情況下，臨床研究並不會對參與者身體造成損害。但是，若參與者出現因研究而導致的身體嚴重不良反應，本臨床研究將承擔因治療該嚴重不良反應而花費的費用。如果參與者在研究過程中出現任何不適，請盡快通知研究人員。除了相關醫療費用之外，其它開支將不獲補償。

研究益處
參與此項臨床研究是完全免費的，參與者在完成所有後評估後，將獲發港幣 1,000 元的交通津貼。參與者有可能因研究而改善老年癡症的症狀，然而此療效並不能被保証。本研究計劃將協助找出最安全和有效的中藥治療阿爾茨海默病。故此，您的參與將有助於老年癡症的治療研究及中醫藥的現代化研究和發展。
私隱保障
在研究開始時，每位參與者將獲隨機分配一個號碼記錄他們的分組編排。有關資料將會
分別存放在密封文件夾及加密的電腦檔案內。整個研究過程中除了研究人員外，其他人
士皆不可接觸有關資料。所有問卷、病人日記及其他相關文件亦只限研究人員查閱。記
錄病程進展的文件將會以代號標示病人的個人資料。所有參與本臨床研究者的姓名、身
份等個人資料均獲保密，並在研究結果發表三年後予以銷毀。

賠償
如果您在參與是次研究時發生其他疾病，本研究小組並不會作賠償安排。但若您在參與
是次研究時發生與試驗藥物直接相關的損害，在有充分理據下您可提出索償。此外，若
在本研究過程中您認為研究者沒有按照上述的協定進行研究，或您認為您的個人權利受
到侵犯，可電郵至 hassc@hkbu.edu.hk 與大學的人體及動物研究委員會作出投訴。

聯絡資料
如果您在參與研究過程中有任何疑問，可與蔡嘉傑醫師聯絡。
地址：香港九龍塘香港浸會大學中醫藥學院教學部
電話：0700-8338
電郵：bucmad@hkbu.edu.hk

參與條款
您明白參與是次研究乃出於自己的意願，您可以在研究過程中退出而無需作出賠償。
您的個人資料將在您退出後予以銷毀。

同意聲明
本人已閱讀並明白以上條文，並有機會發問。本人願意及決定參與本研究，並會獲得本
同意書的副本。

參與者/代理人姓名

參與者/代理人簽署

日期

見證人姓名

見證人簽署

日期

研究員姓名

研究員簽署

日期

知情同意書完一
## Appendix 8: Composition table of DTD

<table>
<thead>
<tr>
<th>Chinese</th>
<th>Latin</th>
<th>Medical Properties</th>
<th>Functions</th>
<th>Gram/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>膽南星</td>
<td><em>Rhizoma Pinelliae Pedatisecta</em></td>
<td>Bitter and slightly pungent in flavor, cold in nature, and attributive to the spleen, lung and liver meridians</td>
<td>Clear away heat evil to resolve phlegm, extinguish wind and settle fright</td>
<td>9</td>
</tr>
<tr>
<td>法半夏</td>
<td><em>Rhizoma Pinelliae</em></td>
<td>Pungent in flavor, warm in nature, and attributive to the spleen, lung and stomach meridians</td>
<td>Dry dampness to resolve phlegm, and suppress vomiting</td>
<td>9</td>
</tr>
<tr>
<td>陳皮</td>
<td><em>Pericarpium Citri Reticulatae</em></td>
<td>Pungent and bitter in flavor, warm in nature, and attributive to the spleen and lung meridians</td>
<td>Regulate Qi and fortify the spleen, dry dampness to resolve phlegm</td>
<td>5.4</td>
</tr>
<tr>
<td>茯苓</td>
<td><em>Rhizoma Smilacis</em></td>
<td>Sweet and bland in flavor, neutral in nature, and attributive to the heart, spleen and kidney meridians</td>
<td>Induce diuresis to drain dampness, fortify the spleen and tranquillize</td>
<td>7.2</td>
</tr>
<tr>
<td>枳實</td>
<td><em>Citrus aurantium L.</em></td>
<td>Pungent and bitter in flavor, slightly cold in nature, and attributive to the spleen, stomach</td>
<td>Break Qi to remove accumulation, resolve phlegm to remove stuffiness</td>
<td>7.2</td>
</tr>
<tr>
<td>植物</td>
<td>植物名称</td>
<td>形状</td>
<td>功效</td>
<td>剂量</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>人參</td>
<td><em>Panax ginseng</em> C. A. Mey</td>
<td>Sweet and slightly bitter in flavor, slightly warm in nature, and attributive to the spleen and lungs meridian</td>
<td>Nonify the source Qi, tonify the spleen and nourish the lungs, engender fluid, tranquilize and strengthen memory</td>
<td>3.6</td>
</tr>
<tr>
<td>石菖蒲</td>
<td><em>Rhizoma Acori Talarinowii</em></td>
<td>Pungent in flavor, slightly warm in nature, and attributive to the heart and stomach meridians</td>
<td>Sweep phlegm, Qi-regulating, disperse wind and dispel dampness</td>
<td>3.6</td>
</tr>
<tr>
<td>竹茹</td>
<td><em>Bambusa tuldoioides</em></td>
<td>Sweet in flavor, slightly cold in nature, and attributive to the lung and stomach meridians</td>
<td>Clear heat, resolve phlegm and remove stagnation, relieve agitation and clear the stomach, stop vomiting</td>
<td>2.5</td>
</tr>
<tr>
<td>生薑</td>
<td><em>Rhizoma Zingiberis Recens</em></td>
<td>Pungent in flavor, slightly warm in nature, and attributive to the lung, stomach meridians</td>
<td>Eliminate pathogenic cold, warm stomach and stop vomiting, resolve phlegm and remove stagnation</td>
<td>10</td>
</tr>
<tr>
<td>甘草</td>
<td><em>Radix Glycyrrhiza</em></td>
<td>Sweet in flavor, mild in nature and attributive to the heart, lung, spleen and stomach meridians</td>
<td>Co-ordinate herbs, reduce the toxicity and seizures</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Appendix 9: Chinese version-Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog)

<table>
<thead>
<tr>
<th>Cognitive domains</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Word recall task</td>
<td>/10</td>
</tr>
<tr>
<td>2. Naming objects and fingers</td>
<td>/5</td>
</tr>
<tr>
<td>3. Delayed word recall</td>
<td>/10</td>
</tr>
<tr>
<td>4. Commands</td>
<td>/5</td>
</tr>
<tr>
<td>5. Constructional praxis: figures</td>
<td>/5</td>
</tr>
<tr>
<td>6. Ideational praxis</td>
<td>/5</td>
</tr>
<tr>
<td>7. Orientation</td>
<td>/8</td>
</tr>
<tr>
<td>8. Word recognition test</td>
<td>/12</td>
</tr>
<tr>
<td>9. Remembering test instructions</td>
<td>/5</td>
</tr>
<tr>
<td>10. Spoken language ability</td>
<td>/5</td>
</tr>
<tr>
<td>11. Word finding difficulty</td>
<td>/5</td>
</tr>
<tr>
<td>12. Comprehension</td>
<td>/5</td>
</tr>
<tr>
<td>13. Concentration/ distractibility</td>
<td>/5</td>
</tr>
</tbody>
</table>

Total (11 items): /70
Total (13 items): /85
1. Word Recall 単語回憶

「我國家假一時字詞你記，你大聲讀出來，同理記住佢，遲啲我會再問佢。」
或「我國家假一時字詞你記，你聽完後大聲讀出來，同理記住佢，遲啲我會再問佢。」[如不識字]
大聲讀出每個詞一次，然後即時出聲再讀一次，然後將十個詞盡量讀出來。總共三次試測。

<table>
<thead>
<tr>
<th>第一次</th>
<th>第二次</th>
<th>第三次</th>
</tr>
</thead>
<tbody>
<tr>
<td>能回憶</td>
<td>不能回憶</td>
<td>能回憶</td>
</tr>
<tr>
<td>鬼企</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>五毫子</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>火車軌</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>媽仔</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>國旗</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>皮膚</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>圖書館</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>小麥</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>海</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

不能回憶的詞總數

不能回憶的詞總數

不能回憶的詞總數

平均分數: (0-10)
2. Naming Objects and Fingers 物件名稱和手指名稱

每位測試者會逐一看12件物品，每件看一次，然後說出它的名稱。問題如下：
“這件物品叫做甚麼名稱？”或“這是甚麼？”可以加少許提示:

<table>
<thead>
<tr>
<th>物品</th>
<th>標準提示</th>
<th>正確</th>
<th>不正確</th>
</tr>
</thead>
<tbody>
<tr>
<td>花</td>
<td>生長於花園的生物</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>床</td>
<td>睡眠時用</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>銀雞（哨子）</td>
<td>你吹它會有聲出</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>鉛筆</td>
<td>寫字用</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>哨兵</td>
<td>BB的玩具</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>面具</td>
<td>用來遮面</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>鉶剪</td>
<td>可以剪紙</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>梳</td>
<td>頭髮用</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>荷包</td>
<td>放錢用</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>口琴</td>
<td>樂器一種</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>聽筒</td>
<td>醫生用的儀器</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>夹</td>
<td>用來拿東西的工具</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

被訪者說出他（她）右手每一隻手指的名稱

<table>
<thead>
<tr>
<th>指名</th>
<th>正確</th>
<th>不正確（或說不出）</th>
</tr>
</thead>
<tbody>
<tr>
<td>手指公</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>食指（第二隻手指）</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>中指</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>無名指（第四隻手指）</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>手指尾</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

總共 __________________

分數  
0=0-2 樣東西錯了  
1=3-5 樣東西錯了  
2=6-8 樣東西錯了  
3=9-11 樣東西錯了  
4=12-14 樣東西錯了  
5=15-17 樣東西錯了
2. Delay Recall 延遲回憶測試
病人的分數是在此測試中忘記詞語的次數（最高=10）

<table>
<thead>
<tr>
<th>詞語</th>
<th>能回憶</th>
<th>不能回憶</th>
</tr>
</thead>
<tbody>
<tr>
<td>屋企</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>五亳子</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>火車軌</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>細路仔</td>
<td>□</td>
<td>□</td>
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<tr>
<td>軍隊</td>
<td>□</td>
<td>□</td>
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<tr>
<td>國旗</td>
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<td>□</td>
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<tr>
<td>皮膚</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>圖書館</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>小麥</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>海</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

不能回憶的詞語數目

4. Commands 口頭指令
在每一句指令讀出後，便要求被訪者做到以下行動，若做不到或做錯，便重新再讀一次指令。

<table>
<thead>
<tr>
<th>指令</th>
<th>正確</th>
<th>不正確或做不到</th>
</tr>
</thead>
<tbody>
<tr>
<td>握緊拳頭（右手或左手）</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>先指一下屋頂，跟住指一下地下</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>在椅上面放一支鉛筆，手錶和啤牌，然後說出一下指令</td>
<td></td>
<td></td>
</tr>
<tr>
<td>與支鉛筆放係啤牌上面，跟住再將佢放番原位</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>將隻手錶放係鉛筆嘅邊邊，跟住反轉張啤牌</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>合埋雙眼，用兩隻手指按自己每邊脣頭兩下</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

要完成每一個在劃線上的動作，才代表完成指令

分數：
0=全對
1=1錯，4對
2=2錯，3對
3=3錯，2對
4=4錯，1對
5=全錯

分數：
5. Construction Praxis (Pencil and eraser) 繪圖行為

“寫下一個圖形，你試下係咗張白紙上面規一個同樣嘅圖形”
每次容許兩次試畫，若果兩次皆不能畫出圖形，便作“錯”

<table>
<thead>
<tr>
<th>形式</th>
<th>對</th>
<th>錯 (或畫不到)</th>
<th>分數</th>
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</thead>
<tbody>
<tr>
<td>圓形</td>
<td></td>
<td></td>
<td>0=對</td>
</tr>
<tr>
<td>兩個重疊的長方形</td>
<td></td>
<td></td>
<td>1=1 形狀錯</td>
</tr>
<tr>
<td>菱形</td>
<td></td>
<td></td>
<td>2=2 形狀錯</td>
</tr>
<tr>
<td>立方形</td>
<td></td>
<td></td>
<td>3=3 形狀錯</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4=4 全錯</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5=完全畫不到；畫了一部份；字而無圖形</td>
</tr>
</tbody>
</table>

附註：劃正確的圖形才可取分數。圖形的大小、隔離的寬窄、形狀的長短都不會計算在內。評分準則如下：
1. 圓形：要連繡畫，沒有斷口
2. 兩個重疊的長方形，圖形是四邊，重疊。如*2
3. 菱形，圖形是四邊，四邊邊界長是差不多相同長度，上下對稱，如下*3
4. 立方形，圖形是有三邊形（正面及側面）對角線要平衡；如下*4

![圖形示例](image-url)
6. Ideational Praxis 意向指令行為

“現你有一封寫好嘅信，想你將信信封好，放入信封里面，再把信封封口，在信封上寫上你自己的名字地址，再貼上郵票。”

指出每一步驟是對或錯，如他（她）做不到或不明白，可以重覆說出指示。

| 對 或做得到 | 錯或做不到 | 分數：
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>撰信</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>將信放入信封裡</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>封口</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>寫上姓名、地址</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>表示郵票貼上位置</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

7. Orientation 認知行為

作此測試之前，先拿走（或遮蓋）時鐘，手錶或日曆。可以指出答案是對或錯。

<table>
<thead>
<tr>
<th>對</th>
<th>錯（沒有答）</th>
</tr>
</thead>
<tbody>
<tr>
<td>全名（必須正確）</td>
<td>☐</td>
</tr>
<tr>
<td>星期幾（必須正確）</td>
<td>☐</td>
</tr>
<tr>
<td>日期（±1天）</td>
<td>☐</td>
</tr>
<tr>
<td>月份（必須正確）</td>
<td>☐</td>
</tr>
<tr>
<td>年（必須正確）</td>
<td>☐</td>
</tr>
<tr>
<td>季節（±2星期）</td>
<td>☐</td>
</tr>
<tr>
<td>時間（±1小時）</td>
<td>☐</td>
</tr>
<tr>
<td>地點（例如醫院）</td>
<td>☐</td>
</tr>
</tbody>
</table>

總分

評分=每錯一題計 1 分

註： 可以接受的答案包括日期（±1天），季節（下一季的一周指內或上一季的兩周之內），時間（1 小時至內），地點（可以說出地點部分的名稱）
8. Word Recognition 認字

“我依家俾一啲字你聽，你大聲讀出來同埋記住佢” 或 “而家讀一啲字你聽，你聽完跟我講一次，然後記住佢” [如病人不識字，由職員讀出]

甲) 第一次
12 個字: 河流 事件 皇后 位置 鴿子 信心 雨傘 提示 飛彈 代理權 蟲蝶 標準

完成測試上述 12 個字後，便說 “我而家再俾另一啲字你聽，有一啲字你頭先已經睇過，有啲就無睇過，你話俾我聽有無睇過嘅?” 或 “我而家再俾另一啲字你聽，有一啲頭先你已經睇過，有啲就無睇過，你話俾我聽有無睇過?” [如病人不識字，由職員讀出]

“呢個字頭先有無睇過 (睇過)? 然後 呢個呢?” 如病人不記得問題，可以重覆問題。請記下每次的提示。

乙) 第二次 (同樣的 11 個字)
河流 事件 皇后 位置 鴿子 信心 雨傘 提示 飛彈 代理權 蟲蝶 標準

丙) 第三次 (同樣的 11 個字)
河流 事件 皇后 位置 鴿子 信心 雨傘 提示 飛彈 代理權 蟲蝶 標準

深色是先前睇過 (睇過) 的名。在病人的答案中 √ 圓形代表錯的答案。若要重複提示問題，便在提示一方格以 √ 表示。
<table>
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<tr>
<th>有</th>
<th>没有</th>
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<th>有</th>
<th>没有</th>
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<th>没有</th>
<th>提示</th>
</tr>
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<td>河流</td>
<td>□ □ □</td>
<td>植物</td>
</tr>
</tbody>
</table>

分數 = 錯的總數或 “12”(以最少為瘠石)

第一次 (A): 分數 ______提示 (次數) ______
第二次 (A): 分數 ______提示 ______
第三次 (A): 分數 ______提示 ______

總共提示
(用筆筆問題 8) ______

分數 (0-12) (註: 三次平均數): ______
9. Remembering Test Instructions 在問題 8 的測試過程中，評估病人記憶問題的能力。
分數:
0 = 不需提醒
1 = 非常輕微，忘記一次
2 = 輕微，提示兩次
3 = 中度，提示三至四次
4 = 嚴重，提示五至六次
5 = 非常嚴重，提示七次以上

分數：

10. Spoken Language Ability 語言表達的能力
對被訪者給予一個整體總評分（如清晰程度、容易明白的程度等質素）
0 = 無困難
1 = 非常輕微困難
2 = 輕微困難（少於四分之一）
3 = 中度困難（四分之一至一半）
4 = 中度嚴重（一半以上）
5 = 非常嚴重（只能說單字或沒有內容的說話）

分數：

11. Word Finding Difficulty in Spontaneous Speech 說話時的用字困難
評估被訪者說話時是否有選詞方面的困難
分數 0=用字無困難
1=非常輕微困難
2=輕微困難（用其他字代替）
3=中等困難（少了一些字又不會用其他字代替）
4=中等嚴重（少了許多字）
5=非常嚴重（差不多完全沒有內容，空洞的發音，說 1 或 2 字）

分數：
12. Comprehension of Speech 理解語言的能力

評估病人理解語言的能力，口頭指令的行動不用計算在內

分數
0=無困難
1=非常輕微， 1-2 次不明白
2=輕微 3-5 次不明白
3=中等要重覆說多次
4=嚴重， 只能答是否等
5=非常嚴重， 很少適當地回答問題，而又不是因言語貧乏原因

分數：

Alzheimer’s Disease 認知部分（ADAS-Cog）

總分 Item 1-12（0-70）：

13. Concentration 注意力不集中

評估病人有無注意力接受測試，或注意力受到分散的情況

分數
0=無困難
1=非常輕微， 1 次
2=輕微 2-3 次
3=中等 4-5 次
4=嚴重， 大部分時間不能集中精神
5=非常嚴重， 完全不能完成測試的工作

分數：
Appendix 10: Chinese version-Mini-Mental State Examination (MMSE)

失智功能障礙評估量表 (CDAD)

姓名：__________________ 性別：__________________
年齡：__________________ 教育程度：__________________

請註明所有身體和感官障礙：__________________

受訪者：__________________ 與評估對象的關係：__________________
評審員：__________________ 日期：__________________

起動力 包括決定及/或開始行動的能力，這不但講求個人的自發性，亦須考慮該活動是否在合適的時間和地點進行。

計劃及組織力 包括認識整個活動中不同組成部分的能力，能把它們按合適的次序連接起來，並制定行動的策略和在行動前預備好所需物料。此外，它還包括監察活動過程的能力，即能於需要時解決問題和作出決定以修正錯誤的能力。

有效執行能力 包括完成整個活動的能力，能否在安全及可接受的方式下完成活動也是其中一個重要的因素。

在過去的兩個星期，__________________（評估對象的姓名），在沒有協助和提醒下：

<table>
<thead>
<tr>
<th>1. 個人衛生</th>
<th>評分：是=1 否=0 不適用=N/A</th>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. 主動洗臉</td>
<td></td>
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<tr>
<td>b. 主動洗腳</td>
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<tr>
<td>c. 主動刷牙或清洗假牙</td>
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<tr>
<td>d. 主動清洗及梳理頭髮</td>
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<tr>
<td>e. 準備水、毛巾和肥皂來清洗自己或洗澡</td>
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</tr>
<tr>
<td>f. 可安全徹底的清洗和梳理身體的各部位</td>
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<tr>
<td>g. 自己刷牙或清洗假牙</td>
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<tr>
<td>h. 自己清洗及梳理頭髮</td>
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</tbody>
</table>
### 2. 穿衣

<table>
<thead>
<tr>
<th>評分</th>
<th>是 = 1</th>
<th>否 = 0</th>
<th>不適用 = N/A</th>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
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<tbody>
<tr>
<td>a.</td>
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### 3. 大小便

<table>
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<th>評分</th>
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<th>不適用 = N/A</th>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
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<tbody>
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<td>a.</td>
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<td>b.</td>
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<td>c.</td>
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### 4. 進食

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<tr>
<th>評分</th>
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<th>否 = 0</th>
<th>不適用 = N/A</th>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
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</thead>
<tbody>
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<td>a.</td>
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<td>d.</td>
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</tbody>
</table>

### 5. 凱爾飯餐

<table>
<thead>
<tr>
<th>評分</th>
<th>是 = 1</th>
<th>否 = 0</th>
<th>不適用 = N/A</th>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
</thead>
<tbody>
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<td>a.</td>
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<td>b.</td>
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<tr>
<td>c.</td>
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</tr>
</tbody>
</table>
### 6. 通電話
評分：是 1 否 0 不適用 N/A

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

a. 在恰當的時間試著與人通電話
b. 正確地記下和撥打電話號碼（家庭和常見的電話）
c. 恰當地進行電話對話
da. 適當地記下和傳達電話訊息（若因教育程度影響，或在病發前從未做到，請填不適用）

### 7. 外出
評分：是 1 否 0 不適用 N/A

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
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<tbody>
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</tbody>
</table>

a. 在合適的時間外出（散步、探訪、購物）
b. 適當地安排一天外出活動，包括選擇交通工具、帶夠錢、決定目的地、考慮天氣情況、帶夠所需金錢、準備所需物品
c. 自行外出到一個熟悉的地方而不迷路
da. 安全地搭乘適當的交通工具（巴士、計程車、地鐵、火車等）
e. 自行出外買所需東西並可自己回家

### 8. 財務
評分：是 1 否 0 不適用 N/A

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
</thead>
<tbody>
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</table>

a. 關注個人事務如財務（若因教育程度影響，或在病發前從未做到，請填不適用）
b. 自行管理財務，如付賬、處理支票、銀行存摺、賬單
c. 有效地使用金錢（如買東西，知道找錢是否正確）

### 9. 服藥
評分：是 1 否 0 不適用 N/A

(若不需服藥，或拒絕服藥，請填不適用)

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

a. 主動在正確的時間服藥（包括考慮服藥的需要）
b. 在合適的地方取出所需的藥物，並以適當的方法服用
c. 依處方服藥（正確劑量）
### 10. 家務
評分：是 = 1  否 = 0  不適用 = N/A

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
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</tbody>
</table>

- a. 對以前經常做的家庭雜務仍有興趣做
- b. 適當地計劃和安排過去經常做的家庭雜務
- c. 有效地完成過去經常做的家庭雜務
- d. 有需要時能安全地預留家中

### 11. 娛樂
評分：是 = 1  否 = 0  不適用 = N/A

<table>
<thead>
<tr>
<th>起動力</th>
<th>計劃及組織力</th>
<th>有效執行能力</th>
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</table>

- a. 對過去經常參與的餘暇活動有興趣
- b. 適當地計劃和安排過去曾經參與的餘暇活動
- c. 有效地完成過去經常參與的餘暇活動

### 總評：

<table>
<thead>
<tr>
<th>副題總分/通用項目</th>
<th>/</th>
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</thead>
<tbody>
<tr>
<td>副題百分比</td>
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<tr>
<td>失智功能障礙評估總分/通用項目</td>
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<tr>
<td>失智功能障礙評估百分比</td>
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</tbody>
</table>

CURRICULUM VITAE

Academic qualifications of the thesis author, Mr. CHUA Ka Kit, Tony:

- Received the degree of Bachelor of Chinese Medicine and BSc (Hons) Biomedical Science from Hong Kong Baptist University, November 2011.

August 2015