THE EFFECT OF ACUPRESSURE FOR MANAGING AGITATION IN NURSING HOME RESIDENTS WITH DEMENTIA: RANDOMIZED CONTROLLED TRIAL

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The effect of acupressure for managing agitation in nursing home residents with dementia: Randomized controlled trial

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CERTIFICATE OF ORGINIALITY

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Abstract

Introduction

Agitation is commonly observed in people with dementia (PWD). It has many negative impacts on the PWD themselves, their caregivers, and society. Acupressure is a therapeutic modality which originates from traditional Chinese medicine (TCM). Preliminary evidence supports its effectiveness and feasibility. However, there are many issues related to the effects of acupressure which are still unknown. This study aimed at examining the effects of acupressure on agitation and stress, the mediating effects of acupressure on agitation by stress, and the sustainability of the effects of acupressure.

Methods

To develop the intervention protocol and research design through evidence-based procedures, this study followed the Medical Research Council 2008 guideline for developing and evaluating complex interventions. This study used three methods sequentially to develop the study: literature review, Delphi process, and pilot study. A randomized controlled trial (RCT) was then used to answer the research question.

The RCT blinded both assessors and participants, and used parallel groups. The participants were allocated to three groups in a 1:1:1 ratio by permuted block randomization. The intervention was acupressure, which was compared with two controlled conditions: sham and usual care.

In the acupressure group, participants received acupressure at five acupoints: Fengchi (GB20), Baihui (GV20), Shenmen (HT7), Niguan (PC6), and Yingtang (EX-HN3). A course of acupressure lasted for two weeks and was implemented twice a day on five days per week. Each session lasted for 10 minutes. In the sham group, participants received the sham protocol, which was the same as the acupressure protocol except that five non-acupoints were used. In the usual care group, participants received no active interventions. The primary outcome was agitation as measured by the Cohen-Mansfield Agitation Inventory (CMAI). The secondary outcome was stress as measured by salivary cortisol. Outcome variables were measured at the baseline (T_0) and the 3rd (T_1), 5th (T_2), and 8th weeks (T_3) after the baseline. The general estimating equation (GEE) and structured equation modeling (SEM) were employed for statistical analysis.

Results

The study recruited 119 eligible subjects from 12 residential care homes in Hong Kong. In the GEE analysis, a significant interaction effect (i.e. group by time) was only observed on the outcome of stress (X^2=14.811, p=0.022); none was observed on agitation. In the pair-wise analysis between time points in the acupressure group, there was significant agitation reduction in T_2 (MD=-6.84, p<0.001) and stress reduction in T_1 (MD=-0.27μg/dL, p<0.001) and T_2 (MD=-0.21 μg/dL, p=0.001) compared with the baseline. The agitation and stress levels in the acupressure group were not observed to be significantly different at T_3 compared with the baseline. In the SEM mediation analysis, stress was not observed to play a significant mediating role leading acupressure to reduce agitation.

Conclusion

This study confirmed that acupressure significantly reduces cortisol levels in agitated PWD, but does not reduce their agitation. Although significant effect on cortisol reduction was observed, the hypothesis that stress is a cause of agitation in PWD nor there is a sustained effect of acupressure on both stress and agitation cannot be confirmed.

Publications

Journal papers

Kwan, R. Y. C., Leung, M. C. P., & Lai, C. K. Y. The effect of acupressure on agitation and salivary cortisol in people with dementia in residential care homes: A pilot study. *Journal of Alternative and Complementary Medicine.* doi:10.1089/acm.2016.0062 [Epub ahead of print]

Kwan, R. Y. C., Leung, M. C. P., & Lai, C. K. Y. (2014) Acupressure for agitation in nursing home residents with dementia: study protocol for a randomized controlled trial, *Trials, 15:410.* doi:10.1186/1745-6215-15-410.

Kwan, Y. C. R., & Lai, K. Y. C. (2013) Can smartphones enhance telephone-based cognitive assessment (TBCA)? *International Journal of Environmental Research and Public Health, 10*(12), 7110-7125.

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Conference papers

Kwan, R. Y. C. & Lai, C. K. Y. (2015, September 28). *Development of an acupressure treatment protocol by consensus for agitated nursing home residents with dementia: A Delphi process.* Oral session presented at the 3rd International Nursing Congress of Armenia, Yerevan Armenia.

Kwan, R. Y. C., Leung, M. C. P. & Lai, C. K. Y. (2014, Nov 7-9). *The preliminary results of a clinical trial on the effect of acupressure for agitation in nursing home residents with dementia.* Poster session presented at the Alzheimer's Disease International Asia Pacific Conference, New Delhi India.

Lai, C. K. Y. & Kwan, R. Y. C. (2014, Nov 29-30). *Practice and outcomes of the Health and Cognitive Assessment Service (HeCAS) in a tertiary education institute in Hong Kong.* Oral session presented at the 9th Pan-pacific Conference on Rehabilitation cum 21st Annual Congress of Gerontology, Hong Kong China.

Kwan, R. Y. C., Lai, C. K. Y., & Leung, M. C. P. (2014, July 24-28*). Methods of developing and evaluating an acupressure protocol for managing agitation in dementia.* Poster session (invited) presented at the 25th STTI Honor Society of Nursing, International Nursing Research Congress, Hong Kong China.

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Kwan, R. Y. C. & Lai, C. K. Y. (2013, Feb 21-22). *The use of advanced practice training as an integral part of doctoral education.* Oral session presented at the 16th East Asian Forum of Nursing Scholars (EAFONS), Bangkok Thailand

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List of Abbreviations

ADL	Activities of daily living
AP	Acupressure group
BPSD	Behavioral and psychological symptoms of dementia
CMAI	Cohen-Mansfield Agitation Inventory
HPA	Hypothalamus-pituitary-adrenocortical
MBI	Modified Barthel Index
MMSE	Mini-mental state exam
NPI	Neuropsychiatric Inventory
PLST	Progressively lowered stress threshold
PWD	People with dementia
RCH	Residential care home
RCT	Randomized controlled trial
SC	Salivary cortisol
SM	Sham group
T_0	Baseline
T_1	The 3rd week after baseline, or the 1st week after completion of the intervention
T_2	The 5th week after baseline, or the 3rd week after completion of the intervention
T_3	The 8th week after baseline, or the 5th week after completion of the intervention
TCM	Traditional Chinese medicine

UC Usual-care group

Statistical Acronyms

95%CI	Ninety-five percent confidence interval
CFI	Comparative fit index
E	Estimate of effect (standardized)
GEE	Generalized estimating equation
IQR	Inter-quartile range
LSD	Less significance difference
MD	Mean difference
mITT	Modified intention to treat
N	Number of samples
NFI	Normed fit index
PP	Per protocol
p	Probability value
r	Pearson’s product-moment correlation coefficient
SD	Standard deviation
SE	Standard error
SEM	Structured equation modeling
SES	Standardized effect size
SRMR	Standardized root mean-square residual
X^2	Chi-square

List of Appendices

Chapter 1 Introduction

Dementia is a clinical syndrome in which there is deterioration in cognitive ability and ability to perform everyday activities (WHO, 2015). It is also known as a neurocognitive disorder with key clinical features of progressive and irreversible cognitive function decline affecting daily functioning (American Psychiatric Association, 2013).

In the course of dementia, psycho-behavioral symptoms commonly occur in people with dementia (PWD). There are many different terms describing these psycho-behavioral symptoms in dementia, including behavioral and psychological symptoms of dementia (BPSD), neuropsychiatric symptoms (NPS), and agitation. These terms are not used specifically to describe a particular psycho-behavioral symptom. Rather, they usually describe a cluster of psycho-behavioral symptoms commonly observed in the PWD. Agitation can also be viewed as a symptom in the cluster of symptoms in BPSD and NPS. To a certain extent these terms overlap with each other conceptually. They are not the same concepts but describe these psycho-behavioral symptoms in dementia from different perspectives.

Agitation is one of the most commonly used terms to describe psycho-behavioral symptoms in PWD in recent decades (Jost et al, 1996; Margallo-Lana, 2007; Lyketsos et al, 2002; Ballard et al, 2009). To date, agitation in dementia has been established as a mature concept that is commonly used to describe these psycho-behavioral symptoms and researched for proper symptom management (Jakobson et al, 2015; Liu & Howard, 2015; Kong & Park, 2015).

In the past two decades, the prevalence of agitation has varied in the community: 22% (Lyketsos et al, 2000) and 40% (Sadak et al, 2014) in the United States, 85% in Hong Kong (Choy et al, 2001), and 86.1% in China (Wang et al, 2003). The prevalence of agitation also varies in nursing homes: 75.4% in Norway (Testad et al, 2007) and 90.8% in mainland China (Wang et al, 2003). A recent review paper showed that the prevalence of NPS, among which agitation was one of the most prevalent symptoms, in nursing home residents with dementia was 82% (Selbæk et al, 2013). The figures vary mainly because different definitions of agitation are used in different studies, and because the studies were conducted in different geographical regions and settings. Nevertheless, the figures show that agitation has been very commonly observed among PWD across settings in recent decades, and that this situation continues today.

The aforementioned evidence shows that agitation in dementia is an established concept which is commonly used in the context of dementia care to describe a cluster of psycho-behavioral symptoms. To date, agitation in dementia is still being actively researched for proper management. This study aimed at further investigating proper management of agitation in dementia by basing it on previously generated knowledge. To achieve this aim, a literature review was performed to explore what had already been learned on agitation in dementia and what was unknown in the literature but worthy of study in further research. The extensive literature review showed that acupressure is one of many therapeutic modalities with potential to be developed for managing agitation in PWD. It may also be a culturally acceptable and useful intervention for the management of

agitation of PWD in the Chinese population. This study discusses how the acupressure protocol and research design were developed. The main purpose of this study focused on examining the effect of acupressure in managing agitation in the nursing home residents with dementia in the Chinese population.

This proposed study argued that acupressure has potential to be developed as an intervention alternative for managing agitation in dementia but there were some knowledge gaps, which were either about unclear effects of acupressure or invalid effects of acupressure reported the previous studies caused by methodological flaws. This study aimed at examining the unclear effects of acupressure by using methods closing the methodological loopholes identified in the previous studies. Specifically, this study asked four research questions:

1. Will acupressure reduce the agitation level of agitated nursing home residents with dementia over time as compared with the controlled conditions?

2. Will acupressure reduce the stress level of agitated nursing home residents with dementia over time as compared with the controlled conditions?

3. If acupressure reduces agitation in nursing home residents with dementia, will the agitation-reducing effect of acupressure be mediated by stress?

4. If acupressure reduces agitation and stress in nursing home residents with dementia, will the effect of acupressure no reducing agitation and stress be sustained over time?

Including this chapter, there are totally seven chapters: introduction, literature review, development of the study, main study, results, discussion and conclusion. Chapter 2, the literature review, aims at exploring the knowledge available on this topic and identifying the knowledge gap worthy of further investigation. This chapter begins with a discussion of the significance and concept of agitation in dementia, followed by its causes and the available interventions. The concept of acupressure as a therapeutic modality and the reasons why it is worthy of further research in the management of agitation in dementia are then discussed, and the development of the research question is explicated.

Chapter 3, the development of the study, discusses the process of identifying a proper study design through evidence-based procedures to generate new knowledge to fill the gap identified in the literature review. The chapter begins by discussing the methods and procedures used for the development of the study design, following this with a discussion of how Delphi technique and the pilot study were used sequentially to lead to the design of this study. Finally, the construction of a conceptual framework and the generation of a testable research hypothesis are discussed.

The aim of chapter 4, the main study, is to elucidate what methods were used in setting up an experiment in order to answer the research question of the study. The chapter begins with a description of the operational definitions of the variables, followed by a discussion of the methods used throughout the RCT.

The aim of chapter 5 is to descriptively report the results of the RCT. The figures are first described separately according to the nature of the participants' characteristics and hypothesis testing. Results related to the sensitivity analysis between analysis protocols are then reported.

Chapter 6, the discussion, considers how to interpret the results of the RCT examining the effect of acupressure in managing agitation in PWD. The chapter begins with a description of the participants' profile, followed by a discussion of the answers to the research questions using the data from the RCT. The meaning of the findings in terms of the research questions, the implications, and the significance of this study are discussed. The chapter then discusses how the study contributes to the theory development, concluding by addressing its strengths and limitations. In chapter 7, the conclusion, the aim is to summarize the key messages of the study.

Chapter 2 Literature Review

This chapter aims at reviewing the literature to discuss concepts related to the use of acupressure in managing agitation in dementia. This literature review begins with a discussion of the significance and concept of agitation in dementia. It is followed by its causes and the available interventions managing agitation in dementia. Finally, a discussion of why acupressure is possibly effective to manage agitation in dementia and the knowledge gap on this topic is given.

2.1 Significance of Agitation in Dementia

Agitation is a clinical problem because it has many negative impacts on the people with dementia themselves, their caregivers, and society as a whole. Cognitive and functional decline is expected in the trajectory of dementia. As the disease progresses, PWD become less capable of performing cognitive tasks and activities of daily living (ADL). Agitation is significantly and negatively associated with functional ability (Rosenberg et al, 2011; Zahodne et al, 2015) and even a faster decline in cognitive and functional ability (Scarmeas et al, 2007). This evidence shows that agitation may be associated with further acceleration of cognitive and functional decline in PWD.

Quality of life is a multi-dimensional and complex concept which is an important focus of the care of PWD. Evidence has shown that agitation can lead to a decrease in quality of life for nursing home residents with dementia, probably due to caregivers' low level of knowledge and skills in behavior management (Hurt et al, 2008). A more recent study (Karttunen et al, 2011) found a significant

association between agitation and poor caregiver-rated quality of life of the PWD. However, agitation was not significantly associated with the PWD's self-rated quality of life. The validity of the instruments measuring PWDs' quality of life is controversial and possibly responsible for this incoherent observation. Evidence as to whether the caregiver-rated or the PWD's self-rated quality of life is more valid was therefore inconclusive. However, the evidence at least showed that agitation is associated with deterioration in quality-of-life related clues observable by the caregivers of PWD.

In the United States, before the nursing home culture-change movement that began around 1997 (Rahman & Schnelle, 2008), nursing home care was reported to be based on the medical model of care, with an over-emphasis on the safety of the residents and the consequent use of restrictive methods (e.g. physical and chemical restraints) on agitated nursing home residents with dementia to ensure their safety and prevent them from hurting other people or themselves. In recent decades, evidence of the ineffectiveness and adverse effects of such methods has been growing. The adverse effects include direct injuries, fatal entrapment, decreased mobility, and reduced psychological well being (Pellfolk et al, 2010; Möhler et al, 2011). In recent decades, endeavors have been made to create many effective care alternatives to manage behavioral problems, instead of using physical restraints (De Bellis et al, 2013; Testad et al, 2015). Nevertheless, a recent study still reported that behavioral problems and dementia are significant risk factors for the use of physical restraints in nursing home residents (Kwan et al, 2015). This evidence shows that agitation in dementia is still being managed by restrictive methods today, in spite of

the availability of many other alternatives to manage agitation in dementia. The adverse effects of physical restraint continue to have an impact on PWD with agitation.

Apart from the negative impact on the PWD, agitation also dramatically increases the burden on formal caregivers (Sink et al, 2005). Studies show that agitation frequency has a significant effect on the distress and burden level of formal caregivers in nursing homes, including nurses and care assistants (Gaugler et al, 2009; Huang et al, 2012). Formal caregivers felt more stressed in handling the agitation of PWD (Matsumoto et al, 2007; Miyamoto et al, 2010), probably because they had limited information about the life history of the PWD and had difficulty communicating with them (Edberg et al, 2008). As a result, the health and quality of life of the formal caregivers of agitated PWD are threatened (Molyneux et al, 2008; Carretero et al, 2009).

Agitation is also one of many risk factors in the institutionalization of PWD (Scarmeas et al, 2007), probably because the care of agitated PWD demands extra time and skills, which are difficult to provide in a home-based setting. In a study in the United Kingdom, the mean excess cost associated with agitation per person with dementia was found to account directly and indirectly for 12% of the health and social care costs of PWD (Moris et al, 2015). This shows that agitation in dementia may have markedly increased the cost of dementia care in our society.

The aforementioned evidence points to a conclusion that agitation in dementia is a clinical problem which negatively impacts on PWD, their caregivers, and

society. Agitation in dementia is worthy of thorough research for better management. This literature review chapter will discuss the concept, causes, and interventions of agitation in dementia identified in the literature. It will then discuss the reasons why acupressure is singled out of the different therapeutic modalities as being worthy of further research. Next, theories and evidence on the use of acupressure as a therapeutic modality will be discussed. Finally, after the literature review, the knowledge gap on the topic of using acupressure in managing agitation in dementia will be presented.

2.2 Concept of Agitation in Dementia

Agitation in dementia appears widely in academic papers as it is a frequently manifested symptom in PWD. The definitions of agitation in dementia in different articles are not exactly the same. The concept of agitation in dementia varies slightly in different definitions and studies. Therefore, the concept of agitation in dementia should first be clarified in order to conduct an appropriate study of this condition.

A concept is a sign or symbol that possesses common attributes (Ausubel et al, 1978), that expresses the same idea by using various sets of words (Rodgers et al, 2000; Walker & Avant, 2005). A critical attribute is a description of the core characteristics which appear over and over again when the concept is defined or described (Walker & Avant, 2005).

2.2.1 Critical attributes

Agitation in dementia has been discussed often in the last three decades. In order to illustrate the core concept of this study, which is agitation in dementia, this study partially follows Rodgers' evolutionary method of concept analysis (2000). Given that the purpose of this analysis was mainly to identify the critical attributes for the purpose of identifying an appropriate operational definition for this study, some other procedures suggested by Rodgers, such as related terms, antecedents, examples, and consequences, were not performed.

By reviewing the literature from the last three decades (i.e. 1980-2015) in the following electronic databases: MEDLINE, CINAHL, and PsychINFO, and in a purposive hand-search, a large number of articles were retrieved. Most were about evaluating the effects of interventions (e.g. drugs and non-pharmacological therapies) using agitation as an outcome. There was very little discussion of the concept of agitation in dementia. Of the vast number of papers, 13 articles (Barnes & Raskind, 1980; American Psychiatric Association, 1980; Cohen-Mansfield, 1986; Rosen, 1994; Algase, 1996; Kopecky & Yudofsky, 1999; Logsdon et al, 1999; Camberg et al, 1999; Volicer & Hurley, 1999; Bogner et al, 2000; Kong, 2005; Cohen-Mansfield, 2008; Cummings et al, 2015) were purposefully selected for analysis, as they all contained discussions on the concept of agitation or definitions of agitation in dementia. It was concluded from these 13 articles that agitation in dementia appeared to possess three critical attributes. First, agitation is observable. Second, agitation is excessive, disruptive, and inappropriate. Third, agitation is not caused by apparent needs.

2.2.1.1 Observable

Agitation most commonly appeared to describe an activity or behavior. For example: verbal, motor, vocal activity (Cohen-Mansfield, 1986); motor, vocal, behavior (Kopecky & Yudofsky, 1999); and motor activity, verbal aggression, physical aggression, or evidencing behaviors that cause excess disability (Cummings et al, 2015). The nature of agitation includes behaviors or activities that are observable. Three types of activities or behaviors were used to describe the agitation in dementia: verbal, vocal and motor. Some definitions used all three: verbal, vocal, or motor activity, (Cohen-Mansfield, 1986), while others used only two: vocal or motor behavior (Rosen et al, 1994). Verbal activities refer to speaking words with conceivable meanings and talking to self or others. Vocal activities refer to making sounds by mouth, which may not carry conceivable meanings, such as murmuring or shouting. Motor activities refer to movement of body parts, no matter whether it is meaningful or meaningless, such as wandering or rubbing body parts or hitting people. The abovementioned verbalization, vocalization, and behaviors are all observable.

On top of the observable signs, some definitions of agitation included psychological components as well (Camberg et al, 1999; Volicer & Hurley, 1999; Bogner et al, 2000; Logsdon et al, 1999). For example: “with a feeling of inner tension” (American Psychiatric Association, 1980), and “experiencing an unpleasant state of excitement” (Volicer & Hurley, 1999). A psychological component is an experience which is only perceived by the subjects themselves. The psychological component is only evident when the person expresses it, because

it cannot be observed by others. Volicer and Hurley (1999) argued that the psychological nature of the agitation may subconsciously be expressed by behaviors. Agitation was defined by Volicer and Hurley (1999) as "observed behaviors that communicate to others that the patient is experiencing an unpleasant state of excitement". They explained that there is a psychological component in the concept of agitation, which can be observed when the person expresses it in their behaviors. More recently, Cummings and colleagues (2015) defined a core component of agitation in dementia as "exhibiting behavior consistent with emotional distress".

In the attribute of *observable,* agitation in dementia includes both agitation of an observable behavioral nature and non-observable psychological agitation that may eventually be manifested in behavioral presentations. The activity or behavior may include verbal, vocal or motor manifestations.

2.2.1.2 Excessive, disruptive, and inappropriate

The definitions of agitation formed in the literature describe the behavioral and psychological nature of its manifestation using a wide variety of different vocabulary. However, the various definitions all aim at distinguishing the agitation from its normal counterpart, which is a non-agitated psycho-behavioral state. Different vocabulary was used to describe the distinctive features that distinguish the agitated from the normal state. The three of these descriptors that appear most commonly in the literature are *excessive* (American Psychiatric Association, 1980),

disruptive (Rosen et al, 1992), and *inappropriate* (Cohen-Mansfield & Billig, 1986). They describe how agitation is identified as being different from normal behaviors.

Excessive refers to a characteristic of the agitated behaviors which can be interpreted in terms of increased frequency, duration, and intensity (Barnes & Raskind, 1980). It means that when the observed behaviors increase in frequency, duration, or intensity when compared with the normal state of the person, the person may be judged to have agitation.

Disruptive refers to the characteristics of agitated behaviors that can be interpreted by the outcomes of the behaviors. In other words, when the outcomes of a person's behaviors influence others or the person, or when others feel that they are being disrupted (Rosen et al, 1992), the person may be judged to have agitation (Cohen-Mansfield, 2008).

Inappropriate is more complex. According to Cohen-Mansfield and Billig (1986), there are three categories of inappropriateness: being abusive or aggressive towards oneself or others, performing appropriate behaviors with inappropriate frequency, and being inappropriate according to social standards for the specific situation. Rosen and colleagues (1992) described a similar concept of inappropriate behaviors as those which can make the PWD unsafe and/or interfere with the delivery of care in a particular environment. When a person behaves inappropriately and their behaviors belong to any one of the above categories of inappropriateness, the person may be judged to have agitation.

In this attribute, I have attempted to describe agitated behaviors as distinct from normal behaviors. There are many words to describe its distinctiveness. However, the three words that are most commonly used are excessive, disruptive, and inappropriate.

2.2.1.3 Not caused by apparent needs

Some of the problematic behaviors of older people with cognitive impairment are caused when some of their basic needs have not been met by the PWD or their caregivers (Algase, 1996). These problematic behaviors are called need-driven behaviors. The following is an example of a need-driven behavior. A person keeps crying and shouting. This person cries and shouts because he finds the environment too noisy. A quiet environment is a basic need of residents in a nursing home. When this need is not satisfied, the person may express his/her need for a quiet environment by certain behaviors. These behaviors may aim at communicating to others that a quiet environment is needed, particularly in the case of those who are cognitively impaired. Cummings and colleagues (2015) also state that "evidencing behaviors are not solely attributable to another disorder". These needs may include a need for treatment for apparent physical or mental illnesses as well. After their needs have been satisfied, the problematic behaviors subside. Such behaviors cannot be interpreted as agitation.

In the literature, it has been argued that need-driven behaviors are different and should be differentiated from agitation. This argument appears in many definitions of agitation in dementia. For example: "Inappropriate activity that is not explained

by needs" (Cohen-Mansfield and Billig, 1986), and "Evidencing behaviors are not solely attributable to another disorder" (Cummings et al, 2015). This means that when the inappropriate activity is identified, further assessment should be performed to see if the behaviors are caused by the person's needs. If that is the case, the person cannot be judged to have agitation. Some definitions even further explicate in the definition that interventions should be performed first to satisfy the needs. For example: "Observed patient behaviors [that] remain after interventions to reduce internal or external stimuli" (Volicer & Hurley et al, 1999). This definition means that the person can only be said to have agitation if interventions to satisfy their needs have been attempted but have failed to control the behaviors.

Clinically, need-driven behavior is not easy to be distinguished from agitation. This is because some needs and subtle illnesses cannot be easily identified or satisfied. Arguing that all needs should be met before a person with problematic behaviors can be identified as having agitation is practically infeasible. Nevertheless, agitation is conceptually different from need-driven behaviors, even though in practice we may not clearly differentiate between them by clinical observations. Agitation should be evident only when observed behaviors remain after apparent needs have been satisfied.

In summary, agitation in dementia is a psycho-behavioral state. The behavioral nature is observable, while the psychological nature is observable when the person expresses it by behaviors. The agitated behaviors can be described as behaviors that are different from the normal because they are excessive, disruptive and inappropriate. However, these deviated behaviors can be a way for people with

cognitive impairment to communicate their needs to others. These behaviors are therefore called need-driven behaviors, and are conceptually different from agitation. Need-driven behaviors and agitation can be difficult to differentiate in PWD who cannot articulate their needs clearly. Agitation should be evident only when observed behaviors remain after apparent needs have been satisfied.

The term agitation has been used widely in the literature and variations on the understanding were observed in different studies. This section clarified and defined the concept of agitation in dementia for this study. It is important as it serves as the theoretical understanding on the targeted clinical problem (i.e. agitation in PWD) to be resolved for this study. Also, selection of instrument to measure this concept bases on this understanding on the agitation in PWD.

2.2.2 Agitation in dementia in traditional Chinese medicine

The health beliefs and way of living of Chinese people are strongly influenced by the Chinese philosophy and culture; they value traditional Chinese medicine (TCM) as much as Western medicine (Smith and Bauer-Wu, 2012). As mentioned earlier, agitation is a concept developed in Western countries, where there is much literature describing and explaining this condition. This is also a prevalent phenomenon among Chinese PWD (Xue et al, 2013). In order to study agitation in dementia among the Chinese, the concept of agitation in dementia needs to be explicated from the perspective of TCM.

A systematic search was performed in attempt to identify papers discussing agitation in dementia from the TCM perspective. Keywords of “agitated or

agitation" and "Traditional Chinese Medicine or TCM" and "dementia or demented" were used on the following English electronic databases: MEDLINE, CINAHL, and PsycINFO. Keywords of "激越 or 躁" (i.e. synonyms of agitation) and "中醫" (i.e. TCM) and "癡呆症 or 痴呆症 or 失智症" (i.e. synonyms of dementia) were used in the Chinese electronic database, China Journals Full Text Database. Publications from 1980 to 2012 were searched. Agitation in dementia was found to be non-existent in the TCM literature, although there were some papers on dementia. No papers were identified that specifically discussed the concept of *agitation in dementia* from the perspective of TCM. It is very likely that this specific clinical condition has not been studied from the perspective of TCM. One paper (Teng, 2011) was identified as discussing agitation from the perspective of TCM, but this paper did not discuss agitation specifically in the context of PWD.

According to Teng (2011), agitation under the concept of TCM belongs to the realm of *fan-zao-zhuangtai* (i.e. an agitated state). *Fan* means a feeling of restlessness. It is a perceived feeling, internal, and may not be perceived by others easily. *Zao* means restlessness of the body parts. The body parts, especially the limbs, cannot help moving. It is external and can be easily observed by others. In TCM, agitation is a psycho-behavioral syndrome that refers to not feeling well, feeling restless, feeling bored, feeling uncomfortable, feeling emotionally unwell, loss of temper, not being able to stay still and having to keep moving, and not feeling comfortable in any position (Teng, 2011).

Agitation is only briefly defined in the TCM literature, as there only one paper (Teng, 2011) has been identified. The cluster of symptoms of agitation is described in the literature but no detailed meaning is given. From the limited description, by comparing the description of agitation in the sole TCM paper identified with the concept of agitation developed from the Western literature discussed earlier, it can be noted that the concept of agitation (i.e. *fan-zau-zhaungtai*) in the TCM literature is comparable to that in Western literature. They share common attributes of the concept of agitation, namely the behavioral and psychological parts. In the behavioral part, the descriptions of behaviors are very similar to the Western concept in that there is movement of body parts. However, the verbal and vocal components are not described. In the psychological part, the descriptions are also very similar to those in the Western concept, that it is a perceived feeling that others may not be aware of. However, the assessment and interpretation of the internal feelings is not explained in the Chinese concept. In addition, the definition of agitation in the TCM literature identifies the abnormality only by giving examples (e.g., the person cannot refrain from moving their body). No detailed explanation was given of the differentiation of agitation as an abnormal syndrome.

In summary, no papers were identified that discussed the concept of agitation in dementia. Only one paper was identified as defining agitation from the perspective of TCM, and this was not in the context of dementia. However, the definition in this one paper (Teng, 2011) is very similar to the definitions of agitation in dementia identified in the Western literature. Basically, the attributes of the concept of agitation in dementia in the Western literature cover all the attributes

of agitation described in the TCM paper (Teng, 2011). Agitation from the TCM perspective may be an evolving concept in its early stages, yet it is consistent with the definition of agitation in dementia in the western literature. Therefore, this knowledge was used subsequently to guide the development of an intervention for managing agitation in dementia from the perspective of TCM.

2.3 Causes of Agitation in Dementia

In this section, the causes of agitation in dementia will be explored and discussed. Different theorists explain the causes of agitation in dementia differently from their professional perspectives. There are many theories explaining the causes of agitation in dementia. The following discussion highlights a few important theories in relation to the purpose of this study, including physiological theory, the progressively lowered stress threshold theory, the unmet need theory, and the TCM meridian theory.

2.3.1 Physiological theory

This theory explains that agitation is caused by organic pathologies. The most common cause of dementia is Alzheimer's disease, which affects 60-80% of PWD (Alzheimer's Association, 2013). By reviewing the available evidence, Humpel (2011) explains Alzheimer's disease in a physiological way. In Alzheimer's disease, there are two hallmark pathologies in the cerebral neurons. They are amyloid plaques and neurofibrillary tangles.

The formation of the amyloid plagues is mainly related to the beta-amyloid peptides. The amyloid cascade hypothesis (Swerdlow, 2007) tried to explain how

amyloid plaques were formed and how their formation is linked to dementia. Amyloid precursor protein (APP) is one of many proteins available on the neuronal cell membrane that is associated with normal cell membrane metabolism. In a normal biochemical process, cleavages of the APP occur in a normal pathway. For reasons that remain unclear for now (e.g. APP mutations), some harmful APP cleavages occur. In these cleavages, beta-amyloid peptide (e.g. Aβ42) is released to the extracellular space of the neuron. These beta-amyloid peptides stick with each other extracellular to the neuron to form the plaque deposition. The accumulation of these beta-amyloid peptides is believed to interfere with neuron-to-neuron communication at synapses and eventually contribute to neuronal death.

The formation of the neurofibrillary tangles is mainly related to the Tau protein. Martin and colleagues (2013) explain that the Tau protein normally binds to microtubules and neurofilaments in the neurons to form the neuronal cytoskeleton. For reasons that are still not entirely understood (e.g. phosphatase downregulation, formation of the beta-amyloid plaque), abnormal phosphorylation of the Tau protein occurs and causes the formation of abnormal Tau proteins. These abnormal Tau proteins interact with the neurofilaments and microtubules and aggregate with each other inside the neuron. This disrupts the stability of the neuronal cytoskeleton to form the neurofibrillary tangles, which eventually contributes to neuronal death.

Although the exact roles of Tau-protein and beta-amyloid protein in the onset and progression of dementia are not yet fully understood (van Norden et al, 2012), amyloid-β and total Tau protein levels in cerebral-spinal fluid (CSF) represent the most advanced and accepted method of diagnosing probable Alzheimer's disease

with high accuracy; changes in these levels can accurately reflect the intensity of the neuronal degeneration (Blennow et al, 2010). Recent studies have shown that these biomarkers (i.e. amyloid-β and total Tau protein in CSF) not only reflect the intensity of the dementia but are also associated with the level of agitation in people with Alzheimer's disease (Bloniecki et al, 2014).

Apart from the beta-amyloid and Tau protein models, an earlier study also found associations between increased activity of dopaminergic neurotransmission and altered serotonergic modulation of dopminergic neurotransission in the cerebral neurons, and agitated behavior in PWD (Engelborghs et al, 2008).

These findings suggest that neuronal degenerative changes involving neuro-cellular physiology and the synaptic neurotransmission system may play a role in the occurrence of agitation in dementia, although the evidence is still unable to explain clearly how physiological changes in the neurons lead to agitation.

2.3.2 Stress theory

Stress is a state of disturbed homeostasis (Filaretova, 2012). The disturbing forces or threats to the homeostasis are called stressor, and the counteracting forces to the stressors are called adaptive response (Chrousos et al, 2013). Stressors can be both physical (e.g. diseases, pain, injury) or emotional (e.g. psychological loss, uncertainty) in nature. In response to the stressors, our body react accordingly to produce adaptive response. The adaptive response comprises both physiological (e.g. neurohormal changes), behavioral (e.g. problem solving behaviors) components, which is known coping behaviors (Chrousos et al, 2013). Therefore,

both physical and emotional stressors may trigger our body to exert adaptive responses which may comprises both physiological and behavioral changes.

Short-term acute stress is an adaptive response to stimuli in the environment that it is important for organism to survive and main characteristics of life, but chronic stress is maladaptive that it causes noxious for both brain and behaviors (Lupien et al, 2009).

From the physiological perspective on understanding stress, when the brain detects a stressor, a coordinated physiological response involving autonomic, neuroendorcrine, metabolic, and immune systems components is activated (Lupien et al, 2009). Frodl and O'Keane (2013) explained that one of the key systems in stress response that has been extensively studied is hypothalamus-pituitary-adrenocortical (HPA) axis, which is a neuroendocrine system. When threat is perceived, the hypothalamus releases corticotropin releasing hormone (CRH) and arginine vasopressin (AVP). This triggers the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. This subsequently leads to production of cortisol by the adrenal cortex. The cortisol also negatively feedbacks to the axis by binding to the glucocorticoid receptors at various levels (e.g. pituitary, hypothalamus, hippocampus) so as to down-regulate the cortisol secretion and the HPA axis back to a homeostatic state.

Ageing associated neuronal damages in the brain and chronic stress triggers hyper-activation of the HPA axis leading to increased basal cortisol release (Prederville et al, 2014). Prederville and colleagues (2014) further explained that

the neuronal impairment of the brain related to aging (e.g. deficient of neurotrophic factors, peripheral immune cell infiltration, blood-brain barrier breakdown) and prolonged high level of cortisol related to chronic stress reduce central glucocorticoid receptor expression. As a result, the function of HPA axis suppressing cortisol secretion in response to the high level of circulating cortisol (i.e. negative feedback) is impaired and this therefore causes increased basal cortisol release.

Both animal (Holmes et al, 2010) and human studies (Lupien et al, 2005) showed that cumulative exposure of the brain to increased cortisol concentration is associated with decline in hippocampal volume, cognitive functions (e.g. episodic memory performance) and behaviors (e.g. anxiety and depression related behaviors). Studies showed that high level of chronic stress with hypersecretion of cortisol in old people increases vulnerability of Alzheimer's disease and elevates circulating cortisol (e.g. cortisol level over time and basal cortisol level), which correlates hippocampal atrophy with faster cognitive decline (Lupien et al, 1998; Joshi & Pratico, 2013; Notarianni, 2013). The effect of hippocampal atrophy and decline in cognitive function caused by chronic stress with prolonged exposure glucocorticoid to the brain is known as glucocorticoid cascade hypothesis (Sapolsky et al, 1986), or later renamed as neurotoxicity hypothesis (Gilbertson et al, 2002). Some studies further showed the consequences of glucocorticoid cascade do not just cause cognitive impairment but also some age maladaptive behaviors, such as late-life anxiety disorder (Hek et al, 2013) and reduced sociability (Adam et al, 2006).

In conclusion, when an ageing brain with chronic stress added on the older people, cognitive impairment and behavioral problems can be resulted. One of the key physiological pathways involved in this stress associated process is call HPA axis. This stress induced cognitive impairment and behavioral problems is known as glucocorticoid cascade hypothesis. This hypothesis has pointed out that PWD may possibly have experienced chronic stress. The behavioral problems (e.g. agitation) may possibly be the result of chronic stress.

2.3.3 Progressively lowered stress threshold theory

Living with a diagnosis of dementia is stressful. Stress can be caused by the problems derived from memory loss, a poor sense of security, poor autonomy, inadequate stimulation, and a poor sense of living a meaningful life (Steeman et al, 2006). The memory loss also interferes with coping strategies, so that it may cause frustration, uncertainty and fear; in this way, stress can be further exacerbated (Steeman et al, 2006).

The progressively lowered stress threshold theory (PLST; Hall & Buckwalter, 1987; Smith et al, 2006) explains agitation in dementia as being initiated from an internal progressively lowered stress threshold. Perceived stress is the net difference between external stressors (e.g. noise) and coping ability. When a person's perceived stress level exceeds a threshold, maladaptive behaviors (e.g. agitation) will occur. According to the PLST (Hall & Buckwalter, 1987), different people have different stress thresholds. However, the stress thresholds of PWD decline progressively over time as their dementia progresses. As a result, the

perceived stress level of PWD is more likely to exceed the stress threshold over time as their dementia advances. When the perceived stress level of the PWD exceeds the stress threshold, it results in agitation. Figure 2.1 shows a schematic illustration of the PLST.

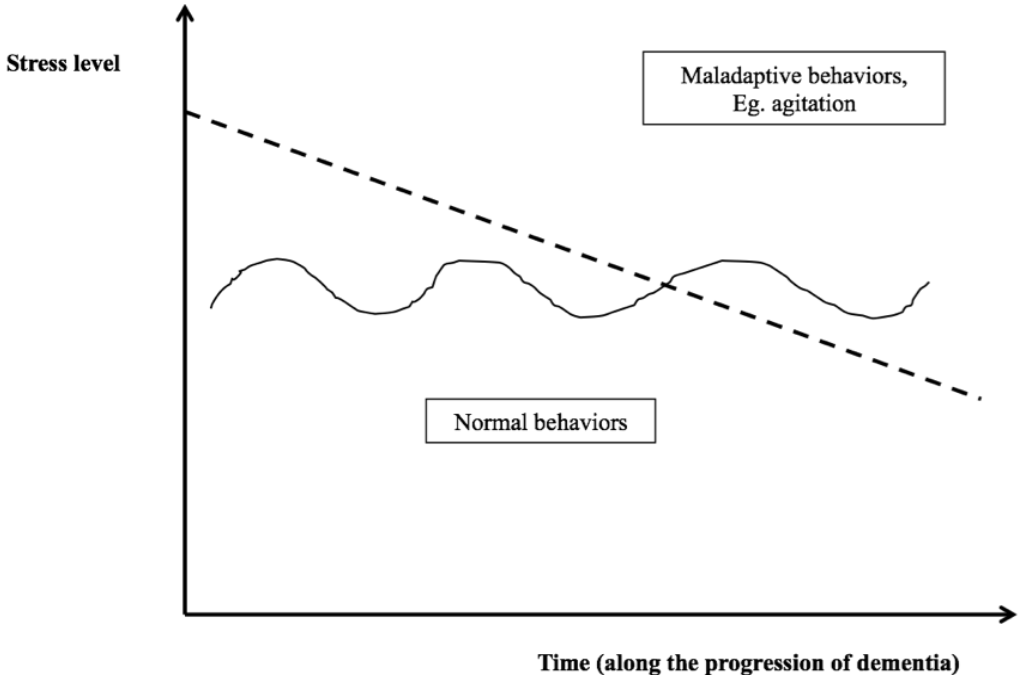


Figure 2.1. Schematic illustration of progressively lowered stress threshold theory. The dotted line represents the stress threshold in people with dementia over time. The sinusoidal line represents the alternating perceived stress level in people with dementia over time.

2.3.4 Unmet need theory

The unmet need theory – which was briefly discussed earlier in the concept of agitation – explains that dementia-related behaviors occur because of the inability of the caregiver to understand the needs and the afflicted people to make their needs known. These needs can include physical diseases, human interaction, and environmental stimulations. Behavior is an attempt to communicate physical or

psychic distress when unmet needs arise (Algase et al, 1996). According to this theory, agitated behavior is the presentation of the PWD in their attempt to communicate the physical and psychic distress of unmet needs.

PWD are commonly at an advanced age, which is associated with a high prevalence of pain based on complex medical conditions such as musculoskeletal disease (Pickering et al, 2006). Pain may remain unrecognized and untreated due to patients' limited cognitive function (Herr et al, 2006). Uncontrolled pain can be an unmet need that causes agitation (Zieber et al, 2005; Nguyen et al, 2008). Recent studies have shown that pain treatment successfully reduces agitation, particularly in the case of verbally agitated behaviors (Husebo et al, 2011; Husebo et al, 2014).

Environment and mode of care play significant roles in satisfying the needs of PWD. A study showed that a lower level of agitation is associated with engagement with live human and inanimate social stimuli, while a higher level of agitation is also associated with unclear speech (Cohen-Mansfield et al, 2012). These findings may explain why PWD need to interact in some way with people and their environment. However, their unclear speech secondary to the dementia may prevent such needs from being met, thereby causing agitation.

Although the argument that agitation is caused by unmet needs is supported by evidence, this theory obviously contradicts the widely accepted definition of agitation in dementia, namely that it is an inappropriate behavior not attributable to unmet needs (Cohen-Mansfield & Billig, 1986; Cohen-Mansfield et al, 1995). Nevertheless, many needs are unapparent because of communication or

interpretation difficulties (Cohen-Mansfield & Billig, 1986). Therefore, unmet needs can be the causes of agitation in dementia because they may not be apparent to others.

2.3.5 Traditional Chinese medicine meridian theory

Explaining the causes of agitation from the perspective of TCM meridian theory should be preceded by a discussion of how TCM views health, the body, and therapy. TCM has a unique concept of physiology in understanding the human body. It has a special interpretation of disorders of the human body. Lu and colleagues (2004) explained that TCM does not solely seek specific pathogenic causes or pathological changes in a specific organ. It looks for disturbances among the self-controlled systems by analyzing all symptoms and signs. Therefore, agitation under the therapeutic concept of TCM is a symptom caused by a disturbance of an inter-connecting self-controlled system constructed by the meridian, *qi*, acupoints and *zangfu*.

In TCM meridian theory (Cheng and Deng, 1987; Cook & Wilcox, 1997), the meridian is a network that is distributed throughout the body like the vascular system. Meridians embrace many paths through which the energy called *qi* passes. They run through many acupoints and the TCM body system called *zangfu.* The *qi* runs through the meridian to reach and nourish the *zangfu*,which includes the *heart*, *lung*, *spleen*, *liver*, and *kidney*. The *zangfu* uses the common names of the organs in Western anatomical science. However, these names have totally different meanings in TCM. The *zangfu* thrives when sufficient *qi is* supplied through the meridians.

However, when the flow of *qi* is disturbed for some reason, the *zangfu* does not function well, resulting in a *zangfu* imbalance. Various illnesses and clinical symptoms may result. However, these structures have been criticized as elusive despite considerable efforts to understand their anatomy and physiology (National Institute of Health Consensus Statement, 1997).

There are many types of *zangfu* imbalance, which can also be referred as TCM pathological syndromes and identified by syndrome differentiation (Jiang et al, 2012). Agitation in dementia can be explained as a consequence of a z*angfu* imbalance (i.e. TCM pathological syndrome) caused by impaired *qi* flow inside the meridians of the related *zangfu*. According to Teng (2011), the TCM pathological syndromes causing agitation can commonly be divided into four types: *re-xie-rao-xin* (i.e. 熱邪擾心), *yin-xue-kui-xu* (i.e. 陰血虧虛), *yin-qi-fu-yue* (i.e. 陽氣浮越), and *xin-pi-liang-xu* (i.e. 心脾兩虛).

In summary, the causes of agitation in dementia are complex. Different theories and individual studies have tried to explain the causes of agitation in dementia from their own discipline-specific perspectives. However, no single theory has been able to completely explain why PWD suffer from agitation. The causes of agitation in dementia are multi-factorial, and different theories may overlap. To summarize the theories in the literature, agitation is likely to be caused by the interacting products of individual factors (e.g. neuronal degeneration, pain, stress, and *qi* disturbance) and contextual factors (e.g. needs that are unmet by caregivers and the environment) (Bidewell & Chang, 2011). Therefore, when

designing interventions to mitigate the agitation in PWD, one or some of these theories should be applied.

2.4 Interventions for Agitation in Dementia

In the past, endeavors have been made to devise interventions to treat agitation in dementia. Some of them specifically targeted the different hypothetical causes of agitation in dementia, while others have no strong theoretical backup but have long been used in the community. However, the effect varies considerably among the different kinds of interventions, as discussed below. The interventions can generally be categorized into pharmacological and non-pharmacological interventions.

2.4.1 Pharmacological interventions

As mentioned above in relation to the physiological causes of agitation, agitation in dementia can be caused by deregulation in the neurotransmitters (e.g. dopamine and serotonin) secondary to neuronal degeneration. Based on this hypothesis, several kinds of drug regulating the serotonergic function have been studied and tested. One such type of drug is the Selective Serotonin Reuptake Inhibitor (SSRI), such as sertraline and citalopram. A recent Cochrane review of 9 trials including 692 individuals showed that there is some evidence to support its use, however further studies are needed to support its effectiveness and safety (Seitz et al, 2011). SSRIs are already considered to be relatively safe drugs when compared with other drugs commonly used for agitation, such as anti-psychotics (Kirshner, 2011). However, SSRI is also associated with a high fracture risk (Gagne et al, 2011).

Based on other similar neuro-biochemical hypotheses, many other kinds of drugs regulating various different neuro-transmitting pathways could also be used. Indeed, these drugs have actually been used for treating agitation in the past. Yet Cochrane reviews yielded very similar conclusions, namely that there is no strong evidence of their effectiveness in reducing agitation, but the drugs are associated with some serious adverse effects. For example: valproate failed to show any improvement in agitation in dementia but was associated with harmful effects, such as falling and infection (Lonergan & Luxenberg, 2009); haloperidol showed no evidence of improvement in agitation in dementia (Lonergan et al, 2002) but was associated with harmful effects, such as extra-pyramidal side effects (Allain et al, 2000); atypical anti-psychotics (e.g. quetiapine and resperidone) failed to reduce aggression but were associated with higher incidence of stroke and extra-pyramidal side effects (Ballard & Waite, 2006).

Since drugs are easy to administer, they have been used extensively to treat agitation in dementia in the past. Given the fact that the effect of drugs on this aspect of dementia is unclear, and that drugs are commonly associated with some serious adverse effects, an alternative with a better balance between benefits and risks is needed. Non-pharmacological interventions have increasingly aroused the interest of clinicians and researchers in managing agitation in dementia, as they are associated with fewer risks (Livingston et al, 2005).

2.4.2 Non-pharmacological interventions

There are many non-pharmacological interventions used to manage dementia behavioral symptoms (e.g. agitation). Unlike pharmacological therapies, some of the non-pharmacological interventions were not developed along the lines of clear theoretical models (Kong et al, 2009). However, others were developed according to some assumptive theoretical models (Cohen-Mansfield, 2001; Volicer & Hurley, 2003), such as the progressively lowered stress threshold model (Hall & Buckwalter, 1987), learning and behavioral models (commonly referred to as antecedent-behavior-consequences models) (Smith & Iwata, 1997), operant conditioning theory (Skinner, 1953), the need-driven dementia-compromised behavior model (commonly referred to as the unmet needs model) (Algase et al, 1996), person-centered care theory (Kitwood, 1997), and the habilitation approach model (Raia, 1999).

There are usually no gate-keeping mechanisms (e.g. licensure or registration) controlling the clinical use of non-pharmacological interventions, thus they are usually used in the clinical setting in a liberal fashion. For this reason, a vast number of non-pharmacological interventions have been used or researched in recent decades. Below is a discussion of the effectiveness of various non-pharmacological interventions.

2.4.2.1 Categorization of non-pharmacological interventions

There are many different non-pharmacological interventions, commonly categorized by their highly diverse therapeutic natures. In order to better discuss this high volume of non-pharmacological interventions, they are discussed by

categories according to their therapeutic natures, roughly divided by previous researchers (Cohen-Mansfield, 2001; Livingston et al, 2014) into: sensory interventions, social contact interventions, behavioral therapy, structured activities, environmental interventions, medical/nursing care interventions, caregiver training, and individualized care.

Sensory interventions are primarily aimed at exerting sensory stimulation on the PWD in order to achieve the therapeutic effects. These sensory stimulations include visual, auditory and tactile approaches. The therapeutic belief of sensory intervention is likely based on the hypothesis that agitation is caused by receiving inadequate sensory stimulation secondary to the sensory deprivation commonly associated with old age and which usually occurs to precede the onset of dementia (Behrman et al, 2014). Sensory interventions theoretically exert their effects by enhancing the sensation of the PWD who may have sensory deprivation. Interventions adopting the sensory stimulation approach included thermal baths (Dunn et al, 2002), music (Denney, 1997; Cooke et al, 2010; Lin et al, 2011; Sung et al, 2012), light therapy (Satlin et al, 1992; Ancoli-Israel et al, 2002; Burns et al, 2009), massage (Rowe & Alfred, 1999; Remington et al, 2002), therapeutic touch (Hawranik, 2008; Woods et al, 2005; Woods et al, 2009), aromatherapy (Ballard et al, 2002; Lin et al, 2007; Burns et al, 2011), Snoezelen therapy (Van Weert, 2005), and acupressure (Lin et al, 2009).

Social contact interventions are primarily aimed at enhancing interaction between PWD and others in order to achieve therapeutic effects. This social contact may include interaction with either real or simulated targets. The interaction can be

achieved through verbal exchange and touch. The therapeutic belief of social contact intervention is likely based on the hypothesis that the social contact needs of PWD, who commonly have communicative disability secondary to cognitive impairment (Ridder & Gummesen, 2015), are not being adequately fulfilled. Agitation may result from these unmet needs (Algase et al, 1996). Social intervention exerts its effects by enabling the PWD to socially interact with others. Interventions adopting this approach may include one-on-one social interaction (Cohen-Mansfield & Werner, 1997) and simulated presence (Camberg et al, 1999).

Behavioral therapy primarily aims at modifying the behaviors of PWD by using various skills and methods based on different psychological theories, such as operant conditioning theory (Skinner, 1953). Taking the use of operant conditioning theory as an example, in order to achieve behavioral modification, the interventionist may have to identify desirable and undesirable behaviors. They then positively reinforce the desirable and negatively reinforce the undesirable behaviors so as to modify the undesirable behaviors (i.e. agitation) of the PWD. Interventions adopting this approach include the behavioral therapy used by Doyle and colleagues (1997), who reinforced quiet behavior based on individual preferences.

Structured activities aim at providing well-planned activities on a regular basis. The therapeutic belief of structured activities is likely to be based on the hypothesis that the agitation of PWD is triggered by boredom in the nursing home (Buettner et al, 1996), because PWD lack the cognitive capacity to join the usual activities in nursing homes. Structured activities exert their effects by reducing boredom through adjusting the level to enhance the feasibility of participation by PWD.

Interventions adopting this approach include recreational interventions such as sorting and sewing (Aronstein et al, 1996), and outdoor gardening (Cohen-Mansfield & Werner, 1999).

Environmental interventions aim at modifying the living environment of PWD in nursing homes. The therapeutic belief of environmental intervention is based on the hypothesis that agitation is the result of an interplay between the PWD and the environment (Cohen-Mansfield, 2001). By modifying the environment to be more accommodating to the needs of people with cognitive and functional impairment such as PWD (e.g. wandering needs), agitation can be reduced. Interventions adopting this approach include setting up wandering areas (McMinn & Hinton, 2000) and natural environments (Whall et al, 1997).

Medical and nursing care interventions are aimed at providing therapy to enhance the physical health of PWD and their quality of care. The therapeutic belief of medical and nursing care intervention is based on a hypothesis that PWD may have unapparent physical needs (e.g. pain, urinary urge, discomfort) caused by diseases and nursing care. The agitation of PWD can be caused by these unmet needs (Algase, 1996). By intentionally modifying these probable physical problems, the agitation can be reduced. Interventions adopting this approach may include pain management (Douzjian et al, 1998), removal of restraints (Middleton et al, 1999), avoiding noise, accompanying the person to the toilet, communication, walking movement, and administering beverages (Oppikofer & Geschwindner, 2014).

Caregiver training aims at equipping caregivers with appropriate skills in caring for agitated PWD. The therapeutic belief of caregiver intervention is based on a hypothesis that agitation is the result of interaction between PWD and their caregivers (Cohen-Mansfield, 2001). Modifying caregivers' skills means that their care is less likely to induce agitation of PWD. Interventions adopting this approach may include comprehensive training of paid care workers (Hagen & Sayers, 1995; Proctor et al, 1999; Magai et al, 2002; Finnema et al, 2005), or focusing on a particular skill, such as communication (McCallion et al, 1999).

Individualized care aims at identifying the individuality of the PWD (e.g. physical illnesses, preferences, functional level, and interest) and providing care that accommodates their individuality. The therapeutic belief of individualized care intervention is based on the person-centered care model (Kitwood, 1997), according to which the causes of agitation of different PWD can be the result of an ignorance of their individuality or individualized causes. Interventions can only be effective if the individualized causes of the agitation are treated. Interventions that adopt this approach may include providing activities or interventions matching the interest and functional level of the agitated PWD (Meares & Draper, 1999; Moniz-Cook et al, 2003; Kolanowski et al, 2011) and providing treatment plans that match their needs (Cohen-Mansfield, 2007).

2.4.2.2 Efficacy of various non-pharmacological interventions

Given the tremendous number of non-pharmacological interventions used and researched to manage agitation in PWD in the past two decades, efforts have been

made to summarize the efficacy of the various interventions in managing psycho-behavioral problems in PWD by reviewing past studies (Cohen-Mansfield, 2001; Turner, 2005; Kong et al, 2009; Olazaran et al, 2010; Brodaty & Arasaratnam, 2012; Livingston et al, 2014; Oppikofer & Geschwindner, 2014). However, the purposes of these review papers were not the same. The nature of the non-pharmacological intervention studies was also very diverse, for example using different study designs and nomenclatures. In the review papers, different authors categorized the non-pharmacological interventions differently. Some categorized the interventions by their theoretical assumptions and others by their administration targets. Many review papers gave only qualitative descriptions of the effects of the different non-pharmacological interventions in managing agitation in PWD. Such descriptive reviews provide no information as to which non-pharmacological interventions are more efficacious than others. Only two of the review papers (Kong et al, 2009; Livingston et al, 2014) conducted meta-analyses to compare the efficacy of different non-pharmacological interventions by categories focusing on reducing agitation in PWD. Below is a discussion of the efficacy of the different non-pharmacological interventions in managing agitation in PWD, by category, based on the papers that conducted meta-analyses for effect comparisons.

Kong and colleagues (2009) reviewed papers using randomized controlled trials as the study design and focusing on non-pharmacological interventions specifically for agitation in dementia only. Their review paper conducted a meta-analysis to compare the efficacy of each category of NPI in reducing agitation. Fourteen clinical trials were identified to examine a total of 13 different kinds of

NPI specifically targeting agitation in dementia. Kong and colleagues (2009) categorized the non-pharmacological interventions into seven groups by their intervention natures, which include: sensory intervention, social contact, activities, environmental modification, caregiver training, combination therapy, and behavioral therapy.

In the meta-analysis (Kong et al, 2009) of the seven types of intervention, it was noted that only the category of sensory intervention was found to be more effective in reducing agitation in dementia when compared with usual care. The interventions in the sensory intervention group included aromatherapy (Ballard et al., 2002), thermal bath (Dunn et al., 2002), and music and massage (Remington, 2002). They all demonstrated favorable effects on reducing agitation in dementia patients, while all other categories of intervention failed to demonstrate such effects because their results were either insignificant or inconsistent between studies.

More recently, Livingston and colleagues (2014) reviewed more updated papers examining the efficacy of non-pharmacological interventions in managing agitation in dementia. A meta-analysis was also performed to examine which categories of non-pharmacological intervention are able to reduce agitation. This review paper (Livingston et al, 2014) identified 33 papers using RCT as the study design to examine the efficacy of different NPT in reducing agitation in PWD. It was found that activities matched to the interest and function of PWD (Kolanowski et al, 2011) and sensory intervention were found to be more effective in reducing agitation in dementia when compared with controls. These sensory interventions included using music (Lin et al, 2011; Sung et al, 2012) and acupressure (Lin et al,

2009). It was also found (Livingston et al, 2014) that staff training was effective in reducing agitation in dementia compared with controls. These staff training interventions all used the person-centered care model (Kitwood, 1997) as the training foundation (McCallion et al, 1999; Deudon et al, 2009; Chenoweth et al, 2009).

To summarize the evidence on the efficacy of non-pharmacological interventions, a tremendous number of such interventions have been used previously for managing agitation in PWD. Probably because the development of the interventions was not based on the same therapeutic model or development methods, no clear categorizations of non-pharmacological interventions with good consensus have been identified in the literature. However, many non-pharmacological interventions were observed to have promising effects on reducing agitation in PWD. Three categories show particularly promising effects on reducing agitation in PWD. The first is activities matched with the interests and functional level of the PWD. The second is sensory interventions for agitated PWD, particularly music, acupressure, massage, thermal bathing, and aromatherapy. The third is caregiver training using the person-centered care model as the theoretical basis. These three elements (i.e. sensory stimulation, matching the therapy to the interests of the PWD, and caregiver training with consideration of individuality) may be the active ingredients contributing to the effectiveness of the above non-pharmacological interventions in managing agitation in dementia.

2.4.3 Discussion on selecting appropriate non-pharmacological interventions for agitation in dementia

Although there are a number of established interventions that have demonstrated favorable effects on agitation in dementia, there are still many factors apart from the effect to be considered when deciding the appropriate intervention to be used. After taking such factors into account, further studies can move on to researching the most appropriate and effective interventions to manage agitation in PWD. To select the most appropriate treatment using an evidence-based approach, a good balance must be struck between benefit and harm (Glasziou & Irwig, 1995). However, this principle has been criticized as being overly simplistic, ignoring the patient's preferences regarding optimal care (DaCruz, 2002). An optimal intervention should consider the potential benefit of the intervention, the risk of harm or safety of the intervention, cost, and personal interest (Haynes et al, 2002). Therefore, an appropriate intervention should have considered all these factors: effectiveness, safety, cost, and preference.

2.4.3.1 Effectiveness

Based on the literature, the cause of agitation in dementia is multi-factorial, non-specific and individualized. Interventions seem to have targeted only a few hypothetical causes of agitation in dementia. No single intervention has been found to be effective across contexts. Yet the aforementioned conclusion about the efficacy of various non-pharmacological interventions shows us that interventions comprising sensory stimulation, consideration of the person's interests, and

consideration of the individuality of the PWD had significant effects. Therefore, in selecting non-pharmacological interventions, those embracing these properties should be given priority.

2.4.3.2 Safety

The safety issue refers to the risk and severity of the adverse effects. Some adverse effects can also occur in non-pharmacological interventions, as stated in the literature, although non-pharmacological interventions are usually regarded as safer than drugs. These possible adverse effects may include that increased stimulation can increase agitation and aggression in some individuals receiving sensory stimulating interventions (Robinson et al, 2007). There is a dearth of papers and systematic reviews identifying trials that directly compare safety among various interventions to manage the behavioral symptoms of dementia (O'Neil et al, 2011). The exact risks of various adverse effects from the non-pharmacological interventions are therefore unknown, but adverse effects have rarely been observed or reported in non-pharmacological interventional studies.

2.4.3.3 Cost

The cost of an intervention can vary widely among non-pharmacological interventions. The costs can be classified into tangible and intangible. Obviously, the tangible cost of many non-pharmacological interventions is low because they do not usually require expensive instruments or consumables. However, the intangible cost of non-pharmacological interventions can be high, because the cost of manpower and specialized skill training can be expensive. As a result, the cost

difference can vary widely because some non-pharmacological interventions demand a higher level of manpower and skills. For example, an individualized intervention (Cohen-Mansfield et al, 2007) is expected to be relatively more costly because it demands specialized skills to assess the individualized needs (or causes of agitation) so that the individualized intervention can be devised accordingly. Therapeutic touch (Woods, 2002) and acupressure (Lin et al, 2009), by contrast, are expected to be relatively less costly because they demand less specialized skill and can possibly be carried out by nurses or family caregivers after some training. However, very few studies have directly compared the cost-effectiveness of different non-pharmacological interventions (O'Neil et al, 2011). Therefore, the cost of the various interventions (including both tangible and intangible) is unknown, although some may cost less than others.

2.4.3.4 Preferences

The intervention preference can be influenced by culture. Before the intervention can take effect, the participant should agree to it and believe that it works. However, many of the western interventions were developed in their own culture (e.g. aromatherapy using western essential oils). Chinese philosophies strongly influence Chinese beliefs about health, and the Chinese place equal value on the therapeutic effects of TCM and those of western medicine (Chen, 2001). A therapeutic idea should be harmonious to Chinese philosophies in order for Chinese patients to accept it or choose to participate. Another study (Chan et al, 2003) showed that Hong Kong people (particularly those over 55, not wealthy and not well educated) believe less in the effectiveness of western medicine-based

treatment than in TCM. Hong Kong nursing home residents admit Chinese people over 65 years of age. The belief of effectiveness in western medicine-based treatment may be even lower. Although there is no evidence as to which type of intervention is preferable to PWD, the above studies (Chen, 2001; Chan et al, 2003) suggest that Hong Kong Chinese nursing home residents with dementia prefer therapy that is more harmonious with Chinese philosophy. Among the interventions identified in the literature search, acupressure is the only Chinese philosophy-based intervention that has been examined for its effectiveness in an RCT (Lin et al, 2009) and showed favorable effects.

To summarize the principles discussed in selecting an appropriate NPT for managing agitation in dementia, some interventions showed preliminarily promising effects. No single intervention has yet been demonstrated to be effective across settings. Although there are not yet any ideal interventions available to manage agitation in dementia, those that are potentially ideal should be identified for further study.

An ideal intervention for managing agitation in dementia should be effective, safe, inexpensive, and harmonious with the preferences of the PWD. Evidence has shown that effective non-pharmacological interventions for reducing agitation in dementia usually include a sensory component (eg. aromatherapy, massage, and acupressure). There is no evidence of serious adverse effects in these non-pharmacological interventions. Individualized interventions may be more effective but they are expensive, while some non-individualized non-pharmacological interventions may be less costly (eg. acupressure and therapeutic touch).

Preferences are usually derived from cultural values. Acupressure is distinct from other non-pharmacological interventions in the sense that it is the only intervention derived from TCM, which is consistent with Chinese health-related values and beliefs. After considering the principles of selecting appropriate non-pharmacological interventions, acupressure may be an appropriate non-pharmacological intervention with therapeutic potential for managing agitation in Chinese PWD. Acupressure is worthy of further study.

2.5 Acupressure and Agitation in Dementia

This section will focus on discussing the use of acupressure as a therapeutic modality in managing agitation in PWD. Theories explaining why acupressure can exert therapeutic outcomes will first be discussed. Then, evidence from clinical research on examining the therapeutic effect of acupressure will be presented, followed by a discussion of the clinical research examining the effect of acupressure specifically for managing agitation in PWD. Finally, the knowledge gap in the use of acupressure for agitation in dementia will be discussed.

2.5.1 Theories of acupressure

Acupressure is the application of pressure on specific acupoints on the body to treat a wide range of conditions or to promote individual well-being (Weaver, 1985). It is a traditional therapy that originates from east Asian culture but from which many variants have evolved.

Acupressure can be viewed as one of the methods of administering acupuncture (Mayer, 2000). Theoretically, acupuncture can be administered by

various methods, such as needle (i.e. classical acupuncture), electrical stimulation (i.e. electroacupuncture), heat (i.e. moxibustion), or manual pressure (i.e. acupressure). Acupressure can also be viewed as a descendent of Chinese manipulative therapy (Beal, 1999), namely *tui-na* (推拿). It is a word that appears in texts written in the Ming Dynasty. Tui-na comprises two skills: *tui* (推) and *na* (拿). *Tui* (推) means push and *na* (拿) means squeeze and lift. Acupressure can also be viewed as *Anma* (按摩) and *Shi-atsu* (指壓), which are traditional Japanese forms of manipulative therapy (Beal, 1999). *Amma* (按摩) means Japanese massage by using the traditional meridian theory under the influence of the Chinese *Tui-na*. *Shi-atsu* comprises two meanings. *Shi* (指) means finger and *atsu* (壓) means pressure. *Shi-atsu* means applying pressure by fingers. It combines traditional Asian forms of body work and other forms of manipulation similar to those employed in chiropractic and osteopathic medicine.

Basically, acupressure is a therapy with many variants (e.g. *Tui-na*, manual acupuncture, *Shi-atsu*, *Anma*). Generally, these variants have also been called acupressure in the literature (Beal, 1999; Robinson, 2011). Different variants of acupressure have different theoretical accordance and methods of administration. Nevertheless, all the acupressure variants operate by applying manual pressure on acupoints in the body according to acupoint or meridian theory, to treat a wide range of conditions. However, the choice of body parts on which to apply pressure, the techniques and the theoretical accordance are quite different among the different variants of acupressure.

Acupressure is a therapy for which a number of theories explain its hypothetical mechanism of action (Birch & Felt, 1999). However, no single theory can fully explain the mechanism of action, and many of these hypothetical mechanisms of action have not been empirically tested. That is to say, the exact mechanism of action is unknown at the physiological level. Nevertheless, there are two main major theories that appear frequently in the literature and have attempted to explain its action. They are bio-chemical theory and TCM theory.

2.5.1.1 Bio-chemical theory

Bio-chemical theory explains that acupressure is a therapy that can trigger a series of neuro-hormonal reactions in the body. For example, the endorphins hypothesis (Mayer & Watkins, 1981; Cheng et al, 1979) explained that the stimulation of some acupoints can trigger the release of a morphine-like substrate (e.g. beta-endorphin or enkephalin) in the central nervous system and circulating plasma. This has many effects, such as analgesia and relaxation.

Another hypothesis (Moyer et al, 2004) explained that tactile stimulation in body tissues by acupressure can cause complex neuro-hormonal responses in the HPA axis. This stimulation is distributed through the brain and can be interpreted as a relaxation response (Lawton, 2003). It is thought that tactile stimulation can counteract the overproduction of cortisol by influencing the secretion of corticotrophin from the HPA axis and subsequently decreasing the cortisol (Remington, 2002) and increasing the endorphins (Moyer et al, 2004) so as to

promote relaxation. By regulating the hormone related to stress, relaxation is promoted. Acupressure may possibly reduce stress through the HPA pathway.

This tactile stimulation hypothesis is also supported by empirical evidence that tactile stimulation-based therapy (TSBT) can possibly reduce stress. A study showed that massage therapy can be useful in lowering a patient's stress (Labrique-Walusis et al, 2010). The TSBT also caused reduction of cortisol. Another study showed that therapeutic touch decreased the salivary and urinary cortisol over time after the treatment (Woods & Dimond, 2002), although a recent systematic review with meta-analysis argued that the reduction of cortisol after massage therapy is minimal and statistically insignificant (Moyer et al, 2011). The statistically insignificant difference may possibly be related to the small sample size of the studies and the non-standardized method of cortisol measurement or analysis. Before more studies are available to falsify this hypothetical mechanism of action, this tactile stimulation hypothesis is still being used to support many recent TSBT (e.g. massage) studies that have shown favorable results (Wu et al, 2014; Bennett et al, 2015). When conducting acupressure, tactile stimulation is an undividable component in the process of acupoint activation. This tactile stimulation component may theoretically lead to stress reduction in the PWD.

2.5.1.2 Traditional Chinese medicine meridian theory

In TCM meridian theory (Lu et al, 2004), the human body is a complicated system that can be identified as a structure of different closely related sub-systems or *zangfu* (臟腑), as mentioned above. The energy or *qi* (氣) flows along the

meridian to contribute the connection among the *zangfu* in order to achieve a state of balance among the *zangfu*. As a result, a healthy state is achieved.

TCM understands the therapeutic mechanism of diseases by achieving the integrity of the system and dynamic balance between the *zangfu* (Lu et al, 2004). The external information or symptom is an expression of problems in the internal system. In other words, the clinical symptom of a disease (e.g. agitation in dementia) is an expression of the imbalance between the *zangfu*. A therapeutic effect can be produced by improving the inter-connections between the *zangfu*. When the inter-connection between *zangfu* is balanced, symptoms are not expressed (Lu et al, 2004). The TCM meridian theory (Ulett et al, 1998) further explains that meridians connect many acupoints. *Qi* flow along these meridians aims to nourish the *zangfu*. When the *qi* flow stagnates in these meridians, the *zangfu* is malnourished, causing clinical symptoms or diseases. By stimulating these acupoints, the *qi* flow along the meridian can be re-established or the inter-connection between *zangfu* improved. The function of the *zangfu* (臟腑) can in turn be improved. As a result, the clinical symptom of the disease (e.g. agitation in dementia) will not be observed, or will be observed to have been alleviated.

The TCM meridian theory and bio-chemical theory co-explain how acupressure works to produce therapeutic effects. The advantage of bio-chemical theory is that all the involved hormones are measurable, so that hormonal changes resulting from acupressure can be clearly tracked. However, it does not specifically explain the mechanism of action of acupressure. The essence of acupressure is to produce a therapeutic effect by stimulating the acupoints. However, the reasons

why stimulating the acupoints can lead to bio-chemical change have never appeared in literature discussing the bio-chemical theory. This is probably because acupoints are not perceivable locations on our body in the sense of anatomy in western medicine, therefore they are unable to be empirically studied. Yet the bio-chemical change is well supported by the observable symptom improvement after the acupuncture or acupressure (Salehi et al, 2015), as directed by TCM meridian theory.

On the other hand, TCM meridian theory explains very specifically why stimulating acupoints by acupressure and which acupoints to be stimulated can lead to therapeutic outcomes. However, many of the variables in TCM meridian theory are not empirically measurable. For example, the change of *qi* is not measurable and the meridian is not empirically observable. In order to track changes in the TCM variables, multiple attempts have been made to visualize these changes by advanced imaging and bio-chemical technologies. For example, researchers have anatomically identified the Bonghan Ducts, which very much resemble the meridian web in our body (Longhurst, 2010); ultrasonic and nuclear images show the existence of suspected acupoints in connective tissues (Langevin & Yandow, 2002; Ren et al, 2010), bio-chemical marker changes correlate with changes in TCM syndromes (Zhao et al, 2008).

Nevertheless, research endeavors still do not provide a concrete and measurable mechanism to explain how acupressure changes our body so that therapeutic effects can be achieved. The mechanism of action of acupressure is still unclear. Basic science research has ascertained some physiological effects in the

central and peripheral nervous system and changes in neuro-endocrine function (National Institute of Health Consensus, 1997). Therefore, there is evidence that acupressure may change the physiological environment of our body, which may in turn result in some therapeutic effects. Yet the exact mechanism of how acupressure can achieve specific therapeutic effects is still unknown.

In summary, bio-chemical theory and TCM meridian theory seemingly cannot independently and fully explain why acupressure can produce therapeutic effects (e.g. reduction of pain and agitation in dementia). However, both theories seem to complement each other in explaining that acupressure can be therapeutic. In theory, acupressure can possibly be used to treat a wide range of diseases or clinical symptoms (e.g. reducing agitation in dementia). However, more empirical research is needed to support these theories.

2.5.2 Research on acupressure

The therapeutic effects of acupressure as predicted by the theories have actually been widely observed in many clinical studies. Many clinical studies have examined its therapeutic effect in treating a wide range of diseases and clinical symptoms. A systematic review (Robinson et al, 2011) showed that acupressure and shi-atsu demonstrated effectiveness on a wide range of clinical symptoms or diseases: pain (dysmenorrheal, labor pain, back and neck pain, minor trauma, injection pain, headache, dental pain), nausea and vomiting (post-operative, chemotherapy, pregnancy), renal disease, sleep and alertness, mental health, chronic respiratory condition, anesthesia or consciousness, stroke, body weight,

visual impairment, cancer, angina, gastrointestinal motility, nocturnal enuresis, peripheral arterial occlusive disease, and diabetes symptoms.

There is strong and favorable evidence to support the effectiveness of acupressure/shi-atsu on pain (particularly dysmenorrhea, lower back pain and labor pain), post-operative nausea and vomiting, and quality evidence for sleep in the institutionalized elderly (Robinson et al, 2011). Evidence on the effects of acupressure on dementia symptoms is minimal because there are still too few quality studies that have researched this area, although favorable effects were observed in the few studies that have been carried out (Yang et al, 2007; Lin et al, 2009).

Acupressure is a traditional east Asian therapy, therefore studies on acupressure may be published in languages other than English. Given it originates from TCM meridian theory, Chinese literature should also be reviewed. A systematic literature search was performed in the China Journals Full Text Database, which is a comprehensive database containing more than 5000 Chinese scientific journals. Chinese publications within the period from 1980 to 2015 were searched. The key words used included 穴位按壓 (i.e. acupressure) and 指壓 (i.e. shi-atsu). The purpose of this systematic literature search was to identify the therapeutic use of acupressure from studies published in Chinese.

A total of 2389 articles were identified. Acupressure had been used to treat a wide range of diseases or clinical symptoms, such as obstetrical symptoms, sleep problems, and post-operative nausea and vomiting. However, out of the 2389

articles, after limiting the key words to 老人 (i.e. older people) or 老年 (i.e. the elderly) or 痴呆症 (i.e. a Chinese terminological variant of dementia) or 癡呆症 (i.e. another Chinese terminological variant of dementia) or 失智症 (i.e. a third Chinese terminological variant of dementia), only 6 articles were identified, none of which were about the use of acupressure in managing agitation in PWD. All of them were about improving the cognitive function or memory of PWD. Studies published in Chinese showed that acupressure had also been used and researched in China to manage the clinical symptoms of PWD. However, the use of acupressure specifically for agitation in PWD has not been adequately studied, based on our findings in the Chinese publications.

2.5.3 Research on acupressure for agitation in dementia

In order to further appraise the current studies specifically addressing the use of acupressure in managing agitation in dementia, a systematic literature search was performed. To identify articles published in English, the following keywords and databases were used. The English keywords used included “agitation”, or “agitated”; and “dementia”, or “demented”; and “acupressure”, or “acupuncture”, or “meridian”, or “massage”. The following English electronic databases were searched: MEDLINE, CINAHL, PsycINFO, Cochrane, the British Nursing Index, PubMed, and AMED. To identify articles published in Chinese, the following keywords and databases were used: “行為問題” (i.e. behavior problems), or “激越” (i.e. a term for agitation), or “躁動” (i.e. a term for agitation); and “痴呆症” (i.e. a term for dementia), or “癡呆症” (i.e. a term for dementia), or “失智症” (i.e.

a term for dementia); and “針灸” (i.e. acupuncture), or “穴位按壓” (i.e. acupressure) or “推拿” (i.e. Tuina), or “指壓” (i.e. shi-atsu), or “穴位” (i.e. acupoint). The China Journals Full Text Database was searched. Both English and Chinese article searches were limited to publications in the last three decades, specifically from 1980-2011. All abstracts identified were reviewed. When potentially eligible studies were identified in the review of abstracts, full texts were retrieved. We selected only experimental studies about the effects of acupressure or acupuncture for agitation in dementia. Finally, only four relevant studies were retrieved, namely studies 1, 2, 3, and 4, as shown in Table 2.1.

Table 2.1

Summary of studies of using acupressure/acupuncture to manage agitation in PWD

No.	Authors	Design	N	Participant	Intervention	Outcomes
1	Arai et al, 2010	Pre-post test	4	Post-op PWD	Auricular acupuncture	*Agitation, by DOS
2	Millea & Reed, 2004	RCT	18	Agitated PWD	Acupuncture by needle, c/w placebo and usual care	*Agitation, by NPI
3	Yang et al, 2007	Pre-post test	20	Agitated PWD	Acupressure	*Agitation, by CMAI
4	Lin et al, 2009	Cross-over RCT	133	Agitated PWD	Acupressure, c/w Montessori activities and presence	*Agitation, by CMAI

*Statistically significant, RCT=randomized controlled trial, Sig.=significant, PWD=people with dementia, DOS=Delirium Observation Scale, NPI=neuropsychiatric inventory, CMAI=Cohen-Mansfield Agitation Inventory

Study 1 (Arai et al, 2010) was about the use of auricular acupuncture to prevent postoperative agitation in older patients. The auricular acupuncture used in this study was to apply occlusive press needles on the acupoints – “Shenmen” and

"Point Zero" - on the ear of the subjects continuously until post-operation day 9. The press needles were changed every three days. The working principle of auricular acupuncture was not clearly explained but was reported to be based also on TCM theory related balance of five organs, which is similar to the TCM meridian theory discussed earlier in section 2.2.4. This was a quasi-experimental study with four subjects only. Three out of the four subjects had dementia. The agitation was measured by the Delirium Observation Scale (DOS). Measurement was done five times, once before the operation and four times afterwards. Three subjects demonstrated reduction of agitation when compared with the baseline. This study demonstrated that the use of auricular acupuncture could reduce agitation in dementia. However, in this study, the intervention was not acupressure. Auricular acupuncture shares similar theoretical TCM working principle which involves meridian and acupoints, but it involves different implementation techniques and different system of meridian which is limitedly located in the ears only. Also, the sample size was very small (n=4) and the design was poor, so that many threats to the internal validity of the study were not eliminated. For example, no randomization or blinding were done, and there were uncontrolled confounders (i.e. no control groups).

Study 2 (Millea & Reed, 2004) was about the use of acupuncture in the treatment of Alzheimer's Disease complicated by agitation. The acupuncture used in this study was to apply needles on five acupoints: ear Shenmen, Baihui (GV20), Neiguan (PC6), Shenmen (HT7), and Yintang (EX-HN3). The needles were taped in place for 20 minutes twice weekly for 2 weeks. For the hypothetical working

principle of acupuncture in this study, it was explained that acupressure may decrease overall sympathetic tone in the autonomous nervous system and raise the agitation threshold. The selection of acupoints was made reference on a protocol suggested in a TCM textbook of acupuncture and moxibustion (Cheng, 1999). It was a randomized controlled trial with 18 subjects (nine married couples), all of whom were PWD. There were three groups, an acupuncture group (four pairs of subjects), a placebo group (two pairs of subjects) and a usual care group (three pairs of subjects). The Neuropsychiatric Inventory (NPI) was used as the measure outcome of the agitation. The agitation was measured before and after the intervention, with the results showing that the reduction in the total NPI median score was significantly larger in the acupuncture group when compared with the placebo and usual care groups. This result indicated that acupuncture can reduce agitation in dementia. The design of this study was relatively good in terms of controlling confounders, since it used randomization and a placebo group control. However, this study used needle acupuncture as the intervention. Needle acupuncture is different from acupressure in terms of implementation although their working principles share the same TCM meridian theory. Also, NPI was used as the outcome measure. NPI may include psychiatric symptoms (e.g. delusion and hallucination) and it is supposed to measure behavioral disposition (especially when the total score is used), although NPI was also described as measuring agitation in dementia. In addition, the total sample size was too small (N=18) and the sample size in each group was also small (n=4 in the placebo group) rendering the result less than convincing.

Study 3 (Yang et al, 2007) was about the efficacy of acupressure for decreasing agitated behavior in dementia. The acupressure used in this study was to apply pressure by fingers on five acupoints: Fengchi (GB20), Baihui (GV20), Shenmen (HT7), Niguan (PC6), and Sanyinjiao (SP6). The acupressure was carried out twice daily, five days a week, for four weeks. Each acupressure session lasted for 15 minutes – two minutes for each acupoint and five minutes for warm-up activity (e.g. holding, rubbing and pressing the palms and finger joints on both hands for 5 minutes). This was also a quasi-experimental study with 20 PWD. The outcome was agitation measured by CMAI. Agitation was measured before and after the intervention, followed by a one-week treatment free period. After the one-week treatment free period, agitation was measured again before and after a control protocol (i.e. visiting and conversation for four weeks). Results showed a reduction in agitation after the acupressure protocol and an increase in agitation after the control protocol. The reduction of agitation after the acupressure compared with increase of agitation after the treatment protocol was significantly different. This result indicated that acupressure can reduce agitation in dementia. However, there may have been selection bias. How subjects were selected and recruited was not reported. There was only one group of subjects. Without randomization of group allocation, many possible confounders were not controlled. Also, the CMAI data collector was the head nurse who knew that the subjects had received acupressure (i.e. there was no blinding); the measurement bias could not be eliminated. Although the attrition rate was well reported in this study, the attrition was severe. 11 out of 31 subjects dropped out for various reasons, giving a high rate of attrition.

In addition, the sample of 20 subjects was not large enough for the results to be convincing.

The study 4 (Lin et al, 2009) was about the use of acupressure to decrease agitation in PWD. The acupressure used in this study was to apply pressure by fingers on five acupoints: Fengchi (GB20), Baihui (GV20), Shenmen (HT7), Niguan (PC6), and Sanyinjiao (SP6). The acupressure was carried out once daily, six days a week, for four weeks. Each acupressure session lasted for 15 minutes – two minutes for each acupoint (i.e. 10 minutes altogether for the five acupoints used) and five minutes for warm-up activity (e.g. holding, rubbing, and pressing the palms and finger joints). This was a cross-over randomized controlled trial to compare the effect of acupressure on agitation among 133 dementia nursing home residents. There were two control groups in this study. The first was Montessori activity program (e.g. scooping, pouring, squeezing) scheduled six times a week for four weeks. The second was being-present (e.g. conversation) for a 15-minute period each day for six days a week for four weeks. Agitation was measured by CMAI before and after the acupressure/control protocol. The result showed a significant decrease in CMAI total score, and two CMAI sub-scores (i.e. aggressive behaviors and physically non-aggressive behaviors) in the PWD compared with the control conditions (i.e. Montessori activities and being present). This study showed a favorable result that acupressure significantly reduced agitation in dementia. Adequate efforts to control confounders were noted, such as the use of randomization, blinding, and control groups. The sample size was relatively appropriate (N=133), although the post-hoc power was not reported. However, the

use of the cross-over design without adequate understanding of the effect sustainability may have amplified the therapeutic effect by the carry-forward-effect. How the effect of the given dose of intervention was delineated from the possible carry-forward-effect was not reported. Also, the attrition and the principles of analyzing data (e.g. intention-to-treat or treat-per-protocol) were not reported. Therefore, the possible confounding effects from attrition bias and study protocol violation were unknown.

To summarize the evidence in the systematic review on the effect of using acupressure/acupuncture for managing agitation in PWD, all four papers identified reported favorable effects in managing agitation in PWD. However, study 1 and 2 did not actually use acupressure, although the auricular acupuncture and acupuncture used in these two studies also based on stimulation of acupoints. Yet, the implementation procedures are very different. In study 3 and 4, both of them used acupressure as their interventions that they coherently showed that acupressure is an effective intervention to reduce agitation in PWD. However, the methodological flaws discussed above may have limited their validity. For example, study 3 failed to use randomization for group allocation or blinding for outcome measurement, while study 4 failed to address the possible carry-forward effect contamination and report the attrition rate. The favorable effectiveness of the use of acupressure may be threatened by the studies' biases (e.g. expectation bias without blinding and withdrawal bias without good management of attrition). Given that there are few studies in this area, the effectiveness of using acupressure in managing agitation in dementia is not clear.

2.5.4 The knowledge gap on the use of acupressure for agitation in dementia

The literature review showed that agitation is a common problem with negative impacts on PWD and their caregivers. To date, as mentioned above, non-pharmacological intervention is believed to be a more appropriate approach to manage agitation in dementia compared with the use of pharmacological agents. However, there is no evidence showing that a single non-pharmacological intervention can be effective in managing agitation in dementia across contexts. Non-pharmacological intervention is observed to be more effective if it comprises sensory stimulating components, caregiver training components with theoretical grounds on the person-centered care model, and consideration of the person's individuality (e.g. interests and functional level). Apart from effectiveness, safety, cost, and preference are also important factors to consider for the non-pharmacological intervention to be used feasibly. This understanding of non-pharmacological interventions for managing agitation in dementia gives rise to the need to develop a variety of non-pharmacological interventions. In this way, more effective NPT can be made available to accommodate the diverse individual needs of agitated PWD.

In the literature, evidence shows that acupressure may have many potential benefits in terms of hypothetical effectiveness (i.e. favorable results from the preliminary studies) and feasibility advantages (i.e. it is likely to be more acceptable to Chinese older people and less costly), and thus is worthy of being developed as a therapeutic modality in managing agitation in PWD. The preliminary evidence supports further research and development in the use of

acupressure. The following discussion looks at which angle is worth studying on the topic of using acupressure to manage agitation in PWD, and asks specific research questions.

Fønnebø and colleagues (2007) proposed a framework for studying interventions using complementary and alternative medicine (CAM). This framework proposes to study CAM (e.g. acupressure) using a sequence of the following steps: level of utilization, safety, effectiveness, efficacy of components, and mechanism at the bio-chemical level.

This CAM study framework (Fønnebø et al, 2007) showed that the topic of using acupressure to manage agitation in PWD can be studied from five angles: level of utilization, safety, effectiveness, efficacy of components, and mechanism at the bio-chemical level. These five angles do not necessarily need to be studied in a strictly chronological sequence; this framework is intended to guide CAM research only (Fønnebø et at, 2007). For example, the use of a CAM intervention is not controlled at the clinical level by any gate-keeping policies. The CAM intervention is usually being widely used already. It makes more sense to study whether the CAM invention is effective first, before its bio-chemical mechanism is examined. In order to identify which angle is more worthy of study on this topic, the five angles on the topic of the use of acupressure in managing agitation in PWD are discussed below with reference to the current evidence.

2.5.4.1 Level of utilization

Level of utilization refers to how many and what segments of the patient population use it (Fønnebø et al, 2007). In the systematic search, no studies were found that reported the demographics and patterns of use of acupressure in managing agitation in dementia. Nevertheless, one of the articles identified reported that many Taiwanese older people have received acupressure throughout their life (Yang et al, 2007). Also, nurses and family members expressed a keen interest in the use of acupressure (Lin et al, 2009). Therefore, acupressure is already being used at the clinical level, although its level of utilization is not fully known.

2.5.4.2 Safety

Safety refers to the risk of adverse effects (Fønnebø et al, 2007). In the systematic search, no studies were found that specifically reported safety issues in the use of acupressure in managing agitation in dementia. Acupuncture, which works in a similar way to acupressure through stimulation of acupoints, was observed to cause tiredness (2-41%) in the participants (Ernst & White, 2001). Over-stimulation could increase agitation and aggression in some individuals (Robinson et al, 2007). Nevertheless, there were no adverse effects reported in the acupressure study on agitated PWD (Yang et al, 2007; Lin et al, 2009). This evidence shows us that acupressure is not associated with serious adverse effects, an aspect that was not reported in previous studies.

2.5.4.3 Effectiveness

Effectiveness refers to the effect on outcomes of the whole treatment system, both in combination with and as an alternative to conventional care (Fønnebø et al,

2007). In the systematic search, two trials were identified that evaluated the effectiveness of acupressure primarily in managing agitation in PWD. Studies 3 and 4 (Yang et al, 2007; Lin et al, 2009) yielded positive results, with acupressure significantly reducing agitation in PWD. As mentioned above, the favorable effect may still be threatened by possible methodological biases, such as amplification of the therapeutic effect by the carry-forward effect. Therefore, preliminary evidence suggests that acupressure is effective. However, the possibility of effect amplification by the carry-forward effect in Lin and colleagues' study (2009) cannot be eliminated. The effectiveness sustainability over time is still unknown.

2.5.4.4 Efficacy of components

Efficacy of components refers to the effect of a specific component of the therapy instead of the whole treatment system (Fønnebø et al, 2007). There are many possible active components in acupressure, such as communicative interaction between participants and interventionists throughout the intervention period (e.g. casual or warm-up chatting and shaking hands), acupoint stimulation, tactile stimulation, and usual care. These components, which cannot be separated from the acupressure protocol itself, may independently or complementarily contribute to the effect of the acupressure. For example, the agitation reduction can be due to the combined effect of acupoint stimulation and tactile stimulation. The effect can also be solely from the acupoint stimulation, with the co-existing components (i.e. tactile stimulation or communicative interaction) playing a negligible role.

In study 3 (Yang et al, 2007), the effect of acupressure was compared with that of visiting and conversation. In study 4 (Lin et al, 2009) the effect of acupressure was compared with presence (i.e. just being with the person). Both study 3 (Yang et al, 2007) and study 4 (Lin et al, 2009) reduced agitation in PWD significantly using acupressure, when compared with presence, visiting and conversation. This may indicate that the communicative interaction component of the acupressure protocol is not a major active component of the acupressure protocol. However, in both study 3 (Yang et al, 2007) and study 4 (Lin et al, 2009), the tactile stimulation component obviously existed in the protocols of both studies 3 and 4. There were warm-up activities for five minutes in the acupressure protocols but not in the control protocol of both studies 3 and 4. The warm-up activities involved hand rubbing and pressing. Acupressure also involving pressing on the skin. These activities have already exerted tactile stimulation. However, efficacy of the tactile stimulation component was not tested. The tactile stimulation component may contribute mainly or complementarily to the effects of acupressure, although the extent is not known. This was supported by evidence in massage studies (Moyer et al, 2011; Moyle et al, 2011) that tactile stimulation by massage may also be active in reducing stress and agitation.

2.5.4.5 Mechanism at bio-chemical level

Mechanism refers to how treatment outcomes can be explained at the bio-chemical level (Fønnebø et al, 2007). In both studies (Yang et al, 2007; Lin et al, 2009) from the systematic search, the treatment outcome of the acupressure was explained by the TCM meridian theory. The TCM meridian theory explained that

acupressure is a non-invasive variation of acupuncture involving constant pressure to stimulate acupoints of the human body in order to balance *qi* and thereby promote individual well-being (Weaver, 1985). The mechanism was not explained in detail, nor discussed at the biological level. A discussion of the bio-chemical mechanism whereby acupressure reduces dementia-related symptoms (e.g. agitation) is lacking. Therefore, the mechanism of acupressure at the bio-chemical level in reducing agitation in dementia is unknown.

To summarize the knowledge and knowledge gap in literature on the use of acupressure in managing agitation in dementia after the appraisal according to the CAM framework (Fønnebø et al, 2007), it is certain that acupressure has already been used at the clinical level to manage agitation in PWD, though the exact level of utilization is not known. Acupressure is not associated with serious adverse effects, though the possible risks are still unknown. Preliminary evidence indicated that acupressure is effective in reducing agitation in PWD, but its effectiveness may be threatened by a possible carry-forward effect as the effect sustainability of acupressure in reducing agitation is not known. Preliminary evidence also showed that the main efficacy components may not be attributed to the communicative interaction in the acupressure protocol (e.g. being present, visiting, and conversation), as a quality study showed that acupressure is significantly more effective in reducing agitation in PWD compared with the communicative interaction control (Lin et al, 2009). However, it is still uncertain whether the main efficacy component comes from the activation of acupoints as predicted by the TCM meridian theory, tactile stimulation as predicted by the tactile stimulation

hypothesis, or others. The therapeutic mechanism of acupressure at the bio-chemical level is basically unknown.

After appraising the knowledge on the use of acupressure for agitation in dementia in the literature, it can be concluded that acupressure is worthy of further research because preliminary evidence supports that it is already being used and is safe and effective. Further studies on this topic should focus on the unknown aspects, which include the utilization of acupressure in clinical settings, the possible risks, the effectiveness after considering the effect sustainability, the main efficacy components apart from the communicative interaction, and the mechanism at the bio-chemical level.

2.6 Summary

Agitation in dementia is a psycho-behavioral clinical syndrome described as observable, excessive, inappropriate, disruptive and not explained by apparent needs. The causes of agitation are multiple and can be explained by different theories, from different perspectives. The theories offer preliminary support for the use of acupressure to reduce agitation and stress levels in PWD.

There are many interventions available to manage agitation in dementia, which can generally be divided into two groups: pharmacological and non-pharmacological interventions. There is no strong evidence showing that drugs are effective in managing agitation in dementia. Yet, severe adverse effects are evident in many of the drugs. There is also no strong evidence supporting which non-pharmacological intervention is solely effective across contexts, but there were no

severe adverse effects reported in previous studies on the use of non-pharmacological interventions. There may be evidence that effective non-pharmacological interventions comprise sensory stimulating components, caregiver training components that are theoretically grounded on the person-centered care model, and consideration for the person's individuality (e.g. interests and functional level). Apart from the effectiveness, safety, cost, and preference are also important factors to consider for the NPT to be used feasibly.

Acupressure is a non-pharmacological intervention that originates from the Chinese culture and is believed to be theoretically effective in managing a range of clinical syndromes. Acupressure also bears tactile stimulation components like massage, which may possibly exert a relaxing and stress-reducing effect through moderation of the HPA axis. There is evidence that acupressure can trigger neuro-hormonal responses in our body, which may possibly have therapeutic effects.

In the literature, there are only two studies examining the effect of acupressure specifically in managing agitation in PWD. These two studies showed promising effect of acupressure in reducing agitation of PWD, although their results were limited by some methodological flaws. Preliminary evidence has shown that acupressure has already been used to manage agitation in PWD clinically, is not associated with serious adverse effects, and is effective, and that its efficacy is unlikely to come from the communicative interaction component of the acupressure protocol. However, the following aspects are still unknown: the utilization of acupressure in clinical settings, the possible risks, effectiveness after considering the effect sustainability, the main efficacy components apart from the social

interaction, and the mechanism at the bio-chemical level. Therefore, further studies are needed in order to understand these unknown areas related to the use of acupressure in managing agitation in dementia.

Chapter 3 Development of the Study

Based on the literature review, some aspects of the use of acupressure in managing agitation in PWD are unknown but worthy of further study. Among these areas, the effectiveness of acupressure, its effect sustainability, its efficacious components, and its effect at the bio-chemical level attracted my interest. Therefore, the aim of this study was to find answers on these four issues.

Prior to finding answers on these four issues and in order to distil them into testable research hypotheses, an intervention protocol and experiment had to be developed by evidence-based methods. The Medical Research Council (MRC) proposed a guideline for the development and evaluation of complex interventions such as acupressure (Craig et al, 2008). This provides an appropriate method for evaluating and developing an intervention protocol for acupressure study based on evidence. The research questions related to these four issues will be clearly specified after the development of the study, because the hypothetical relationships between the variables involved in this study will only be understood thereafter.

This chapter describes how the study was developed with reference to the MRC guideline 2008, beginning with an outline of the MRC guideline 2008 (Craig et al, 2008). Following the MRC guideline 2008 (Craig et al, 2008), a literature review to identify related theories and evidence will be presented, followed by a discussion on the use of Delphi technique to gain consensus on the acupressure protocol. Finally, the use of a pilot study to test procedures and make estimations about certain dimensions of the study will be discussed.

3.1 The MRC Guideline 2008

In the MRC 2008 guideline, as shown in Figure 3.1, there are four steps: development, feasibility and piloting, evaluation, and implementation. In the development stage, evidence and related theories of a complex intervention should first be identified, and the process and outcomes of the complex intervention modeled. In the feasibility and piloting stage, procedures are tested and important estimations of the study made (e.g. recruitment rate, sample size). In the evaluation stage, the effectiveness of the intervention protocol is assessed and the change process is understood. In the implementation stage, the intervention should be disseminated. At that point, long-term surveillance and monitoring on its effectiveness and safety should be carried out. These four stages form a reversible cycle, with studies moving back and forth between the stages. If a study identifies problems that make it impossible to move on to the next stage, it can move back to the previous stage.

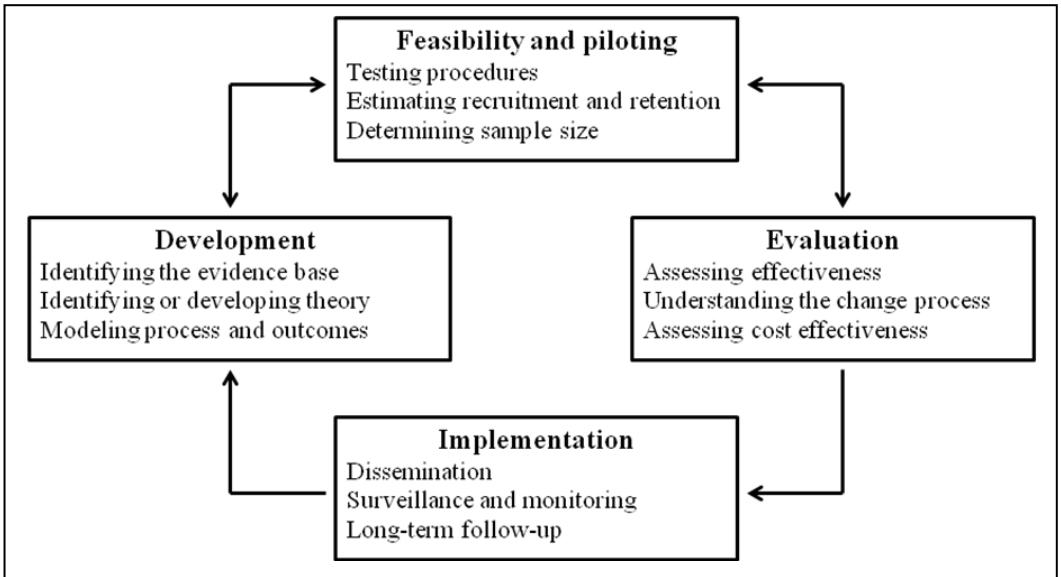


Figure 3.1. Guideline to Develop and Evaluate Complex Intervention proposed by Medical Research Council 2008

This study, as shown in Table 3.1, used three methods to research the effects of acupressure in managing agitation in dementia by following the guideline suggested by the MRC (Craig et al, 2008). The three methods are the literature review, Delphi technique, and pilot study. These three methods were purposefully implemented in a sequential order. Data generated from one method informed the design of the subsequent method. The literature review was the first method to identify evidence and theories. Delphi technique was the second method, which was used to gain consensus on the acupressure protocol among a panel of TCM experts. The pilot study was the third method of testing procedures and making estimations. After the intervention protocol had been developed and the optimal procedures of the study decided, a randomized controlled trial was used to answer the research questions.

Table 3.1

Methods used to develop and evaluate the effect of acupressure following the MRC guideline 2008

MRC's suggested guideline		Methods			
Stage	Purpose	LR	DT	PS	RCT
1. Development	Identifying theories and evidence	x			
	Gaining consensus on the acupressure protocol		x		
2. Feasibility and piloting	Testing procedures and making estimations			x	
3. Evaluation	Answering the research questions				x

MRC=Medical Research Council, LR=literature review, DT=Delphi technique, PS=pilot study, RCT=randomized controlled trial

3.2 Identifying Theories and Evidence

In order to develop a study on the topic of using acupressure in managing agitation in PWD, it is essential to conceptualize a framework which theoretically explains how an intervention leads to the outcomes (Solomon et al, 2008). In this study, this means how acupressure can lead to the reduction of agitation in PWD. It is also essential to know which intervention ingredients (e.g. selection of acupoints, dosage, and technique specification) should be included in the acupressure protocol. To this end, a literature review was conducted.

3.2.1 Literature review

In Chapter 2, the literature review aimed at identifying the concept of agitation in dementia, causes of agitation in dementia, interventions for agitation in dementia, and acupressure for agitation in dementia. In this section, this literature review was done for a different purpose. The purpose was to explore for existing theories or hypotheses which backed up theoretically how acupressure may possibly lead to the reduction of agitation. So as to develop an acupressure protocol and the study procedures for further evaluation of its effects. This was an explorative literature review and therefore there were no search criteria (e.g. keywords and publication years) known in prior.

3.2.2 Results

In the explorative review, four related theories and hypotheses were identified to explain how acupressure can possibly lead to the reduction of agitation in PWD. The four related theories and hypothesis are the stress hypothesis, the tactile

stimulation hypothesis, the progressively lowered stress-threshold model, and TCM meridian theory.

3.2.2.1 Stress hypothesis

According to the aforementioned glucocorticoid cascade hypothesis or neurotoxicity hypothesis (Gilbertson et al, 2002) and Predevelle's explication of the deleterious effect of aging on the brain (Prenderville et al, 2014), neuronal degeneration in ageing and chronic stress in the life span of the older people damage the negative feedback regulation of the HPA axis. It causes higher level of basal cortisol concentration. The high level of basal cortisol concentration further alters the brain plasticity (e.g. causing hippocampal atrophy) to accelerate cognitive decline and causes behavioral problems. Empirical studies also supported that older people with Alzheimer's disease have higher level of basal glucocorticoid level compared with the people without dementia (Umegaki et al, 2000; Giubilei et al, 2001). It is therefore hypothesized that PWD usually have experienced chronic stress, dysregulated HPA axis, and higher level of basal glucocorticoid level. This is known as "stress hypothesis" in this study.

3.2.2.2 Tactile stimulation hypothesis

As discussed in Chapter 2 under section 2.4.1.1, tactile stimulation can possibly lead to reduction of cortisol through the HPA axis (Lawton, 2003; Moyer et al, 2004; Remington, 2002). This hypothesis can also be supported by the observations that massage and therapeutic touch can reduce cortisol level (Woods & Dimond, 2002; Labrique-Walusis et al, 2010; Moyer et al, 2011). Given that

acupressure also exerts a certain level of tactile stimulation, it can be hypothesized that acupressure may also reduce cortisol level by its tactile stimulation property.

3.2.2.3 PLST model

Chapter 2, section 2.2.2 discussed how PWD may experience a progressively lowered stress threshold. When the stress level exceeds the stress threshold, maladaptive behaviors (e.g. agitation) occur. PWD who have their stress threshold progressively lowered by dementia are therefore thought to be prone to having stress levels that exceed the stress threshold. This may also imply that agitation in PWD is caused by high levels of stress, which is also coherent with what was explained in the aforementioned stress hypothesis. This theory is supported by a preliminary study in which agitation decreased along with cortisol level following touch therapy (Woods & Dimond, 2002), although evidence of this association is still scarce.

3.2.2.4 TCM meridian theory

As discussed in Chapter 2, section 2.2.4, agitation can be a clinical symptom which is an expression of *zangfu* imbalance or TCM pathological syndromes. TCM meridian theory (Cheng & Deng, 1987; Cook & Wilcox, 1997) explains that the *zangfu* balance is achieved by adequate supply of *qi* through the meridians. Acupoints are distributed widely over the meridians. By stimulating the related acupoints on the meridians running through the involved imbalanced *zangfu*, the *zangfu* balance can be re-established. As a result, the clinical symptom (e.g. agitation) can be resolved.

3.2.3 The conceptual framework of the study

The conceptual framework in an experimental study is a set of hypothetical relationships between concepts or variables used in research to outline possible courses of action (Solomon et al, 2008). The literature review shows three key concepts or variables involved in this study: acupressure, stress and agitation. The following discusses the hypothetical relationships between these three variables as derived from the literature, so as to construct a conceptual framework to outline the possible courses of action in this study.

The hypothetical relationship between stress and agitation is shown in Figure 3.2. It can be hypothesized that agitation in dementia can be caused by *zangfu* imbalance related to *qi* flow stagnation in the relevant meridians as predicted by the aforementioned TCM meridian theory. Stress level is usually higher with overproduction of cortisol in PWD because of the neural damage (e.g. to the hippocampus) as predicted by the aforementioned stress hypothesis. High level of stress that exceeds the stress-threshold can cause agitation, as predicted by the PLST model.

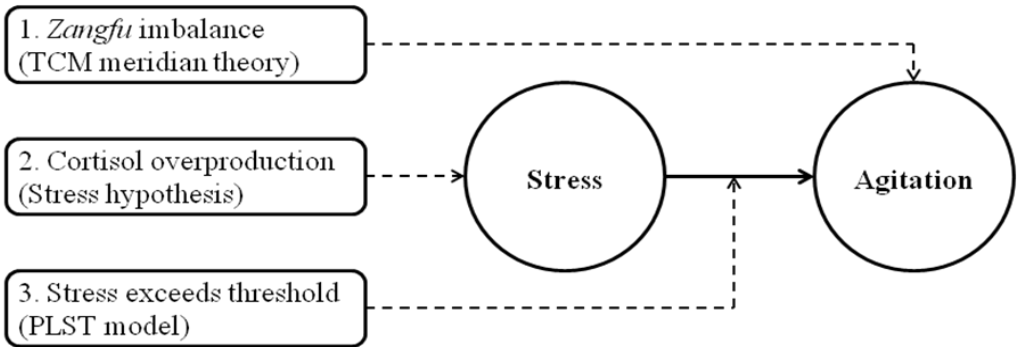


Figure 3.2. Schematic illustration of the hypothetical relationship between stress and agitation in PWD.

As shown in Figure 3.3, acupressure may reduce cortisol or stress levels by tactile stimulation as predicted by the *tactile stimulation hypothesis*. When cortisol and stress are reduced to a level below the stress threshold, agitation can be reduced.

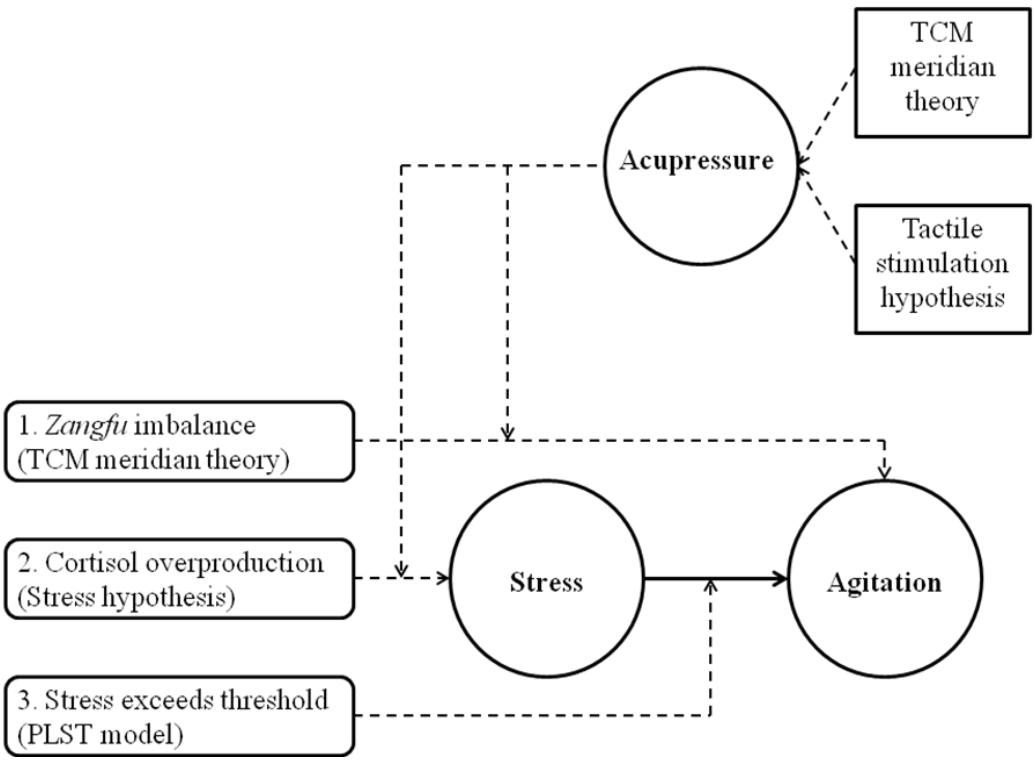


Figure 3.3. The hypothetical relationship between acupressure, stress, and agitation in PWD.

In summary, it is conceptualized that agitation in dementia may be partly caused by *zangfu* imbalance, as predicted by the TCM meridian theory. Over-production of stress hormone (i.e. cortisol) is common in PWD as a result of chronic stress and the neuronal degeneration secondary to dementia, as predicted by the stress hypothesis. Agitation may also be partly caused by high stress levels that exceed the hypothetical stress threshold, as predicted by the PLST model. Hypothetically, acupressure on one hand can counteract the over-production of cortisol as well as to bring down the stress level of PWD as predicted by the tactile stimulation hypothesis. When the stress level goes below the hypothetical stress threshold, agitation can be reduced as predicted by the PLST hypothesis. Acupressure on the other hand can rectify *zangfu* imbalance by stimulating the acupoints as predicted by TCM meridian theory. As a result, agitation can be reduced. Therefore, as shown in Figure 3.4, it is conceptualized that acupressure can partially exert a direct effect on reducing agitation in PWD, and partially exert an indirect effect on reducing agitation in PWD by mediating the stress level.

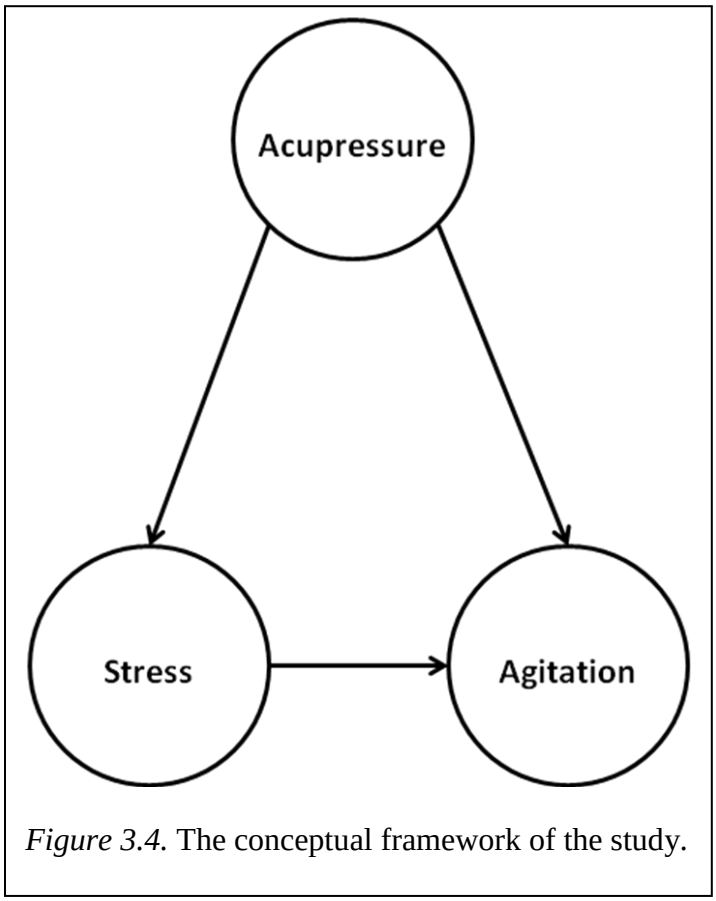


Figure 3.4. The conceptual framework of the study.

However, this conceptual framework is merely hypothetical and based on conclusions drawn from the literature. The framework explains why acupressure is believed to be effective in leading to agitation reduction in PWD. The validity of this conceptual framework has to be tested.

3.3 Developing the Acupressure Protocol through Delphi Procedures

After the literature review, relevant theories and hypotheses were identified to support how acupressure can hypothetically lead to the reduction of agitation. The next step was to develop an intervention protocol through evidence-based procedures. As discussed in the literature review, there is a dearth of studies examining the effect of using acupressure to manage agitation in PWD. There is no well-established acupressure protocol for treating agitation in dementia.

Development of a theoretically effective acupressure protocol by evidence-based procedures is therefore important before the effect of acupressure can be examined.

An intervention protocol is made up of many intervention ingredients, which have to be specified and selected by evidence-based procedures so that its effect can be fully demonstrated (Craig et al, 2008). Taking an acupressure protocol as an example, it has to be specified which acupoints are to be used, how long each acupoint should be pressed, how many sessions of acupressure are to be regarded as a complete course of therapy, and so on. There are far too many intervention ingredients that have to be specified before the effect of an intervention protocol can be evaluated. Without a well established intervention protocol whose effect is well supported by evidence, the intervention ingredients cannot be specified by following guidelines or a literature review.

Delphi technique is an approach to gain consensus among a panel of experts that is normally achieved through a series of rounds where information is fed back to panel members (Keeney et al, 2001). By using Delphi technique, intervention ingredients (e.g. selection of acupoints, dosage, and technique specification) can be specified through consensus by a panel of experts after repeated cycles of consultation.

3.3.1 Delphi technique

In this study, the use of Delphi technique aimed at developing an acupressure protocol with good consensus from a panel of experts. To start this process, available background information related to the development of the acupressure

protocol was first identified from the literature. Qualified experts were then selected to form the panel of experts. Finally, the panel of experts was purposefully consulted by cycles until good consensus was reached regarding the acupressure protocol to be adopted.

3.3.1.1 Preparation of background information

As discussed in Chapter 2, only two papers have been published specifically examining the effect of acupressure in managing agitation in PWD and with statistically significant results (Yang et al, 2007; Lin et al, 2009). The review of Chinese-language literature revealed no papers specifically discussing the concept of agitation in dementia from the perspective of TCM. One paper discussed the concept of agitation from the perspective of TCM and possible or common TCM pathological syndromes (i.e. the types of *zangfu* imbalance) causing the agitation (Teng, 2010), but the discussion was not specifically in the context of PWD. Yet, as mentioned above, the concept of agitation in Teng's paper (2010) was highly comparable with the concept of agitation in dementia reported in the Western literature. Therefore, the concept of agitation from the perspective of TCM and the TCM pathological syndromes reported in Teng's paper, together with the intervention ingredients used in the aforementioned two similar papers which showed favorable results (Yang et al, 2007; Lin et al, 2009), were considered to be important points of reference for the subsequent consultations using Delphi technique. Information about the specifics of the acupressure interventions in these three papers (Yang et al, 2007; Lin et al, 2009; Teng, 2010) was extracted. This information was summarized and used as background information to orient the

experts and aid their decision making on suggested intervention ingredients in the acupressure protocol.

3.2.1.2 The expert panel

This study invited experts according to several selection criteria. All experts had to hold a bachelor degree's in TCM, be registered TCM practitioners in either Hong Kong or mainland China, and have at least five years of post-registration experience including practicing acupuncture. The experts had preferably but not necessarily received post-registration training in acupuncture therapy, or had experience using acupuncture on people with dementia (PWD). These selection criteria ensured that the expert panel had sufficient knowledge and credentials to give theoretically relevant and practical recommendations on the intervention protocol.

3.3.1.3 The Delphi process

The first step in the Delphi process was to send each panel expert an invitation letter, instructions, anonymous bibliography of the experts, background information on the study summarized from the literature review, and consultative questions. This email invitation was followed by telephone calls. The consultative questions asked the experts about the selection of intervention ingredients with reference to their expert knowledge in TCM theory (e.g. TCM meridian theory, TCM syndrome differentiation), clinical experience (e.g. common TCM syndromes in the agitation of PWD, acupoints or specific techniques showing promising effects), and the

background information of the study provided. The identities of all the experts in the panel were blinded to the others to ensure anonymity.

In the first Delphi round, the expert panel was invited to read the information provided to them, to freely suggest intervention ingredients of an acupressure protocol which may reduce the agitation of elderly people with dementia, and to give narrative comments or justifications for the suggested intervention ingredients. The aim of the first round was to identify all the possible effective intervention ingredients that the expert panel found essential, as well as their justifications for the suggested intervention items.

After the consultation in the first Delphi round, the suggestions made by the expert panel were analyzed by the researcher. In the analysis, the level of agreement on each suggested intervention ingredient was summarized and represented by a percentage. The narrative comments justifying the use of the intervention ingredients were also summarized. The researcher had to determine whether the intervention ingredients proposed were clear and adequate for an acupressure protocol to be implemented by people without TCM training. The researcher also had to determine whether the suggested ingredients received good consensus from the panel experts.

A good consensus in this Delphi process was defined to be above 80% of agreement. Although the $\geqslant$80% threshold for consensus we used in this study was arbitrary, the threshold for setting agreement $\geqslant$70-80% as good consensus had been used in other Delphi studies (van Steenkiste et al, 2002; Yang et al, 2013). If

the researcher found that the intervention items suggested by the expert panel did not show clarity, adequacy or agreement, further consultative questions were asked to the panel again in the next Delphi round. After the analysis, new consultative questions, a summary statement containing the suggested intervention ingredients with figures of level of agreement on each suggested intervention ingredient, and narrative comments were sent to the panel experts again for the second round of Delphi.

In the second Delphi round, the expert panel was first asked to read all information provided and any new consultative questions asked by the researcher. The panel was then asked individually to rate whether they agreed with the intervention items suggested by the expert panel in the first round. Each expert could change their suggestions or even suggest new intervention ingredients after reading the information provided in the first Delphi round. Each expert was also asked to give comments or justifications for the intervention ingredients that they suggested or supported.

The aim of the second round was to identify new and important intervention ingredients if any, and to achieve a level of agreement on the suggested intervention ingredients. Similar to the procedures in the first Delphi round, the researcher analyzed the suggestions from the expert panel, summarized the level of agreement on each intervention item by percentage, summarized the comments on the intervention ingredients, and asked new consultative questions if there are any. This Delphi process went on until all selected intervention ingredients received over 80% of agreement from the expert panel and no more new questions on the

intervention protocol asked by the researcher. The schematic flow chart of the Delphi process is shown in Figure 3.5.

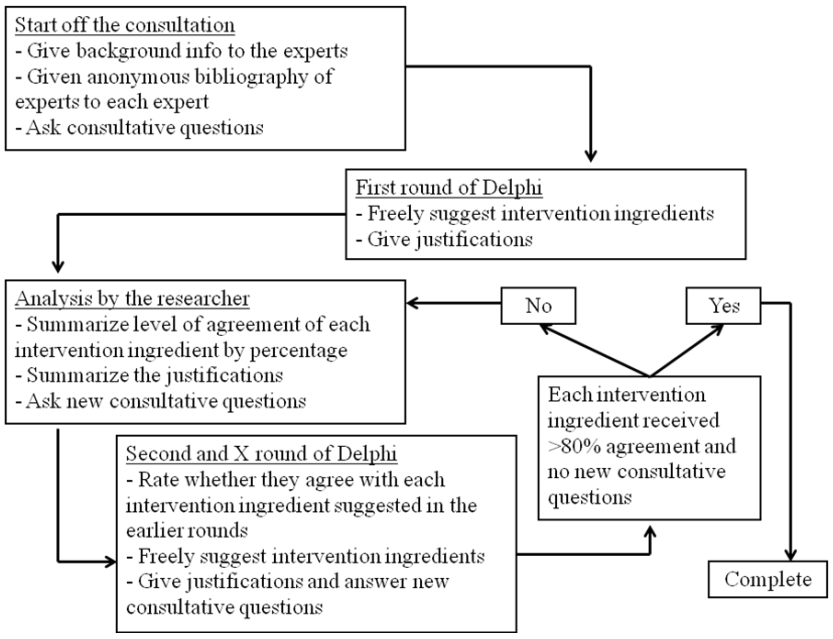


Figure 3.5. The Delphi process flow chart

3.3.2 Procedures

By purposive invitation, six TCM practitioners meeting the selection criteria were invited and agreed to be panel experts. The professional qualification and practice experience of the panel experts is shown in Table 3.2.

The majority of them was registered as TCM practitioners in Hong Kong (83.4%) and had practiced in Hong Kong (83.3%). All had a bachelor's degree in TCM and two had attained master's degree level (33.3%). One expert had a post-graduation qualification specializing in acupuncture (16.7%). All of them sometimes or occasionally practiced acupuncture on PWD, and the mean number of years that they had practiced acupuncture was 16.8.

Table 3.2

Professional qualifications and practice experience of the panel experts

Professional qualifications and practice experience	(N=6)
TCM registration location, n (%)	
Hong Kong	3 (50.0)
Hong Kong and Taiwan	1 (16.7)
Hong Kong and mainland China	1 (16.7)
Mainland China	1 (16.7)
Current practicing location, n (%)	
Hong Kong	5 (83.3)
China	1 (16.7)
Highest TCM academic qualification, n (%)	
Bachelor's degree	4 (66.7)
Master's degree	2 (33.3)
Post-grad qualification specializing in acupuncture, n (%)	
Master's degree	1 (16.7)
Experience practicing acupuncture on PWD, n (%)	
Often	0 (0)
Sometimes	3 (50.0)
Occasionally	3 (50.0)
Never	0 (0)
Number of years practicing acupuncture, mean (SD)	16.8 (10.7)

TCM=traditional Chinese medicine

3.3.3 Results of the Delphi procedures

Three rounds of Delphi came up with good consensus on all the intervention ingredients needed for an acupressure protocol. The following section discusses the results of three rounds of Delphi.

3.3.3.1 First round Delphi

The expert panel in the first round of Delphi freely gave suggestions on all kinds of intervention ingredients, which could be categorized into the selection of acupoints, duration of each session, duration of whole course, and frequency.

As shown in Table 3.3, there were 11 suggestions on the selection of acupoints, two suggestions on the duration of each session, two suggestions on the duration of the whole course, and two suggestions on the frequency proposed by the expert panel. The acupoints suggested by more than 50% of the experts were: Baihui (GV20) (100%), Shenmen (HT7) (100%), Fengchi (GB20) (83.3%), Neiguan (PC6) (66.7%), and Shanyinjiao (SP6) (66.7%). The majority of the experts suggested that the duration of each session should be 15 minutes (83.3%), the duration of the whole course should be four weeks (83.3%), and the frequency should be once a day for five days a week (83.3%). All of these suggestions had been used in previous acupressure studies (Yang et al, 2007; Lin et al, 2009).

Table: 3.3

Summary of intervention ingredients suggested in the first round Delphi

Intervention items	No. of experts suggested (N=6)
Selection of acupoints, (%)	
Baihui (GV20)*	6 (100%)
Shenmen (HT7)*	6 (100%)
Fengchi (GB20)*	5 (100%)
Neiguan (PC6)*	4 (66.7%)
Shanyinjiao (SP6)*	4 (66.7%)
Taichong (LR3)	2 (33.3%)
Fenglong (ST40)	2 (33.3%)
Yintang (EX-HN3)	1 (16.7%)
Hegu (LI4)	1 (16.7%)
Qimen (LR14)	1 (16.7%)
Daling (PC7)	1 (16.7%)
Duration of each session, (%)	
15 minutes*	5 (83.3%)
No specific suggestions	1 (16.7%)
Duration of whole course, (%)	
Four weeks*	5 (83.3%)
No specific suggestions	1 (16.7%)
Frequency, (%)	
Once a day, 5 times a week*	5 (83.3%)
Once every 2 days, 3 times a week	1 (16.7%)

*Intervention items used in other studies

In the narrative comments, the panel experts reported that their selection of acupoints to use was justifiable by TCM theory. All experts in the panel justified the dosage by what had been used previously in similar studies with significant results. Two experts commented that they had suggested the dosage according to their experience, particularly in terms of the duration and frequency. Duration and frequency of dosage could be important factors accounting for the efficacy of acupressure, but they were not well justified by TCM theory. There was also no

strong empirical evidence showing which duration and frequency was more effective than the others.

To analyze the suggestions made by the panel in the first round of Delphi, many items had not yet reached consensus. Only three acupoints reached over 80% agreement: Baihui (GV20), Shenmen (HT7), and Fengchi (GB20). For the dosage, there was strong consensus (83.3%) on using 15 minutes per session, a course of four weeks, and once a day and five times a week.

Upon clarification with the expert panel individually through emails, it was found that acupoints managing a particular syndrome can be categorized by effects into *essential* (主), *auxiliary* (輔), and not useful. *Essential* acupoints are the most important and should be used, while the *auxiliary* are less important and play the role of intensifying the effect. However, the panel did not specify the categories by effects of the acupoints in the first round of Delphi.

The qualitative comments from the expert panel justified the dosage suggestion based mainly on what had been used previously. One expert said that the duration was not easily justified by TCM theory. The others justified their suggestions on duration and frequency mainly on what had been previously used and whether the same approach could be practically implemented on agitated people with dementia. Therefore, concluding from the narrative comments, the dosage of the intervention could not be determined by consensus from the panel experts' experience and expertise.

Apart from the dosage, the researcher also found that some other useful intervention ingredients were not suggested by the expert panel in the first round of Delphi, such as the ideal number of acupoints and specific techniques for the acupressure (e.g. rhythmic or constant pressure). The researcher also considered that 15 minutes per session may be too long for agitated PWD to tolerate. These issues were formulated into three consultative questions and then brought to the panel experts again in the second Delphi round as shown in Table 3.4.

Table 3.4

Consultative questions for the second Delphi round

The three consultative questions put to the expert panel in the second round of Delphi
1. What is the ideal number of acupoints? 2. What are the specific techniques used in delivering the acupressure? 3. 15 minutes may be too long for the PWD to tolerate, what is your suggestion to resolve this problem?

In the second round of Delphi, the expert panel was asked to rate the acupoints suggested in the first round as essential, auxiliary, or not useful. The panel was also asked to answer the above consultative questions, give justifications for their rating, and give new suggestions if necessary.

3.3.3.2 Second round Delphi

The rating of acupoints in the second Delphi round is shown in Table 3.5. All of the experts rated Baihui (GV20) as essential, and more than half rated Shenmen (HT7) and Yingtang (EX-HN3) as either essential or auxiliary (66.7%). Half of the experts rated Fengchi (GB20), Neiguan (PC6), Taichong (LR3), Hegu (LI4), and Fenglong (ST40) as either essential or auxiliary (50%).

Table 3.5

Rating of acupoints in the second round Delphi

Acupoints	No. of experts proposed, N=6 (%)			
	Essential	Auxiliary	Not Useful	Not Rated
Baihui (GV20)	6 (100)	0 (0)	0 (0)	0 (0)
Shenmen (HT7)	3 (50.0)	1 (16.7)	0 (0)	2 (33.3)
Yintang (EX-HN3)	3 (50.0)	1 (16.7)	0 (0)	2 (33.3)
Fengchi (GB20)	3 (50.0)	0 (0)	0 (0)	3 (50.0)
Neiguan (PC6)	2 (33.3)	1 (16.7)	0 (0)	3 (50.0)
Taichong (LR3)	1 (16.7)	2 (33.3)	0 (0)	3 (50.0)
Hegu (LI4)	1 (16.7)	2 (33.3)	0 (0)	3 (50.0)
Fenglong (ST40)	0 (0)	3 (50)	0 (0)	3 (50.0)
Daling (PC7)	0 (0)	2 (33.3)	0 (0)	4 (66.6)
Jusanli (ST36)	0 (0)	2 (33.3)	0 (0)	4 (66.6)
Shanyinjiao (SP6)	0 (0)	1 (16.7)	0 (0)	5 (83.3)
Qimen (LR14)	0 (0)	1 (16.7)	0 (0)	5 (83.3)

In response to the researcher's consultative question about the ideal number of acupoints to use, some experts suggested an exact number of acupoints, while other experts suggested a range of numbers of acupoints as shown in Table 3.6. Using five acupoints as ideal was suggested by the largest number of experts (83.3%).

Table 3.6

Ideal number of acupoints in the second round Delphi

No. of acupoints	No. of experts suggested, N=6 (%)
4	1 (16.7)
5	5 (83.3)
6	1 (16.7)
7	2 (33.3)
8	2 (33.3)
9	1 (16.7)

For the consultative question about the specific techniques, different experts gave different suggestions but their responses complemented each other. To summarize their suggestions, one should apply pressure on the acupoints following a light-strong-light pattern as shown in Figure 3.6. Pressure should be increased gradually until it reaches the optimal level, sustained at the optimal level, and decreased gradually. The implementation should be ended by a kneading on the pressed acupoints. When the pressure increases to a level where the *deqi* sensation begins to be obviously felt by the participants or observed by the interventionist, the level of pressure is regarded as optimal. The *deqi* sensation was defined by soreness, numbness, distention, heaviness (Yang et al, 2013) reported by the participants or relevant behaviors (e.g. frowning, withdrawing) observed by the interventionists. The panel suggested using an approach of sustained pressure at the optimal level instead of altering pressure above and below the optimal level, which is also reported to be commonly used. The reason was that the former is easier for people with minimal TCM training to implement, and it keeps the confounding factor of technique variation among sessions to a minimum. The justification for the finger kneading was that it reduces unfavorable sensation after an acupoint is pressed for a prolonged period of time.

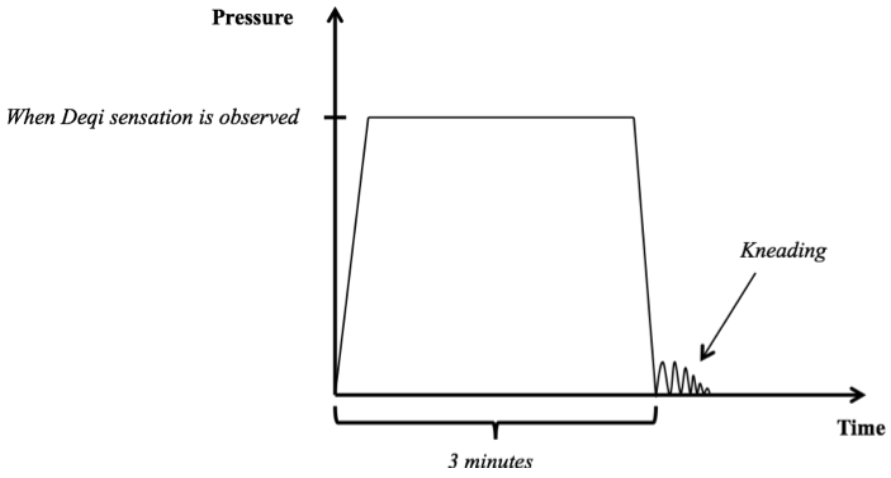


Figure 3.6. Schematic illustration of pressure change on acupoints over time during the acupressure

To resolve the problem that each session was too long, one expert suggested pressing two acupoints simultaneously in order to shorten the time for each acupressure session. For bilateral acupoints, which means when two identical acupoints are located on bilateral sides of the body, only the acupoints on one side should be pressed at a time. Acupoints on either side of the bilateral acupoints can be pressed alternately. Effects could be seen by pressing on each of the acupoints for three minutes per session. The other five experts suggested shortening the duration of pressure on each acupoint.

Analysis of the data in the second round of Delphi revealed a strong consensus (83.3%) on using five acupoints as ideal. The top five acupoints receiving the highest consensus included: Baihui (GV20), Shenman (HT7), Yingtang (EX-HN3), Fengchi (GB20), and Neiguan (PC6). The researcher adopted the suggestion of pressing two acupoints simultaneously instead of directly shortening the duration of

pressure, because with this approach there is no trade-off in the duration of therapy used on each acupoint.

Given that two acupoints could be pressed simultaneously, Shenman (HT7) was paired up with Neiguan (PC6) and Baihui (GV20) with Fengchi (GB20) since their pairs are proximal with each other and the paired acupoints can be pressed simultaneously. A qualitative comment from one of the experts suggested pressing each acupoint for three minutes per session and the effect would be evident. Therefore, Yingtan (EX-HN3) could be pressed independently for three minutes, Baihui (GV20) and Fengchi (GB20) could be pressed simultaneously for three minutes, and Shenman (HT7) and Neiguan (PC6) could be pressed simultaneously for three minutes. The time for a session of acupressure would then be nine minutes altogether.

These suggestions and comments from the expert panel were summarized together with the aforementioned specific techniques into a summary statement. The expert panel was consulted again in the third round of Delphi to obtain consensus on the preliminary protocol generated from the second round. In the third round, the expert panel was asked to indicate by ranking each intervention ingredient along a four-point Likert scale for agreement (“strongly agree”, “agree”, “disagree”, and “strongly disagree”). Each expert was still offered an opportunity to give additional comments or new intervention ingredients after reading the summary statement from the second round.

3.3.3.3 Third round Delphi

In the third round, all items on the statement were rated either strongly agree or agree by the panel, as shown in Table 3.7. To consider the items to be agreed if they were rated by the expert panel to be either strongly agree or agree, an agreement of 100% on the protocol was obtained from the expert panel in the third round of Delphi. No new intervention ingredients or qualitative comments were given in the third round of Delphi. The Delphi process was therefore complete.

Table: 3.7

Agreement on the acupressure protocol by the expert panel in the third round Delphi

Items	Agreement, n=6 (%)			
	Strongly Agree	Agree	Disagree	Strongly Disagree
Selection of acupoints				
Baihui (GV20)	5 (83.3)	1 (16.7)	0 (0)	0 (0)
Shenman (HT7)	5 (83.3)	1 (16.7)	0 (0)	0 (0)
Yingtang (EX-HN3)	2 (33.3)	4 (66.6)	0 (0)	0 (0)
Fengchi (GB20)	4 (66.6)	2 (33.3)	0 (0)	0 (0)
Neiguan (PC6)	4 (66.6)	2 (33.3)	0 (0)	0 (0)
Techniques				
Yingtang (EX-HN3) is pressed independently	0 (0)	6 (100)	0 (0)	0 (0)
Baihui (GV20) and Fengchi (GB20) are pressed simultaneously	0 (0)	6 (100)	0 (0)	0 (0)
Shenman (HT7) and Neiguan (PC6) are pressed simultaneously	0 (0)	6 (100)	0 (0)	0 (0)
Light-strong-light principle	0 (0)	6 (100)	0 (0)	0 (0)
Applying pressure for 3 minutes on each point or set of points	2 (33.3)	4 (66.6)	0 (0)	0 (0)
Sustain the pressure at the level at which the deqi sensation is observed	4 (66.6)	2 (33.3)	0 (0)	0 (0)
Post-pressure finger kneading	2 (33.3)	4 (66.6)	0 (0)	0 (0)

3.3.4 Discussion

Acupressure protocol may have various unknown intervention ingredients, but it was feasible to agree on a protocol with standardized ingredients with a high level of agreement through the Delphi process (Smith et al, 2012; Trevelyan et al, 2014). However, some of the intervention ingredients (i.e. the dosage) could not be identified through consensus in the Delphi process. It was expected that these important ingredients may have to be determined by other methods. These issues will be discussed below.

3.3.4.1 Feasibility of developing the acupressure protocol by consensus

It has been debated in the acupuncture community whether the effect of acupuncture depends on individualized TCM syndrome differentiation (Jiang et al, 2012) to find out the specific TCM pathological syndrome (i.e. zangfu imbalance) and subsequently to determine specific intervention ingredients (e.g. acupoint selection) (Anderson et al, 2007). In this consensus process, the selection of intervention ingredients is based on an assumption that agitation in dementia shares some common TCM pathological syndromes that may be treatable by a set of common acupressure ingredients. This set of common acupressure ingredients may be determined by the expert acupuncturists' professional knowledge and clinical experience.

In this consensus process, it was found that the key intervention ingredients suggested by the experts in the first round were widely divergent. However, the experts were eventually able to come up with a very good consensus on a fixed set

of options on the key intervention ingredients. This observation echoes the understanding that acupressure may be able to achieve its therapeutic effect through different sets of options from among the intervention ingredients (MacPherson et al, 2008). In other words, there is not necessarily a fixed set of theoretically effective intervention ingredients to treat a specific clinical syndrome (e.g. agitation); there can multiple sets of intervention ingredients that are also theoretically effective to treat a specific clinical syndrome. The consensus process through Delphi may have identified just one of a few theoretically effective sets of intervention ingredients. The result of the Delphi process, with good agreement on a set of intervention ingredients, confirmed that one of possibly a few sets of intervention ingredients can be identified through consensus among experts. This also suggests that the abovementioned set of common acupressure ingredients for managing agitation in dementia may exist. This set of common acupressure ingredients can be referred to as a standardized protocol (MacPherson et al, 2008).

This raised the argument as to whether using a standardized protocol is effective compared with the treatment generated after careful individualized TCM syndrome differentiation. To date, there is also a lack of studies comparing the effectiveness of this kind of common set protocol with the individualized protocol in the area of agitation in dementia. Even the effect of acupressure in managing people with dementia is not adequately known. The strength of using this type of standardized protocol generated by consensus is that it provides a pragmatic and evidence-based approach to evaluate the effect of acupressure in the real-world practice by clinical trials (Trevelyan et al, 2014). In addition, a standardized

protocol generated by experts' consensus is more externally generalizable, as it does not require individualized TCM syndrome differentiation before each application of the therapy. This standardized protocol makes this intervention more feasible to implement in the clinical setting, as it can be implemented by lay caregivers.

3.3.4.2 Implications of lack of consensus on the intervention ingredients

Although there was good consensus in the expert panel regarding some of the intervention ingredients, some others (i.e. frequency and duration) could not be proposed according to some of the experts' narrative comments, despite the fact that the frequency of once a day and the duration of four weeks received high agreement (83.3%) among panel members. The expert panel had no strong justification for the suggestions, according to their experience and knowledge of TCM theory. The dose-response relationship of acupressure in dementia care had never been reported. It was not known whether a more frequent or a less frequent intervention dosage would produce a larger effect.

Although the dosage (i.e. frequency and duration) could not be determined by expert consensus, it was decided that the dosage used by previous studies and agreed upon by the expert panel should be used as the best available evidence. The frequencies suggested by the majority of the panel experts (83.3%) in the first round of Delphi and used in other studies (Lin et al, 2006; & Yang et al, 2009) were once daily and twice daily. The duration suggested by majority of the panel experts (83.3%) in the first round of Delphi and used in other studies (Lin et al,

2006; & Yang et al, 2009) was four weeks. Given that the dose-response relationship of acupressure in managing agitation remains unknown, more evidence is needed to justify the dosage used in the main study as optimal. Acupressure is a complex intervention, and whether the dose-response relationship is linear is still uncertain. There is no evidence that a larger dose (i.e. more frequent and for a longer duration) leads to a larger response. Within the range of doses suggested by a majority of the panel experts in the Delphi process and used in other studies, the optimal dosage (i.e. frequency and duration) to be used for the main study is better identified by experimental comparisons of effect among different doses.

A summary of the range of doses used in other studies and suggested by the panel experts showed that the dose-dependent efficacy of acupressure among different durations ranged from one to four weeks, and the frequency ranged from once to twice a day; this was then tested out in the subsequent pilot study by experimental design. The evidence generated was important to determine the dosage (i.e. frequency and duration) for the intervention protocol, in order to evaluate its effects in the randomized controlled trial of the main study.

3.4 Pilot Testing the Study Protocol

Before the acupressure protocol could be evaluated in an RCT, study procedures had to be tested and some estimations made. This section will show how a pilot study was used to identify the undetermined intervention ingredients and appropriate procedures to be used in the RCT.

This pilot study purposefully compared the efficacies of acupressure at different dosages and identified the important feasibility issues needed to design the subsequent RCT. It therefore aimed at identifying the feasibility issues in saliva sample collection, acupressure implementation on the agitated nursing home residents with dementia, as well as the recruitment, the effect change over time, and the efficacies of acupressure when it is delivered in difference dosages. This data enabled the researcher to determine the optimal intervention dose, outcome measure time points, and estimation of sample size and recruitment rate. The intervention protocol and the study procedures of the subsequent randomized controlled trial were determined accordingly.

3.4.1 Operational definitions

This study had three key variables that needed to be defined: acupressure, agitation, and stress.

3.4.1.1 Acupressure

Acupressure was defined as a therapy performed by applying pressure on specific acupoints on the body to treat a wide range of conditions or to promote individual well-being (Weaver, 1985). In this study, the implementation of acupressure referred to the implementation of the aforementioned intervention protocol.

3.4.1.2 Agitation

Agitation was defined as inappropriate verbal, vocal, or motor activity that is not judged by an outside observer to result directly from the needs or confusion of the agitated individual (Cohen-Mansfield and Billig, 1986). CMAI (Cohen-Mansfield, 1991) derived from this definition was used to measure the variable of agitation in this study.

3.4.1.3 Stress

Stress was defined as a state of disturbed homeostasis evoked by physiological or behavioral adaptive response (Filaretova, 2010). Salivary cortisol level was measured for the stress as a proxy. For the rationale of using salivary cortisol as a proxy, methods of analysis, and procedures of collection are reported later in section 3.4.2.4.

3.4.2 Design

This study used a time serial design with multiple groups and was conducted in three residential care homes (RCH) in Hong Kong from May to July 2013. Convenience sampling was used. After screening, nursing home residents fulfilling the selection criteria were invited to participate. Inclusion criteria were being over 65, being documented as having dementia in their medical records, and being identified as having agitated behaviors for at least one month before the time of recruitment according to the criteria of agitation stated in the Instruction Manual for CMAI (Cohen-Mansfield, 1991). Exclusion criteria were skin problems on

acupoints (e.g. skin break down, infection), and musculo-skeletal problems (e.g. amputation of the body parts containing the intervention protocol's acupoints).

To compare the effect among different doses, subjects were divided into groups according to different combinations of frequency and duration. Frequency refers to the number of acupressure sessions performed in a day. Duration refers to the number of weeks that the acupressure lasts. Two frequencies and four durations were used within the range of doses in previous studies (Yang et al, 2007; Lin et al, 2009) and suggested by the expert panel of TCM practitioners in the Delphi process described above. These two factors formed eight combinations. There were totally eight groups in this study, with different frequency-duration combinations ranging from once a day for one week to twice a day for four weeks, as shown in Table 3.8.

Table 3.8

The eight study groups

		Duration			
		1 week	2 weeks	3 weeks	4 weeks
Frequency	Twice a day	2D1W	2D2W	2D3W	2D4W
	Once a day	1D1W	1D2W	1D3W	1D4W

3.4.2.1 The acupressure intervention

The acupressure protocol was developed by the Delphi process described from section 3.3.1 above. The use of acupoints and techniques were discussed earlier and are shown in Table 3.7. The interventions were conducted five days per week on Monday to Friday. There were no interventions on Saturday or Sunday because the interventionists should be on leave and there were fewer staffs in RCH. These

factors made intervention to be implemented on Saturday and Sunday not feasible. The frequency and duration varied among groups. For example, participants in Group 2D1W received acupressure twice a day for one week. To conduct the intervention, the interventionist first identified the acupoints. The acupoint identification method used was based on two textbooks (Cheng, 2003; WHO Regional Office for the Western Pacific, 2008). The acupressure sessions were conducted by two interventionists who were trained laypeople without prior formal TCM training (e.g. certificate courses of TCM, degree in TCM). The two interventionists were undergraduate students studying gerontology.

3.4.2.2 Quality assurance on interventionists

The two interventionists were trained by the TCM experts. All interventionists were instructed to communicate with the participants during the intervention only for the purpose of the study (e.g. explanation of the procedure, instruction for positioning, sensation check against the acupressure). They were instructed to minimize conversations unrelated to the implementation of acupressure with the participants. Upon requests of care by the participants, interventionists were instructed to refer them back to the nursing home staffs.

Both interventionists attended an 8-hour training course consisting of one lecture and two skills workshops provided by the two TCM experts who were involved in the Delphi process of this study. After the training, all interventionists attempted the skill test administered by one of the six members of the TCM expert panel. The test contents included correct identification of the acupoints (e.g. skills

in identifying landmarks and the *deqi* sensation) or non-acupoints, and acupressure techniques (e.g. skills in sustaining the pressure by fingers) or non-acupoints pressing techniques. Interventionists using the acupressure protocol and the sham protocol attended the training separately in order to ensure that they were blinded to the nature of the protocols. The skills were performed on both elderly volunteers and the trainer (i.e. one of the six members of the TCM expert panel). The interventionists passed the test when the skills performed on both the elderly volunteer and the trainer were observed and felt by the trainer to be up to standard. The standard made reference to the skills checklist, which was validated by the TCM expert panel in this study with a content validity index (CVI) of 1.0.

The skills of all the interventionists were monitored in the skill evaluations provided by the research team at the regular monthly meetings. The quality of the intervention in the field was also monitored on an on-going basis. Each interventionist was monitored at least once in each site and once a month at the regular meeting.

3.4.2.3 Data collection

At the baseline, demographic data such as age, gender, length of stay in the RCH, number of psychotropic drugs used, and number of co-morbidities were collected. Level of functioning using the modified Barthel Index Chinese version (mBI) (Leung et al, 2007) and cognitive function using the Mini-Mental State Examinations Cantonese version (MMSE) (Chiu et al, 1994) were collected.

Throughout the study period, as shown in Figure 3.7, the outcome variables were measured weekly, from the baseline week until four weeks after completion of the intervention. Since the duration of the intervention varied among groups, the times of data collection in different groups also varied. All the data was collected by trained research assistants who were registered nurses or nursing students. Details of data collector training will be reported later in section 3.4.2.6.

Groups	Weeks								
	0	1	2	3	4	5	6	7	8
2D1W	x	x	x	x	x	x			
1D1W	x	x	x	x	x	x			
2D2W	x	x	x	x	x	x	x		
1D2W	x	x	x	x	x	x	x		
2D3W	x	x	x	x	x	x	x	x	
1D3W	x	x	x	x	x	x	x	x	
2D4W	x	x	x	x	x	x	x	x	x
1D4W	x	x	x	x	x	x	x	x	x

Figure 3.7. Intervention period and outcome measurement period in different groups; x=data collection; shaded=intervention

3.4.2.4 Primary outcome - agitation

Agitation level was measured by the Hong Kong version of the CMAI for nursing homes (Lai, 2010) and data was collected weekly. The psychometric properties of the CMAI were good when used on PWD in Hong Kong. The internal consistency was high (Cronach's α = 0.83). The content was valid (CVI = 0.86) and the inter-rater reliability good (ICC: 0.82). These factors all favored the

feasibility and comparability of using the CMAI in an interventional study. The instrument is shown in Appendix 1.

The CMAI (Lai, 2010) comprises 21 items with 4 sub-scores reflecting four constructs in the concept of agitation: verbally non-aggressive behaviors (VNAB), verbally aggressive behaviors (VAB), physically non-aggressive behaviors (PNAB), and physically aggressive behaviors (PAB). Each item can be scored from 1 to 8 to reflect the frequency of the particular agitated behavior item. The total score is a summation of the frequency scores of all agitated behaviors, and ranges from 21 to 168, with higher scores reflecting higher levels of agitation. The scale can be used by a trained researcher to interview caregivers (Lai, 2010). The observed period of the agitated behaviors was set to be week of the designated time point. CMAI assessments were conducted once weekly on every Saturday or Sunday in the designated weeks.

3.4.2.5 Secondary outcome - stress

Stress level was measured by salivary cortisol (SC) in this study. The following discusses the rationales, data collection procedures, and methods of analysis.

Rationales

For the PWD, perceived stress may not be validly retrieved by asking them questions because of their cognitive impairment. Other measurements should be considered. When we are under stress, our body mostly evoke physiological response to stressor that HPA axis plays an important role, despite the fact that the

extent of response can vary because of many factors (e.g. variations between older people on central glucocorticoid receptor expression). Cortisol as an end-product of the HPA axis may theoretically reflect the HPA activity extent in response to stress (Arsenault-Lapierre et al, 2012). In this study, it is hypothesized that the extent of stress can be estimated by tracking the change of basal cortisol level. Basal cortisol level reflects the change of stress better and it is defined as a fixed time of sample collection to reduce the impact of diurnal variation in cortisol level and other factors (Henckens et al, 2015). Therefore, the basal cortisol level was used as a physiological marker (i.e. a proxy measurement) for stress in this study.

It is because stress and cortisol is a complex interplay of neurobiological events. Cortisol level varies throughout the day and it is affected by many factors apart from stress. These factors other than stress include HPA axis sensitivity, gender and age (Hellhammer et al, 2008). Given that this study aimed at comparing the change of stress before and after acupressure, these factors are more or less comparable before and after the acupressure for a short period of time. Yet, several methodological factors may also affect the level of cortisol. These factors include but limited to stress induced by sample collection (e.g. venipuncture), time of collection, cortisol awakening response, exercise, eating, post-collection sample contamination (Hellhammer et al, 2008; Kudielka et al, 2009; Woods & Mentes, 2011).

In order to obtain collect stress-free sample, salivary cortisol was measured instead of plasma cortisol. Salivary cortisol was measured also because it makes the measurement for the agitated older people with dementia more feasible. Free

cortisol which is unbound to carrier protein can enter the body fluid from blood through passive diffusion so that it is possible to measure the free cortisol level in all fluids including saliva (VanBruggen et al, 2011). Saliva carries approximately 10% of the total cortisol present in plasma (Schwartz et al, 1998) and salivary cortisol reflects serum cortisol well. In a validation study of a healthy elderly cohort, the correlations between serum and salivary cortisol levels over a day were all significant ($r = 0.54\text{-}0.96$) (Reid et al, 1992). Salivary cortisol therefore is an accepted measure used to assess unbound cortisol (Weibel, 2003) and stress (Hellhammer, 2009).

Cortisol secretion typically follows a diurnal rhythm, which is characterized by a peak after waking followed by a decline in level throughout the day and similar pattern is also observed in PWD (Woods et al, 2008). Cortisol awakening response describe a physiological phenomenon that there is a sharp increase of cortisol level after awakening, peaked at around 30 minutes, and its level gradually return to baseline approximately 60 minutes post-awakening (Fries et al, 2009; Clow et al, 2010). As a result, the cortisol level varies throughout the day normally. Given that this study aimed at identifying chronic stress reflected by basal cortisol level, sample is the best to be collected at the fixed time point at the baseline which is better to be in the morning, 60 minutes after awakening, and before eating and exercises.

Despite the fact that cortisol does not only respond to stress but affected by many confounding factors such as personal characteristics and methodological considerations, is still regarded as moderately associated with stress (Hellhammer

et al, 2009). Yet, the methodological consideration should be well adjusted in order to use salivary cortisol to track the change of stress. Therefore, salivary cortisol was used to measure as a proxy of stress in this study.

Data collection procedures

Saliva samples were collected using the Salimetrics® Oral Swab (SOS). The SOS was held in the oral cavity of the participant for two to five minutes. Collected saliva samples were kept in Salimetrics® storage tubes and frozen at or below -20^{o}C within two hours. During transportation, the samples were kept in an insulated container with ice packs.

Salivary samples were collected on twice weekly on two consecutive days (i.e. Saturday and Sunday) of the designated weeks. The two values of samples were averaged to represent the SC level reading of a participant in a particular week. Given that cortisol level can be affected by many uncontrollable factors of the participants (e.g. activities and psychological/physical conditions), using two averaged samples collected on two consecutive days aimed at minimizing the variances other than stress as suggested in a study (Woods & Mentes, 2011).

In the nursing home, the activities, breakfast, and wakeup time was tightly structured. Residents in the RCH in Hong Kong were usually waken up at approximately 06:00 for the morning round (e.g. face washing, toileting, and oral care). All salivary samples were collected in the morning at 07:00-08:00 (i.e. at least 60 minutes after waking) before oral care, breakfast and all forms of activities (e.g. morning exercise). These saliva collection specifications aimed at minimizing

the variances contributed by diurnal cortisol secretion pattern, cortisol awakening response, and other factors which were reported in studies (Kudielka et al, 2009; Hellhammer et al, 2009; Woods & Mentes, 2011; Kovach et al, 2011; Woods et al, 2011) to be able to possibly alter the cortisol secretion and analysis accuracy.

Methods of analysis

On the day of analysis, the saliva samples were thawed at room temperature and centrifuged at a rate of 3000 rotations-per-minute for 15 minutes to extract the saliva for enzyme-linked immunosorbent assay (ELISA). The ELISA was performed by me under direct supervision of a registered medical laboratory technologist, who had both bachelor and master degrees in medical laboratory science and was studying his doctoral degree. The data collection, storage, and analysis procedures followed the manufacturer's guidelines (Salimetrics, 2008; Salimetrics, 2014). The This kit requires 25 micro-liters of saliva and has a sensitivity of less than 0.003 µg/dL and a calibration range of 0.012 µg /dL – 3.000 µg /dL. Coefficient of variation (CV) equals 6.41% across 12 tests and intra-assay variability CV equals 3.65% (Woods et al, 2011). These figures indicate that this kit is highly reliable.

3.4.2.6 Quality assurance on data collection

Each data collector also attended an 8-hour training course consisting of one lecture and two skill workshops provided by the researcher. All data collectors were trained by the researcher according to the data collection guideline of the study, as shown in Appendix 5. This was designed with reference to all of the

original instruction manuals of the instruments. This training was intended to ensure compliance with the study protocol.

After the training, data collectors passed the test if they collected data on both the elderly volunteer and the researcher up to a certain standard. The standard was that they collected the data on the elderly volunteers and other data collectors with 100% accuracy with reference to the data collection guideline of this study as rated by the researcher, as well as demonstrating good inter-rater reliability (i.e. IRR=1.0) on each questionnaire with the researcher.

The skills of all data collectors were monitored in the skill evaluations provided by the research team at the regular monthly meetings. The quality of the data collection in the field was also monitored on an on-going basis. Each data collector was monitored at least once in each site and once a month at the regular meeting.

Each time the data collection was monitored, each data collector took turns collecting a complete set of data (i.e. clinical data, CMAI, and salivary samples) at baseline on the study participants in the field or the researcher/other data collectors at the regular meeting. For the saliva sample collection, each collector was observed by an assessor while conducting saliva sampling. The assessor was either the researcher or a fully trained research team member. The assessor rated whether the data collectors conducted the procedures as depicted in the data collection guideline of the study, as shown in Appendix 5 with reference to the saliva collection instructions provided by the manufacturer (Salimetrics, 2008).

For data collection using questionnaires, each data collector took turns collecting a complete set of data by questionnaires, while all of the other data collectors observed the data collection procedures and filled out the same set of questionnaires. All data was then compared among the data collectors for whether the findings were the same. Inter-rater reliability was then constructed on each questionnaire. Discrepancies were discussed and methods for consensus on data collection and interpretation were made afterwards until all the issues caused by the discrepancies were resolved and inter-rater-reliability index reached 1.0.

Remedial training sessions were provided on site or in the regular meeting if skills were observed that deviated even slightly from the research protocol. Uncollected data due to various reasons such as drop-out or withdrawal were recorded until completion of the study.

3.4.2.7 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 20 for Windows software (IBM Corp, 2012). The results of continuous data were presented as mean with standard deviation or median with inter-quartile range (IQR). Results of the nominal data were presented as frequency with percentage. Because of the small sample size, non-parametric tests were used for comparison. The median differences of the outcomes (i.e. the difference between a reading at an interval and at the baseline) of all groups were reported in order to identify the peak effect occurring interval. At the peak effect occurring interval, the median changes of the outcomes (i.e. the difference between the reading at the peak effect occurring

interval and at the baseline) were compared among groups by duration and frequency. Continuous data were compared between groups using the Kruskal-Wallis test, the Wilcoxon signed-ranks test, and the Mann-Whitney U test. Significance was defined as $p < 0.05$ with a two-sided test. Missing data were replaced by the last-observation-carried-forward principle (Portney & Watkins, 2009).

3.4.2.8 Ethics

Written informed consent by proxy and assent from the potential participant were obtained before they were formally admitted to the study. After consent had been obtained, baseline data collection started. This pilot study was approved by the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University (application number: HSEARS20120920001) as a part of the main study.

3.4.3 Procedures

In the three RCHs that agreed to participate, 403 residents were screened for eligibility and 368 did not meet the eligibility criteria. The remaining 35 residents were found eligible and were contacted one by one. Ten eligible residents declined to participate, either themselves or via their families. Finally, 25 eligible residents were recruited to give a recruitment rate of 6.2%. These 25 eligible residents were non-randomly allocated into groups. Twenty-four participants completed the intervention and one participant in the 3W1D group discontinued

the intervention without giving a reason. This single case of withdrawal gave an attrition rate of 4%. The flow of participants is shown in Figure 3.8.

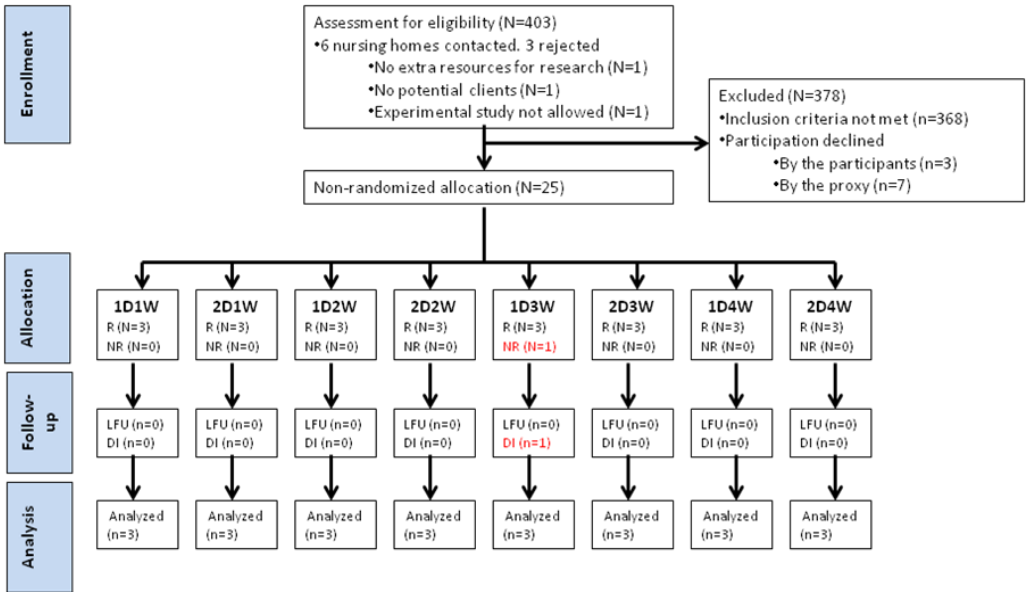


Figure 3.8. Participants flow chart. R=received acupressure; NR=did not receive acupressure; LFU=lost to follow up; DI=discontinued intervention

3.4.4 Results

This section will report the demographic and clinical data at baseline, feasibility issues on saliva sample collection and acupressure implementation, the effect change of acupressure on agitation and stress over time, and the efficacy of different doses of acupressure.

3.4.4.1 Demographic and clinical data at baseline

As shown in Table 3.9, the mean age of the 24 participants was 82.83 (SD: 6.94). The majority (n=18) were female (75%). The mean length of stay in the

RCH was 33.08 months (SD: 20.94). The mean MMSE score was 6.61 (SD: 6.32), the mean mBI score was 20.83 (SD: 24.13), and the mean CMAI score was 43.67 at baseline (SD: 10.57). The majority of the subjects were taking one to three psychotropic drugs at baseline (75%).

Table 3.9

Demographic and clinical data at baseline

Characteristics	No. of participants (N=24)
Age, mean years (SD)	82.83 (6.94)
Gender, n (%)	
Female	18 (75)
Male	6 (25)
LOS in RCH, mean months (SD)	33.08 (20.94)
*MMSE, mean (SD)	6.61 (6.32)
mBI, mean (SD)	20.83 (24.13)
CMAI, mean (SD)	43.67 (10.57)
No. of psychotropic drugs used, n (%)	
0	2 (8.33)
1-3	18 (75)
4-6	4 (16.67)

* Only 23 participants completed the MMSE, because one participant refused

RCH=residential care home; MMSE=mini-mental state examination; mBI=modified Barthel index; CMAI=Cohen-Mansfield Agitation Inventory

3.4.4.2 Feasibility issues

Valid salivary sample return rate

For the saliva sample collection as shown in Figure 3.9, out of the 24 subjects with twice-weekly repeated measurements, 360 salivary cortisol samples were expected to have been collected. However, 161 samples were either not collected or excluded. Some samples were not collected because participants refused to give

a saliva sample. Others were excluded because the returned saliva collecting swabs contained no saliva samples even after an adequate period in the oral cavity as stipulated by the Salimetrics® saliva collection guideline (Salimetrics, 2008). The remaining 199 samples completed the ELIZA chemical analysis. Of these, seven were discarded, five because the salivary cortisol level exceeded 3.0 µg/dL due to possible contamination based on the manufacturer's protocol, and two because of duplicate labeling. In the end, 192 saliva samples were appropriate for data analysis. The rate of valid SC data returned was 53.33%.

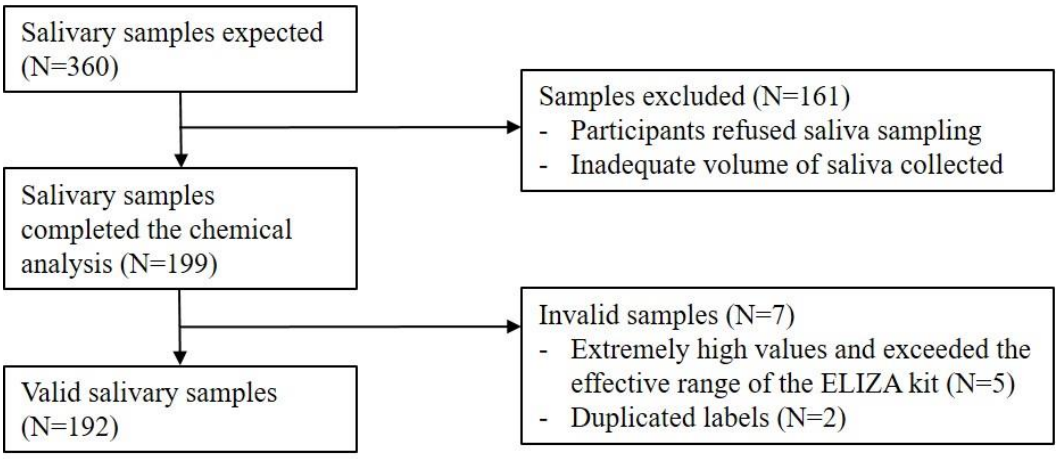


Figure 3.9. Flow chart of valid salivary samples collected

As mentioned above, some participants yielded very small saliva samples because of their persistent dry mouth (n=4 participants) or consistent refusal (n=2 participants). They yielded less than 10 percent of the expected number of saliva samples, and no saliva could be collected at the baseline. Their samples were excluded from data analysis (8 salivary samples from 6 participants). The salivary

cortisol data of 184 salivary samples from 18 eligible participants were used for data analysis, as shown in Figure 3.10.

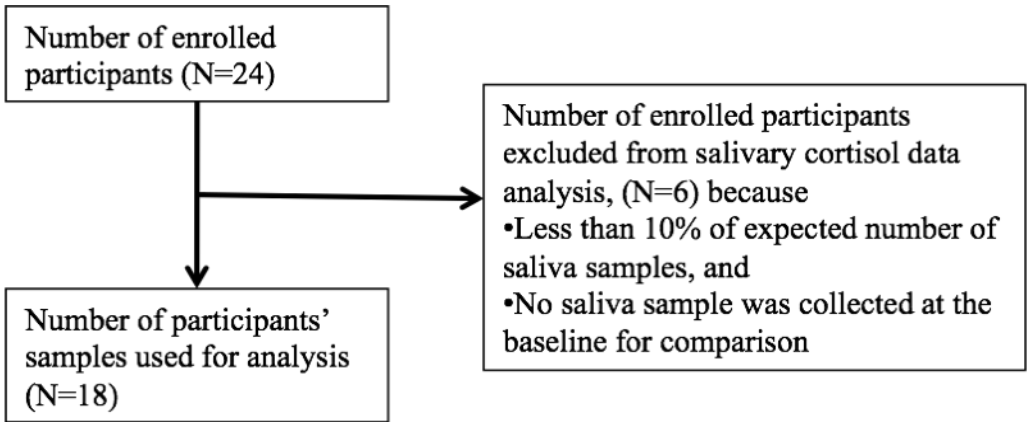


Figure 3.10. Participants giving valid salivary sample selection flow chart

Compliance with the intervention protocol

In this study, it was expected that 450 sessions of acupressure would be provided to the 24 participants in eight groups. Fifty-four sessions were not conducted because participants were not available when the interventionists visited them (e.g. medical appointment or family gathering), or participants or their families occasionally refused due to episodic bad mood, transient illnesses, or hospitalization of participants. There were 396 sessions completed with a compliance-by-session rate of 88.0%.

Participants were regarded as having complied with the intervention only if they had completed 80% or more of the expected number of sessions. Nineteen out of 24 participants complied. The compliance-by-participant rate was 79.2%.

3.4.4.3 Effect change over time on agitation and stress

On agitation as measured by CMAI

The pattern of changes in agitation for all groups over time is shown in Table 3.10 and Figure 3.11. In the first week after the commencement of acupressure, agitation was reduced markedly. This effect diminished in weeks 2 and 3, and surged again in weeks 4, 5 and 6. The effect diminished gradually after week 6 and tailed off in week 8. The peak effect was observed in week 5. The reduction of median CMAI score was significant in weeks 1 (median difference=-9.0, p <0.001), 4 (median difference=-9.0, p=0.001), 5 (median difference=-9.5, p<0.001), and 6 (median difference=-8.0, p<0.001).

Table 3.10

Changes in median CMAI score in all groups over time

Week	N	Median CMAI (IQR)	Median change in CMAI c/w baseline (IQR)	Statistics+
1	24	31.00(15.25)	-9.00(1.25)	p<0.001*
2	24	41.50(20.00)	-3.50(14.00)	p=0.401
3	24	43.00(16.75)	-3.00(12.00)	p=0.258
4	24	29.00(13.25)	-9.00(16.00)	p=0.001*
5	24	30.00(13.25)	-9.50(14.25)	p<0.001*
6	18	32.50(9.25)	-8.00(8.50)	p<0.001*
7	12	38.50(16.75)	-5.00(9.50)	p=0.056
8	6	44.50(19.25)	4.00(13.75)	p=0.463

*statistically significant, +by Wilcoxon Signed Ranks Test, IQR=inter-quartile range, CMAI=Cohen-Mansfield Agitation Inventory

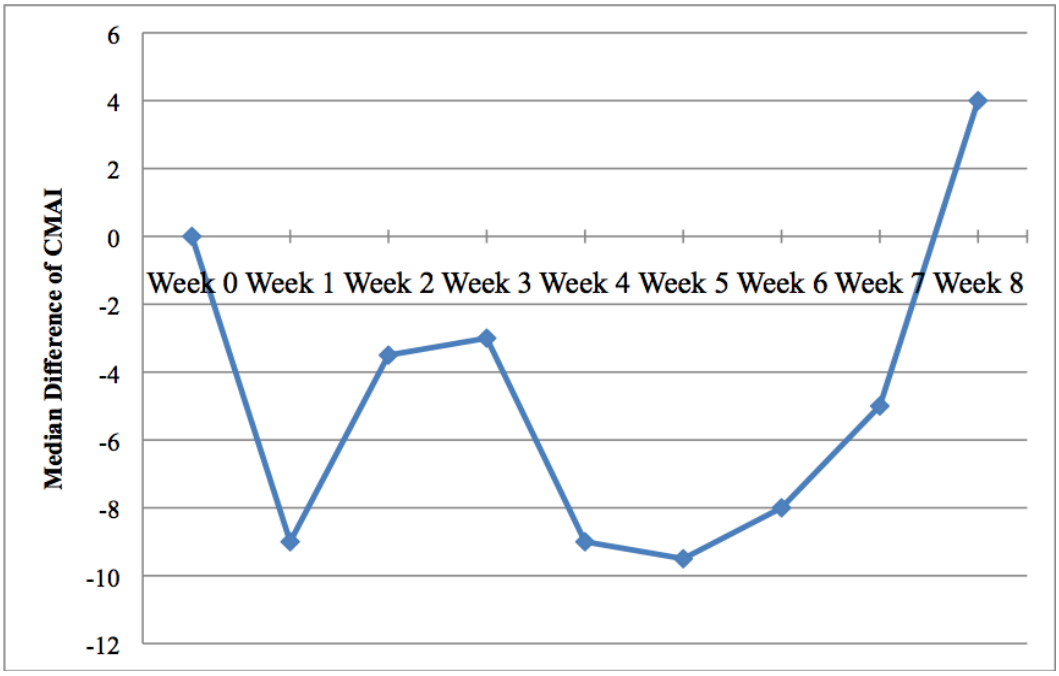


Figure 3.11. Graphical illustration of the changes in median CMAI score of all groups over time. CMAI=Cohen-Mansfield Agitation Inventory

On stress as measured by salivary cortisol (SC) level

The pattern of changes in SC level of all groups over time is shown in Table 3.11 and Figure 3.12. SC level was slightly reduced in the first week of acupressure. It was progressively reduced in weeks 2 and 3, and reached a trough in week 4, surging back markedly from weeks 5 to 7. It decreased again sharply in week 8. Reductions in median SC level were observed in most of the intervals except weeks 5 and 7. The reduction of median SC concentration was significant in weeks 1 (median difference=-0.08μg/dL, p =0.011) and 4 (median difference=-0.30μg/dL, p=0.010).

Table 3.11

Changes in median salivary cortisol level (μg/dL) in all groups over time

Week	N	Median SC level (IQR)	Median change in SC level c/w baseline (IQR)	Statistics[+]
1	18	0.48(0.33)	-0.08(0.31)	p=0.011*
2	18	0.44(0.33)	-0.07(0.44)	p=0.227
3	18	0.45(0.39)	-0.11(0.66)	p=0.298
4	18	0.38(0.22)	-0.30(0.64)	p=0.010*
5	18	0.44(0.54)	0.01(0.47)	p=0.492
6	13	0.49(0.29)	-0.02(0.24)	p=0.421
7	10	0.68(0.35)	0.07(0.60)	p=0.683
8	5	0.43(0.88)	-0.33(1.815)	p=0.500

*statistically significant, +by Wilcoxon Signed Ranks Test, IQR=inter-quartile range, SC=salivary cortisol

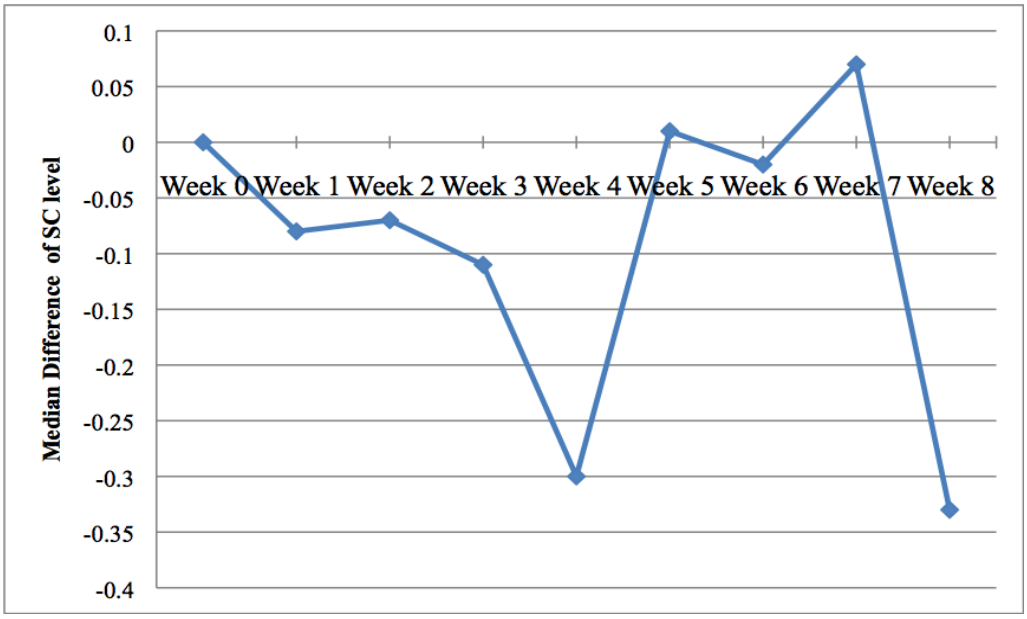


Figure 3.12. Graphical illustration of the changes in median SC level for all groups over time. SC=salivary cortisol

3.4.4.4 Efficacy of the acupressure at various doses

The efficacy of the acupressure at various dosages was compared among groups by factors (i.e. duration and frequency) at the peak effect occuring interval. Peak effect was observed for agitation (as measured by CMAI) in week 5 and for stress (as measured by SC) in week 4.

Comparison among various dosages for the primary outcome – CMAI

Changes in CMAI score compared with the baseline were significantly different in the 1-week (median difference = -11.5; p=0.046) and 2-week groups (median difference = -14; p=0.026) as shown in Table 3.12, and more significant (i.e. a smaller p-value) in the 2-week group than in the 1-week group. There were no significant differences among the other groups (i.e. the 3-week and 4-week groups).

Table 3.12

Changes in CMAI score in week 5 compared with baseline for the four groups of different durations

Groups by duration	N	Median CMAI (IQR)	Median change in CMAI c/w baseline (IQR)	Statistics[+]
1 week	6	27.00 (12.00)	-11.50 (14.00)	p=0.046*
2 weeks	6	27.50 (13.25)	-14.00 (5.75)	p=0.026*
3 weeks	6	33.00 (20.50)	-16.50 (32.75)	p=0.116
4 weeks	6	38.00 (17.25)	-1.00 (14.00)	p=0.463

*statistically significant, + by Wilcoxon Signed Ranks Test, IQR=inter-quartile range, CMAI=Cohen-Mansfield Agitation Inventory

Changes in CMAI score compared with the baseline were significantly different in groups receiving the intervention once (median difference = -12.00; p = 0.019) or twice a day (median difference = -9.00; p = 0.005), as shown in Table 3.13, and the reduction was more significant (i.e. a smaller p-value) in the twice-a-day group than in the once-a-day group.

Table 3.13

Changes in CMAI score in week 5 compared with baseline for the two different frequency groups

Groups by frequency	N	Median CMAI (IQR)	Median change in CMAI c/w baseline (IQR)	Statistics[+]
Once a day	12	30.00 (19.25)	-12.00 (16.75)	p=0.019*
Twice a day	12	31.00 (13.50)	-9.00 (20.5)	p=0.005*

*statistically significant, +by Wilcoxon Signed Ranks Test, IQR=inter-quartile range, CMAI=Cohen-Mansfield Agitation Inventory

Comparison among various dosages for the secondary outcome – SC level

As shown in Table 3.14, there were no significant differences in SC concentration between the baseline and week 4 in the once-a-day group. However, there was a significant difference in SC concentration in the twice-a-day group (median difference = -0.37μg/dL; p = 0.015).

Table 3.14

Changes in SC level (μg/dL) in week 4 compared with baseline for the two different frequency groups

Groups by frequency	N	Median SC level (IQR)	Median change in SC level c/w baseline (IQR)	Statistics[+]
Once-per-day	9	0.40 (0.26)	-0.02 (0.49)	p=0.314
Twice-per-day	9	0.34 (0.29)	-0.37 (0.73)	p=0.015*

*statistically significant, +by Wilcoxon Signed Ranks Test, IQR=inter-quartile range, SC=salivary cortisol

3.4.5 Discussion

The findings from the pilot study provided important references for the subsequent main study in terms of sample size estimation and recruitment strategies, optimal acupressure dosage to be used, time points for measuring outcomes, and data collection and intervention implementation strategies. These issues will be discussed below.

3.4.5.1 Sample size estimation and recruitment strategies

The effect size in this pilot study ranged from 0.58 to 1.03 (the Cohen's d). This was lower compared with a previous study in which the Cohen's d was 1.71 (Yang et al, 2007). This could be because the baseline agitation level was lower in this study (CMAI mean: 43.67) compared with that of Yang and colleagues (CMAI mean: 79.3). Attrition in this study was 4%, lower than in a previous study that reported 10% attrition (Lin et al, 2009). This could be because the duration of the intervention in many groups was shorter compared with that in Lin and colleagues' study (2009). The recruitment rate was not reported in earlier studies. In this study, 25 eligible participants were successfully recruited from a screening

of 403 residents in three nursing homes, and the recruitment rate in this pilot study was therefore 6.2%.

These findings had a few implications for the subsequent RCT. The first is related to sample size estimation. This pilot study found that the effect size was much smaller than that reported in the previous study (Yang et al, 2007). To be conservative, the lower effect size (i.e. Cohen's d=0.58-1.03) was used to estimate for the sample size of the subsequent RCT. Second, attrition in this study was lower than that reported in the previous study (Lin et al, 2009). Again, to be conservative, a larger attrition rate (i.e. 10%) was used to estimate the sample size of the subsequent RCT. Third, the recruitment rate was noted to be only 6.2%. This figure was used to estimate the number of RCH that needed to be invited in order to achieve the target sample size.

3.4.5.2 Optimal acupressure dosage estimation

This study found that relatively shorter duration (i.e. one or two weeks) and higher frequency interventions (i.e. twice a day) showed a more significant difference in effect. There were 396 sessions completed (i.e. 88%) and 19 participants completed over 80% of expected sessions out of 24 participants in all groups (i.e. 79.2%). Some sessions were missed for various reasons (e.g. family gatherings, medical appointments, or hospitalization). The shorter duration of treament may favor better compliance. Based on this study's findings, it was recommended to administer acupressure twice a day for two weeks for optimal results in the subsequent RCT.

3.4.5.3 Outcome measurement time points

For the primary outcome (i.e. agitation), the peak effect was observed at week 5 and tailed off completely by week 8. In order to capture the peak effect in the subsequent RCT, outcomes should be measured at week 5 and the delayed effect at week 8 after commencing the intervention.

3.4.5.4 Data collection and intervention implementation strategies

In this study, almost half of the SC samples could not be collected because of dry mouth in the elderly. Hydration is the most important factor influencing saliva production (de Almeida et al, 2008). In the main study, it was therefore necessary to ensure that participants were well hydrated in order to perform successful saliva collection.

Refusal of saliva collection was consistent over time among certain participants. Experience and skills in sampling saliva from agitated PWD were accumulated from the pilot study. For example, saliva sampling should involve the formal caregivers who closely take care of the residents. Saliva sampling should be completed quickly enough to avoid collecting saliva at breakfast time, because residents prefer to eat than to cooperate with saliva sampling during breakfast. These strategies were used by data collectors in order to reduce the number of saliva samples that could not be collected in the main study.

The participant compliance rate was satisfactory (79.2%). Missing sessions were mainly due to participants' episodic illness and mood change. One participant

refused more than half of the expected sessions. Clear explanations to both potential participants and their families, and care in obtaining consent from potential participants during recruitment were thus found to be important in improving compliance among the recruited subjects. All eligible subjects received short testing sessions of acupressure in order to prevent multiple refusals of acupressure sessions in the study, but some strongly disliked the sensation of acupressure. If eligible subjects strongly refused the short testing sessions, they should not be recruited in order to reduce the possible attrition.

3.5 Summary

The development of the study followed the MRC guideline of 2008. Three methods were used to develop the study, namely a literature review, Delphi technique, and a pilot study. These three methods were purposefully performed in sequential order in order to make use of the evidence generated from one stage to inform the purposes and procedures of the next.

A literature review was used to identify the theories and evidence. Four theories and hypotheses were identified to explain why acupressure could lead to a reduction of agitation in people with dementia. These theories and hypotheses included the stress hypothesis, tactile stimulation hypothesis, progressively lowered stress threshold model, and TCM meridian theory. These theories and hypotheses co-constructed that acupressure may directly reduce agitation by rectifying the *zangfu* imbalance and indirectly reducing agitation by lowering stress to a level to below the stress thresholds of the PWD.

Delphi technique was used to develop the intervention protocol by seeking consensus from an expert panel. The Delphi process identified a standardized protocol with high level of agreement on all the intervention ingredients. However, the Delphi process also found that the frequency and duration of the intervention protocol could not be determined by the expert panel's consensus.

A pilot study was used to test the procedures and estimate the subsequent main study. The pilot study identified evidence needed to guide the main study in terms of sample estimation and recruitment strategies, optimal dosage selection, outcome measurement intervals, and data collection and intervention implementation strategies.

Using the evidence generated by these three stages, an evidence-based acupressure protocol and study procedures were identified. These acupressure protocol and study procedures were now ready for use when the researcher attempted to answer the research questions.

Chapter 4 The Main Study

This chapter discusses the formulation of testable research questions in the areas where evidence was lacking and which attracted my interest. An outline of the method of using an RCT to answer the research questions is then presented.

4.1 Research Questions

This study attempted to answer the following questions:

1. Will acupressure reduce the agitation level of agitated nursing home residents with dementia over time as compared with the control conditions?
2. Will acupressure reduce the stress level of agitated nursing home residents with dementia over time as compared with the control conditions?
3. If acupressure reduces agitation in nursing home residents with dementia, will the agitation-reducing effect of acupressure be mediated by stress?
4. If acupressure reduces agitation and stress in nursing home residents with dementia, will the effect of acupressure on reducing agitation and stress be sustained over time?

4.2 Methods

4.2.1 Design

This study employed the design of a randomized controlled trial (RCT), as shown in Figure 4.1. Participants were randomly allocated into three parallel groups in a 1:1:1 ratio: the acupressure group, the sham group, and the usual-care

group. The intervention was the acupressure protocol, while the controlled conditions were the sham and usual care. The intervention lasted for two weeks. Outcomes were measured at the baseline (i.e. T_0), and at the 3rd (i.e. T_1), 5th (i.e. T_2), and 8th (i.e. T_3) weeks after the commencement of the intervention. All the data was collected by trained research assistants who were registered nurses or nursing students. Training of data collectors will be reported later in the section

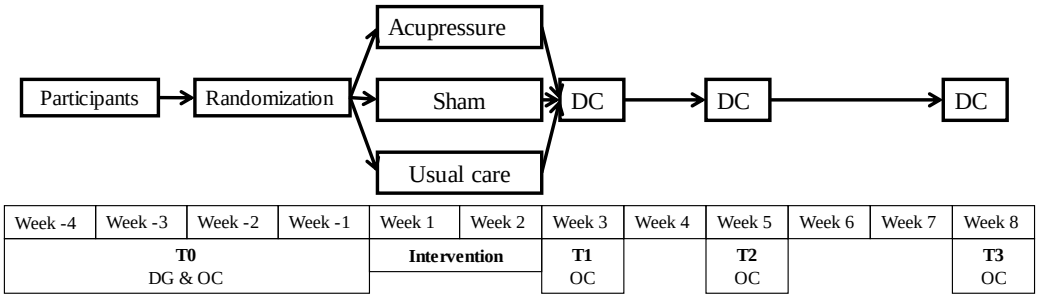


Figure 4.1. Design of the RCT. Acupressure=acupressure protocol lasted for two weeks; sham=sham protocol lasted for two weeks; usual care=usual care lasted for two weeks; DC=data collection; T0=baseline; T1=the 3rd week after the commencement of the intervention; T2=the 5th week after the commencement of the intervention; T3=the 8th week after the commencement of the intervention; DG=demographic/clinical variables; OC=outcome variables

4.2.2 Sample

4.2.2.1 Sample size estimation

According to the pilot study and the previous similar studies (Yang et al, 2007; Lin et al, 2009), sample size was estimated by priori power analysis using G*Power. With assumptions (i.e. α =0.05, power=0.8, three groups, within-between interaction effect), estimated effect size (i.e. f=0.14) and attrition rate (i.e. 10%), the total number of participants needed to demonstrate a significant

interaction effect among three groups in a randomized controlled trial was 99. Thirty-three participants were thus needed for each group.

4.2.2.2 Sampling and recruitment procedures

This study employed the probability cluster sampling method (Portney & Watkins, 2009). One RCH was regarded as a cluster. The sampling frame was constructed from the list of RCHs registered under the Social Welfare Department (2013). The RCHs were only put in the sampling frame if they were eligible for this study. The eligibility criteria for RCHs were that they had more than 100 beds and they provided beds for moderately or severely functionally impaired elders (i.e. they had to be care and attention or nursing homes). Invitation letters were sent to all eligible RCHs in Hong Kong and followed up by telephone calls. From the list of RCHs who were interested and eligible to participate, a target number of RCHs (or clusters) were randomly selected.

The targeted number of RCHs provided a sufficient number of participants with reference to the estimations of recruitment rate and sample size of the study. Given that all eligible RCH should have at least 100 participants, the eligible RCH might have more than 100 participants. Assuming that there were 150 residents in each participating RCH on average and the recruitment rate was 6.2% as estimated from the pilot study, 111 participants would need to be recruited from 12 RCHs. These 111 participants from the 12 RCHs could provide the necessary number of participants, which was 99. Therefore, we randomly selected 12 eligible RCHs out of the list of eligible RCHs that showed an interest in participating in this study.

4.2.2.3 Eligibility criteria

This study used almost the same eligibility criteria as the pilot study, except that it added the exclusion criterion of having received acupuncture/acupressure within eight weeks prior to the day of recruitment. The reason for excluding people who had received acupuncture/acupressure was that any effects from the previous sessions of acupuncture/acupressure might carry forward to the study period, contaminating the true effects of the acupressure protocol being examined in this study. Eight weeks were used because it was observed in the pilot study that the effect was not observable eight weeks after commencement of the acupressure. Details of the eligibility criteria are given in section 4.3.2.4.

4.2.3 Setting

This study was conducted in residential care homes (RCH). In Hong Kong, there are four types of RCH for older people registered under the licensing system of the Hong Kong Social Welfare Department all of which provide beds that are fully or partially funded by the government. The four types are hostels for the elderly, homes for the aged, care and attention homes for the elderly, and nursing homes. This categorization was made according to the functional level of the residents. The older people with the highest functional level reside in hostels for the elderly, while those with the lowest level reside in nursing homes. Older people who are eligible to be admitted to hostels for the elderly and homes for the aged have no or only a mild impairment level in functioning, while those who are eligible for admission to the care and attention and nursing homes have moderate

to severe impairment levels in functioning under the Standardized Care Need Assessment Mechanism for Elderly Services (Hong Kong Social Welfare Department, 2014).

In this study, only residents in care and attention homes for the elderly and nursing homes were recruited. This was because residents in these two facilities were generally more functionally and cognitively impaired, therefore more residents with dementia were likely to be recruited from these homes.

4.2.4 Interventions

There were two types of intervention in this study: acupressure and the control conditions. There were also two control conditions: sham and usual care. They made up of three groups for testing. The following gives details on how these three groups were operated. To ensure the quality of the study during the study period, some training and monitoring was provided to interventionists. The quality assurance for the measures also reported below.

4.2.4.1 Acupressure

The acupressure protocol used in this study was similar to that used in the pilot study, as discussed in section 3.4.2.1. The use of acupoints and techniques were discussed earlier and are shown in Table 3.7. The only differences were that we used twice a day (i.e. AM sessions at 08:00-12:00, PM sessions at 14:00-18:00) as the frequency and two weeks (i.e. five days per week, from Monday to Friday) as the duration. As explained above, the frequency and duration used in the acupressure protocol were determined by the results of the literature review, the

experts' consensus, and the pilot study. Details of the intervention protocol are given in Appendix 2.

4.2.4.2 Control conditions – sham and usual-care

A "control" is a reference condition to be compared with the intervention in order to identify the intervention effect. An intervention is made up of many intervention components and its effect is always the result of combining all the intervention components. In order to examine the effect of an intervention, the effect of an individual component or a set of combined components have to be clearly defined in the design of an RCT (Collins et al, 2014). As mentioned above, I was also interested in the efficacy of the intervention components in acupressure, and this area had not been examined before. This study examined the effect of an individual component as well as that of a set of combined components.

The theoretically active component of acupressure was the activation of acupoints, as discussed before. However, at the time of activating the acupoints by acupressure, exerting tactile stimulation was unavoidable. We discussed earlier that tactile stimulation may possibly reduce stress, thereby in turn reducing agitation. In order to examine the effect of the theoretically active component of acupressure, a control condition of sham treatment was designed to theoretically comprise all the intervention components of the acupressure protocol except for the acupoint activation. In order to examine the effect of the acupressure as a set of combined components (i.e. acupoint activation, tactile stimulation, and other possibly unknown components), a control condition of usual care was designed. In

this study, two control conditions were designed: sham and usual care. The theoretical intervention components of the interventions in different groups are shown in Figure 4.2.

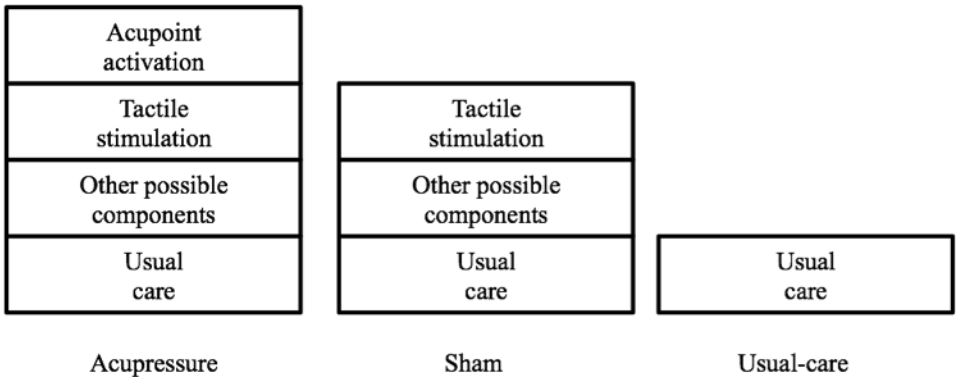


Figure 4.2. Theoretical intervention components of the interventions in different groups

Sham group

In this group, participants received a sham intervention following the sham protocol. This sham protocol was almost identical to the acupressure protocol except for the points on which the interventionists applied pressure. In the sham protocol, the interventionists applied pressure on non-acupoints. Theoretically, they provided the same kind of tactile stimulation without activating the acupoints. By comparing the acupressure group with the sham group, the effect of the intervention component of acupoint activation in the acupressure protocol could be identified. The non-acupoints were far away from all acupoints depicted in the abovementioned two textbooks (Cheng, 2003; WHO Regional Office for the Western Pacific, 2008) which were used to guide the identification of acupoints in

this study. The selection of non-acupoints also received complete agreement from the expert panel. The sham protocol is described in more detail in Appendix 3.

Usual care

In this group, participants received no added interventions. They only received the usual care provided by the RCH. For example, the RCH residents received basic personal care, participated in recreational activities, and received various activity programs provided by their individual nursing homes. Some agitated nursing home residents were put in physical restraints or on psychotropic drugs. The type of usual care given was not manipulated by the researchers.

4.2.4.3 Intervention quality assurance

Two laypeople were recruited as interventionists in the main study. Both of them had received some basic trainings for working as care assistants in nursing home before joining this study, had not received any formal TCM trainings, and had not participated in the pilot study. Selection of laypeople as interventionist without formal TCM training and without participating in the pilot study was because we intended to blind the interventionists against the protocol label (i.e. acupressure or sham). The training methods and standard are the same as that reported in the pilot in section 3.4.2.1.

One interventionist was trained according to the Acupressure Protocol as shown in Appendix 2 and another interventionist was trained according to the Sham Protocol as shown in Appendix 3. Each interventionist was responsible to

carry out only one protocol on the participants in this study. Each interventionist therefore carried out the intervention in all the nursing homes.

Each time the intervention implementation was monitored, the interventionists were observed by an assessor while performing acupressure on the study participants in the field or on the researcher in the regular meeting. The assessor was the researcher or a fully trained research team member. They had completed the training identical to the one provided to the interventionists by one TCM panel expert according to a skill checklist derived from the validated intervention protocol. The assessor rated the skill performance according to the skill checklist shown in Appendix 6 with reference to the acupressure protocol shown in Appendix 2. If the assessors have had questions, they would consult the research team with the presence of members from the TCM expert panel for clarifications. So as the remedial training could be planned accordingly.

The skill checklist of the acupressure protocol, as shown in Appendix 6, comprised 15 items, each with a possible score from 1 to 4. Higher scores indicated higher levels of appropriateness. The skill checklist of the sham protocol, as shown in Appendix 7, comprised 14 items with the same possible score for each item as that of the acupressure protocol. Interventionists passed the test if they performed the protocol 100% correctly as assessed by the trainer. To prevent fatigue, an interventionist was assigned to conduct acupressure for a maximum of 10 sessions per day, and adequate rest time between sessions was provided.

Remedial training sessions were provided on site or at the regular meetings if skills were observed that deviated even slightly from the research protocol. Undelivered interventions due to various reasons such as drop-out or withdrawal were recorded until completion of the study.

4.2.5 Measures

There were two types of measures in this study. They were outcome variables and variables of participants' characteristics. To ensure the quality of the study during the study period, some training and monitoring was provided to data collectors. The quality assurance for the measures also reported below.

4.2.5.1 Outcome – agitation and stress

There were two outcome variables (or dependent variables). The primary was agitation as measured by CMAI. The secondary was stress as measured by salivary cortisol.

Primary outcome - agitation

Agitation level was measured by the Hong Kong version of the CMAI for nursing homes (Lai, 2010) and data was collected weekly. The description of the CMAI psychometric properties have been given in the pilot study in section 3.4.2.4. CMAI assessments were conducted once weekly on every Saturday or Sunday in the designated weeks.

Secondary outcome - stress

Stress level was measured by salivary cortisol (SC). Salivary samples were collected on once weekly on either Saturday and Sunday of the designated weeks. One salivary sample was collected in the designated week instead of two as in the pilot study. It was because the variation between two consecutive samples were small in the pilot study with median difference of 0.16μg/dL (range:0.001-1.19) and strong correlation ($r=0.77$, $p<0.001$). For the rationales of using SC as a proxy measure for stress, procedures of data collection, and methods of analysis, they were the same as that in the pilot and were reported in section 3.4.2.5.

4.2.5.2 Participants' characteristics at baseline

There were two common reasons for profiling participants' characteristics. The first was to assess the comparability of the groups and the second was to assess the external validity of the trial results (Furler et al, 2012). Below is a discussion of the participants' characteristics that were collected. Participants' characteristics were categorized into demographic and clinical data. The demographic and clinical data were measured at baseline (i.e. T_0) before randomization, within a two-week period after recruitment but prior to implementation of the interventions.

The demographic data collected included gender, age, and duration of the nursing home stay. Clinical data included the cognitive function, functional status, number of chronic illness, physical restraint use frequency, family involvement level, and activity engagement level. Details of the demographic and clinical data collection at baseline are stated on the Demographic and Clinical Data Collection Form in Appendix 4.

Cognitive function

Cognitive function was measured by the Mini-mental State Examination (MMSE; Folstein et al, 1975), which is a brief cognitive test that takes less than 10 minutes to complete. It covers five domains of cognitive function: orientation, attention and calculation, recall, and visual construction. The MMSE has been translated into Chinese and validated in Hong Kong (Chiu et al, 1994). In the MMSE (Chiu et al, 1994), the possible score ranges from 0-30. The MMSE (Chiu et al, 1994) is reliable with high internal consistency (Cronbach's alpha = 0.86) and high inter-rater reliability (ICC = 0.99). The discriminant validity to distinguish people with normal cognitive function from the cognitively impaired is high (97.9% correctly classified).

Functional status

Functional status was measured by the modified Barthel Index (MBI; Shah, 1989). The MBI was translated and validated in Hong Kong (Leung et al, 2007). It covers a total of 10 types of activities of daily living (ADL): personal hygiene, bathing, feeding, toileting, walking stairs, dressing, bowel control, bladder control, walking, and transfer between bed and wheelchair. The score range is 0-100. Higher scores indicate a higher level of independence in performing ADL or functioning. The MBI is highly reliable, with high inter-rater reliability (kappa values 0.81-1.00) and high internal consistency (Cronbach's alpha = 0.93). It has good structural validity (two factor model explained 75.7% of total variance).

Use of psychotropic drugs

The psychotropic drugs inclusion criteria in the study made reference to a relevant study (Maguire et al, 2013). The criteria included all the drugs indexed in the British National Formulary (BNF) under the categories of hypnotics, anxiolytics, and antipsychotics.

Use of physical restraint

Physical restraint was defined as any device, material or equipment attached to or near a person's body which cannot be controlled or easily removed by the person and which deliberately prevents or is deliberately intended to prevent a person's free body movement to a position of choice and a person's normal access to their body (Retsas, 1998).

To measure the frequency of the physical restraint, a single-item five-point Likert scale was developed specifically for this study with a scale range of 0-4. Point 0 meant "never used", point 1 meant "rarely used", which was defined as used when needed and the resident was restrained for less than 10% of the day, point 2 meant "sometimes used", which was defined as the resident being restrained for less than 50% but more than 10% of the day, point 3 meant "often used", which was defined as the resident being restrained for less than 80% but more than 50% of the day, and point 4 meant "persistently used" and was defined as the resident being restrained for more than 80% of the day except on special occasions (e.g. for bathing).

There are many types of restraint and this Likert scale made reference to what was used in other studies (Hofmann & Hahn, 2014), including belt, limb holders,

bed restraint, chair restraint, over-chair table, sleep suits, special sheets, overalls, mittens, and tapes for restraint purposes. The data collectors of this study measured the participants' frequency of physical restraint use by reading their physical restraint charts with verbal clarification to the nurses in the nursing home.

Family visits

The family visit item was measured in terms of frequency. Family visits were defined as visits by family members only. Visits by volunteers and friends were not counted.

To measure the frequency of family visits, a single-item five-point Likert scale was developed specifically for this study with a scale range of 0-4. Point 0 meant "never visited", point 1 meant "less than once a week", point 2 meant "once or twice a week", point 3 meant "three to six times a week", and point 4 meant "more than six times a week". The data collectors of this study measured the participants' frequency of family visits by reading their family visit records with verbal clarification to the nurses in the nursing home.

Engagement in activities

Engagement in activities was measured by both frequency and duration per week. Activities were defined as those formally arranged by the RCH, only because other informal activities were not known by the formal caregivers working in the RCH.

To measure the frequency of activities, a single-item five-point Likert scale was developed specifically for this study with a scale range of 0-4. Point 0 meant "never participated", point 1 meant "less than once a week", point 2 meant the resident participated "once or twice a week", point 3 meant "three to six times a week", and point 4 meant "more than six times a week".

To measure the during of activities, a single-item five-point Likert scale was developed specifically for this study with a scale range of 0-4. Point 0 meant "never participated", point 1 meant "less than five hours a week", point 2 meant "five to nine hours a week", point 3 meant "ten to fifteen hours a week", and point 4 meant "more than fifteen hours a week".

The data collectors of this study measured the participants' frequency and duration of activities by reading their activity records with verbal clarification to the nurses in the nursing home.

4.2.5.3 Data collection quality assurance

Data collectors were trained research assistants who were registered nurses or nursing students. For the training for the research assistants, it was the same as that in the pilot study and reported in section 3.4.2.6.

4.2.6 Randomization

Permuted block randomization was employed in this study. A block size of 12 of every consecutively enrolled participant was set. A block size of 12 is considered to be a longer block size, and was selected because it preserves the

unpredictability better (Meinert, 2012). To generate a random sequence, a total sample size was estimated first. The number of blocks was determined by preserving two blocks more than the estimated sample size in this study. Given that the sample size was estimated to be 99 and two more blocks had to be reserved, it finally generated a random list of 132 group labels with 11 blocks.

Labels were then assigned to the different groups: number 1 was assigned to the acupressure group, number 2 to the sham group, and number 3 to the usual-care group. A permuted block sequence of the three codes (i.e. 1, 2 and 3) representing the three experimental groups was generated by the web-based generator at www.randomization.com (Randomization.com, 2014). After a list of codes had been generated, the list was checked carefully to see if the ratio of the three labels in every block equaled 1:1:1.

To guarantee the allocation concealment, the whole randomization procedure was carried out by an independent research assistant (i.e. the random-list keeper) who did not participate in any other parts of the research. Throughout the study period, the independent research assistant generated the randomization list and kept the list. The random-list keeper was the only person who knew the randomized group sequence, so that it was concealed to all members of the research team.

To implement the randomization, information on the recruited participants (i.e. name, age, gender) was sent to the random-list keeper by email after the recruitment, which was done by the data collectors and the researcher. The

random-list keeper assigned a group label to each participant according to the randomization list and sent the information back to the researcher by email. The random-list keeper was blinded to the meaning of the group label and the clinical conditions of the participants, and had only basic information (i.e. name, age, gender) in order to prevent possible duplication of participant's names.

4.2.7 Blinding

The participants, interventionists, data collectors, nursing home staff (i.e. the formal caregivers providing the CMAI data), and statistician were blinded to the group labels.

Participants were not told about whether they had been assigned to the acupressure group or the sham group. Since the nature or feelings of acupressure and sham were very similar and the participants could not differentiate, and because they were not told to which group they had been assigned, they were blinded to the group labels. However, the blinding was only possible between the acupressure and sham groups. The participants could not be blinded against the group label if they were assigned to the usual-care group.

The interventionists were people without prior TCM or acupressure training. Every interventionist was taught to carry out only one protocol, which was either the acupressure protocol or the sham protocol. The interventionists were not told which protocol was the acupressure one. All the points in the protocols were coded, and they were not told the names and purposes of the points. Since the interventionists had no prior TCM knowledge and were not told the name of the

protocol they were implementing, they were blinded against the group labels of the acupressure and sham groups.

Data collectors, nursing home staff, and the statistician were simply not told to which group the participants had been assigned. Since the group label could not be naturally observed by these people and they were not told to which group the participants were assigned, these people were blinded against the group label.

4.2.8 Statistical analysis

Data analysis was performed by using SPSS version 21.0 (IBM Corp, 2012) and R (R Core Team, 2014) software. The level of significance was set as $p < 0.05$. In multiple pair-wise comparisons, the level of significance was adjusted by using Bonferroni adjustment (Ludbrook, 1998). All the data was checked for normality of distribution. The Kolmogorov-Smirnov (KS) test was used to test for the normality of distribution of all the data. Data fulfilling the assumptions of using parametric tests (e.g. normality, adequate sample number in a group) was reported using the mean with standard deviation. Continuous data not fulfilling the assumptions of using parametric tests was reported by using both mean with standard deviation and median with inter-quartile range. Categorical data is reported using frequency with percentage.

4.2.8.1 Checking demographic and clinical data equivalence at baseline between groups

The demographic and clinical data at baseline were described by groups (i.e. acupressure, sham-acupressure, and usual-care) separately and altogether.

Demographic and clinical data at baseline was analyzed to measure the equivalence among the three groups by using Chi-square for the categorical data and ANOVA for the continuous data.

4.2.8.2 Identification of co-variates

Given that there were no co-variates known in this study previously, possible co-variates for statistical adjustment on the effects were identified within the study from the demographic and clinical variables at baseline. Identification was based on whether there was a strong association between the demographic and clinical variables and the outcome variables at baseline.

The demographic and clinical variables were analyzed for their association with the primary outcome (i.e. agitation as measured by CMAI) and secondary outcome (i.e. stress as measured by salivary cortisol level) measured at baseline. Pearson's r was used for continuous demographic and clinical variables, while eta squared was used for categorical demographic and clinical variables to examine the strength of association. If the association between the demographic and clinical data and the primary outcome was found to be strong, which was defined as having large strength (i.e. Pearson's r >0.5 or eta squared >0.16) (Cohen, 1988), they were included in the analysis as covariates to statistically adjust the effect regardless of the lack of a statistically significant difference among the three groups (Pocock et al, 2002).

4.2.8.3 Hypothesis testing to answer the research questions

The generalized estimating equation (GEE) is robust to the normality assumption (Overall et al, 2004) and therefore was used to analyze the outcome data regardless the distribution of the outcome data. The average of outcomes (i.e. agitation and stress) within a cluster (i.e. a group and a time point) with possible missing data were reported in the estimated marginal means calculated by the GEE model. The standard errors, mean difference, p-value, and 95%CI for mean difference computed by the GEE model were also reported. GEE was used to answer the following three research questions:

1. Will acupressure reduce the agitation level of agitated nursing home residents with dementia over time as compared with the control conditions?

2. Will acupressure reduce the stress level of agitated nursing home residents with dementia over time as compared with the control conditions?

3. If acupressure reduces agitation and stress in nursing home residents with dementia, will the effect of acupressure on reducing agitation and stress be sustained over time?

The GEE compared the changes in agitation and stress over time between groups by computing the interaction effects. That is to say, the dependent variables were agitation as measured by CMAI and stress as measured by salivary cortisol level. The independent variables were group, time points, and group cross time point interaction. If these interaction effects were significant and the follow-up tests showed that agitation and stress were significantly further reduced after the

intervention in the acupressure group than in the controls, the acupressure could be identified as effective in reducing stress and agitation.

If the acupressure could reduce agitation and stress more significantly compared with the control condition after the intervention, and the reduction of agitation and stress after the intervention could be observed to be significantly different in T_2 and T_3; the effects of acupressure could be said to be sustainable for at least 5 weeks after the intervention.

Mediation analysis by structured equation modeling (SEM) was used to answer the fourth research question:

4. If acupressure reduces agitation in nursing home residents with dementia, is the agitation-reducing effect of acupressure mediated by stress?

The SEM mediation analysis followed Gunzler and colleagues' mediation analysis method (2013). The total effect of an intervention is comprised of direct and indirect effects (i.e. total effect = direct effect + indirect effect). The indirect effect explains the amount of mediation. In this case, before examining the mediation effect, the total effect, which was the causal path from acupressure to agitation, was examined at three different time points after the intervention (i.e. T_1, T_2, and T_3). If the total effect, which is the causal path from acupressure to agitation at any particular time point, was significant, then the stress would be added to the model as a mediator for the mediation analysis.

To test the mediating effect of stress between intervention and agitation, as shown in Figure 4.3, the three variables of interventions, stress, and agitation had

to be defined in the SEM. The interventions variable was an ordinal level of measurement. Number 3 was assigned to the acupressure group, which was assumed to comprise the therapeutic components of acupoint stimulation, tactile stimulation, other possible components, and usual care. Number 2 was assigned to the sham group, which was assumed to comprise the therapeutic components of tactile stimulation, other possible components, and usual care. Number 1 was assigned to the usual-care group, which was assumed to comprise usual care only. The higher ordinal level of the group factor represented the greater number of therapeutic components it comprised, as discussed in section 4.2.4. The variable of

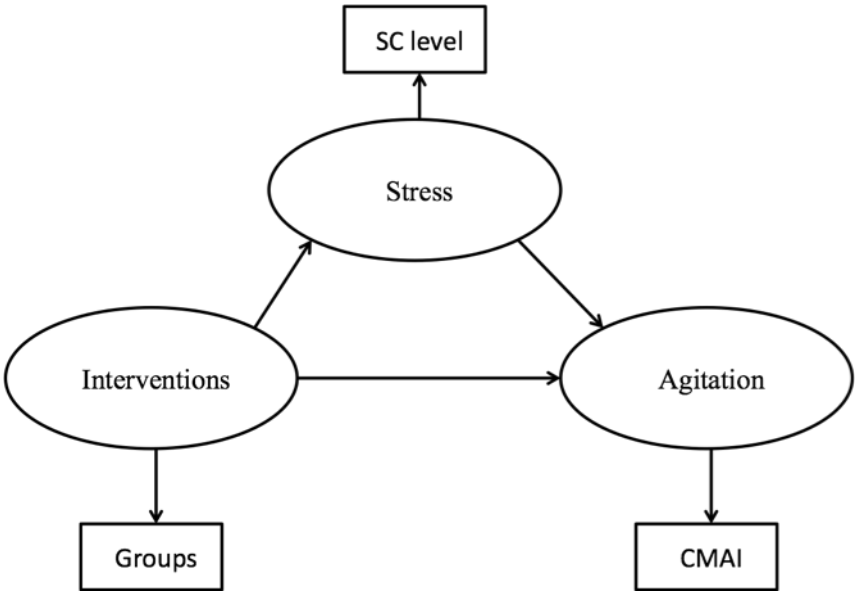


Figure 4.3. Mediation model being tested. SC=salivary cortisol, CMAI=Cohen-Mansfield Agitation Inventory

Three models using data at three time points after the intervention (i.e. T_1, T_2, and T_3) were constructed for mediation analysis. In any one of the models, when significant causal paths from acupressure to stress and from stress to agitation were observed concurrently at any one of the time points, acupressure was suggested to reduce agitation by mediating stress. The effect of each path was represented as a standardized estimate ranging from -1.0 to 1.0. Their standard errors and p-values were reported. Goodness-of-fit indexes including Chi-square (i.e. X^2), the normed fit index (i.e. NFI), the comparative fit index (i.e. CFI), and the standardized root mean square residual (i.e. SRMR) were also reported to explain how well the empirical data could support the model at different time points.

4.2.8.4 Handling missing data

Missing data was estimated within the GEE without replacement, based on the assumption that the missingness was random or not associated with the independent factors (i.e. group and time) of the study (Little & Rubin, 2014; Paik, 1997). The Chi-square test was used to check whether the missingness of the missing data was associated with the independent factors (i.e. groups and time points). If missingness was not at random or associated with the dependent factors (i.e. groups and time points), the missing data was replaced by multiple imputation before being entered into the GEE analysis (Paik, 1997). If the missingness was random, an incomplete set of data was used and the missing data was estimated within the GEE model (Paik, 1997).

4.2.8.5 Sensitivity analysis

According to the compliance with the intervention, participants were divided into a complier group with satisfactory compliance and a non-complier group with unsatisfactory compliance. To define participants as compliers or non-compliers with the intervention protocol (i.e. the acupressure and sham protocols), a cut-off of 80% completion of the assigned intervention protocol was used. The 80% cut-off had been commonly used in other RCT (Ye et al, 2014). Analyses including non-compliers and excluding non-compliers were performed separately. These two analyses were modified intention-to-treat (mITT) and per-protocol (PP) analysis.

Intention-to-treat analysis includes all randomized patients in the group to which they were randomly assigned regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol (Fisher et al, 1990). However, some factors such as whether treatment actually started play a significant role on the effect of intervention. Including participants who have not started the intervention in the intervention group may markedly diminish the treatment effect. The mITT allows researchers a subjective approach in adjusting the entry criteria to analysis, which may lead to inaccurate results (Gupta, 2011). There are no agreed principles for selecting participants for mITT analysis. The participants included in the mITT analysis in this study were those who were all randomized into groups after the collection of baseline data and did not withdraw before the commencement of the intervention or refuse to provide data.

The participants included in the PP analysis were those who fulfilled the criteria of mITT and were identified as compliers only. Non-compliers were excluded from the PP analysis. Sensitivity tests were done to compare the differences in the interpretation of results between the mITT and PP analysis in order to examine whether different conclusions can be drawn based on the variations in study protocol compliance. Conducting these two analyses separately aimed at providing more information on the effect of the intervention, considering possible confounders such as non-compliance (Gupta, 2011).

4.2.9 Ethical consideration

The study protocol was reviewed and approved by the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University under reference number HSEARS20120920001. Several steps were taken to ensure that the ethical issues of the study were well considered. These steps included consenting and assenting, the unmasking of group labels, options for compensation, data confidentiality, and monitoring for adverse effects.

4.2.9.1 Consenting and assenting

In the preparatory phase, all RCH which agreed to participate were instructed to help with the preliminary screening according to the selection criteria. A group of potentially eligible participants were identified by the RCH staff, and they and their next-of-kin were then asked whether they would agree to pass their contact information to the research for a detailed screening. Next, a group of potentially eligible participants who agreed and/or whose next-of-kin agreed was identified.

Finally, the researcher contacted them for face-to-face screenings and recruitment in the RCH.

In the recruitment phase, before the randomization, all the next-of-kin of subjects screened to be eligible were informed of the details of the study, including the intervention and data collection procedures, and the potential risk and benefits. All eligible subjects were likewise informed of the same details, as described in the Acupressure Information Sheet shown in Appendix 8. The participants and their next-of-kin were clearly told about the equal chance of allocation to any one of the three groups before signing the informed consent. They were also told prior to the randomization that they would be offered compensatory acupressure sessions if they were assigned to either the sham or usual-care groups. The group labels were strictly concealed to the participants, next-of-kin, data collectors, and nursing home staff throughout the study period, and only revealed after completion of the study. The participants were recruited if they signed the written informed consent or consented to participate in another way (i.e. nodding, verbalizing, or not refusing when acupressure was performed on them), or if their next-of-kin signed the written informed consent as a proxy consent (Karlawish et al, 2002). The Acupressure Consent Form is shown in Appendix 9.

4.2.9.2 Unmasking of group label

Unmasking refers to revealing the group label to participants and their next-of-kin after completion of the study. Unmasking was done by the researcher, who contacted all the next-of-kin and RCH staff involved via telephone. RCH staffs

were invited to convey the group allocation status to the participants face-to-face. Emergency unmasking before the pre-determined completion time of the study was allowed only in emergency situations, such as the occurrence of suspected adverse effects related to acupressure.

4.2.9.3 Options for compensation

After the unmasking, if the participants were assigned to either the sham or usual-care groups, they could receive free courses of acupressure identical to the one conducted in the acupressure group. In case the family members wanted to continue the acupressure on the participants by themselves after the study, workshops were provided to them. The results of the effects of the acupressure were also reported to the participants and their next-of-kin upon request. The results were reported to the related family by the researcher through telephone.

4.2.9.4 Data confidentiality

After the data collection, data collectors returned the data in hard copy to the researcher's office and the saliva samples to the laboratory. The office and the lab were lock-protected. Only the researcher and related data collectors had access rights to this office and this laboratory. The hard copies of the data were subsequently placed in a locked cabinet for which the researcher had the only key. The data on the hard copies were then entered into the computer by the researcher. The computer in his office was also password-protected, and only the researcher had the password. These endeavors were to ensure that the confidentiality of the participants' data was protected.

4.2.9.5 Adverse effects monitoring and management

Although no severe adverse effects had previously been reported in relation to acupressure or the procedures of the study, we still endeavored to monitor for any possible adverse effects. Regular site-visits were conducted at least once per RCH during the intervention period, there was one telephone follow-up after completion of the last round of data collection at T_3, and separate regular monthly meetings were held with both the interventionists and the data collectors.

At these meetings, we aimed to discuss any possible adverse effects identified by the participants, their families, or the RCH staff. We also monitored any possible adverse effects from the perspective of the interventionists and data collectors. When suspected adverse effects were identified, all data collectors, interventionists, participants' family members, and RCH staff were provided with the telephone number of the researcher, so that they could discuss the matter with the researcher immediately. If the researcher could not exclude the possibility that the adverse effects were related to the intervention or to the study procedures, the involved participants were removed from the study. If there was clear evidence of any threat to the safety of the participant, the trial was terminated.

4.3 Procedures

This section discusses how the study was carried out: the study cycles, RCH recruitment, participant recruitment, intervention fidelity, intervention compliance, missing data and data quality, statistical assumption check, harms, and post-study management.

4.3.1 Study cycles

In order to recruit a sufficient number of participants in multiple RCH and balance the manpower demands, the whole study was completed through six study cycles as shown in Appendix 10. Two RCHs participated concurrently in each cycle, so that totally 12 RCHs participated. The period of each cycle partially overlapped with the next in order to efficiently utilize the manpower and study venues. Each study cycle lasted for 10 weeks, including a 2-week baseline period, a 2-week intervention period, and a 6-week follow-up period. The six study cycles lasted for 30 weeks in total. The participant recruitment of the main study commenced in Dec 2013 and was completed in Jun 2014.

4.3.2 RCH recruitment

As shown in Figure 4.4, there were 284 eligible RCHs on the list of RCH provided by Hong Kong Social Welfare Department and finalized on Jun 30, 2012. There were 123 RCHs providing fewer than 100 beds, two RCHs located on outlying islands, and two RCHs excluded from participation in the pilot study. In the end, 157 eligible RCHs were invited to participate in this study.

Out of the 157 invited RCHs, 122 did not reply. There were 35 RCHs that replied, with 18 RCH agreeing and 17 RCHs declining to join. Of the 18 RCHs that agreed, we randomly drew 12 RCHs to participate in this study in order to make sure that adequate samples were recruited as planned in the sample size estimation. However, one of them declined to join the study after listening to

details of the collaboration; one more RCH was randomly drawn to replace the drop out. In the end, 12 RCHs joined this study.

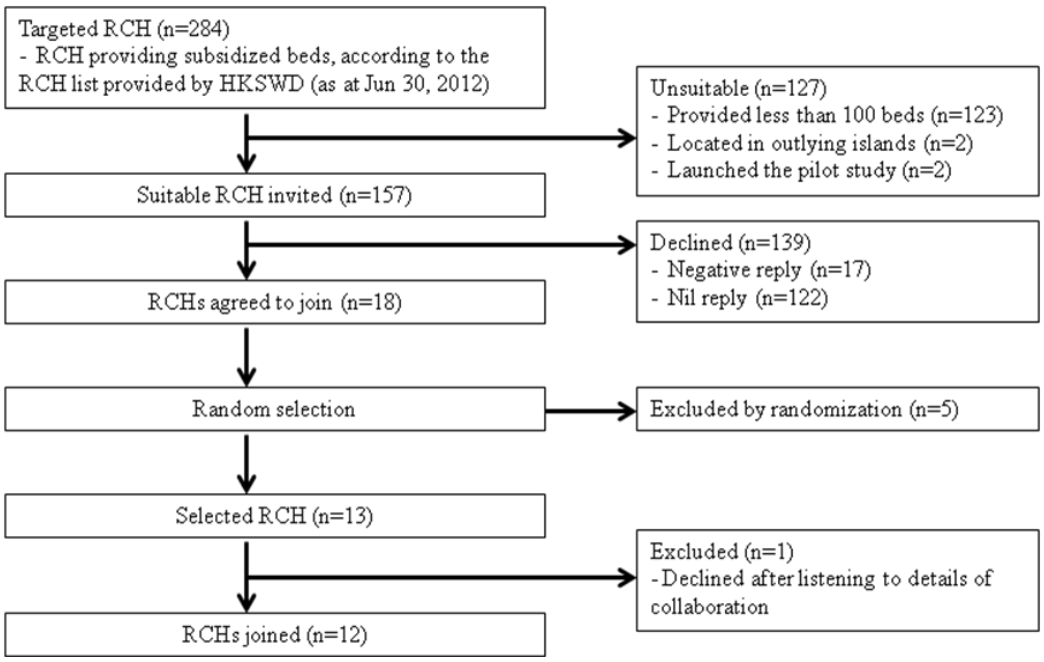


Figure 4.4. RCH recruitment flow chart. RCH=Residential care home; HKSWD=Hong Kong Social Welfare Department

4.3.3 Participant recruitment

As shown in Figure 4.5, a total of 2014 residents were assessed for eligibility in the 12 eligible RCH that agreed to participate. After the eligibility screening, 1838 residents were screened out as ineligible, while 176 residents were eligible. Among these 176 eligible residents, 55 were excluded because the family refused (n=39), the family could not be contacted (n=10), the clients refused (n=3), or the clients were hospitalized during the period of baseline data collection (n=3). There were 121 subjects randomized into three groups: an acupressure group (n=40), a sham group (n=41), and a usual-care group (n=40).

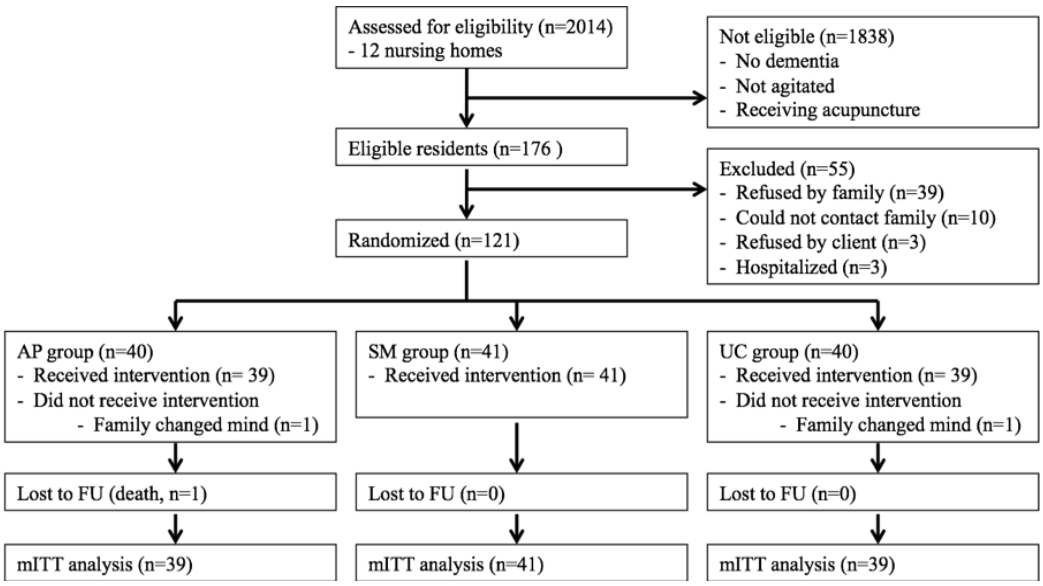


Figure 4.5. Participant flow chart following Consolidated Standards of Reporting Trials Guidelines 2010. AP=acupressure; SM=sham; UC=usual care; FU=follow-up. mITT=modified intention-to-treat

The acupressure protocol was commenced on 39 participants in the acupressure group, but not on one assigned participant. The reason for not commencing the intervention on that participant was that the family withdrew consent after the baseline data collection, without giving reasons. The family did not allow us to use the participant's data for research purposes. During the study period, one participant was lost to follow-up because s/he passed away before completion of the intervention. This participant was included for mITT analysis. This group comprised 39 participants in the final mITT analysis.

The sham-acupressure was implemented on all 41 participants in the sham group. No participants were lost to follow-up. This group included 41 participants in the final mITT analysis.

In the usual-care group, 40 participants received usual care and one left during the study period, shortly after the group allocation, because the family withdrew consent without giving reasons. The family did not allow us to use the participant's data for research purposes. During the study period, no participants were lost to follow up. The group included 39 participants in the final mITT analysis.

4.3.4 Intervention fidelity

The intervention fidelity of both the acupressure and sham protocols during the study period was monitored by an assessor. The assessor rated the intervention fidelity according to the skill checklists validated by the expert panel during the study period. This checklist was exactly the same as the one used to examine the skill of the interventionists in the aforementioned training, as shown in Appendix 4 and Appendix 5. The checker was a registered nurse who completed the same training for the interventionists on both acupressure and sham protocols by the same expert trainer (i.e. one of the expert panel members) in a separate occasion. The checker also participated in the pilot study and had gained thorough experience through rounds of discussion with the expert trainer on the issues related intervention fidelity rating difficulties in the pilot study. Whenever the checker was uncertain about the intervention fidelity rating, the checker was instructed to consult the expert trainer.

There were totally six on-site skill evaluations conducted in six RCHs, with one evaluation conducted in each RCH. Out of the six on-site evaluations, all items were rated to be equal to or over 3 (i.e. appropriately carried out), with a mean

score of 3.02. Out of the six on-site evaluations, all items were rated to be equal to or over 3, with a mean score of 3.04.

4.3.5 Intervention compliance

The 39 participants in the acupressure group were expected to attend 20 sessions. There were 780 sessions in total for these 39 participants. Upon completion of the study, 717 out of the 780 expected sessions had been completed by the 39 participants. The overall compliance rate by session was 91.9%. 32 out of the 39 participants in the acupressure group (82.1%) completed more than 80% of the expected sessions of acupressure. Seven participants counted as non-compliers as they could not complete more than 80% of the expected sessions of acupressure. One participant was not included as a complier for analysis because s/he passed away before completion of the study. Six participants refused more than 20% of the expected number of sessions.

41 participants in the sham group were expected to attend 20 sessions, making a total of 820 sessions offered to these 41 participants. Upon completion of the study, they had completed 755 of the expected 820 sessions. The overall compliance rate by session was 92.1%. 37 participants out of 41 in the sham group (90.2%) completed more than 80% of the expected sham sessions. Four were counted as non-compliers as they could not complete more than 80% of the expected sessions in the sham group. In all four cases, the reason for non-compliance was their refusal to complete more than 20% of the expected number of sessions.

4.3.6 Missing data

There were two types of data: demographic and clinical data, and outcome data. There was no missing demographic or clinical data.

For the CMAI outcome data, 476 pieces of data were collected from 119 participants at the four expected time points. Upon completion of the study, four out of 467 expected pieces of CMAI outcome data were missing (n=4). The reasons were that one participant passed away, contributing to two pieces of missing data (n=2), and that two participants were hospitalized, contributing to another two pieces of missing data (n=2). The missing data rate of the CMAI was 0.8%.

As shown in Figure 4.6, 476 pieces of salivary cortisol data were collected from 119 participants at the four expected time points. Upon completion of the study, one participant passed away, contributing to two pieces of missing data (n=2). 36 samples could not be collected (n=36) because the collection was refused by the participants or they were unavailable due to medical follow-up, hospitalization, or family activities. Out of the 438 saliva swabs collected, some (n=222) were found to contain nil or inadequate volume (i.e. less than 50μL) of saliva after centrifuging. 216 saliva samples completed the chemical analysis for cortisol level. After completion of the chemical analysis, one sample (n=1) produced a reading out of the range guaranteed by the Salimetics® ELIZA kit. There were eventually 215 valid saliva samples (45.2%) after chemical analysis, out of the 476 samples expected.

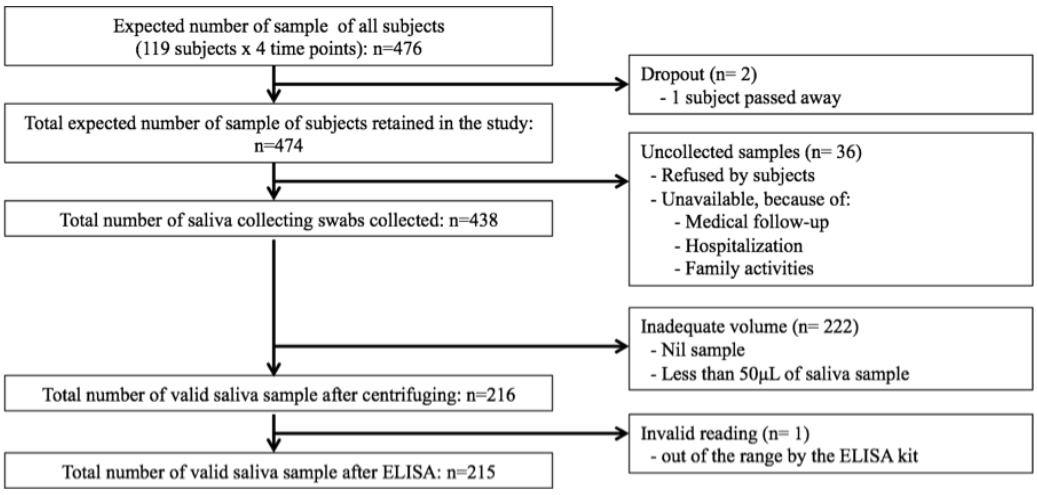


Figure 4.6. Missing data of saliva sample. ELISA=Enzyme Linked Immunosorbent Assay

The distribution of missing/invalid data was comparable among groups. For the CMAI and psychotropic drug use, the differences were very minimal across groups because the overall missing/invalid data rate was very low (CMAI: 0.8%). For the saliva samples, the overall missing/invalid data was very high, as shown in Tables 4.1 and 4.2. There were 261 invalid/missing samples (54.8%) recorded. There were 84 (32.2%) invalid/missing samples in the acupressure group, 90 (34.5%) in the sham group, and 87 (33.3%) in the usual-care group. Yet, there was no significant difference in the number of missing saliva samples between groups and between time points.

Table 4.1

Missing and invalid salivary samples by groups

By groups, % N=261			Statistics[+]
AC	SM	UC	
84 (32.2)	90 (34.5)	87 (33.3)	p=0.903

+Chi-square test; AC: acupressure group; SM: sham-acupressure group; UC: usual-care group

Table 4.2

Missing salivary samples by time points

By time points, % N=261				Statistics[+]
T_0	T_1	T_2	T_3	
55 (21.1)	68 (26.1)	65 (24.9)	73 (28.0)	p=0.130

+Chi-square test; T_0=baseline; T_1= 3rd week after the commencement of the intervention;

T_2= 4th week after the commencement of the intervention; T_3= 8th week after the commencement of the intervention

4.3.7 Data quality

The outcome data collection quality of the CMAI during the study period was monitored by six on-site concurrent inter-rater tests between the researcher and the data collectors in three different centers during the study period. The inter-rater reliability was good (IRR=1.0). The quality of the salivary sample collection during the study period was monitored by the research team member six times in six different RCHs. The data collectors were observed to have followed the data collection guideline of the study 100% correctly.

4.3.8 Statistical assumption check

Kolmogorov-Smirnov test was used to check for the normality of all the continuous data (i.e. demographic and clinical data and outcome data) at the baseline. Only the distribution of age was identified as normal (p=0.084), while the distribution of the remaining continuous data was identified as not normal (p<0.001). Therefore, age was reported by mean with standard deviation as it fulfilled the parametric assumption of normal distribution. The other continuous data were reported by both mean with standard deviation and median with inter-

quartile range, as they did not fulfill the parametric assumption of normal distribution.

All demographic and clinical variables were tested for their association with the outcomes (i.e. CMAI and cortisol level) at baseline. There was no strong (i.e. $r > 0.5$, eta squared >0.13) or significant (i.e. $p < 0.05$) association between the demographic and clinical variables and the outcomes at baseline. There was no strong evidence that the demographic and clinical variables at baseline played significant roles as covariates. It was assumed that the demographic and clinical variables did not cause changes in the outcome variables. Therefore, they were not put into the statistical analysis as covariates to adjust the results in this study in the GEE analysis. No covariates were selected to statistically adjust the effect of the interventions.

For the missing data, as mentioned above and shown in Tables 4.1 and 4.2, there was no association between the frequency of the missing and independent factors (i.e. group and time) identified. Missing data was assumed to be missing-at-random (MAR). Data were analyzed by GEE as an incomplete data set with the assumption of missing-at-random as planned. The average of the outcome with missing data in a cluster (i.e. within a group or within a time point) was reported as estimated marginal means calculated by GEE.

4.3.9 Harms

We visited each RCH once in during the intervention period and called the RCH in-charge once after completion of the last round of data collection by

telephone. We received no major complaints causing premature termination of the intervention by family and nursing home staff related to the study (i.e. the interventions and data collection).

In our monthly regular meeting with the data collectors and interventionists, site-visits, and telephone follow-up, some minor adverse effects were observed. The most frequent minor adverse effects reported were that fingernail marks and mild redness on the skin were observed on the client immediately after the intervention. We investigated whether they were caused by the long fingernails of the interventionists. We checked the fingernails of the interventionists at the venue at each on-site monitoring, and found that the fingernail marks on the clients were not related to the length of the interventionists' fingernails. Fingernail marks were still observed even after the acupressure was performed by interventionists with short fingernails. However, the fingernail marks and redness on the skin often faded quickly, and no complaints were made by the clients or their families in this regard.

According to the interview with the interventionist, some participants strongly refused the intervention because they did not want people to touch or bother them for no obvious reason. Some participants reported that they refused to receive the intervention because they did not believe that it could help them. Others asked the interventionist to stop the intervention because it caused pain.

To manage intervention refusal, we tried to ask the formal caregivers who were familiar with them to accompany the participants and during the acupressure

sessions, to explain aspects of the intervention while it was under way. This was because we believed that the participants might not trust the strange interventionists. Some of them accepted the acupressure when accompanied by their familiar caregivers, but some still refused even after explanations by their familiar formal caregivers. We approached the clients again after completion of the interventions on other participants. If they still refused, we ceased the acupressure session but continued for all the subsequent sessions. Many refusals were just episodic.

Pain is a normal *deqi* sensation during the acupressure when acupoints are activated (Yang et al, 2013). But when the pain was reported to be too intense, our interventionists tried to reduce the level of pressure in order to identify the optimal pressure to the level when the *deqi* sensation was just felt. Many of the participants would tolerate the pain after the reduction of pressure. Some still strongly refused once pain had been caused. If they refused because of pain even after reduction of pressure, we left them for a while and went back to them after completing the intervention on other participants. If they still refused, we stopped that session of acupressure for them but continued for all the subsequent sessions. Many refusals for pain were also episodic.

4.3.10 Post-study management

It was agreed that there should be an option of compensation to the participants assigned to the sham and usual-care groups, as well as a verbal report of the result given to the participant's family. After data collection, the involved

family and nursing home staff were contacted. 92 participants' families (77.3%) showed an interest in knowing the results. 84 families (70.6%) were successfully contacted and had the results reported to them verbally via telephone. The verbal report over the phone included information about the group label and a simple interpretation of the changes in agitation and cortisol levels over time. Eight participants (6.7%) could not be contacted after repeated phone calls. Compensatory sessions of acupressure were provided upon the family's request after completion of the study.

4.4 Summary

A randomized controlled trial was used to answer the four research questions of this study. Participants were allocated by permuted-block randomization into three groups: acupressure group, sham group as a control condition, and usual care group as another control condition. The primary outcome variable was agitation, as measured by CMAI, and the secondary outcome variable was stress, as measured by salivary cortisol. These outcome variables were measured at four time points: the baseline (T_0), the 3rd week (T_1), the 5th week (T_2), and the 8th (T_3) week after the baseline.

The randomized list of group labels was concealed by deploying an independent research assistant to manage the list. Measures ensuring blinding were implemented on the participants, interventionist, data collectors, RCH staff, and statistician. The blinding of the participants could only be done in the sham and acupressure groups.

Training and monitoring measures were implemented to ensure the quality of the study on intervention implementation and data collection. All interventionists and data collectors passed the required tests before they were certified to be competent in their roles. Monitoring was done on site as well as through regular meetings.

Statistical assumption tests were performed to inform the appropriate selection of statistical analysis strategies. GEE was used to analyze the data for answering research questions 1 to 3, while SEM mediation analysis was used to answer research question number 4.

There were 12 RCHs in Hong Kong that fulfilled the eligibility criteria to be sampled and invited to participate in this study. There were 121 eligible and consented participants recruited into this study, which was implemented in six cycles. The data of 119 participants were included in the mITT analysis. The intervention fidelity and intervention compliance were highly satisfactory. Missing data was quite prominent on the salivary cortisol, yet there were no differences in the amount of missing data between groups and time points. The intervention fidelity and the data quality were good.

Chapter 5 Results

This chapter begins with a discussion of participants' characteristics, followed by results of the hypothesis testing in accordance with the research questions. Finally, a sensitivity test was discussed.

5.1 Participants' Characteristics at Baseline

As shown in Table 5.1, there were 11 demographic and clinical variables at baseline. The majority of participants were female (76%). Their mean age was 86.5 (SD: 6.3), median length of stay in the RCH was 32.0 (IQR: 98.0) months, median MMSE was 6.0 (IQR: 9.0), median mBI was 24.0 (IQR: 61.0), median number of chronic illnesses was 4.0 (IQR: 2.0), and median number of psychotropic drugs used was 2.0 (IQR: 1.0). The majority were put in physical restraints all the time (37.0%), and the majority were visited by family members less than once a week (42.0%). Most were engaged in activities less than once a week (27.7%) and for less than five hours per week (51.3%). There were no significant differences in these demographic and clinical variables among the groups at baseline.

Table 5.1:

Demographic and clinical variables at baseline

Characteristics	All (n=119)		AC (n=39)		SM (n=41)		UC (n=39)		Statistics	p-value
Gender (%)										
Male	27	(22.3)	8	(20.5)	12	(29.3)	7	(17.9)	X^2= 1.612	p=0.446
Female	92	(76.0)	31	(79.5)	29	(70.7)	32	(82.1)		
Age (SD)										
Mean	86.5	(6.3)	86.9	(6.1)	85.6	(6.9)	87.1	(5.9)	F=0.689	p=0.500
Length of stay[#], months										
Mean (SD)	64.4	(71.7)	54.8	(73.3)	70.9	(80.1)	67.1	(60.7)	F=0.545	p=0.582
Median (IQR)	32.0	(98.0)	28.0	(62)	34.0	(104)	45.0	(114)	X^2=2.464	p=0.292
MMSE[#], PR=0-30										
Mean (SD)	7.0	(7.9)	7.4	(5.8)	7.8	(11.3)	5.6	(4.9)	F=0.877	p=0.419
Median (IQR)	6.0	(9.0)	7.0	(8.0)	6.0	(8.0)	6.0	(8.0)	X^2=1.747	p=0.417
mBI[#], PR=0-100										
Mean (SD)	35.9	(33.1)	41.7	(34.1)	29.1	(30.9)	37.2	(33.8)	F=1.495	p=0.229
Median (IQR)	24.0	(61.0)	33.0	(71.0)	15.0	(45.0)	26.0	(66.0)	X^2=2.607	p=0.272
No. of chronic illnesses[#]										
Mean (SD)	4.1	(1.9)	4.1	(2.0)	4.3	(2.0)	3.9	(1.8)	F=0.467	p=0.628
Median (IQR)	4.0	(2.0)	4.0	(2.0)	4.0	(2.0)	3.0	(2.0)	X^2=1.009	p=0.604
No. of psychotropic drugs used[#]										
Mean (SD)	1.5	(1.1)	1.56	(1.0)	1.7	(1.2)	1.2	(1.1)	F=1.816	p=0.167
Median (IQR)	2.0	(1.0)	2.0	(1.0)	2.0	(1.0)	1.0	(2.0)	X^2=3.644	p=0.162

Frequency of physical restraint use (%)									X^2=8.593	p=0.378
Never used	31	(26.1)	11	(28.2)	10	(24.4)	10	(25.6)		
Rarely used, < 10% of time,	9	(7.6)	5	(12.8)	2	(4.9)	2	(5.1)		
Sometimes used, 10%-50% of time	13	(10.9)	5	(12.8)	6	(14.6)	2	(5.1)		
Often used, 50%-80% of time	22	(18.5)	3	(7.7)	8	(19.5)	11	(28.2)		
Used all the time, >80% of time	44	(37.0)	15	(38.5)	15	(36.6)	14	(35.9)		
No. of family visits (%)									X^2=8.334	p=0.402
Never visit	8	(6.7)	2	(5.0)	4	(9.8)	2	(5.1)		
< 1 time per week	50	(42.0)	15	(37.5)	17	(41.5)	18	(46.2)		
1-2 times per week	29	(24.4)	7	(17.5)	9	(22.0)	13	(33.3)		
3-6 times per week	16	(13.4)	7	(17.5)	7	(17.1)	2	(5.1)		
> 6 times per week	16	(13.4)	8	(20)	4	(9.8)	4	(10.3)		
Frequency of activities (%)									X^2=2.907	p=0.940
Never participate	22	(18.5)	9	(23.1)	7	(17.1)	6	(15.4)		
< 1 time per week	33	(27.7)	9	(23.1)	12	(29.3)	12	(30.8)		
1-2 times per week	20	(16.8)	6	(15.4)	9	(22.0)	5	(12.8)		
3-6 times per week	25	(21.0)	8	(20.5)	8	(19.5)	9	(23.1)		
> 6 times per week	19	(16.0)	7	(17.9)	5	(12.2)	7	(17.9)		
Duration of activities (%)									X^2=3.320	p=0.913
Never participate	22	(18.5)	9	(23.1)	7	(17.1)	6	(15.4)		
< 5 hours per week	61	(51.3)	18	(46.2)	23	(56.1)	20	(51.3)		
5-9 hours per week	17	(14.3)	5	(12.8)	5	(12.2)	7	(17.9)		
10-15 hours per week	12	(10.1)	4	(10.3)	3	(7.3)	5	(12.8)		
> 15 hours per week	7	(5.9)	3	(7.7)	3	(7.3)	1	(2.6)		

Continuous data found to have no normal distribution by Kolmogorov-Smirnov Test; *statistically significant; AP= acupressure group; SM=sham group; UC=usual-care group; PR=possible range

MMSE=mini-mental state exam; mBI=modified Barthel index

There were two outcome variables at baseline, as reported below in Table 5.2. The primary outcome was agitation, as measured by CMAI. The secondary outcome was stress, as measured by salivary cortisol level. There was no significant correlation between agitation and stress at baseline (r=-0.138, p=0.276).

A total of 119 CMAI samples were collected at baseline. The median total score was 43.0 (IQR: 22.0), median VNAB score was 12.0 (IQR: 10.0), median VAB score was 7.0 (IQR: 5.0), median PNAB score was 13.0 (IQR: 8.0), and median PAB score was 10.0 (IQR: 10.0). There were no significant differences in any of the CMAI scores between groups.

There were 64 salivary samples collected at baseline. The median salivary cortisol level was 0.39 (IQR: 0.35). There were no significant differences in salivary cortisol level between groups.

Table 4.4:

Outcome variables at baseline

Characteristics	All (n=119)		AP (n=39)		SM (n=41)		UC (n=39)		Statistics	p-value
CMAI[#], PR=21-168										
Total mean (SD)	47.6	(16.4)	46.1	(15.4)	47.4	(17.4)	49.2	(16.6)	F=0.336	p=0.715
Total median (IQR)	43.0	(22.0)	41.0	(17.0)	41.0	(23.0)	45.0	(23.0)	X^2=0.972	p=0.615
VNAB mean (SD)	13.1	(6.8)	12.4	(6.0)	13.1	(7.7)	13.8	(6.8)	F=0.397	p=0.673
VNAB median (IQR)	12.0	(10.0)	12.0	(10.0)	11.0	(12.0)	12.0	(9.0)	X^2=0.830	p=0.660
VAB mean (SD)	7.9	(4.4)	7.6	(3.6)	7.2	(4.4)	8.9	(4.9)	F=1.536	p=0.220
VAB median (IQR)	7.0	(5.0)	7.0	(4.0)	6.0	(7.0)	9.0	(7.0)	X^2=2.849	p=0.241
PNAB mean (SD)	14.3	(6.7)	14.2	(7.3)	13.6	(6.1)	15.1	(6.9)	F=0.525	p=0.593
PNAB median (IQR)	13.0	(8.0)	12.0	(8.0)	12.0	(9.0)	13.0	(7.0)	X^2=1.567	p=0.457
PAB mean (SD)	12.2	(6.9)	11.8	(6.2)	13.5	(8.1)	11.4	(6.2)	F=1.057	p=0.351
PAB median (IQR)	10.0	(10.0)	11.0	(10.0)	12.0	(9.5)	10.0	(9.0)	X^2=1.401	p=0.496
Salivary cortisol[#], µ g/dL										
Mean (SD)	0.45	(0.30)	0.52	(0.37)	0.42	(0.24)	0.41	(0.27)	F=0.902	p=0.411
Median (IQR)	0.39	(0.35)	0.35	(0.53)	0.40	(0.19)	0.39	(0.32)	X^2=0.496	p=0.780

Continuous data found to have non-normal distribution by Kolmogorov-Smirnov Test, *statistically significant; AP= acupressure group, SM=sham group, UC=usual-care group

PR=possible range; CMAI=Cohen-Mansfield Agitation Inventory; VNAB=verbal non-aggressive behaviors; VAB=verbal aggressive behaviors; PNAB=physical non-aggressive behaviors; PAB=physical aggressive behaviors

5.2 Hypothesis Testing

The research questions put four hypotheses to the test, related to the effects on agitation, the effects on stress, the mediation effects on agitation through stress, and the sustainability of the effects. The following testing was based on the participants eligible to be selected into the modified intention-to-treat analysis.

5.2.1 Research question 1 - the effects on agitation

Agitation was measured by the CMAI. In order to understand the effect difference of acupressure on the overall agitation and agitation subtypes, the effects on agitation were analyzed separately by CMAI total score and CMAI sub-scores: VNAB score, VAB score, PNAB score and PAB score.

5.2.1.1 CMAI total score

As shown in Table 5.3 and Figure 5.1, the GEE model showed no significant interaction effect between groups and time points on the CMAI total score, although the effect was almost statistically significant (X^2=12.486, p=0.052). There was significant difference over time points (X^2=14.735, p=0.002), but there was no statistically significant difference between groups.

Table 5.3:

Comparing CMAI total scores between groups over time

Effect types	Statistics
CMAI total	
Time (T_0, T_1, T_2, T_3)	X^2=14.735, p=0.002*
Group (AP, SM, UC)	X^2=1.351, p=0.509
Time x Group	X^2=12.486, p=0.052

*statistically significant; AP=acupressure; SM=sham acupressure; UC=usual care;

T_0=baseline; T_1= 3rd week after commencement of the intervention;

T_2=5th week after commencement of the intervention:

T_3=8th week after commencement of the intervention

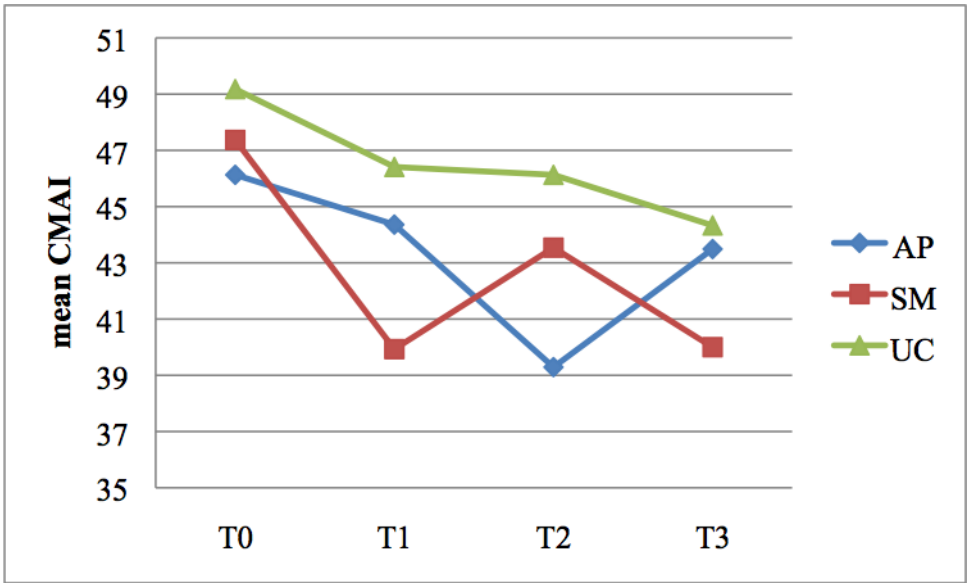


Figure 5.1: Graphical illustration of comparison of changes in CMAI scores over time points by groups. CMAI=Cohen-Mansfield Agitation Inventory; AP=acupressure group, SM=sham group; UC=usual-care group; T0=baseline; T1=3rd week after commencement of the intervention; T2=5th week after commencement of the intervention; T3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing CMAI scores between time points by groups is shown in Table 5.4, comparing the CMAI total scores at T_1, T_2, and T_3 with T_0 separately by group. In the acupressure group, the CMAI total score at T_2 (MD=-6.84, 95%CI: -10.60, -3.08) was observed to be significantly lower than that at T_0. CMAI total scores at T_1 and T_3 were observed to be not significantly different compared with T_0. In the sham group, the CMAI total scores at T_1 (MD=-7.44, 95%CI: -12.63, -2.25) and T_3 (MD=-7.37, 95%CI: -11.45, -3.28) were observed to be significantly lower than at T_0. The CMAI total score at T_2 was observed to be not significantly different compared with T_0. In the usual-care group, CMAI scores at T_1, T_2 and T_3 were observed to be not significantly different from that at T_0.

Table 5.4:

Comparing CMAI total scores between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
CMAI total				
AP				
	$T_1 - T_0$	-1.77 (2.78)	-7.22, 3.68	p=0.525
	$T_2 - T_0$	-6.84 (1.92)	-10.60, -3.08	p<0.001*
	$T_3 - T_0$	-2.64 (2.51)	-7.57, 2.29	p=0.293
SM				
	$T_1 - T_0$	-7.44 (2.65)	-12.63, -2.25	p=0.005*
	$T_2 - T_0$	-3.83 (2.36)	-8.46, 0.80	p=0.105
	$T_3 - T_0$	-7.37 (2.09)	-11.45, -3.28	p<0.001*
UC				
	$T_1 - T_0$	-2.77 (2.44)	-7.54, 2.00	p=0.255
	$T_2 - T_0$	-3.05 (2.58)	-8.12, 2.01	p=0.238
	$T_3 - T_0$	-4.85 (2.66)	-10.05, 0.36	p=0.068

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group; SM=sham group; UC=usual-care group; T_0=baseline; T_1=3rd week after commencement of the intervention; T_2=5th week after commencement of the intervention; T_3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing CMAI scores between groups by time points after completion of the intervention is shown in Table 5.5: the CMAI total scores were compared between the acupressure group and the two control groups separately at the time points after completion of the intervention (i.e. T_1, T_2, and T_3). There were no significant differences observed between the acupressure group and either of the control groups at any of the time points after completion of the intervention.

Table 5.5

Comparing CMAI total score between groups by time points after completion of the intervention

Pair-wise comparison		MD (SE)	95%CI	Statistics+
CMAI Total				
T_1	AP – UC	-2.05 (3.72)	-9.35, 5.24	p=0.581
	AP – SM	4.43 (3.38)	-2.19, 11.05	p=0.189
T_2	AP – UC	-6.84 (4.00)	-14.66, 1.00	p=0.087
	AP – SM	-4.25 (3.55)	-11.2, 2.70	p=0.231
T_3	AP – UC	-0.85 (4.19)	-9.06, 7.36	p=0.840
	AP – SM	3.49 (3.29)	-2.96, 9.94	p=0.289

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group, SM=sham group, UC=usual-care group

5.2.1.2 CMAI sub-scores

In order to examine the possible specific effect of acupressure on the sub-types of agitation, the sub-scores of CMAI were analyzed separately. The following section presents the analysis of the effect of acupressure on the four sub-scores of the CMAI: VNAB score, VAB score, PNAB score, and PAB score.

VNAB score

As shown in Table 5.6, the GEE model showed no significant interaction effect between groups and time points on the VNAB score. There was a significant difference across time points (X^2=17.093, p=0.001), but no significant difference between groups.

Table 5.6:

Comparing VNAB scores between groups over time

Effect types	Statistics
VNAB	
Time (T_0, T_1, T_2, T_3)	X^2=17.093, p=0.001*
Group (AP, SM, UC)	X^2=2.337, p=0.311
Time x Group	X^2=7.326, p=0.292

* Statistically significant; VNAB=verbally non-aggressive behaviors; AP=acupressure; SM=sham; UC=usual care; T_0=baseline;
T_1=3rd week after commencement of the intervention;
T_2=5th week after commencement of the intervention;
T_3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing VNAB scores between time points by groups is shown in Table 5.7, in which the VNAB scores at T_1, T_2, and T_3 are compared with that in T_0 separately in different groups. In the acupressure group, the VNAB scores in T_1, T_2 and T_3 were observed to have no significant difference compared with that at T_0. In the sham group, the VNAB score at T_1 was observed to be significantly lower than at T_0 (MD=-3.63, 95%CI: -5.97, -1.30), the VNAB score at T_2 was observed to be not significantly different from that in T_0, and the VNAB score at T_3 was significantly lower than that at T_0 (MD=-3.55, 95%CI: -5.52, -1.57). In the usual-care group, the VNAB scores at T_1, T_2, and T_3 were observed to have no significant difference compared with that at T_0.

Table 5.7:

Comparing VNAB scores between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
VNAB				
AP				
	$T_1 - T_0$	-0.82 (1.00)	1.13, -2.77	p=0.409
	$T_2 - T_0$	-1.67 (0.88)	0.05, -3.40	p=0.057
	$T_3 - T_0$	-0.54 (0.88)	1.18, -2.27	p=0.537
SM				
	$T_1 - T_0$	-3.63 (1.19)	-1.30, -5.97	p=0.002*
	$T_2 - T_0$	-2.51 (1.05)	-0.46, -4.56	p=0.016
	$T_3 - T_0$	-3.55 (1.01)	-1.57, -5.52	p<0.001*
UC				
	$T_1 - T_0$	-2.41 (1.00)	-0.46, -4.37	p=0.016
	$T_2 - T_0$	-2.05 (1.30)	0.49, -4.59	p=0.113
	$T_3 - T_0$	-1.64 (0.87)	0.07, -3.35	p=0.060

+LSD-test; *statistically significant after Bonferroni adjustment; AP= acupressure group; SM=sham group; UC=usual-care group;

VNAB=verbally non-aggressive behaviors; T_0=baseline; T_1=3rd week after commencement of the intervention; T_2=5th week after commencement of the intervention: T_3=8th week after commencement of the intervention

PNAB score

As shown in Table 5.8, the GEE model showed no significant interaction effect between groups and time points on the PNAB score. There was no statistically significant difference between time points and groups.

Table 5.8:

Comparing PNAB scores between groups over time

Effect types	Statistics
PNAB	
Time (T_0, T_1, T_2, T_3)	X^2=3.514, p=0.319
Group (AP, SM, UC)	X^2=2.767, p=0.251
Time x Group	X^2=5.946, p=0.429

AP=acupressure group, SM=sham-acupressure group, UC=usual-care group;
PNAB=physically non-aggressive behavior; T_0=baseline;
T_1=3rd week after commencement of the intervention;
T_2=5th week after commencement of the intervention;
T_3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing PNAB scores between time points by groups is shown in Table 5.9. The PNAB scores at T_1, T_2, and T_3 were compared with that at T_0 separately in different groups. In the acupressure group, the PNAB score at T_2 was observed to be significantly lower than that at T_0 (MD=-2.57, 95%CI: -4.32, -0.83). PNAB scores at T_1 and T_3 were observed to be not significantly different from those at T_0. In the sham and usual-care groups, the PNAB scores at T_1, T_2 and T_3 were observed to be not significantly different from those at T_0.

Table 5.9:

Comparing PNAB scores between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
PNAB				
AP				
	$T_1 - T_0$	-1.62 (1.07)	-3.71, 0.47	p=0.130
	$T_2 - T_0$	-2.57 (0.90)	-4.32, -0.83	p=0.004*
	$T_3 - T_0$	-1.07 (1.06)	-3.15, 1.01	p=0.314
SM				
	$T_1 - T_0$	-0.78 (0.92)	-2.59, 1.02	p=0.397
	$T_2 - T_0$	-0.39 (0.94)	-2.22, 1.44	p=0.676
	$T_3 - T_0$	-1.11 (0.91)	-2.90, 0.68	p=0.224
UC				
	$T_1 - T_0$	0.38 (1.11)	-1.79, 2.56	p=0.728
	$T_2 - T_0$	-0.31 (1.20)	-2.64, 2.03	p=0.796
	$T_3 - T_0$	-0.36 (1.21)	-2.73, 2.01	p=0.767

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group, SM=sham group, UC=usual-care group; PNAB=physically non-aggressive behaviors

VAB score

As shown in Table 5.10, the GEE model showed that there was no significant interaction effect between groups and time points in terms of the VAB scores. There was no statistically significant difference between time points and between groups.

Table 5.10:

Comparing VAB scores between groups over time

Effect types	Statistics
VAB	
Time (T_0, T_1, T_2, T_3)	X^2=2.755, p=0.431
Group (AP, SM, UC)	X^2=1.137, p=0.566
Time x Group	X^2=10.636, p=0.100

AP=acupressure group, SM=sham group, UC=usual-care group; VAB=verbally aggressive behaviors;

T_0=baseline; T_1=3rd week after commencement of the intervention;

T_2=5th week after commencement of the intervention;

T_3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing VAB scores between time points by groups is shown in Table 5.11. The VAB scores at T_1, T_2, and T_3 were compared with T_0 separately in different groups. In the acupressure and sham groups, the VAB scores at T_1, T_2 and T_3 are observed to have no significant difference compared with those at T_0. In the usual-care group, the VAB score at T_3 was observed to be significantly lower than that at T_0 (MD=-1.82, 95%CI: -3.16, -0.48). The VAB scores at both T_1 and T_2 were observed to have no significant difference compared with that at T_0.

Table 5.11:

Comparing VAB scores between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
VAB				
AP				
	$T_1 - T_0$	0.15 (0.69)	-1.20, 1.51	p=0.823
	$T_2 - T_0$	-0.85 (0.61)	-2.04, 0.34	p=0.161
	$T_3 - T_0$	-0.15 (0.81)	-1.73, 1.42	p=0.848
SM				
	$T_1 - T_0$	-0.71 (0.57)	-1.83, 0.41	p=0.216
	$T_2 - T_0$	0.37 (0.60)	-0.80, 1.54	p=0.540
	$T_3 - T_0$	-0.04 (0.61)	-1.24, 1.15	p=0.942
UC				
	$T_1 - T_0$	-0.79 (0.95)	-2.66, 1.07	p=0.404
	$T_2 - T_0$	-0.74 (0.77)	-2.24, 0.76	p=0.331
	$T_3 - T_0$	-1.82 (0.68)	-3.16, -0.48	p=0.008*

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure, SM=sham, UC=usual care

VAB=verbally aggressive behaviors

PAB score

As shown in Table 5.12, the GEE model showed that there were no significant interaction effect between groups and time points in terms of the PAB score. There were no statistically significant differences between time points or between groups.

Table 5.12:

Comparing PAB scores between groups over

Effect types	Statistics
PAB	
Time (T_0, T_1, T_2, T_3)	X^2=7.567, p= 0.056
Group (AP, SM, UC)	X^2=0.456, p=0.796
Time x Group	X^2=10.688, p=0.099

AP=acupressure group, SM=sham group, UC=usual-care group; PAB=physically aggressive behaviors;

T_0=baseline; T_1=3rd week after commencement of the intervention;

T_2=5th week after commencement of the intervention;

T_3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing PAB scores between time points by groups is shown in Table 5.13. The PAB scores at T_1, T_2, and T_3 were compared with that at T_0 separately in different groups. In the acupressure, sham, and usual-care groups; PAB scores in T_1, T_2 and T_3 were observed to be not significantly different from those at T_0.

Table 5.13:

Comparing PAB scores between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics+
PAB				
AP				
	$T_1 - T_0$	0.51 (1.17)	-1.78, 2.80	p=0.661
	$T_2 - T_0$	-1.74 (0.88)	-3.47, 0.01	p=0.049
	$T_3 - T_0$	-0.87 (1.06)	-2.95, 1.20	p=0.408
SM				
	$T_1 - T_0$	-2.32 (1.06)	-4.40, -0.24	p=0.029
	$T_2 - T_0$	-1.29 (1.15)	-3.55, 0.97	p=0.262
	$T_3 - T_0$	-2.66 (1.09)	-4.79, -0.53	p=0.014
UC				
	$T_1 - T_0$	0.05 (0.85)	-1.61, 1.71	p=0.952
	$T_2 - T_0$	0.05 (0.87)	-1.65, 1.75	p=0.953
	$T_3 - T_0$	-1.03 (0.78)	-2.56, 0.51	p=0.190

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group; SM=sham group; UC=usual-care group; PAB=physically aggressive behaviors

5.2.2 Research question 2 – the effects on stress

As shown in Table 5.14 and Figure 5.2, the GEE model showed a significant interaction effect between groups and time points in terms of salivary cortisol level (X^2=14.811, p=0.022). There were no significant differences between groups or time points.

Table 5.14:

Comparing SC levels (µg/dL) between groups over time

Effect types	Statistics
SC level	
Time (T_0, T_1, T_2, T_3)	X^2=3.274, p=0.351
Group (AP, SM, UC)	X^2=2.611, p=0.271
Time x Group	X^2=14.811, p=0.022*

*statistically significant; AP=acupressure group, SM=sham group, UC=usual-care group;

T_0=baseline; T_1=3rd week after commencement of the intervention;

T_2=5th week after commencement of the intervention;

T_3=8th week after commencement of the intervention

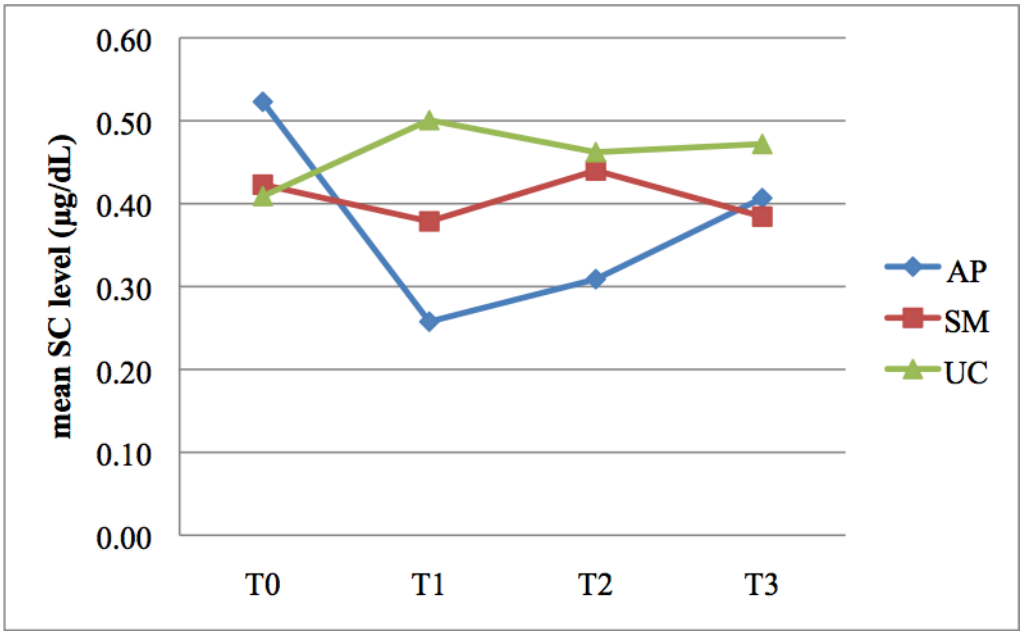


Figure 5.2. Graphical illustration of the comparison of changes in SC level over time by groups. SC=salivary cortisol; AP=acupressure group; SM=sham group; UC=usual-care group; T0=baseline; T1=3rd week after commencement of the intervention; T2=5th week after commencement of the intervention; T3=8th week after commencement of the intervention

The pair-wise sub-group analysis comparing SC level between time points by groups is shown in Table 5.15. The SC levels at T_1, T_2, and T_3 were compared with that at T_0 separately in different groups. In the acupressure group, the SC level at T_1 was observed to be significantly lower than that at T_0 (MD=-0.27, 95%CI: -0.41, -0.12), and the SC level at T_2 was observed to be significantly lower than that at T_0 (MD=-0.21, 95%CI: -0.34, -0.08). The SC level at T_3 was observed to be not significantly different compared with that at T_0. In both the sham and usual-care groups, the SC levels T_1, T_2, and T_3 showed no significant differences compared with those at T_0 in the same group.

Table 5.15:

Comparing SC levels (μg/dL) between time points by groups

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
SC level				
AP				
	$T_1 - T_0$	-0.27 (0.08)	-0.41, -0.12	p<0.001*
	$T_2 - T_0$	-0.21 (0.07)	-0.34, -0.08	p=0.001*
	$T_3 - T_0$	-0.12 (0.09)	-0.29, 0.05	p=0.180
SM				
	$T_1 - T_0$	-0.04 (0.06)	-0.19, 0.08	p=0.485
	$T_2 - T_0$	0.02 (0.04)	-0.06, 0.09	p=0.642
	$T_3 - T_0$	-0.04 (0.05)	-0.15, 0.07	p=0.483
UC				
	$T_1 - T_0$	0.09 (0.09)	-0.09, 0.28	p=0.328
	$T_2 - T_0$	0.05 (0.08)	-0.10, 0.21	p=0.494
	$T_3 - T_0$	0.06 (0.11)	-0.15, 0.29	p=0.567

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group, SM=sham group, UC=usual-care group

The pair-wise sub-group analysis comparing SC levels between groups by time points after completion of the intervention is shown in Table 5.16, in which SC

levels are compared between the acupressure group and the two control groups separately at the time points after completion of the intervention (i.e. T_1, T_2, and T_3). The only significant difference observed was between the AP and UC groups at T_1.

Table 5.16

Comparing SC levels (µg/dL) between groups by time points after completion of intervention

Pair-wise comparison		MD (SE)	95%CI	Statistics[+]
SC level				
T_1	AP – UC	-0.24 (0.09)	-0.42, -0.07	p=0.007*
	AP – SM	-0.12 (0.05)	-0.23, -0.02	p=0.023
T_2	AP – UC	-0.15 (0.08)	-0.31, 0.01	p=0.058
	AP – SM	-0.13 (0.07)	-0.27, 0.01	p=0.062
T_3	AP – UC	-0.07 (0.13)	-0.32, 0.19	p=0.611
	AP – SM	0.02 (0.09)	-0.16, 0.21	p=0.813

+LSD-test; *statistically significant after Bonferroni adjustment; AP=acupressure group, SM=sham group, UC=usual-care group

5.2.3 Research question 3 - the mediation effects on agitation through stress

Before examining the indirect effect, the total effect was first examined. As discussed in the statistical analysis plan in section 4.2.10.3, the total effect equals the sum of the direct and indirect effects (i.e. the mediation effect). If the total effect is insignificant (i.e. too small), the indirect effect will not be significant.

The SEM analyses examining the total effects on the causal paths from interventions to agitation were statistically insignificant at all three time points after completion of the intervention (i.e. T_1, T_2, and T_3). The total effects by standardized estimates whose score range was -1 to 1 were measured to be 0.09 at T_1, 0.15 at T_2, and -0.04 at T_3, which were all statistically insignificant. Given that there were no

significant total effects on the causal paths from the interventions to agitation, there were no mediation effects between the intervention and the agitation.

Although the total effects on the causal paths from interventions to agitation were not statistically significant, SEM analyses examining the mediation or indirect effects were still performed. Model 1 refers to using the set of data collected at T_1. Model 2 refers to using the set of data collected at T_2. Model 3 refers to using the set of data collected at T_3. All three models showed very good Goodness-of-fit indexes: Model 1 (X^2=2.15; NFI= 0.92; CFI: 1.0; SRMR=0.07), Model 2 (X^2=0.32; NFI=0.97; CFI=1.0; SRMR=0.03), and Model 3 (X^2<0.001, NFI= 0.99, CFI=1.0; SRMR<0.01). As shown in Table 5.17 and Figures 5.3, 5.4, and 5.5, there were no significant causal paths from acupressure to stress or from stress to agitation at the same time. Therefore, there was no significant indirect effect from acupressure to agitation by mediating stress in the three models.

Table 5.17:

The three models examining the mediation effect of acupressure on agitation through stress

					Goodness-of-fit indexes			
	Time	Path	E (SE)	p-value	X^2	NFI	CFI	SRMR
Model 1	T_1	I -> A	0.02 (0.10)	p=0.831	2.15	0.92	1	0.07
		I -> S	-0.42 (0.09)	p<0.001*				
		S ->A	-0.17 (0.09)	p=0.059				
Model 2	T_2	I -> A	-0.17 (0.09)	p=0.068	0.32	0.97	1	0.03
		I -> S	-0.26 (0.09)	p=0.005*				
		S -> A	0.07 (0.09)	p=0.444				
Model 3	T_3	I -> A	-0.03 (0.09)	p=0.767	<0.01	0.99	1	<0.01
		I -> S	-0.09 (0.09)	p=0.344				
		S -> A	0.07 (0.09)	p=0.483				

E= estimate of effect; SE=standard error; I=interventions; A=agitation; S=stress; NFI= normed fit index; CFI=comparative fit index; SRMR=standardized root mean-square residual

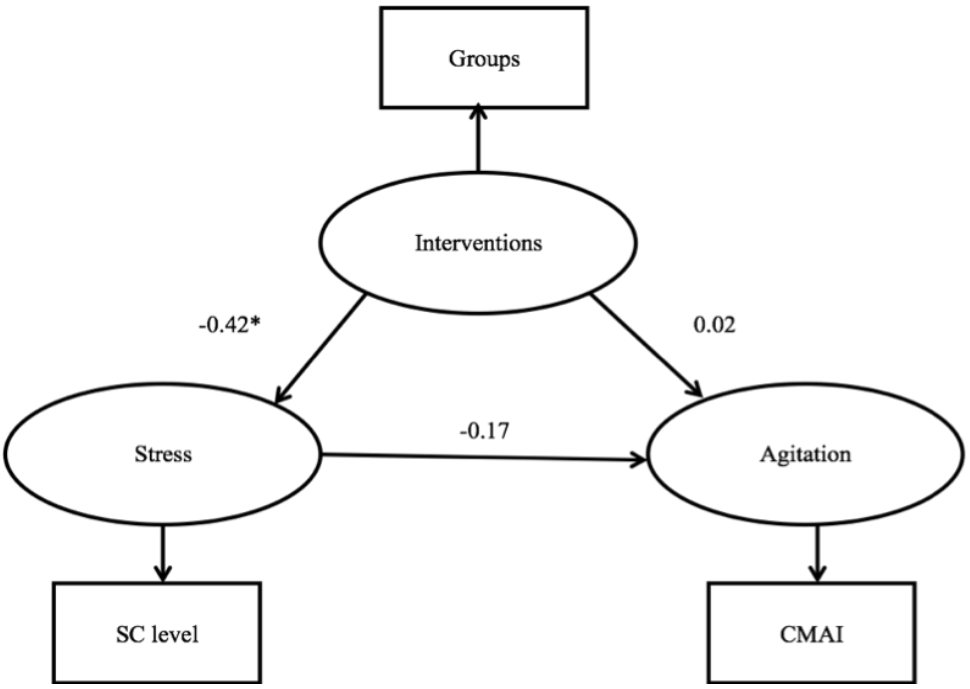


Figure 5.3. Model 1 in T_1. SC=salivary cortisol, CMAI=Cohen-Mansfield Agitation Inventory

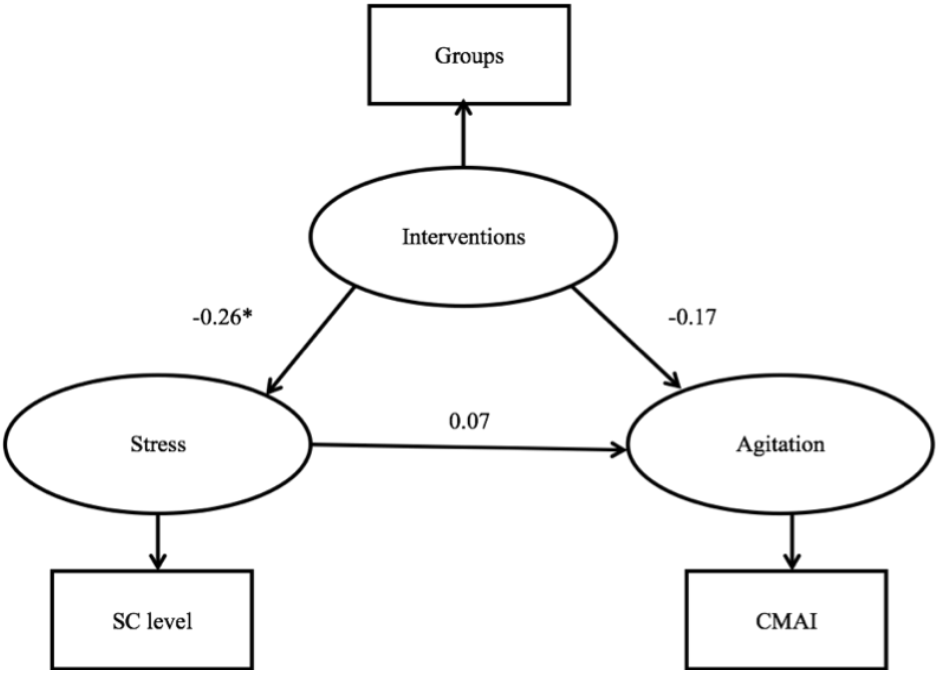


Figure 5.4. Model 2 in T_2. SC=salivary cortisol, CMAI=Cohen-Mansfield Agitation Inventory

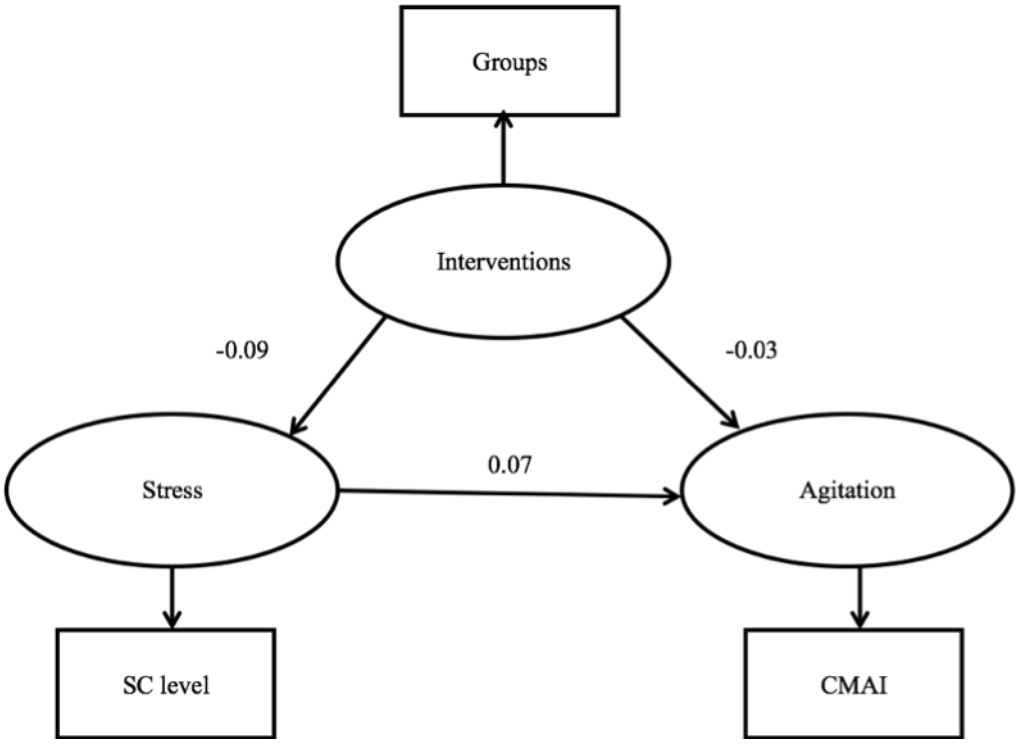


Figure 5.5. Model 3 in T_3. SC=salivary cortisol, CMAI=Cohen-Mansfield Agitation Inventory

5.2.4 Research question 4 - the sustainability of the effects

For the effect of acupressure on agitation, as shown in Table 5.4, the agitation reduction in the acupressure group compared with the baseline was just significant at T_2, but was not sustained until T_3. For the effect of acupressure on stress as shown in Table 5.14, in the acupressure group, the salivary cortisol level reduction compared with the baseline was significant at T_1 and T_2, but not sustained until T_3.

5.3 Sensitivity Analysis

The sensitivity test in this study aimed at comparing the difference between two methods of analysis: modified intention-to-treat (mITT) and per-protocol (PP).

As shown in Table 5.18, in the mITT population, there were 39 participants in the acupressure group, 41 in the sham-acupressure group, and 39 in the usual-care group. In the PP population, there were 32 participants in the acupressure group, 37 in the sham-acupressure group, and 39 in the usual-care group.

Table 5.18:

Participant distribution between analysis methods by groups

Group	mITT analysis (n=119)	PP analysis (n=108)
AP	39	32
SM	41	37
UC	39	39

PP=per-protocol; mITT=modified intention-to-treat; AP=acupressure group; SM=sham group; UC=usual-care group

By comparing the results from these two analysis methods, as shown in Tables 5.19 and 5.20, there were no differences of statistical significance between the two analysis methods in terms of the primary and secondary outcomes.

Table 5.19

Comparing the results of the CMAI total scores between PP and mITT

	CMAI total scores			
	PP		mITT	
Group	X^2= 0.936	p=0.626	X^2= 1.351	p=0.509
Time	X^2=14.838	p=0.002*	X^2=14.735	p=0.002*
Group*Time	X^2= 9.349	p=0.155	X^2= 12.486	p=0.052
	MD (SD)	Statistics$^+$	MD (SD)	Statistics$^+$
AP				
$T_1 – T_0$	-1.74 (2.57)	p=0.497	-1.77 (2.78)	p=0.525
$T_2 – T_0$	-5.85 (1.71)	p=0.001*	-6.84 (1.92)	p<0.001*
$T_3 – T_0$	-2.34 (2.26)	p=0.302	-2.64 (2.51)	p=0.293
SM				
$T_1 – T_0$	-7.58 (3.00)	p=0.010*	-7.44 (2.65)	p=0.005*
$T_2 – T_0$	-4.11 (2.66)	p=0.122	-3.83 (2.36)	p=0.105
$T_3 – T_0$	-7.92 (2.29)	p=0.001*	-7.37 (2.09)	p<0.001*
UC				
$T_1 – T_0$	-2.77 (2.44)	p=0.255	-2.77 (2.44)	p=0.255
$T_2 – T_0$	-3.05 (2.58)	p=0.238	-3.05 (2.58)	p=0.238
$T_3 – T_0$	-4.85 (2.66)	p=0.068	-4.85 (2.66)	p=0.068

+LSD-test; *statistically significant after Bonferroni adjustment; PP=per-protocol; mITT=modified intention-to-treat; AP=acupressure group; SM=sham group; UC=usual-care group; MD=mean difference

Table 5.20

*Comparing the results on the SC levels*μ*) g/dL) between PP and mITT*

	Salivary cortisol level (μg/dL)			
	PP		mITT	
Group	X^2= 2.357	p=0.308	X^2= 2.611	p=0.271
Time	X^2=3.468	p=0.325	X^2=3.274	p=0.351
Group*Time	X^2= 14.191	p=0.028*	X^2= 14.811	p=0.022*
	MD (SD)	Statistics+	MD (SD)	Statistics+
AP				
$T_1 – T_0$	-0.28 (0.08)	p=0.001*	-0.27 (0.08)	p<0.001*
$T_2 – T_0$	-0.23 (0.07)	p=0.002*	-0.21 (0.07)	p=0.001*
$T_3 – T_0$	-0.15 (0.09)	p=0.092	-0.12 (0.09)	p=0.180
SM				
$T_1 – T_0$	-0.03 (0.06)	p=0.673	-0.04 (0.06)	p=0.485
$T_2 – T_0$	0.01 (0.04)	p=0.811	0.02 (0.04)	p=0.642
$T_3 – T_0$	-0.05 (0.05)	p=0.353	-0.04 (0.05)	p=0.483
UC				
$T_1 – T_0$	0.09 (0.09)	p=0.328	0.09 (0.09)	p=0.328
$T_2 – T_0$	0.05 (0.08)	p=0.494	0.05 (0.08)	p=0.494
$T_3 – T_0$	0.06 (0.11)	p=0.567	0.06 (0.11)	p=0.567

+LSD-test; *statistically significant after Bonferroni adjustment; PP=per-protocol; mITT=modified intention-to-treat; AP=acupressure group; SM=sham group; UC=usual-care group; MD=mean difference

5.4 Summary

The study showed that there was a significant reduction of agitation within both the acupressure and sham groups, but no significant interaction effects (i.e. group by time) were observed. There was a significant reduction of stress only in the acupressure group, with a significant interaction effect (i.e. group by time) observed. The results of the study did not find a significant total effect of acupressure on agitation reduction. Therefore there was no mediation effect of acupressure on agitation. Stress was not a mediator causing reduction of agitation in PWD. Acupressure significantly reduced stress but not agitation. The effect of

stress reduction was only observed in the week immediately after the intervention compared with the controls; it did not sustain at the follow-up observation at T_3. In the sensitivity analysis, there was no difference in the interpretations of all the results between the mITT and PP analysis.

Chapter 6 Discussion

This chapter begins by discussing the participants' characteristics and continues by presenting the answers and findings to the research questions. Other findings are then discussed. Finally, the implications, strengths and limitations of this study are presented.

6.1 Participants' Characteristics

The purpose of profiling the participants' characteristics was to show comparability of groups and assess the external validity of the trial results (Furler et al, 2012). The comparability of participants' characteristics was reported earlier; this section aimes at discussing the external validity by comparing the participants' characteristics in this study with similar populations (i.e. agitated nursing home residents with dementia) reported in other studies. This helps to understand how the results of this study are valid to be generalized.

6.1.1 Demographic variables

6.1.1.1 Age and gender

In Hong Kong, a large-scale local study (Lee et al, 2009) including 1819 nursing home residents sampled from 533 private and 130 subsidized nursing homes, reported that females made up 73.3% of the nursing home population? and the mean age was 78.2 years old. In the United States, the National Center for Health Statistics (Harris-Kojetin et al, 2013) reported that 67.7% of the nursing home residents were female, 85.1% were aged 65 or older, and 42.3% were 85 or older. Studies targeting agitated nursing home residents with dementia reported that

there were 54.5% female residents with a mean age of 77.3 in Taiwan (Ho et al, 2011) and 75% female residents with a mean age of 87 in Western countries (Husebo et al, 2011).

In this study, there were more female than male participants. 76% of all participants were female. The mean age of the participants in this study was 86.5 years old. The gender distribution for the participants in this study was comparable with the general population and with agitated PWD in nursing homes reported in other studies. As regards their age, the agitated nursing home residents with dementia in this study (i.e. 86.5 years old) were older than the general population in nursing homes in Hong Kong (i.e. 78.2 years old). The age range of agitated nursing home residents reported in other countries was wide (i.e. 77.3-87). The mean age of the participants in this study (i.e. 86.5) was more or less comparable with the age range reported in other studies conducted in different regions.

6.1.1.2 Length of stay

In Hong Kong, the same abovementioned large-scale local study (Lee et al, 2009) reported that the mean length of stay (LOS) was 90.2 months. In United States, a national nursing home survey (Jones et al, 2009) reported that the mean LOS of the nursing home residents was 27.8 months. In Taiwan, a study targeting agitated nursing home residents with dementia reported that the LOS was 45 months (Ho et al, 2011). There were no local studies reporting LOS specifically with regard to agitated nursing home residents with dementia.

In this study, participants had a mean LOS of 64.4 (SD: 71.7) months. A comparison with the findings from other studies on general nursing home residents showed that the LOS of general nursing home residents in Hong Kong (i.e. 90.2 months) was much longer than that in United States (i.e. 27.8 months). The LOS of the participants in this study (i.e. 64.4 months) was longer than in a similar population in Taiwan (i.e. 45 months), but shorter than for general residents in Hong Kong (i.e. 90.2 months).

From these findings, it can be concluded that geographical factors play a large role in the LOS of nursing home residents. Hong Kong nursing home residents generally have a longer LOS, disregarding the nature of dementia or agitation.

6.1.2 Clinical variables

6.1.2.1 Functional status

Poor functional status can be associated with agitation in PWD (Chen et al, 2014). In Hong Kong, the abovementioned large-scale local study (Lee et al, 2009) showed that the functional status of nursing home residents was quite poor. Their functional status was measured by the MDS-ADL sub-scale on a scale of 0-6. The lower the score, the more dependent the resident was on others for performing ADL. The mean score was 2.0 (SD: 2.3). In the United States, the National Center for Health Statistics (Centers for Disease Control and Prevention, 2013) reported that 56-96.1% of residents needed a variety of ADL assistance. In Norway (Husebo et al, 2011), the functional status specifically of agitated nursing home residents with dementia was also quite poor. Their functional status was measured by the

Activities of Daily Living on a scale of 0-20. Lower scores indicated greater dependence on others in performing ADL. The mean score was 7-8.

In this study, the functional status measured by mean mBI was 35.9 (SD: 33.1) on a scale of 0-100. Lower scores indicated a higher level of dependence in performing ADL, showing that the functional status of the participants in this study was similarly poor compared with the general and agitated nursing home residents in other regions.

6.1.2.2 Cognitive function

The decline in cognitive function in PWD may cause agitation, as mentioned above (Hall & Buckwalter, 1987; Chen et al, 2014). In Hong Kong (Lee et al, 2009), the large-scale local study mentioned earlier showed that the cognitive function of general nursing home residents was between borderline intact and mild impairment. Cognitive function was measured by MDS-CPS on a scale of 0-6. Lower scores indicate better cognitive function. The mean MDS-CPS was measured as 1.6 (SD: 1.6). In Western countries (Cohen-Mansfield et al, 2007; ver der Ploeg et al, 2013), the cognitive function of agitated nursing home residents with dementia was measured by the MMSE on a scale of 0-30. It was measured as 6 to 9.5, meaning severely impaired.

The cognitive function of the participants in this study, measured by mean MMSE, was 7.0 (SD: 7.9), showing that the severity of cognitive impairment of the participants in this study was poor, similar to that of agitated nursing home residents with dementia in western countries. However, the participants in this

study had all been diagnosed with dementia, thus their cognitive function was expected to be worse than that of general nursing home residents in Hong Kong.

6.1.2.3 Chronic medical illnesses

Chronic medical illness is associated with problem behaviors in dementia, such as agitation (Ronsenberg & Lyketsos, 2011). In Hong Kong, a large-scale study with 1603 general nursing home residents aged over 60 (Chen et al, 2008) showed that 85% of them had chronic illnesses. 55% of the residents had more than one chronic illness. The mean number of chronic medical illnesses of agitated nursing home residents with dementia was found to be 2.7 in Taiwan (Ho et al, 2011) and 8.9 in Israel (Cohen-Mansfield et al, 2014).

Participants in this study had a mean number of 4.1 chronic medical illnesses (SD: 1.9), which was similar compared with the general nursing home residents in Hong Kong, as the majority of them (85%) had one or more chronic medical illnesses. However, participants in this study had more chronic illness (i.e. 4.1) than agitated nursing home residents with dementia in Taiwan (i.e. 2.7) and fewer compared with those in Israel (i.e. 8.9). It can be concluded that there are no clear differences in the number of chronic illnesses of the participants in this study compared with general nursing home residents in Hong Kong and agitated nursing home residents with dementia in other countries.

6.1.2.4 Psychotropic drug use

Psychotropic drugs have commonly been used to manage agitation, as mentioned above (Seitz et al, 2011, Kirshner, 2011; Gagne et al, 2011). In Hong

Kong, 28% of general nursing home residents had been prescribed with antipsychotics (Feng et al, 2009). In the Netherlands, 66% of nursing home residents in dementia special care units had been prescribed with psychotropic drugs to manage their psycho-behavioral symptoms (Wetzels et al, 2011). In Norway, 25-50% of agitated nursing home residents with dementia had been prescribed with psychotropic drugs to manage their psycho-behavioral symptoms (Husebo et al, 2011).

In this study, 92 participants (77.3%) had been prescribed with psychotropic drugs. The mean number of drugs used in this study was 1.5 (SD: 1.1), showing that the use of psychotropic drugs for managing psycho-behavioral symptoms was more common in the participants of this study than with general nursing home residents in Hong Kong (28%) and agitated nursing home residents with dementia in Western countries (25%-66%).

6.1.2.5 Physical restraint

Physical restraint is commonly used on PWD with behavioral problems such as agitation (Kwan et al, 2015). In Hong Kong (Feng et al, 2009), a large-scale study on general nursing home residents - including 1914 nursing home residents in 14 nursing homes - showed that 25% of general nursing home residents were put in physical restraints. In Germany (Meyer et al, 2009), a large-scale study of 2367 nursing home residents showed that the prevalence of residents with at least one physical restraint was 26.2%. In Taiwan, prevalence of the use of physical restraint

on agitated nursing home residents with dementia ranged from 7.7-54.4% (Lin et al, 2009; Ho et al, 2011).

In this study, 88 participants (73.9%) had been put in physical restraints. Compared with general nursing home residents, The prevalence of using physical restraint on agitated residents with dementia was greater compared with the rate of restraint use on both the general nursing home resident population in Hong Kong and on agitated residents with dementia in other countries. This shows that the use of physical restraint was more common on the participants in this study than on either general nursing home residents or agitated nursing home residents with dementia in both Hong Kong and other countries.

6.1.2.6 Family visits

Passmore (2014) argued that one of the underlying causes of agitation could be inadequate family involvement or support, which was measured by number of family visits. In Hong Kong (Cheng, 2009), a small-scale study showed that a majority (52.2%) of nursing home residents were visited by their family less than once a month. Another study (Gräske et al, 2015) examined family visits specifically with regard to nursing home residents with dementia. The majority of residents were visited several times a week (41.3%). Only 11.6% of residents with dementia were visited by their family less than once a month.

Eight participants in this study (6.7%) were never visited by their family. The majority (51.2%) were visited by their family at least once a week. Because different units were used to measure the frequency of family visits, it was not easy

to compare the findings of this study with other studies precisely. However, it could be generally concluded that participants in this study were more frequently visited by their family than general nursing home residents in Hong Kong.

6.1.2.7 Engagement in activities

Cognitive impairment is a significant factor impacting the activity engagement level of nursing home residents (Kolanowski et al, 2006), in that PWD are more prone to be engaged in a lower level of activity. Activity engagement is an essential need of PWD in nursing homes. Lack of engagement in activity was reported to cause agitation because of unmet needs (Trahan et al, 2014). There is a dearth of studies examining the activity engagement level of nursing home residents in Hong Kong. In the United States, a study examining the activity engagement of nursing home residents with dementia showed that 45% of subjects engaged in few or no facility activities (Buettner & Fitzsimmons, 2003).

In this study, 46.2% of participants engaged in few or no activities (i.e. less than one per week). This finding was comparable to the activity engagement levels of nursing home residents with dementia reported in other studies.

To summarize their demographic and clinical characteristics, the participants in this study had more or less the same age, gender distribution, functional status, cognitive function, number of chronic illnesses, and activity engagement level as similar populations reported in other studies. However, the participants in this study had longer length of stay, used more psychotropic drugs, were more often put under physical restraint, and received more family visits than similar populations reported

in other studies. These characteristics should be considered before generalizing the findings of this study to other contexts.

6.1.3 Outcome variables

6.1.3.1 Agitation

In Hong Kong, a small-scale local study (Kwok et al, 2013) showed that the mean CMAI score of community-dwelling PWD ranged from 41.5-45.5. In other similar studies, the mean score of the CMAI ranged from 39.3-60.6 (Lin et al, 2009; Husebo et al, 2011; Ho et al, 2011).

The mean CMAI total score of this study at baseline was 47.6. In the literature, it was found that agitation severity varied across regions and studies. This can be partially explained by different locally validated versions of the CMAI used in different studies. This is because the possible score ranges of different versions of the CMAI are different. This study used a validated Hong Kong version of the CMAI (Lai, 2010) with 21 items (score range: 21-168). The versions used in the aforementioned studies were all CMAI (Cohen-Mansfield & Libin, 2004) with 29 items (score range: 29-232). The instrument used in this study could be expected to result in scores from 8-64 points lower compared with the version of CMAI used in the above studies. After considering the scoring difference among different versions of the CMAI, the agitation level of the participants in this study was in the middle of the CMAI range reported in the previous studies. This showed that participants in the study had similar agitation levels to those in other studies. Participants in this

study also demonstrated higher levels of agitation compared with community-dwelling PWD.

6.1.3.2 Stress

In Hong Kong, there is a dearth of studies examining the cortisol levels of PWD. In Canada, a study of 635 community-dwelling subjects showed that the morning salivary cortisol level of elders without cognitive impairment was 0.22 µ g/dL, and that of elders with cognitive impairment without specification of a formal dementia diagnosis was 0.23 µ g/dL (Potvin et al, 2013). In the United States, another study reported that the early morning salivary cortisol levels of nursing home residents with advanced dementia were 0.44 µ g/dL and 0.48 µ g/dL (Woods et al, 2008).

The mean salivary cortisol level of the participants at baseline was found to be 0.45 µ g/dL (SD: 0.30). The saliva sample was collected consistently early in the morning (07:00 to 08:00). Compared with the previous studies whose samples were also collected at similar times in community-dwelling older people, it showed that participants in this study demonstrated higher levels of salivary cortisol compared with community-dwelling older people with or without cognitive impairment (Potvin et al, 2013). The salivary cortisol level of the participants of this study (i.e. 0.45 µ g/dL) was very comparable with that of agitated nursing home residents with dementia (i.e. 0.44 µ g/dL and 0.48 µ g/dL) reported in an earlier study (Woods et al, 2008). Due to the limited number of studies on salivary cortisol in PWD, a precise comparison cannot be made. There were inconsistent observations on the salivary

cortisol levels of people with cognitive impairment, with 0.23 μ g/dL found in the community and 0.44-0.48 μ g/dL in nursing homes. It was unclear whether the different observations were related to the severity of the dementia (i.e. cognitive impairment with specification of the severity compared with advanced dementia), to the context (i.e. community-dwelling compared with nursing home dwelling), or to other factors. However, a preliminary conclusion can be drawn from this study and the previous studies, namely that agitated nursing home residents diagnosed with dementia have similarly high levels of salivary cortisol.

6.2 Other Findings

Besides answering the research questions, this study also yielded some meaningful findings that were important to discuss. These other findings were related to the intervention components of acupressure, the effect size of acupressure, the possible effect onset time of acupressure, the feasibility advantages of acupressure, the hyposalivation of agitated nursing home residents with dementia, and the high administration of psychotropic drugs prescribed on an as-needed basis.

6.2.1 The intervention components of acupressure

Acupressure/acupuncture is a complex intervention that may comprise a basket of undividable therapeutic components (Macpherson & Kaptchuk, 1997). The theoretically active component of acupressure according to TCM meridian theory is the acupoint activation, which makes it different from other similar manual-based therapy (e.g. massage). In this study, acupressure was designed to comprise the theoretically active component of acupoint activation. However, acupressure also

unavoidably comprised other components, including tactile stimulation and other possible components such as placebo effects and social interaction during the intervention. During the course of acupressure, usual care (e.g. facility activities and socialization) was also provided to the participants. In order to determine the effect of the hypothetical intervention component of acupressure (i.e. acupoint activation), a sham group was purposely set up to comprise acupressure-comparable components while sparing the hypothetical intervention component (i.e. acupoint activation). In order to also know whether the effect of acupressure is attributable to a combined set of different inter-related therapeutic components in acupressure, the usual-care group was also set up purposefully.

For the effect of acupressure on agitation, the significant reduction in the acupressure group at T_2 (MD: -6.84, p=<0.001; at T_2) led to the conclusion that the combined set of all therapeutic components in acupressure (i.e. acupoint activation, tactile stimulation, other possible components, and usual care) was effective in reducing agitation. However, the insignificant interaction effect between group and time might indicate that the agitation-reducing effect of acupressure contributed by its hypothetical active component (i.e. acupoint activation) was not significantly larger than that of the control conditions (i.e. the sham and usual care groups). Reduction of agitation was also observed in the control conditions, which included sham (MD: -3.83, p=0.105; in T_2) and usual care groups (MD: -3.05, p=0.238, in T_2), although the reductions were not significant.

These observations sent the message that agitation would gradually diminish over time in the controlled condition (i.e. sham and usual care). Although the

reduction over time was not significant under controlled conditions, acupressure by its hypothetical active component (i.e. acupoint activation) could not show a significantly larger effect on agitation reduction compared with sham and usual care. The hypothetically active component of acupressure (i.e. acupoint activation) did not demonstrate a significantly and distinguishably large agitation-reducing effect compared with the other components, which were already available in the control conditions (i.e. the sham and usual-care groups).

For the effect of acupressure on stress, the significant reduction of salivary cortisol in the acupressure group compared with the baseline at T_1 (MD: -0.27μg/dL, 95%CI: -0.41, -0.12) and T_2 (MD: -0.21μg/dL, 95%CI: -0.34, -0.08) led to the conclusion that the combined set of all therapeutic components in acupressure was effective in reducing stress. The significant interaction effect between group and time indicated that acupressure reduced stress more than the control conditions (i.e. sham acupressure and usual care). To look more closely at the extent of stress reduction between groups at different time points, the extent of stress reduction in the acupressure group was observed to be only significantly different from that of the usual-care group at T_1 (-0.24μg/dL, p=0.007), and was not significantly different from that of the sham group at T_1. The extent of stress reduction in the acupressure group was not observed to be significant compared with the control groups at any other time points. The significant difference of the reduction of salivary cortisol level between acupressure and usual care at T_1 concluded that the hypothetical components of acupressure on top of usual care (i.e. acupoint activation, tactile stimulation, and other possible components) could

demonstrate a significantly and distinguishably larger stress-reducing effect compared with the usual care. The insignificant difference of the reduction of salivary cortisol level between acupressure and sham at all time points concluded that acupoint activation was not a distinguishable component causing stress reduction. The stress-reducing effect of acupressure might be caused by an interaction between a bunch of intervention components including acupoint activation, tactile stimulation and other possible components. Acupoint activation might have played a role in stress reduction, but it was not significantly an independent component.

6.2.2 The effect size of acupressure

Although the effect of acupressure on nursing home residents with dementia was insignificant, this could probably be because the effect size was too small to be observed in this study design. In order to appraise the effect size of the acupressure, its effects were also compared with other NPT. For better comparison across studies with different outcome measures and instruments, the effect size was expressed in standardized effect size (SES) by Cohen's d (Cohen, 1988).

For the agitation-reducing effect, the within-group SES of the acupressure in T_2, where a significant difference from the baseline was observed, was 0.47. A similar study (Lin et al, 2009) compared the agitation-reducing effect of acupressure with Montessori activities and being-presence on agitated nursing home residents with dementia. It was found that the within-group SES was 0.46. The within-group effect sizes between this study and that of Lin and colleagues

(2009) were very comparable. However, as mentioned above, agitation reduction was also observed in the control conditions. Looking at the within-group effect may not clearly reveal the net effect of acupressure. The between-group effect may be more informative. Lin and colleagues' study (2009) did not provide enough figures to compute the between-group effect for direct comparison.

A systematic review identified randomized controlled trials examining the effects of non-pharmacological interventions for agitation in dementia, which computed the between-group effects of some non-pharmacological interventions (Livingston et al, 2014). This review identified evidence by meta-analysis, finding that only a few types of interventions were shown to be statistically efficacious in reducing agitation in PWD. Music therapy was found to be efficacious, and it had immediate effects measured by between-group SES ranging from 0.5 to 0.9. Nursing home staff training was also found to be efficacious, and it had immediate effects measured by between-group SES ranging from 0.3 to 1.8. The between-group (i.e. acupressure and usual-care) SES of acupressure in this study at T_1, T_2 and T_3 were 0.12, 0.38, and 0.05 respectively, and these effects (between group) were statistically insignificant. This comparison showed that acupressure has a very small effect size on agitation reduction in nursing home residents with dementia, compared with other non-pharmacological interventions.

For the stress-reducing effect, the between-group SES of acupressure compared with usual care at T_1, where significant differences were observed, was 1.04. A systematic review (Moyer et al, 2011) showed that the between-groups SES

of massage on reducing the salivary cortisol ranged from 0.05 to 0.3. This clearly showed that acupressure had a much larger cortisol-reducing effect than massage.

6.2.3 Possible effect onset time of acupressure

In the study, the effect onset of acupressure on cortisol reduction was almost immediate, as supported by the fact that significant reduction of salivary cortisol was observed in the week immediately after completion of the intervention (i.e. T_1). Acupressure may have imposed immediate neuro-hormonal changes on the body.

For the effect of agitation reduction, although no significant effect of acupressure on agitation reduction was observed compared with the controls, a significant reduction of agitation compared with the baseline was still observed at T_2 after completion of the intervention. This finding suggests that acupressure may not have its effect onset immediately after completion of the intervention, but in the 5^{th} week after the baseline. This finding was also coherent with observations in previous studies (Yang et al, 2007; Lin et al, 2009) that a significant reduction of agitation was observed in the 5^{th} week after the baseline. These suggests that the effect onset of acupressure may not be immediately observable after completion of the intervention. The agitation reduction effect may only be observable, at the earliest, in the 5^{th} week after the commencement of the acupressure, although the agitation reduction effect in this study was observed to be insignificantly small compared with the control conditions.

6.2.4 Feasibility advantages of acupressure

No serious harmful effects were reported in this study, and the intervention fidelity was highly satisfactory. It was feasible to be implemented by non-professionals by simplified and standardized intervention protocol, as evidenced by the very good intervention fidelity, which was observed to be 100% correctly performed in the on-site visits. Acupressure was also shown to be highly accepted by the agitated nursing home residents with dementia and their families, as the intervention compliance was satisfactory (i.e. 91.9% in the acupressure protocol). Also, the eligible residents' participation refusal rate was low. In 1.7% of cases, participation was refused by the subjects themselves, and in 22.1% of cases the invitation to participate was rejected by residents' family members. Therefore, acupressure implementation on agitated nursing home residents with dementia is highly feasible because it can be accurately performed at the clinical level, as well as being highly accepted by PWD and their family.

6.2.5 Hyposalivation of agitated nursing home residents with dementia

Xerostomia refers to subjective oral dryness; while hyposalivation refers to being objectively assessed as having a low flow of saliva secretion (Sreebny, 2000). Complaints of xerostomia do not necessarily indicate hyposalivation because of sensory dysfunction among elders (Eveson, 2000). But hyposalivation may cause tooth wear, oral soft tissue lesions, oral infection, and reduced quality of life (Bardow et al, 2001; Ikebe et al, 2007; Kagami et al, 2008; Marino et al, 2008).

A systematic review showed that xerostomia prevalence among elders ranged from 13% to 26% in the general population (Orellana et al, 2006). The prevalence of xerostomia specifically in the frail elderly was 57% to 63% (Pajukoski et al, 2001). The prevalence of hyposalivation among the physically disabled elderly residents was 24% (van der Putten et al, 2013).

In this study, out of the 474 expected samples, 222 were collected but yielded nil or inadequate volume of saliva for analysis (46.8%). At baseline, 40.5% of collected samples were found to have nil or inadequate volume saliva for analysis. Hyposalivation was defined as 0.1 ml/min in a study (Sreebny, 2000). In this study, the data collection protocol set the dwelling time of the swab in the oral cavity at 2 to 5 minutes. However, 46.8% of samples collected did not yield more than the required volume of 0.05ml of saliva. This condition matched the definition of hyposalivation in older people set by Sreebny's study (2000), and was obviously higher than the 24% reported in another study (van der Putten et al, 2013). This may show that the hyposalivation problem is more severe in agitated nursing home residents with dementia.

6.2.6 High administration of psychotropic drugs prescribed on as-needed basis

At the time when the data on psychotropic drug use was collected, documented notes showed that many psychotropic drugs were prescribed on an as-needed basis. However, it was observed that most of the psychotropic drugs prescribed for use on an as-needed basis were administered regularly. Although the appropriate administration of psychotropic drugs was beyond the scope of this study, the high

administration of psychotropic drugs prescribed on an as-needed basis to residents in this study may signify over-administration.

6.2.7 Possible threats to the internal validity of the main study

The RCT with ITT analysis has become the gold standard for analyzing the effects of interventions, but its internal validity can be threatened by non-compliance, drop-outs and missing data (Armijo-Olivo et al, 2009). This study recorded the status of these three issues throughout the study period.

In this study, participant compliance, as discussed in section 4.3.5 with regard to the acupressure protocol, was also high, with 82.1% of participants complying with more than 80% of the planned sessions compared with only 49% of participants complying with more than 66.7% of planned psycho-education sessions (Leclerc et al, 2013). In addition, by including only the compliers (i.e. per-protocol analysis) and both compliers and non-compliers (i.e. mITT analysis), there were no differences in the interpretation of the effect on the primary and secondary outcomes of the intervention.

Among the participants under mITT analysis in this study, just one dropout case (0.8%) was recorded, as discussed in section 4.3.3. This was because the resident had died, and the figure was minimal compared with the figure range of 4.8-100% in most studies, with a dropout rate range of 20-40% reported in a systematic review designed to identify the dropout rate of pharmacological and psychological intervention studies (DeJong et al, 2012).

For the missing data, that in the CMAI was minimal (0.8%). However, there was a lot of data missing from the salivary cortisol measurements (54.8%). Given that there is a dearth of salivary cortisol studies conducted on PWD, and that none of the published studies have reported missing data, no comparison can be made to determine the severity of the problem. Nevertheless, the analysis, as discussed in section 4.3.6 about the distribution of missing data across time points and groups, showed that the missing numbers were not significantly different between groups and between time points. The missing data might have been completely at random and not have threatened the internal validity of the RCT, although it markedly reduced the power to show significant differences. Therefore, it can be concluded that the non-compliance, dropout, and missing data in this study were unlikely to have posed a threat to the internal validity of this study.

6.3 Implications

The answers to the research questions of the study, as well as other findings, had several implications for clinical practice, further research, and theory development.

6.3.1 Clinical practice

According to the results of this study, acupressure is not supported for immediate use in managing agitation in PWD in nursing homes, as no significant agitation reduction effects were observed compared with the control conditions. However, there are still some other implications for its use in clinical practice, as acupressure use was observed to be feasible and to have many advantages for use

on agitated PWD in nursing homes. Also, some other findings may suggest that attention is needed when taking care of PWD in the nursing home.

Acupressure is a safe intervention. Having said that, acupressure was shown to be safe only because the interventionists were appropriately trained and many safety monitoring measures were implemented. These included a good quality control mechanism, formal pre-start training, on-going training, on-site monitoring, and the involvement of TCM experts specialized in acupuncture as professional consultants. These points should be well considered before using acupressure on nursing home residents with dementia.

Given that different nursing home residents may have their own preferences regarding the activities or therapies provided by nursing homes, the high acceptance of acupressure by nursing home residents and their families offers nurses and caregivers another good alternative in selecting an appropriate therapy or activity for a nursing home resident with dementia.

This acupressure protocol was designed for laypeople to implement as the interventionists in this study were all laypeople. This study showed that the implementation of the protocol was feasible. This acupressure protocol can be implemented by the caregivers after training as well. Nurses are the important formal care givers of the nursing home residents with dementia. This acupressure protocol is a new and locally validated intervention that it provided nurses a new alternative to safely manage their agitated residents with dementia. This study

therefore provided a new nursing intervention for managing agitation in PWD in nursing home.

During the study period, it was observed that the psychotropic drugs prescribed on an as-needed basis were mostly administered regularly. Also, as mentioned above, the number of psychotropic drugs and the amount of physical restraint use on the agitated nursing home residents were observed to be greater in this study than in other studies. Prescription on an as-needed basis implies that the drug may not be needed regularly, and is expected to be administered only when needed based on the judgment of the nurses. This may imply that there is a lack of training for nurses in local nursing homes with regard to psychotropic drug and physical restraint use. It is suggested that education and training is needed for nurses working in local nursing homes, in order to provide proper care in managing agitation in nursing home residents with dementia.

Hyposalivation has been found to be more prevalent in agitated nursing home residents with dementia than in general nursing home residents. Similarly, although the reasons why agitated nursing home residents with dementia are more commonly observed to have hyposalivation are beyond the scope of this study, this finding should draw the attention of nurses working in nursing homes to the need to provide proper oral care and adequate hydration to their residents. This aims at preventing negative complications in the health of agitated nursing home residents with dementia, such as oral infection and tooth wear.

6.3.2 Further research

The main result of this study showed that acupressure had no effect on agitation reduction in nursing home residents with dementia when compared with control conditions. This result contradicts that of another similar study (Lin et al, 2009), which showed that acupressure has a significant agitation-reducing effect compared with control conditions (i.e. being present and Montessori activities). In order to identify the possible reasons for the difference between these results so that further studies can revise the study protocol for further evaluation, the study designs and intervention protocols between this study and that of Lin and colleagues (2009) were compared.

On careful examination of the study design of Lin and colleagues' research (2009), two main differences were apparent. First, this study used a smaller total sample size compared with that of Lin and colleagues (2009). A total of 119 subjects completed the data analysis of this study, while 133 subjects completed the analysis in Lin and colleagues' study (2009). However, this trial used a parallel group approach, while Lin and colleagues' trial (2009) used a cross-over group approach. Lin and colleagues' cross-over design (2009) increased the sample size in each group for comparison. There were 133 subjects in each group for comparison in Lin and colleagues' study (2009), while there were only 39-41 subjects in each group for comparison in this study.

In terms of the intervention protocol, there were also a few differences between this study and that of Lin and colleagues (2009). In this study, we used Baihui

(DU20), Yingtang (EX-HN3), Fengchi (GB20), Shenmen (HT7), and Niguan (PC6). The previous study (Lin et al, 2009) used Baihui (DU20), Sanyinjiao (SP6), Fengchi (GB20), Shenmen (HT7), and Niguan (PC6). The Sanyinjiao (SP6) used by Lin et al (2009) was replaced by Yingtang (EX-HN3) in this study. Also, the acupressure was implemented for four weeks in the previous study (Lin et al, 2009), while this study implemented it for two weeks only. It is suggested that further studies use a rigorous study design to examine how these intervention ingredient and methodological differences impact on the effects of acupressure.

Another key finding in this study is the significant effect of acupressure on reducing salivary cortisol levels. The physiological mechanism of acupressure has long been a mystery? in acupressure research. This finding supported the idea that acupressure may trigger a neuro-hormonal reaction in the human body. Although it had been proposed in previous studies that neuro-hormonal response in the hypothalamus-pituitary-adrenocortical (HPA) axis can be triggered by manual therapy (Moyer et al, 2011), this study found that acupressure showed a significantly larger effect in reducing salivary cortisol level compared with tactile stimulation provided via other manual therapies (e.g. massage). Also, significant reduction of salivary cortisol over time was only observed in the acupressure group.

This finding suggests that the activation of acupoints in acupressure may play an important role in physiological stress reduction. Although this finding is preliminary and the reduction of salivary cortisol level does not significantly lead to observable clinical benefits (i.e. a reduction in agitation), this is still a pioneer study and suggests that further studies should focus on exploring the effect of acupressure

on the HPA axis. It is also suggested that cortisol be used as a more objective biomarker to track the changes and associations with other possible therapeutic effects of acupressure. These suggested studies may give a better picture of how acupressure works in this context at the physiological level.

Although the result of acupressure for agitation of nursing home residents with dementia on salivary cortisol level was promising in this study, saliva collection on the population of this study was extraordinarily difficult. Previous studies showed that saliva secretion rate can be increased by various methods (e.g. acid and chewing) (van der Putten et al, 2013). However, it is not known whether these methods may alter the accuracy of salivary cortisol detection as stated on the manufacturer's saliva collection manual (Salimetrics, 2008). Further studies are suggested to explore how the saliva yield of this study's population can be increased without infringing the validity of the saliva sample to track changes in cortisol secretion. Also, further studies should explore the feasibility of using other types of human body fluid (e.g. urine) to accurately track changes in cortisol.

This study yielded the observational result that hyposalivation was very common among the population of this study. A previous study showed that the causes of hyposalivation among physically disabled elderly care home residents were the use of psychotropic drugs (De Almeida et al, 2008) and dehydration (Ichikawa et al, 2011). Most of the participants in this study were physically disabled older people, thus these causes may also apply to them. High administration of psychotropic drugs was also observed in this study, and this too may play a role as a cause of hyposalivation. Further studies on agitated nursing

home residents with dementia who demonstrate hyposalivation are suggested. These suggested studies could further investigate specific causes of hyposalivation, so that appropriate care can be delivered.

6.3.3 Theory development

This study employed four theories and hypotheses to construct a conceptual framework in an attempt to explain how acupressure could lead to a reduction of agitation in PWD. These were the stress hypothesis, the tactile stimulation hypothesis, the progressively lowered stress-threshold model, and TCM meridian theory. Below is a discussion of how the findings of this study extend our understanding of these theories and hypotheses.

6.3.3.1 Stress hypothesis

As discussed in the literature review, the stress hypothesis explains that nursing home residents with dementia experience a higher level of stress because the progressively cerebral neuronal damage secondary to dementia impairs the normal cortisol regulation through the HPA axis.

In this study, the mean salivary cortisol collected in the morning at baseline was observed to be 0.45μg/dL. This level was highly comparable with the salivary cortisol level of nursing home residents with dementia (i.e. 0.44-0.48 μg/dL) collected at the same time and reported in another study (Woods et al, 2008). However, when compared with the salivary cortisol level of community-dwelling older people (i.e. 0.23μg/dL) collected at the same time, as reported by Potvin et al (2013), the salivary cortisol level of the agitated nursing home residents with

dementia was noticeably higher. Although it cannot be concluded from these findings that PWD had higher cortisol levels because of cerebral neuronal damage, they at least supported the stress hypothesis that severely cognitively impaired (i.e. mean MMSE=7.0) PWD in nursing homes demonstrated similarly higher morning cortisol levels compared with their counterparts living in the community.

6.3.3.2 Tactile stimulation hypothesis

As discussed in the literature review, the tactile stimulation hypothesis explains that tactile stimulation may trigger a neuro-hormonal response through the HPA axis, causing moderation of cortisol secretion. As a result, cortisol levels can be reduced.

In this study, acupressure significantly reduced cortisol level more compared with usual care. However, acupressure did not reduce cortisol level significantly more than sham acupressure across any of the time points after the intervention. Significantly lower salivary cortisol level in the acupressure group compared with the usual-care group was only observed at T_1 (i.e. -0.24μg/dL, p=0.007). The theoretical intervention component differences between the acupressure group and the usual-care group were acupoint activation, tactile stimulation and other possible components. Acupoint activation could not independently reduce cortisol levels significantly, as there was no significant difference observed between the acupressure and sham groups. Acupressure was only significant when it embraced acupoint activation, tactile stimulation, and other possible components, because the

significant effect difference was only observed between the acupressure and usual-care groups.

These findings were inconclusive as to whether tactile stimulation can reduce the cortisol level of PWD. However, they did at least confirm that the tactile stimulation component in acupressure played a role in possibly synergizing other components (e.g. acupoint stimulation) in acupressure to make it effective in reducing the cortisol level of agitated PWD. Further studies will be needed to answer the question of how much tactile stimulation is enough to exert stress-reducing effects.

6.3.3.3 Progressively lowered stress threshold model

As discussed in the literature review, the PLST model (Hall & Buckwalter, 1987) explains that PWD have a progressively lowered stress threshold because of neuronal damage secondary to dementia. Maladaptive behaviors (e.g. agitation) can occur if the stress level exceeds the stress threshold. This model assumed that stress is a cause of the agitation in PWD.

In this study, at the baseline, there was no significant correlation between agitation and stress (r=-0.138). The salivary cortisol level of the agitated nursing home residents with dementia in this study (0.45 μg/dL) was similar to that of nursing home residents with dementia without a specification of agitation (0.44-0.48 μg/dL). Agitated PWD did not show higher levels of salivary cortisol compared with other nursing home residents with dementia. In the mediation analysis, there was no evidence showing that stress level was associated with

agitation level after the intervention. Although the intervention was significantly associated with stress level after the intervention at T_1 and T_2, the association between stress and agitation was insignificantly weak. These findings suggested that the stress level of the PWD was not associated with their agitation level, stress level was not higher in the agitated PWD compared with other PWD in the nursing home, and a reduction in stress did not lead to a reduction in agitation. Stress measured by salivary cortisol is unlikely to be a cause of agitation in PWD. The evidence in this study did not support what was explained in the PLST model about the relationship between stress and agitation in PWD.

Although the findings of this study do not support PLST model, there could possibly be caused by some methodological factors. First, it was about using cortisol to track the change of stress level of the participants. Given that the perceived stress could not be measured by asking the participants who have cognitive impairment, this study used the post-awakening salivary cortisol level to estimate the stress level. Using cortisol level to reflect change of stress may possible be confounded by many other factors as discussed earlier about the stress hypothesis in section 3.2.2.1, such as HPA axis dysfunction. Second, it was about unknown effect onset time on the two outcome variables (i.e. agitation and stress). Agitation and salivary cortisol were measured in the same week. The measurement time was based on the observation of effect change over time in the pilot study. It was also observed that the effect onset time was not the same on these two outcome variables in the study. The outcome measurement time point in this study based on the observation of the pilot study for the primary outcome (i.e. agitation) only. It

could be possible that the effect onset of these two outcome variables are actually different. Therefore, the cross-sectional associations of the two outcome variables in the same time point were not significant in the SEM analysis. The insignificant result could be related to lag of effect of two outcome variables. When interpreting the findings of this study in relation to the PLST, these factors should be considered.

6.3.3.4 TCM meridian theory

As discussed in the literature review, TCM meridian theory explains that clinical symptoms can be caused by an imbalance among *zangfu* (or TCM body system) functions. Meridians connect with *zangfu,* and *qi* flows along meridians to nourish the z*angfu*. There are many acupoints located on the meridians. The imbalance of *zangfu* functions can be improved by promoting *qi* flow among the meridians by activating (or stimulating) the acupoints through acupressure or acupuncture. As a result, the clinical symptoms (i.e. agitation in dementia) can be reduced.

This study hypothesized some common types of *zangfu* imbalance related to agitation in PWD in Hong Kong through a literature review and consultation of the TCM acupuncture experts. Theoretically appropriate intervention ingredients (e.g. selection of acupoints, techniques, and dosage) according to the TCM meridian theory were then selected by expert consensus (i.e. Delphi process) and empirical testing (i.e. pilot study). This study also used a sham condition for comparison in order to examine the stand-alone efficacy of the active component of acupressure (i.e. acupoint activation), as predicted by TCM meridian theory.

This study showed no significant difference in the agitation-reducing effect between the acupressure and sham groups. This finding therefore did not support that acupoint activation played an independent role in the reduction of agitation as predicted by TCM meridian theory.

Nevertheless, the insignificant result could be due to several causes from the perspective of TCM meridian theory. First, the hypothetically common types of *zangfu* imbalance may not be the specific types that the different individuals in the study actually had. The ineffective intervention observed in study could be because the use of intervention ingredients (e.g. the selection of acupoints) could not be targeted specifically to heal the specific types of *zangfu* imbalance. As a result, the effect was much diminished. Second, even though the acupressure protocol was validated by the TCM experts and was theoretically effective, this study provided no evidence of any change in *zangfu* function/balance or *qi* flow. How *zangfu* function and *qi* flow improvement could lead to a reduction of agitation was not revealed by this study. However, how to confirm whether the selected intervention ingredients were specific and correct for the individuals and how the *zangfu* and *qi* should be measured could be difficult, although it could be arguably identified and measured by individualized physical exams and interviews through TCM syndrome differentiation (Jiang et al, 2012). These issues should be investigated in further studies in order to enrich our understanding of the applicability of TCM meridian theory in the context of dementia care.

6.3.3.5 Others

One of the important observations in this study was that significant reduction of agitation was observed in both acupressure and sham group. However, significant agitation reduction was not observed in the usual care group and there was no significant interaction effect between group and time. Also in Lin and colleagues' study (2009), significant within group agitation reduction was also observed in acupressure group and Montessori's activities but not in being presence with the participants. Therefore, these observations support an assumptive thought that purposeful interaction with the subjects may be therapeutic but non-purposeful interaction (e.g. usual care or being presence) may not be.

Need-driven dementia-compromised model (Algase et al, 1996) which is also known as unmet need theory (Kovach et al, 2005) is a theory commonly referred in the development of many non-pharmacological interventions for managing behavioral problems in PWD (Kolanowski et al, 2011). This model explained that the neuronal damages in the PWD could impair their ability to interact with the people and environment. Their cognitive impairments have restricted their capacities to make their needs known, or the caregivers are unable to comprehend their needs (Kovach et al, 2005). So as their needs cannot be met easily. These needs cannot be apparent most of the time. When these needs are not fulfilled, it may cause agitation or behavioral problems.

Purposeful interaction may possibly have fulfilled the PWD's needs of communicating with people or socialization to mitigate their sense of loneliness,

which may have been commonly one of the basic needs of the PWD that it has been overlooked (Kovach et al, 2005). By fulfilling their needs (e.g. socialization) through purposeful interaction, agitation may be reduced through this pathway.

According to the findings of this study, significant reductions of agitation were observed after both the acupressure and sham groups. This observation may have provided some preliminary evidence on supporting the thought that agitation may be reduced in both the acupressure and sham through their purposeful interactions by fulfilling their needs of socialization, as predicted by the need-driven dementia-compromised behavior model (Algase et al, 1996). Nevertheless, the effect of purposeful interaction may not be large as its effect cannot be delineated from the usual care as evidenced by insignificant interaction effect. However, this study was not setup primarily to examine this effect, further studies are needed in order to test this assumptive thought. Yet, the findings for this study align well with the need-driven dementia-compromised model.

6.4 Strengths of the Study

This section discusses the strengths of the study by explicating why this intervention is positive and has potential to be applied in the clinical setting, which of the research methods used were good at generating new and quality knowledge, and how the study contributed to enhancing our understanding of the theory by empirical data. The strength of the study was discussed from the perspectives of interventions, research methods, and contributions to the theory.

6.4.1 Intervention

Although the evidence from this study did not conclude that acupressure was effective in reducing agitation in PWD compared with the control conditions, it did show that acupressure significantly reduced salivary cortisol level. Acupressure may be effective in managing stress, which may be linked to other health-related parameters of agitated PWD (e.g. behavioral problems and psychosocial well-being). It could be a therapeutic modality with good potential for further development, as it was observed that the nature of acupressure may have embraced many implementation benefits as below.

Acupressure is an inexpensive intervention that many nursing homes can afford. The main resources consumed by acupressure in this study were in training and monitoring the interventionists, but this is just like many other interventions: all interventions consume resources in training and quality assurance. No expensive equipment or highly trained professionals are needed to implement acupressure, as it only requires a pair of skilled hands and a good quality assurance mechanism. These advantages made acupressure an affordable intervention to be implemented on nursing home residents with dementia.

The protocol used in this study was simplified and locally validated. All the procedures needed were standardized and shown to be comprehensible to non-professionals. Compared with other published protocols (Lin et al, 2009; Yang et al, 2007), this protocol specified many procedures. These included methods for gauging the amount of pressure needed, techniques for identifying the optimal pressure to be applied, and standardized training methods. This locally validated

protocol is ready to be used by local nursing homes. The standardized and simplified protocol also favors being used by people without professional training. This may enhance the generalizability and practicability of the intervention protocol.

As mentioned above, agitation was commonly managed by psychotropic drugs and physical restraints, which imposed a lot of risks on agitated PWD without adding significant clinical benefits. Although this study could not provide evidence that it was effective in reducing agitation, acupressure was observed to be very safe in this study. It has potential for further development. If future studies can identify its clinically beneficial effects after revision of the protocol, it may be used to replace some use of psychotropic drugs and physical restraints.

6.4.2 Research methods

This study began by discussing how the acupressure protocol was developed to manage agitation in PWD by a literature review, Delphi process, and a pilot study. Previous similar studies (Yang et al, 2007; Lin et al, 2009) simply stated that the intervention protocol had been developed and validated by a group of experts. The issues of how the dosage was determined, how the techniques were defined, and how the acupoints were selected were not discussed. This study provides a reproducible method to develop an intervention protocol with better rigor.

This is the first study purposefully controlled the possible confounding effects from communication between the interventionists and the PWD. In the acupressure protocol reported in the previous similar studies (Yang et al, 2007; Lin et al, 2009), there were warm-up activities (e.g. hand rubbing, pressing) which were part of their

acupressure protocol. These warm-up activities did not appear in their control conditions and therefore its effect was not controlled. The possible effect from the communication through the warm-up activity may partially contribute to the agitation reducing effect of the acupressure protocol. The acupressure protocol in this study did not comprise any warm-up activities and the interventionists were all instructed to minimize the communications unrelated to acupressure with the participants during the intervention. The results of this study therefore demonstrated purer effects of acupressure compared with earlier studies.

This is the first study to use the parallel trial method. Another study (Lin et al, 2009) used the cross-over group method, which greatly enhanced the sample size in each group. However, without a clear understanding of the delayed effect of acupressure, the result could possibly have been influenced by the carry-forward effect of the acupressure. This study employed a parallel group design, which gave a better picture with consideration of possible variance contributed by the accumulation of the delayed effect of the intervention across study groups.

This is also the first study to employ a repeated measurement design to examine the sustainability of the effect of acupressure in managing agitation in PWD. The result of insignificant differences between groups over the longer period (i.e. at T_3) enriched our understanding that the effect of acupressure may not be sustainable.

This study also discussed many feasibility issues (e.g. the valid rate for collection, hyposalivation problems) related to salivary collection, which have

seldom been reported with regard to agitated PWD in nursing homes. These findings may enlighten the research design and planning for data collection in any further research on PWD that may also employ cortisol as a variable to be measured.

This study was the first to report many important figures, such as the intervention fidelity and compliance. It was also the first to report the result of a sensitivity test by comparing the conclusions made against the analysis methods according to study protocol adherence. These figures provided important clinical references to enable researchers to further study the effect of acupressure on agitation in dementia.

6.4.3 Contributions to theories

According to the understanding of the four theories or hypotheses mentioned earlier, some relationships were hypothesized, as discussed above, between the three key variables in this study: interventions, stress, and agitation. However, the empirical data from this study did not support these relationships. This finding raised queries regarding the applicability of these four theories or hypotheses in the area of agitation in PWD, as discussed earlier.

Nevertheless, this study enriched our understanding by providing new evidence on another set of new hypothetical relationships between stress, agitation and acupressure in the context of dementia care. According to the findings of this study, acupressure is not effective in reducing agitation, but it is effective in triggering neuro-hormonal changes as measured by salivary cortisol. However, the effect of acupressure cannot be significantly explained by the effect from the

activation of acupoints. The active components of acupressure are still unknown, but the effects of acupressure may likely come from an interaction between several intervention components (e.g. activation of acupoints, tactile stimulation, and other possible components).

This study also provided evidence that agitation in dementia is unlikely to be caused by stress or cortisol. This was because the association between stress and agitation before and after the intervention throughout the study period was negligible. The possible agitation-reducing effect of interventions observed in the previous studies (Lin et al, 2009; Yang et al, 2007) might have exerted its effect through different physiological pathways instead of the pathway involving stress or cortisol. Therefore, the new relationships between these three variables may be that acupressure reduces stress only without a significant effect on reducing agitation. There is no association between stress and agitation.

6.5 Limitations and challenges

This section discusses the limitations that readers should consider before generalizing the results of the study to the target population. The limitations and challenges are discussed below from the perspectives of the methods, procedures, intervention, and analysis.

6.5.1 Methods

In this study, random sampling (i.e. cluster sampling) was used to select a sample from the population. An RCH was regarded as a cluster or a unit in the first sampling step. There were 284 RCH invited. However, only 17 RCH agreed to join.

Although we endeavored to apply clustered random sampling principles in order to make the sample heterogenous enough to represent the targeted population, there were eventually 17 RCH (or clusters) that agreed to be randomly sampled. The small proportion of consenting RCH for sampling may have limited the power of the randomness of the sampling. This may also have limited the generalizability of the results to the population of the participating RCH.

The effect size needed for sample size estimation in this study was mainly based on similar published studies. However, only one study (Yang et al, 2007) provided adequate data for effect size (i.e. Cohen's d) estimation. From this study, only the within-group effect size could be calculated. Another source for the effect size needed for sample size estimation in this study was from the pilot study. The pilot study used a time serial design without parallel control groups for comparison. As such, this study under-estimated the sample size needed because it employed only the within-group effect size for the estimation of between-group effect size. Although the actual power could not be calculated, as the statistical analysis employed GEE, it could be estimated by using post-hoc power analysis. To re-compute the sample size needed by G*Power version 3.1.3 (Faul, 2010) in order to achieve significant difference between groups by using a small effect size (i.e. f=0.1), 190 samples were needed. Since only 119 samples were recruited and used for data analysis, this was inadequate to demonstrate the small effect size of the intervention.

6.5.2 Procedures

Saliva sample collection was a big challenge in this study. The low valid saliva sample collection rate became a major threat to the interpretation of the salivary cortisol result. Although this confounding effect could be independent to the outcome factor (i.e. stress as measured by salivary cortisol) because the missing numbers were evenly distributed in each group and time point, the reduced sample number still threatened the statistical power to detect significant differences between groups.

6.5.3 Intervention

The development of the intervention was rigorous, with the dose of the acupressure (i.e. the duration and frequency) obtaining strong consensus from the expert panel. The selection of intervention dosage was based on the results of a pilot study of 24 subjects only. In particular, the duration of the intervention was two weeks, whereas the one used in this study was based on the dosage that had demonstrated the largest effect in the pilot study. However, the group in which the dosage effect was largest had comprised just six participants. The two-week dosage is different from the duration used in previous similar studies (Lin et al, 2009), and demonstrated significant effects compared with the control. The agitation-reducing effect in this study failed to show a significant difference compared with the controls. That the dosage used is not adequate may possibly play a role.

6.6 Summary

To summarize, most of the participants' characteristics in this study were comparable with those of similar populations reported in other studies. They included gender, functional status, cognitive function, chronic medical illness, and activity engagement. However, our participants generally had longer LOS, more psychiatric drug use, more physical restraint use, and more family visits compared with similar populations reported in other studies. The agitation and stress level of the participants at baseline were highly comparable with similar populations reported in other studies.

Acupressure significantly reduced the stress level of agitated nursing home residents with dementia. However, it did not significantly reduce the agitation of nursing home residents with dementia. Acupressure did not reduce agitation by mediating stress. Its effect on both stress and agitation was not sustained.

The effect of acupressure in stress reduction may be attributed to the synergy between its acupoint stimulation, tactile stimulation, or other possible components. Neither the of acupoint activation component nor the tactile simulation component played any significantly independent roles in stress reduction.

The agitation-reducing effect size of acupressure was insignificantly small compared with other NPT, but its stress-reducing effect size was very large compared with massage therapy. Acupressure may achieve its stress-reducing effect onset in the week immediately after the intervention, but the onset of its agitation-reducing effect may not be immediately after completion of the intervention. The

onset of its effect may only be in the 5th week after commencement of the intervention.

Although acupressure was not found to be effective in reducing agitation in PWD, its significant effect on triggering a neuro-hormonal response (i.e. cortisol) may give rise to further investigation into its other possible therapeutic effects, because acupressure is also observed to have many implementation benefits, such as being inexpensive, safe, and highly acceptable. Other incidental findings such as high psychotropic drug use, high physical restraint use, and high hyposalivation rate may inform us that more attention should be paid to PWD in these areas in order to enhance their quality of care.

This study showed incoherent observations on the effects of acupressure in managing agitation. The reasons related to the possible differences in the research protocol are worthy of further research. The key finding that acupressure significantly reduced the salivary cortisol levels of the PWD may have opened up a new direction for exploration of the working mechanism of acupressure at a physiological level. Other incidental findings such as the unsatisfactory data collection of saliva and hyposalivation in PWD may give rise to further investigation of the reasons for these findings.

This study also provided empirical data both to support and to question our beliefs in the applicability of the previously known hypotheses and theories. The empirical data of this study supported the stress and tactile-stimulation hypotheses,

but not the PLST model and TCM meridian theory in the context of agitation in dementia.

This study demonstrated several strengths in having shown the implementation benefits of the intervention, used various research methods to enhance the rigor of the research and enrich our understanding of the use of acupressure to manage agitation in PWD, and contributed to the development of theories, particularly on the relationships between acupressure, stress and agitation. Some limitations related to the methods, procedures, and intervention are also discussed.

Chapter 7 Conclusion

Agitation is commonly observed in nursing home residents with dementia. Agitation has many negative impacts on PWD, their caregivers, and even society. Many interventions have been developed to manage agitation in dementia. Non-pharmacological interventions have been regarded as a preferable therapy for managing agitation in dementia, because they usually have fewer adverse effects. Yet, there is no strong evidence supporting the effectiveness of any particular non-pharmacological intervention.

Acupressure is a non-pharmacological intervention. It is a therapeutic modality that originated in ancient TCM. It is theoretically effective in managing agitation in dementia according to TCM meridian theory. Preliminary evidence showed that acupressure has good potential to be developed as a therapeutic modality for managing agitation in PWD, as it possesses many potentially good properties, such as the fact that it is preliminarily effective, safe, inexpensive, and in harmony with the health beliefs of Chinese populations. However, there are still many issues that remain unresolved, and it is important to understand them before acupressure can confidently be used at the clinical level. These important issues include the efficacious components of acupressure, its effect sustainability, its effect on stress, and its mediation effect on agitation through stress. This study attempted to examine these issues by clinical research.

To develop the intervention protocol and study through evidence-based procedures, this study followed the Medical Research Council 2008 guideline for developing and evaluating complex interventions. To follow this guideline, this

study used three methods to develop the intervention protocol and study: a literature review, Delphi process, and a pilot study. An RCT was conducted to examine the research questions.

The RCT employed the designs of blinding assessors and participants and using parallel groups. The participants were allocated to three groups in a 1:1:1 ration by permuted block randomization. The intervention was acupressure, which was compared with two control conditions of sham and usual care. The intervention lasted for two weeks. Outcomes were measured at the baseline (i.e. T_0), and at the 3rd (i.e. T_1), 5th (i.e. T_2), and 8th (i.e. T_3) weeks after commencement of the intervention. We recruited nursing home residents who were diagnosed as having dementia, over 65 years old, and experiencing agitation.

In the acupressure group, participants received acupressure at five acupoints: Fengchi (GB20), Baihui (GV20), Shenmen (HT7), Niguan (PC6), and Yingtang (EX-HN3). A course of acupressure lasted for two weeks. Acupressure was implemented by trained non-professionals on the participants twice daily and five days per week. Each course of acupressure therefore comprised 20 sessions and each session lasted for 10 minutes. In the sham group, participants received the same protocol as the acupressure group except the acupressure was delivered on five non-acupoints. In the usual care group, participants received no intervention apart from the usual care provided by the nursing homes. The primary outcome was agitation, as measured by the CMAI. The secondary outcome was stress, as measured by salivary cortisol.

The general estimating equation (GEE) was used to compare the effects of acupressure on agitation and stress between groups over time. Structured equation modeling (SEM) was used for the mediation analysis to examine the mediation effect of acupressure on agitation through stress. Missing data was managed according to the missing-at-random principle. The level of significance was set at 0.05. A sensitivity analysis was conducted to examine the impact of violation of the study.

The main results of this study showed that acupressure was not effective in reducing agitation. Acupressure is effective in reducing stress. The stress-reducing effect of acupressure was not sustained until the 8^{th} week after the baseline. Acupressure did not reduce agitation by mediating stress.

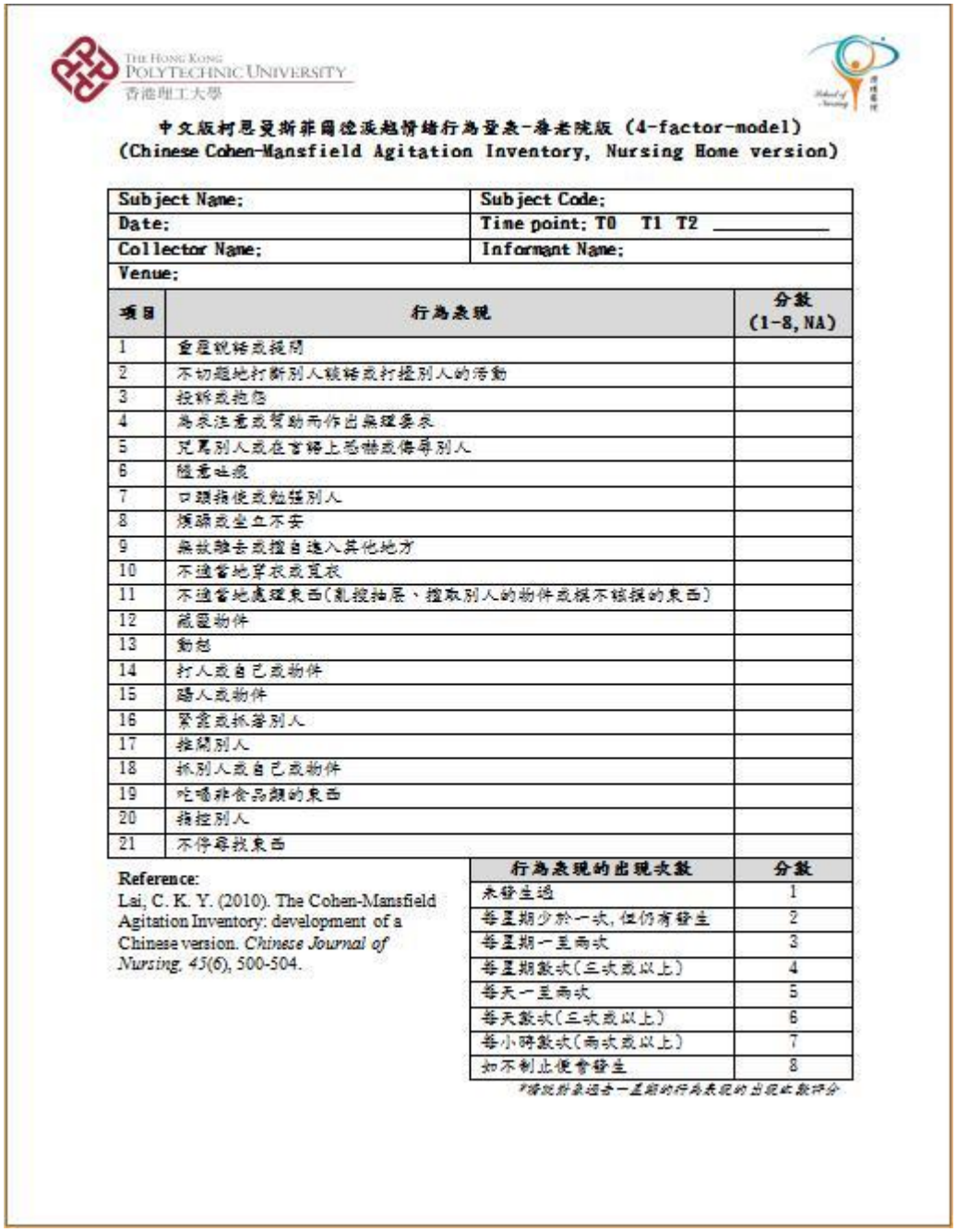
Besides the main results, this study also generated some other meaningful findings. It showed that the active intervention components for the stress-reducing effect of acupressure were likely to be an interaction between several intervention components (e.g. acupoint activation and tactile stimulation). The agitation-reducing effect of acupressure was insignificantly small. However, its stress-reducing effect size was large, even larger than that of massage, as reported in other studies. The stress-reducing effect onset time was almost immediate, in that it was observed in the week immediately after completion of intervention. But the agitation-reducing effect was only observed to peak in the 5^{th} week after the baseline. This study also showed that acupressure was very safe and its implementation by non-professionals highly feasible.

In findings besides those on the acupressure, it was also incidentally found that hyposalivation was prevalent in the participants of this study. The prevalence was much higher than that in general nursing home residents reported in other studies. Also, the use of physical restraints and psychotropic drugs on the participants of this study was also more prevalent compared with that on similar populations reported in other studies.

The knowledge generated from this study gave a few key conclusive messages. First, the evidence does not show that acupressure is effective in reducing agitation in PWD, but acupressure may trigger neuro-hormonal responses involving cortisol. Second, the most distinctive theoretical proposition to support the possible effectiveness of acupressure was acupoint activation. However, the independent effect of acupoint activation was not supported by the evidence of this study. Acupoint activation may have participated as a possible player contributing to the interaction with other intervention components (e.g. tactile stimulation) to trigger the neuro-hormonal responses. It was not an independently active intervention component. Third, the evidence from this study indicated that the stress levels of agitated PWD in nursing homes may be higher, but the evidence does not suggest that stress or cortisol plays a significant role in causing agitation in PWD. This is because the association between stress and agitation had been negligibly minimal before and after the intervention throughout the study period. Fourth, the agitation-reducing effect of acupressure is not consistently observed, so that its effect may not be as certain as once believed. This is because this tightly controlled study does not support the effectiveness of acupressure on agitation reduction in PWD. Fifth,

the effect size of acupressure on agitation reduction was small, reducing its significance when compared with other non-pharmacological interventions. Also, its effect onset was not immediate and its effect was not sustained at the 8th week after the baseline. Sixth, despite its small and insignificant effect size, acupressure has many implementation benefits that favor its further development as a therapeutic modality for agitated PWD. However, evidence from this study does not support the immediate use of the acupressure protocol. Further revision of the acupressure protocol and studies with favorable results are needed to support its possible clinical use in the future. Seventh, high use of psychotropic drugs, high use of physical restraint, and high prevalence of hyposalivation were observed in this study. These incidental findings signal an urgent need for healthcare providers and researchers to look into the reasons and identify possible solutions so that the quality of care of agitated nursing home residents with dementia can be improved.

Appendix 1



THE HONG KONG POLYTECHNIC UNIVERSITY
香港理工大學

中文版柯恩曼斯菲爾德激越躁動行為量表-養老院版 (4-factor-model)
(Chinese Cohen-Mansfield Agitation Inventory, Nursing Home version)

Subject Name:	Subject Code:
Date:	Time point: T0 T1 T2 _____
Collector Name:	Informant Name:
Venue:	

項目	行為表現	分數 (1-8, NA)
1	重複說話或提問	
2	不切題地打斷別人說話或打擾別人的活動	
3	投訴或抱怨	
4	為求注意或幫助而作出無理要求	
5	咒罵別人或在言語上恐嚇或傷害別人	
6	隨意吐痰	
7	口頭指使或勉強別人	
8	煩躁或坐立不安	
9	無故離去或擅自進入其他地方	
10	不適當地穿衣或脫衣	
11	不適當地處理東西(亂搜抽屜、擅取別人的物件或模不相關的東西)	
12	藏匿物件	
13	動怒	
14	打人或自己或物件	
15	踢人或物件	
16	緊盯或抓著別人	
17	推開別人	
18	抓別人或自己或物件	
19	吃喝非食品類的東西	
20	指控別人	
21	不停尋找東西	

行為表現的出現次數	分數
未發生過	1
每星期少於一次, 但仍有發生	2
每星期一至兩次	3
每星期數次(三次或以上)	4
每天一至兩次	5
每天數次(三次或以上)	6
每小時數次(兩次或以上)	7
如不制止便會發生	8

根據對象過去一星期的行為表現的出現次數評分

Reference:
Lai, C. K. Y. (2010). The Cohen-Mansfield Agitation Inventory: development of a Chinese version. *Chinese Journal of Nursing, 45*(6), 500-504.

Appendix 2.1

Acupressure for Managing Agitation in Nursing Home Residents with Dementia: Protocol 1

(For Research Purpose Only)

Research Team Member:

Mr. Rick Kwan *(PhD student, School of Nursing, PolyU)*
Dr. Mason Leung *(Co-supervisor, Department of Rehabilitation Science, PolyU)*
Prof. Esther Mok *(Co-supervisor, School of Nursing, PolyU)*
Prof. Claudia Lai *(Chief supervisor, School of Nursing, PolyU)*

Appendix 2.2

Introduction

The purpose of this protocol is to provide a clinical guidance to deliver a standardized acupressure therapy on the older nursing home residents with dementia for research purpose. This protocol will cover the following contents:

Appendix 2.3

Instructions to Interventionist

Major Duties

You are required to deliver the acupressure intervention according to the instruction depicted in this protocol.

Expectations

You are expected to arrive on time. Time is a very crucial point for the validity of the intervention. For the duty time, you need to refer to the Duty Roster. It can be different among different nursing homes. You are also expected to make sure the identity of the subject is correct. You need to use appropriate methods to check the client's identity (eg. bracelet or confirm with the nursing home staffs). Every time you go to deliver intervention, please make sure that you have cut your fingernails and brought the hand-rub (which will be provided to you) with you.

Post Intervention

After the intervention, you are required to do the documentation on two records:

- On-side Attendance Record
- On-site Individual Progress Record

Appendix 2.4

The Implementation Procedure

Preparation

The interventionist has to spend one minute to self-introduce, explain the procedure, prepare the hands, and position the client.

Introduction

The interventionist can say "Hello! My name is xxxx. I am a research person from School of Nursing, PolyU."

Procedure explanation

The interventionist can say "I come here today to do the acupressure for you. What I am going to do is to use my finger-tips to press on your acupoints. All I want you to do is to relax throughout the whole procedure. When I apply pressure on your acupoints, it may trigger some sensations; such as sore, swollen, numbness, and pain. The sensations usually are not very unpleasant. However, if the sensation is too unpleasant for your, just kindly let me know and I will adjust the extent of pressure. The whole procedure will last for about 10 minutes only."

Hand preparation

The intervention should have washed and warmed the hand properly.

Client positioning

The interventionist should position the client in an up-right-sitting position on the chair. When the intervention positions the client, the interventionist can say "In order to facilitate the procedure to be done effectively, I would ask for your help to remain in a comfortable position."

Appendix 2.5

Acupoint Identification

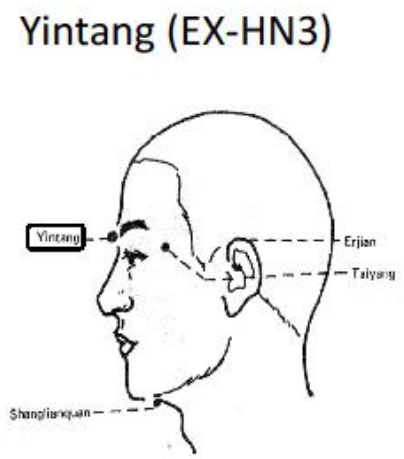
The interventionist has to firstly identify the acupoints. Then, the acupoints should be pressed by the fingertip correctly. There are totally five acupoints.

Appendix 2.6

Yintang (EX-HN3)

Location: midway between the medial ends of the two eyebrows. (Cheng, 2003)

Schematic Illustration (Adopted from Cheng, 2003):

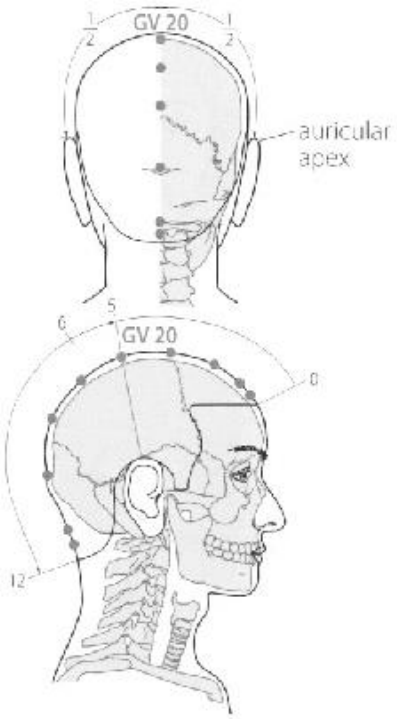


Appendix 2.7

Baihui (GV20)

Location: On the head, 5 B-cun superior to the anterior hairline, on the anterior median line. GV20 is located in the depression 1 B-cun anterior to the midpoint of the line from the antior hairline to the posterior hairline. When the ears are folded, GV20 is located at the midpoint of the connecting line between the auricular apices. (WHO, 2008)

Schematic Illustration (Adopted from WHO, 2008):



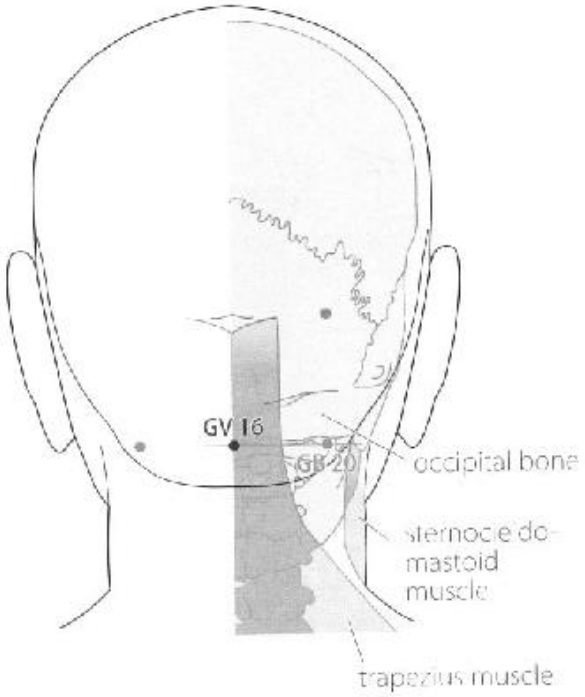
GV20

Appendix 2.8

Fengchi (GB20)

Location: In the anterior region of the neck, inferior to the occipital bone, in the depression between the origins of sternocleidomastoid and the trapezius muscles. (WHO, 2008) It is a dual-acupoints that it comes with a pair on bilateral sides of the anterior region of the neck.

Schematic Illustration (Adopted from WHO, 2008):



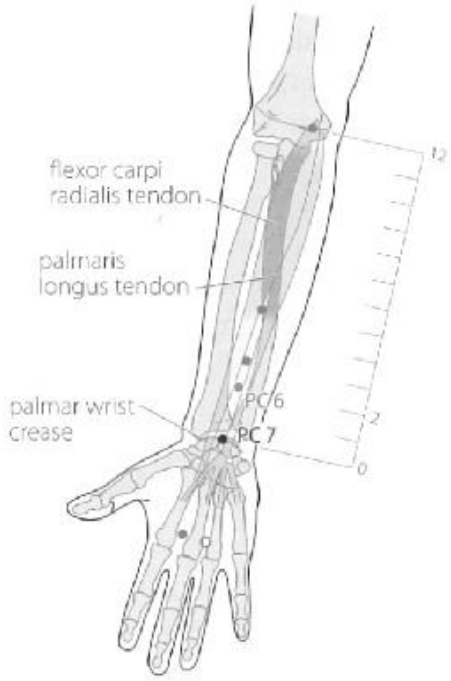
GB20

Appendix 2.9

Neiguan (PC6)

Location: On the anterior aspect of the forearm, between the tendons of the pamlaris longus and the flexor carpi radialis, 2 B-cun proximal to the palmar wrist crease. With the fist clenched, the wrist supinated and the elbow slightly flexed, the tendons become more prominent. If the Palmaris longus tendon is not present, PC6 is medial to the flexor carpi radialis tendon. (WHO, 2008) It is a dual-acupoints that it comes with a pair on both forearms.

Schematic illustration (Adopted from WHO, 2008):



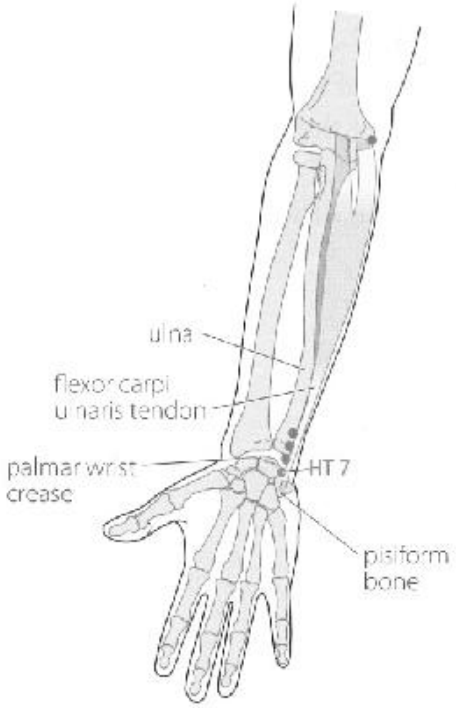
PC6

Appendix 2.10

Shenmen (HT7)

Location: On the anteromedial aspect of the wrist, radial to the flexor carpi ulnaris tendon, on the palmar wrist crease. In the depression radial to the proximal border of the pisiform bone, on the palmar wrist crease. (WHO, 2008) It is a dual-acupoints that it comes with a pair on both wrists.

Schematic Illustration (Adopted from WHO, 2008):



HT7

Appendix 2.11

Implementation

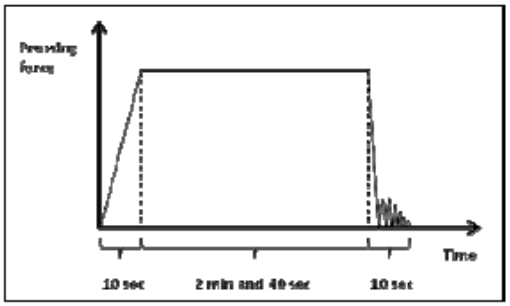
There are two types of techniques: General and specific. General techniques apply to all acupoints, while specific techniques apply to only the related acupoint.

General techniques

After the acupoint has been identified, the interventionist should apply pressure on the acupoint by using the thumb tip. The pressure rhythm should be divided into three phases: light-strong-light principle. First, the interventionist gradually increases the pressing force until reaching the optimal peak. This phase takes ten seconds. Second, sustain optimally peak pressing force for two minutes and forty seconds. . Third, the interventionist gradually decreases the pressing force. By the end of the third phase, the interventionist finger-kneads on the acupoint. This phase takes ten seconds. ***(Figure 1)*** The peak pressing force can vary among different subjects. The peak pressing force is achieved when signs of some sensations (eg. sore, numb, swollen, pain) are noted. These sensations can be expressed by the subject verbally or non-verbally (eg. frowning, withdrawing).

If the point is correct pressed, the subject may have some sensation (eg. sore, numb, swollen, pain). The sensation can be expressed by some non-verbal cues (eg. frowning, withdrawing). It does not always happen because the response can vary among individuals.

Figure 1



Appendix 2.12

Specific techniques

- ***Yintang (EX-HN3)***

  Description: It is a single acupoint. In each therapy, Yintang (EX-HN3) is to be pressed alone.

  Techniques: Stack the middle finger behind the index finger and put the index finger on the Yintang (EX-HN3) and apply force perpendicularly. Use another hand to support the occipital side of the skull to provide counter force.

- ***Baihui (GV20) & Fengchi (GB20)***

  Description: Baihui (GV20) is a single acupoint. Fengchi (GB20) is a dual-acupoints. In each therapy, Baihui (GV20) is to be pressed simultaneously with one side of the Fengchi (GB20). Each side of the Fengchi (GB20) is to be pressed alternatively.

  Technique: Put one thumb on the Baihui (GV20) and apply force vertically downward. The rest of the four fingers spread on the right fronto-parital side of the skull to provide counter force for the Fengchi (GB20). Put another thumb on one side of the Fengchi (GB20) and apply force towards the direction of the nose tip. Both acupoints should be pressed simultaneously.

- ***Neiguan (PC6) & Shenmen (HT7)***

  Description: Both Neiguan (PC6) and Shenmen (HT7) are dual-acupoints. In each therapy, only one side of the Neiguan (PC6) and Shenmen (HT7) is to be pressed. Each side of the Neiguan (PC6) and Shenmen (HT7) is to be pressed alternatively. Both Neiguan (PC6) and Shenmen on the same side are pressed every time simultaneously.

  Technique: Rest the forearm of the subject on a table and flex the hand medially to the ulnar side. Put one thumb tip on the Shenmen (HT7) and apply force towards to radial side. The remaining four fingers grasp on the wrist to provide counter force for Shenmen (HT). Put the tip of one finger (eg. index or middle) on the Neiguan (PC6) and apply force vertically downward. Both acupoints should be pressed simultaneously.

Appendix 2.13

Peri-intervention

During the intervention

The interventionist should monitor the possible adverse effects. Fainting, bruises, and headache may occur. If the adverse effects are significantly evident, stop the intervention and inform the investigator.

Post- intervention

The interventionist should advice the subject to rest (eg. lying flat in a bed or sitting on a chair) for at least 10 minutes. The interventionist also has to advice the caregiver (eg. nurses) to monitor and manage for possible adverse effects (eg. fainting, bruises, and headache) after the intervention. If the above adverse effects are noted by the caregiver, the caregiver should inform the investigator for possible termination of the acupressure.

The subject, family and caregiver should be informed that the post acupressure marks on the acupoints (eg. redness, pitting) are normal. They will disappear soon and they do not cause harm.

Appendix 2.14

Dosage

Each acupoint should be pressed for three minutes. The acupoints should be pressed in a fixed sequence. First, Yintang (EX-HN3) is pressed alone for three minutes. Second, Baihui (GV20) and Fengchi (GB20) are pressed simultaneously for three minutes. Third, Neiguan (PC6) and Shenmen (HT7) are pressed simultaneously for three minutes. The total implementation time is nine minutes. ***(Table 1)***

Table 1

Sequence	Acupoint(s)	Time
1	Yintang (EX-HN3)	3 min
2	Baihui (GV20) & Fengchi (GB20)	3 min
3	Neiguan (PC6) & Shenmen (HT7)	3 min
	Total	9 min

Appendix 2.15

Summary Table

Phase	Procedure	Time	Reference
Preparation	• Introduction • Explanation • Hand preparation • Client positioning	1 min	P. 5
Implementation	*1st set: Yintang (EX-HN3)* • Identification • Apply pressure	3 min	P. 7, 12-13
	2nd set: Baihui (GV20) & Fengchi (GB20) • Identification • Apply pressure simultaneously	3 min	P. 8-9, 12-13
	3rd set: Neiguan (PC6) & Shenmen (HT7) • Identification • Apply pressure simultaneously	3 min	P. 10-11-, 12-13
Post-intervention	Give general advice	1 min	P. 14
	Total time (for one session)	11 min	

Appendix 2.16

Reference

Cheng, X. (2003). *Chinese Acupuncture and Moxibustion (2nd ed).* Foreign Languages Press: Beijing.

WHO Regional Office for the Western Pacific. (2008). *WHO Standard Acupuncture Point Locations in the Western Pacific Region.* World Health Organization: Manila.

Appendix 3.1

Acupressure for Managing Agitation in Nursing Home Residents with Dementia: Protocol 2

(For Research Purpose Only)

Research Team Member:

Mr. Rick Kwan *(PhD student, School of Nursing, PolyU)*
Dr. Mason Leung *(Co-supervisor, Department of Rehabilitation Science, PolyU)*
Prof. Esther Mok *(Co-supervisor, School of Nursing, PolyU)*
Prof. Claudia Lai *(Chief supervisor, School of Nursing, PolyU)*

Appendix 3.2

Introduction

The purpose of this protocol is to provide a clinical guidance to deliver a standardized acupressure therapy on the older nursing home residents with dementia for research purpose. This protocol will cover the following contents:

Appendix 3.3

Instructions to Interventionist

Major Duties

You are required to deliver the acupressure intervention according to the instruction depicted in this protocol.

Expectations

You are expected to arrive on time. Time is a very crucial point for the validity of the intervention. For the duty time, you need to refer to the Duty Roster. It can be different among different nursing homes. You are also expected to make sure the identity of the subject is correct. You need to use appropriate methods to check the client's identity (eg. bracelet or confirm with the nursing home staffs). Every time you go to deliver intervention, please make sure that you have cut your fingernails and brought the hand-rub (which will be provided to you) with you.

Post Intervention

After the intervention, you are required to do the documentation on two records:

- On-site Attendance Record
- On-site Individual Progress Record

Appendix 3.4

The Implementation Procedure

Preparation

The interventionist has to spend one minute to self-introduce, explain the procedure, prepare the hands, and position the client.

Introduction

The interventionist can say "Hello! My name is xxxx. I am a research person from School of Nursing, PolyU."

Explanation

The interventionist can say "I come here today to do the acupressure for you. What I am going to do is to use my finger-tips to press on your acupoints. All I want you to do is to relax throughout the whole procedure. When I apply pressure on your acupoints, it may trigger some sensations; such as sore, swollen, numbness, and pain. The sensations usually are not very unpleasant. However, if the sensation is too unpleasant for your, just kindly let me know and I will adjust the extent of pressure. The whole procedure will last for about 10 minutes only."

Hand preparation

The intervention should have washed and warmed the hand properly.

Client positioning

The interventionist should position the client in an up-right-sitting position on the chair. When the intervention positions the client, the interventionist can say "In order to facilitate the procedure to be done effectively, I would ask for your help to remain in a comfortable position."

Appendix 3.5

Acupoint Identification

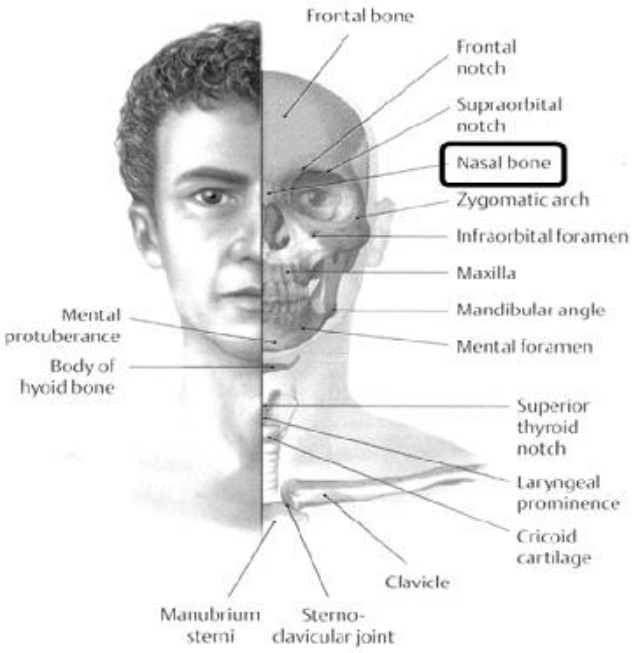
The interventionist has to firstly identify the acupoints. Then, the acupoints should be pressed by the fingertip correctly. There are totally five acupoints.

Appendix 3.6

Point 1

Location: Root of the nose, on middle point of the nasal bone.

Schematic illustration (Adopted from Schuenke et al, 2006)

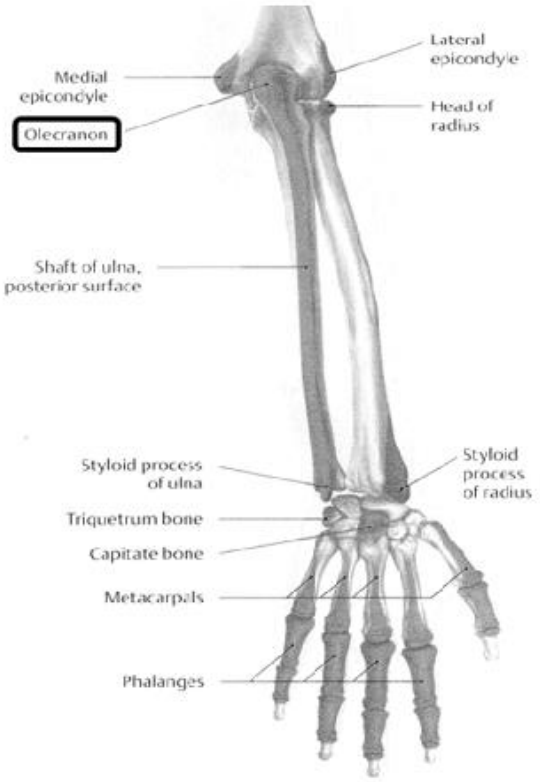


Appendix 3.7

Point 2

Location: Tip of the elbow, Olecranon of the Ulna

Schematic illustration (Adopted from Schuenke et al, 2006)

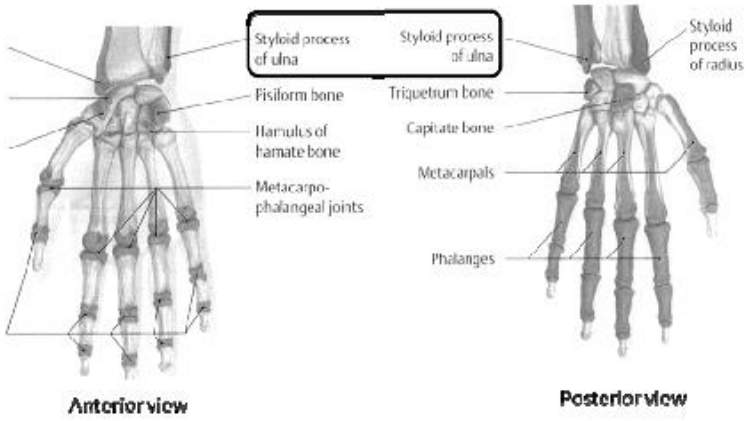


Appendix 3.8

Point 3

Location: Distal end of the ulna, ulnar styloid process

Schematic illustration (Adopted from Schuenke et al, 2006)

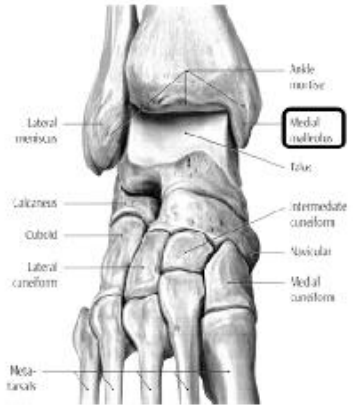


Appendix 3.9

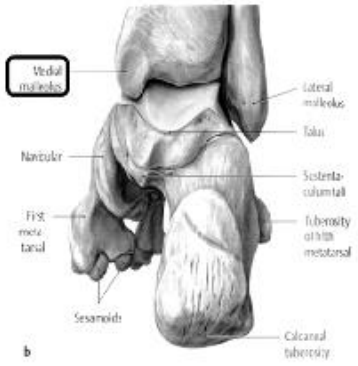
Point 4

Location: Medial malleolus over the ankle

Schematic illustration (Adopted from Schuenke et al, 2006)



Anterior view



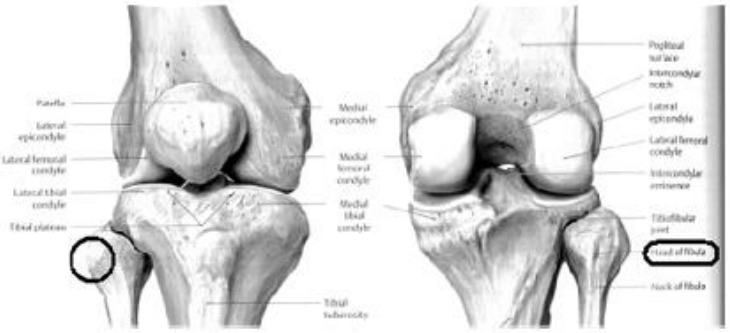
Posterior view

Appendix 3.10

Point 5

Location: Head of fibula

Schematic illustration (Adopted from Schuenke et al, 2006)



Anterior view Posterior view

Appendix 3.11

Implementation

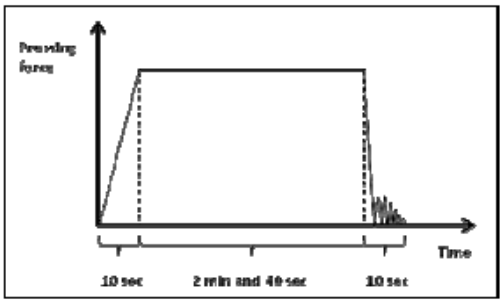
There are two types of techniques: General and specific. General techniques apply to all acupoints, while specific techniques apply to only the related acupoint.

General techniques

After the acupoint has been identified, the interventionist should apply pressure on the acupoint by using the thumb tip. The pressure rhythm should be divided into three phases: light-strong-light principle. First, the interventionist gradually increases the pressing force until reaching the optimal peak. This phase takes ten seconds. Second, sustain optimally peak pressing force for two minutes and forty seconds. . Third, the interventionist gradually decreases the pressing force. By the end of the third phase, the interventionist finger-kneads on the acupoint. This phase takes ten seconds. ***(Figure 1)*** The peak pressing force can vary among different subjects. The peak pressing force is achieved when signs of some sensations (eg. sore, numb, swollen, pain) are noted. These sensations can be expressed by the subject verbally or non-verbally (eg. frowning, withdrawing).

If the point is correct pressed, the subject may have some sensation (eg. sore, numb, swollen, pain). The sensation can be expressed by some non-verbal cues (eg. frowning, withdrawing). It does not always happen because the response can vary among individuals.

Figure 1



Appendix 3.12

Specific techniques

- ***Point 1***

  Description: It is a single acupoint. In each therapy, Point 1 is to be pressed alone.

  Techniques: Stack the middle finger behind the index finger and put the index finger on the point 1 and apply force perpendicularly. Use another hand to support the occipital side of the skull to provide counter force.

- ***Point 2 & Point 3***

  Description: Both Point 2 and Point 3 are dual-acupoints. In each therapy, only one side of the Point 2 and 3 is to be pressed. Each side of the Point 2 and Piont 3 is to be pressed alternatively. Both Point 2 and Point 3 on the same side are pressed every time simultaneously.

  Technique: Rest the forearm of the subject on a table and twist the hand allow the dorsal side of the hand facing up. Put one thumb tip on the Point 2 with and apply force perpendicularly. Use the other 4 fingers on the anterior side of the elbow to provide counter force. Put another thumb tip on the Point 3 and apply force perpendicularly. Use the other 4 fingers on the palmar side of the wrist to provided counter force. Both acupoints should be pressed simultaneously.

- ***Point 4 & Point 5***

  Description: Both Point 4 and Point 5 are dual-acupoints. In each therapy, only one side of the Point 4 and Point 5 is to be pressed. Each side of the Point 4 and Point 5 is to be pressed alternatively. Both Point 4 and Point 5 on the same side are pressed every time simultaneously.

  Technique: Put one middle finger tip on the Point 4 and apply force perpendicularly. Use the other thumb to grasp on the lateral side of the ankle to provide counter force. Put another thumb tip on the Point 5 and apply force perpendicularly. The other fingers grasp on the anterior knee to provide counter force. Both acupoints should be pressed simultaneously.

Appendix 3.13

Peri-Intervention

During the intervention

The interventionist should monitor the possible adverse effects. Fainting, bruises, and headache may occur. If the adverse effects are significantly evident, stop the intervention and inform the investigator.

Post- intervention

The interventionist should advice the subject to rest (eg. lying flat in a bed or sitting on a chair) for at least 10 minutes. The interventionist also has to advice the caregiver (eg. nurses) to monitor and manage for possible adverse effects (eg. fainting, bruises, and headache) after the intervention. If the above adverse effects are noted by the caregiver, the caregiver should inform the investigator for possible termination of the acupressure.

The subject, family and caregiver should be informed that the post acupressure marks on the acupoints (eg. redness, pitting) are normal. They will disappear soon and they do not cause harm.

Appendix 3.14

Dosage

Each acupoint should be pressed for three minutes. The acupoints should be pressed in a fixed sequence. First, Point 1 is pressed alone for three minutes. Second, Point 2 and Point 3 are pressed simultaneously for three minutes. Third, Point 4 and Point 5 are pressed simultaneously for three minutes. The total implementation time is nine minutes. ***(Table 1)***

Table 1

Sequence	Acupoint(s)	Time
1	Point 1	3 min
2	Point 2 & Point 3	3 min
3	Point 4 & Point 5	3 min
	Total	9 min

Appendix 3.15

Summary Table

Phase	Procedure	Time	Reference
Preparation	• Introduction • Explanation • Hand preparation • Client positioning	1 min	P. 4
Implementation	*1st set: Point 1* • Identification • Apply pressure	3 min	P. 6, 12
	2nd set: Point 2 and Point 3 • Identification • Apply pressure simultaneously	3 min	P. 7-8, 12
	3rd set: Point 4 and Point 5 • Identification • Apply pressure simultaneously	3 min	P. 9-10, 12
Post-intervention	Give general advice	1 min	P. 13
	Total time (for one session)	11 min	

Appendix 3.16

Reference

Schuenke, M., Schulte, E., Schumacher, U. (2006). *Atlas of Anatomy: General Anatomy and Musculoskeletal System.* New York: Thieme Stuttgart.

Appendix 4.1

Demographic and Clinical Data

DC Name		**DC Date**	
Subject #:			
Name (Eng):		**Name: (Chi):**	
Gender:			
NH Name:		**Age:**	
NH duration:			
Home Add.:			
Home Tel.:		**Language:**	
Proxy Name:		***Proxy Relat.**	
Proxy Tel:			
HoAPW:			

Medical History	**Drug Name:**	**Dose:**	**Freq.**	**Route:**

** Proxy Relat.: Proxy Relationship*
HoAPW: Hour of Activity per Week

Appendix 4.2

Demographic and Clinical Data 2

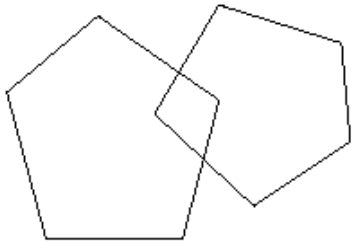
Q1. 使用約束用具 約束用具包括：腰帶,手腕/腳踝帶, 床用約束衣, 椅子用約束衣, 固定的椅上桌, 睡衣, 床單, 褲子, 手套, 帶子 (用以約束院友活動)	0	不曾使用
	1	很少使用 (只是需要時才使用, 院友絕大部份時間可以自由活動)
	2	間中使用 (平均一天少於一半時間使用, 院友仍有自由活動的時間)
	3	經常使用 (平均一天多於一半時間使用, 及院友很少有自由活動時間)
	4	恒常使用 (院了洗澡及短暫休息時沒有使用, 餘下絕大部份時間都使用)
Q2. 家人探訪次數	0	不曾探訪
	1	一個月少於四次
	2	每星期一至兩次
	3	每星期三至六次
	4	每天一次或更多
Q3. 參與活動的次數	0	不曾參與
	1	一個月少於四次
	2	每星期一至兩次
	3	每星期三至六次
	4	每天一次或更多
Q4 每週參與活動的時數	**0**	不曾參與
	1	少於五小時
	2	五至九小時
	3	十至十五小時
	4	多於十五小時

Appendix 4.3

Cognitive Function – MMSE (Cantonese version)

	問題	得分
1.	依家係乜野日子? (年份) (季節) (月份) (幾號) (星期幾)	 ( ) ( ) ( ) ( ) ( )
2.	我地依家係邊度? (九龍/新界/香港) (九龍/新界/香港既邊度) (醫院/邊一科診所/邊條街/邊個屋村) (邊層樓/診所名字/邊一座/中心名字) (病房/邊層樓)	 ( ) ( ) ( ) ( ) ( )
3.	依家我會講三樣野既名，講完之後，請你重複一次 請記住佢地，因為幾分鐘後，我會叫你再講番俾我聽。 (蘋果) (報紙) (火車) 依家請你講番哩三樣野俾我聽。	 ( ) ( ) ( ) 重覆次數:
4.	請你用一百減七，然後再減七，一路減落去，直至我叫你停為止。(減五次後便停) 或:依家我讀幾個數目俾你聽，請你倒轉講番出黎 [4 2 7 3 1] (第一次) (第二次) (第三次) (第四次) (第五次)	 ( ) 1st ( ) 2nd ( ) 3rd ( ) 4th ( ) 5th
5.	我頭先叫你記住既三樣係乜野呀? (蘋果) (報紙) (火車)	 ( ) ( ) ( )
6.	哩樣係乜野? (鉛筆) (手錶)	 ( ) ( )
7.	請你跟我講句說話:[姨丈買魚腸]	( )
8.	依家檯上面有一張紙。 請用你既右手拿起張紙 用兩隻手將紙摺成一半	 ( ) ( )

Appendix 4.4

	然後放番張紙係檯上面	( )
9.	請你讀出張紙上面既字，然後跟住做。 拍手	( )
10.	請你講出任何一句完整既句子俾我聽。例如：[我係一個人]、[今日天氣好好]。	( )
11.	哩處有幅圖，請你照著黎畫啦。 	( )
	總分：	( )

Reference:
Chiu, H., Lee, H. C., Chung, W. S., Kwong, P. K. (1994). Reliability and validity of the Cantonese version of mini-mental state examination: a preliminary study. *Journal of Hong Kong College of Psychiatrists, 4* (Suppl 2), 25S–28S.

Appendix 4.5

Functioning (ADL) – Modified Barthel Index (Chinese version)

項目		得分
個人衛生	**0** – 完全依賴別人去完成整項活動 **1** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **3** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **4** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **5** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
洗澡	**0** – 完全依賴別人去完成整項活動 **1** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **3** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **4** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **5** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
進食	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
如廁	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
上落樓梯	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
穿衣	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
大便控制	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
小便控制	**0** – 完全依賴別人去完成整項活動 **2** – 某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 **5** – 能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 **8** – 除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 **10** – 可以獨立完成整項活動而毋需別人在旁監督、提示或協助	

Appendix 4.6

行走	0 –完全依賴別人去完成整項活動 3 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 8 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 12 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 15 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
床椅轉移	0 –完全依賴別人去完成整項活動 3 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 8 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 12 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 15 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
輪椅操控*	0 –完全依賴別人去完成整項活動 1 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 3 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 4 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 5 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
	總分 (0-100)	

*「輪椅操控」只適用於「行走」項目中被評為「完全不能步行」的人。

Reference:

Leung, S. O. C., & Chan, C. C. H., & Shah, S. (2007). Development of a Chinese version of the Modified Barthel Index – validity and reliability. *Clinical Rehabilitation, 21*, 912-922.

Appendix 5.1

Acupressure for Managing Agitation in Nursing Home Residents with Dementia: A Data Collection Guideline

Appendix 5.2

Introduction

The purpose of this protocol is to provide a clinical guidance to collect data. This protocol will cover the following contents:

Appendix 5.3

Instructions to Data Collector

Major duty

You are required to collect three types of data: 1) Demographic and Clinical Data, 2) CMAI, & 3) Saliva. Please refer to the related documents for the detailed procedures.

Expectations

You are expected to arrive on time. Time is a crucial point for the validity of the data, especially the Saliva. For the exact duty time, you may refer to the Duty Roster. It can be different among different nursing homes. You are expected to ensure the correct identity, appropriate identity check (eg. checking the name on the bracelet) and sampling identity labeling are very important. You are expected to carry the provided equipments (eg. cool box, swabs, etc…) with you every time you go for the Saliva collection.

Data Collection Interval

You are required to collect data at different time intervals: 1) At the time of recruitment, & 2) Every Wednesday and Saturday. At different time intervals, you are required to collect different types of data.

At the time of recruitment

After a nursing home has been confirmed to allow us to recruit subjects, the Coordinator will identify the designated Data Collectors to go with her. The date of recruitment is the best to be on Saturday. After the screening and consenting procedures which are done by the Coordinator, Baseline data collection can commence. You are required to collect all three types of data.

Every Sunday and Saturday

On every Saturday or Sunday, you are required to collect both the CMAI and the Saliva.

Post data collection

Appendix 5.4

Every time after the data collection, you are expected to do documentation and return the samples collected.

Documentation

You are required to document on two types of document:

- On-site Individual Progress Record (to record the progress of the data collection)

Returning Samples

You are required to return all the collected samples within the same day. For the paper type data (eg. Demographic and Clinical Data, CMAI), you should contain the forms in the provided envelop according to the type of data (eg. CMAI in the CMAI envelop) and drop it in my pigeon hole (which is named "Rick Kwan" on the 5/F of PQ core in PolyU campus). For the Saliva, you should return it to the designated box of the fridge (which is located in FG513).

Appendix 5.5

Demographic and Clinical Data Collection Procedure

Preparation

Equipments

- The Demographic and Clinical Data (D&CD) questionnaire
- Pencils or pen

Subject and environment

The environmental factors may influence the performance of the subject. It is the best to identify a quite room to start the data collection.

Explanation

The Data Collector should explain the procedure prior to collecting sample. The Data Collector can say "Hello, my name is XXX. I am a research person from School of Nursing, PolyU. I am going to ask you a feel questions. I would like to ask you to do your best to answer my questions or to do according to my instruction. If you really cannot do it, it is ok. This interview will take around 10 minutes. Are you ready now?"

Procedure

The sequence of the interview should be:

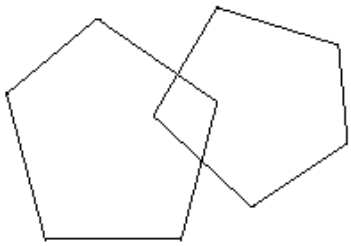
1. MMSE (Ask the subject)
2. MBI (Ask the care givers)
3. Demographic data (Access the info in the patient record, ask the proxy or the subject)

Appendix 5.6

Cognitive Function – MMSE (Cantonese version)

	問題	得分
1.	依家係乜野日子？ (年份) (季節) (月份) (幾號) (星期幾)	 ( ) ( ) ( ) ( ) ( )
2.	我地依家係邊度？ (九龍/新界/香港) (九龍/新界/香港既邊度) (醫院/邊一科診所/邊條街/邊個屋村) (邊層樓/診所名字/邊一座/中心名字) (病房/邊層樓)	 ( ) ( ) ( ) ( ) ( )
3.	依家我會講三樣野既名，講完之後，請你重複一次 請記住佢地，因為幾分鐘後，我會叫你再講番俾我聽。 (蘋果) (報紙) (火車) 依家請你講番哩三樣野俾我聽。	 ( ) ( ) ( ) 重覆次數:
4.	請你用一百減七，然後再減七，一路減落去，直至我叫你停為止。(減五次後便停) 或: 依家我讀幾個數目俾你聽，請你倒轉講番出黎 **[4 2 7 3 1]** (第一次) (第二次) (第三次) (第四次) (第五次)	 ( ) 1st ( ) 2nd ( ) 3rd ( ) 4th ( ) 5th
5.	我頭先叫你記住既三樣係乜野呀？ (蘋果) (報紙) (火車)	 ( ) ( ) ( )
6.	哩樣係乜野？ (鉛筆) (手錶)	 ( ) ( )
7.	請你跟我講句說話：[姨丈買魚腸]	( )
8.	依家檯上面有一張紙。 請用你既右手拿起張紙	 ( ) ( )

Appendix 5.7

	用兩隻手將紙摺成一半 然後放番張紙係檯上面	( )
9.	請你讀出張紙上面既字，然後跟住做。 拍手	( )
10.	請你講出任何一句完整既句子俾我聽。例如：【我係一個人】、【今日天氣好好】。	( )
11.	哩處有幅圖，請你照著黎畫啦。 	( )
	總分:	( )

Reference:
Chiu, H., Lee, H. C., Chung, W. S., Kwong, P. K. (1994). Reliability and validity of the Cantonese version of mini-mental state examination: a preliminary study. *Journal of Hong Kong College of Psychiatrists, 4* (Suppl 2), 25S–28S.

Appendix 5.8

Functioning (ADL) – Modified Barthel Index (Chinese version)

項目		得分
個人衛生	0 –完全依賴別人去完成整項活動 1 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 3 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 4 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 5 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
洗澡	0 –完全依賴別人去完成整項活動 1 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 3 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 4 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 5 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
進食	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
如廁	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
上落樓梯	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
穿衣	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
大便控制	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
小便控制	0 –完全依賴別人去完成整項活動 2 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 5 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 8 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 10 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	

Appendix 5.9

行走	0 –完全依賴別人去完成整項活動 3 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 8 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 12 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 15 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
床椅轉移	0 –完全依賴別人去完成整項活動 3 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 8 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 12 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 15 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
輪椅操控*	0 –完全依賴別人去完成整項活動 1 –某程度上能參與，但在整個活動過程中都需要別人提供協助才能完成。 3 –能參與大部份的活動，但在某些過程中仍需要別人提供協助才能完成整項活動 4 –除了在準備或收拾時需要協助，病人可以獨立完成整項活動；或進行活動時需要別人從旁監督或提示，以策安全。 5 –可以獨立完成整項活動而毋需別人在旁監督、提示或協助	
	總分 (0-100)	

*「輪椅操控」只適用於「行走」項目中被評為「完全不能步行」的人。

Reference:
Leung, S. O. C., & Chan, C. C. H., & Shah, S. (2007). Development of a Chinese version of the Modified Barthel Index – validity and reliability. *Clinical Rehabilitation, 21*, 912-922.

Appendix 5.10

Demographic and Clinical Data

DC Name		**DC Date**	
Subject #:			
Name (Eng):		**Name: (Chi):**	
Gender:			
NH Name:		**Age:**	
NH duration:			
Home Tel.:		**Language:**	
Proxy Name:		***Proxy Relat.**	
Proxy Tel:			
HoAPW:		**Education year**	

Medical History	**Drug Name:**	**Dose:**	**Freq.**	**Route:**

** Proxy Relat.: Proxy Relationship*
YoDDX: Year of Dementia Diagnosis
HoAPW: Hour of Activity per Week

Appendix 5.11

Question Keys

DC Name	The name of the data collector
DC Date	The date of the data collection
Subject #	The code assigned by the Coordinator at the time of recruitment
NH Name	Full name of the Nursing Home
Age	Round down to year, Eg. 86 years and 11 months, write it as "86 yr"
NH duration	Use number of months, Eg. "87 months"
Home Tel.	The telephone of the Nursing Home
Proxy Name	Family is commonly (but not always) the Proxy. If the subject has got a legal guardian, the proxy should be the legal guardian.
Proxy Relat.	The relationship to the client, Eg. "son"
Proxy Tel	The telephone number of the proxy
HoAPW	Hour of Activity per Week. Only the scheduled activities are counted, Eg. Cooking, physiotherapy. Non-scheduled chatting and watching TV are not counted.
Education year	Counting from primary level education. Pre-school level is not counted. Eg. "3 year informal education" is 3 years. "2 year kindergarten" is 0 years. "Primary 5" is 5 years.

Appendix 5.12

CMAI Procedure

Preparation

Equipments

- CMAI questionnaire
- CMAI questionnaire copy for the informant
- Pencil or pen

Environment and informant

It is the best to identify a quite room to conduct the interview. CMAI is an interview asking the care giver who is the most familiar with the behavior of the subject. Therefore, an appropriate informant should be identified. The informant can be the nurse, social workers, activity directors, or health care worker in the nursing home.

Procedure

The Data Collector should explain the procedure prior to collecting sample. The Data Collector can say "My name is xxx. I am a research person from School of Nursing, PolyU. Today we are going to talk about Ms. A. I'm going to ask you some questions about certain specific behaviors that occur in older people. Let me explain what we are going to be doing. The purpose of this evaluation is xxx. The purpose of using this form, the CMAI is to assess agitated behaviors in elderly persons. The reason that I am asking you is that you have the most contact with Ms. A. as her direct caregiver, and so you know her best. Thank you for agreeing to help with this assessment. These questions should take us approximately 20 minutes to complete. I will read you a list of behaviors. Some of these will apply to Ms. A., and some will not. Some of the behaviors listed here on the CMAI may sound like they are negative or bad behaviors, but please answer honestly. We are only trying to figure out how often these behaviors occur, not judge whether a person is good or bad. I am going to read the description for you, and then you tell me how often Ms. A. has behaved this way in the past one week during your work shift. To make it easier to remember the options, I have this CMAI form for you that can remind you of how you should be answering. So as you can see the frequency would be either never; less than once a week; once or twice a week; several times a week; once or twice a day, several times a day, or several times an hour. If a behavior is not applicable then just let me know. Rate only what you see and hear on your shift. I would also like you to look at a copy of the questions that

Appendix 5.13

I'll be asking you. It just might make it easier for you to follow along. Just remember the period to rate is the last one week. Any questions? Great, let's begin. The first behavior is…. How often has Ms. A……..?"

Reference

Cohen-Mansfield, J. (1991). Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI). The Research Institute of the Hebrew Home of Greater Washington: Maryland. Retrieved from http://www.dementia-assessment.com.au/symptoms/CMAI_Manual.pdf

Appendix 5.14

中文版柯恩曼斯菲爾德激越情緒行為量表-養老院版（4-factor-model）

(Chinese Cohen-Mansfield Agitation Inventory, Nursing Home version)

Subject Name:	Subject Code:
Date:	Time point: T0 T1 T2 _____
Collector Name:	Informant Name:
Venue:	

項目	行為表現	分數 (1-8, NA)
1	重覆說話或提問	
2	不切題地打斷別人談話或打擾別人的活動	
3	投訴或抱怨	
4	為求注意或幫助而作出無理要求	
5	咒罵別人或在言語上恐嚇或侮辱別人	
6	隨意吐痰	
7	口頭指使或勉強別人	
8	煩躁或坐立不安	
9	無故離去或擅自進入其他地方	
10	不適當地穿衣或寬衣	
11	不適當地處理東西(亂搜抽屜、擅取別人的物件或模不該摸的東西)	
12	藏匿物件	
13	動怒	
14	打人或自己或物件	
15	踢人或物件	
16	緊靠或抓著別人	
17	推開別人	
18	抓別人或自己或物件	
19	吃喝非食品類的東西	
20	指控別人	
21	不停尋找東西	

行為表現的出現次數	分數
未發生過	1
每星期少於一次,但仍有發生	2
每星期一至兩次	3
每星期數次(三次或以上)	4
每天一至兩次	5
每天數次(三次或以上)	6
每小時數次(兩次或以上)	7
如不制止便會發生	8

*請就對象過去一星期的行為表現的出現次數評分

Appendix 5.15

Reference

Original English version

Cohen-Mansfield, J., Billig, N. (1986). Agitated behaviors in the elderly I: a conceptual review. *Journal of American Geriatric Society, 34*, 711-721.

Chinese version

Lai, J. Y. (2010). The Cohen-Mansfield Agitation Inventory: development of a Chinese version. *Chinese Journal of Nursing, 45*(6), 500-504.

Appendix 5.16

CMAI, Question keys

1.	**Subject Name**	The Full English name of the subject (Last name first), Eg. Kwan Yiu Cho
2.	**Subject Code**	The code assigned to the subject at the time of recruitment
3.	**Date**	The date of date collection, Eg. DD-MM-YYYY (28-03-2013)
4.	**Time point**	The number of measure, Eg. Week 0, Week 1, Week 2, etc…
5.	**Collector Name**	The name of the Data Collector, Full Name, Eg. Chan Siu Man
6.	**Informant Name**	The name of the caregiver providing the data. It can be the nurses or the health care workers, Full Name, Eg. Chan Tai Yi
7.	**Venue**	The name of the nursing home. Use appropriate/standardized name as provided by the Coordinators

1.	**Repetitive sentences or questions**	Repeating the same sentence or question one right after the other, addressed to a particular person or to no one (complaining, even if oriented and possibly warranted is rated under the complaining section)
2.	***Interrupting***	*Inappropriately interrupt the conversation or activities of others.*
3.	**Complaining**	Whining, complaining about self, somatic complaints, personal gripes or complaining about physical environment or other people.
4.	**Constant unwarranted request for attention or help**	Vebal or nonverbal unreasonable nagging, pleading, demanding (indicate also for oriented people).
5.	**Cursing or verbal aggression**	only when using words; swearing, use of obscenity, profanity, unkind speech or criticism, verbal anger, verbal combativeness. Does not include unintelligible noises (rate under screaming or strange noises).
6.	**Spitting (including while feeding)**	Spitting onto floor, other people, etc.; does not include uncontrollable salivating, or spitting into tissue, toilet, or onto ground outside.
7.	***Verbal instructing or forcing others***	Verbally instructing others or forcing somebody to do something.
8.	**General restlessness**	Fidgeting, always moving around in seat, getting up and sitting down inability to sit still.
9.	**Trying to get to a different place**	Inappropriately entering or leaving a place, such as trying to get out of the building, off the property, sneaking out of room, trying to get into locked area, trespassing within unit, offices, or other resident's room or closet.
10.	**Inappropriate dressing or disrobing**	Putting on too many clothes, putting on clothing in a strange manner (eg. putting pants on head), taking off clothing in public or when it is inappropriate (if only genitals are exposed, rate under sexual advances). Does not include a person's

Appendix 5.17

		ability to dress/undress as in ADL's.
11.	**Handling things inappropriately**	Picking up things that don't belong to them, rummaging through drawers, moving furniture, playing with food, fecal smearing.
12.	**Hiding things**	Putting objects out of sight, under or behind something.
13.	**Temper outbursts**	Exhibiting verbal and non-verbal expressions of anger that are more complex and of longer duration that single agitated behaviors. Can include but not limited to hitting, throwing, cursing, etc…
14.	**Hitting**	Physical abuse, striking others, pinching others, banging self/furniture.
15.	**Kicking**	striking forcefully with feet at people or objects
16	**Grabbing onto people**	Snatching, seizing roughly, taking firmly, or yanking
17.	**Pushing**	Forcefully thrusting, shoving, moving putting pressure against another.
18.	**Scratching**	Clawing, scraping with fingernails either other people or self.
19.	**Eating or drinking inappropriate substances**	Putting into mouth and trying to swallow tems that are inappropriate.
20.	***Accusing others***	*Accusing that he is being framed. Someone steals his money/belongings. (Including true or imaginary/hallucinated people)*
21.	***Keep finding things***	Keep finding things

Appendix 5.18

THE HONG KONG POLYTECHNIC UNIVERSITY 香港理工大學

Criteria for agitated/not agitated status

Subject Name: _____ **Subject Code:** _____
Date: _____ **Data Collector Name:** _____

Is the CMAI total score above 30? Yes => recruit, No ⇒ continue the below

Factor 1 – Aggressive behavior				
	Score	Checking question	Yes	No
Q. 5		**ONE** item or more ≥ 4		
Q. 6		**TWO** items or more ≥ 3		
Q. 7		**THREE** items or more ≥ 2		
Q. 14		**TWO** items or more ≥ 2, & **ONE** item ≥ 3		
Q. 15				
Q. 17				
Q. 18		If any **ONE** of the above is true, the client is agitated. Is it true?		

Factor 2 – Physically nonaggressive behavior				
	Score	Checking question	Yes	No
Q. 8		**ONE** item or more ≥ 5		
Q. 9		**TWO** items or more ≥ 4		
Q. 10		**THREE** items or more ≥ 3		
Q. 11		**FOUR** items or more ≥ 2		
Q. 12				
Q. 16				
Q. 19				
Q. 21		If any **ONE** of the above is true, the client is agitated. Is it true?		

Factor 3 – Verbally agitated behavior				
	Score	Checking question	Yes	No
Q. 1		**ONE** item or more ≥ 5		
Q. 2		**TWO** items or more ≥ 4		
Q. 3		**THREE** items or more ≥ 3		
Q. 4		**FOUR** items or more ≥ 2		
Q. 13				
Q. 20				
		If any **ONE** of the above is true, the client is agitated. Is it true?		

Overall Agitation status		
Checking question	Yes	No
If any one of the above factor is true, the client is defined to be agitated. Is it true?		

Appendix 5.19

Saliva Collection Procedure

Preparation

Equipments

- Oral swabs (Salimetrics Oral Swab or Salimetrics Children's Swab)
- Sample Collecting Tubes
- A pair of scissors
- Gloves

Timing

- Wake-up time (at least 1 hour after wake up)
- Meal time (before or at least 1 hour after meal)
- Alcohol (at least 12 hours after alcohol consumption)

Subject

The position does not matter. The subject can be either in a lying or sitting position. In order to prevent dryness or acidity, it is suggested to rinse mouth of the subject by water. This should be done at least 10 minutes prior to the sample collection.

Procedure explanation

The Data Collector should explain the procedure prior to collecting sample. The Data Collector can say "Hello, my name is XXX. I am a research person from School of Nursing, PolyU. I am going to collect some of your saliva sample for research purpose. What I am going to do is to put this tiny cotton swab into your mouth under your tongue. You just have to keep your mouth close for 1 to 2 minutes. You may feel a little bit dryness during the process. But it does not normally cause discomfort. Are you ready now?"

Appendix 5.20

Collection procedure

1. Hand rub and put on gloves
2. Instruct the subject to open the mouth
3. Put the oral swab into the mouth under the tongue
4. Take it out after 1 to 2 minutes
5. Examine if the oral swab is fully soaked with saliva. If not, put it back to wait for another 3 minutes.
6. Repeat step 5 if the swab is still dry. Max collection time (keep the swab in mouth) should not exceed 6 minutes.
7. Put the return swab into the sample collecting tube.
8. If Salimetrics Children's Swab is used, it is too long to put into the tube. Cut it short until it can be placed inside the tube. However, don't cut too short. The volume of saliva will not be adequate if the saliva-soaked swab is too short.
9. Replace cap and snap securely onto tube
10. Label the exterior of the tube (subject code and interval)
11. Place the saliva sample into the cool box provided immediate after collection

Caution

1. Use each swab once only
2. If visible blood is noted in the returned swab, discard the sample and start the procedure over. If the blood is still noted in the second time, inform the Coordinator for possible dropping the data.

Reference

Salimetrics. (2009). Salimetrics Oral Swab (SOS). Retrieved from *http://www.salimetrics.com/documents/S-Sample_collection-Salimetrics_Oral_Swab__SOS_-Illus._Instructions-Rev_12-28-09.pdf*

Salimetrics. (2011). High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit. Retrieved from *http://www.salimetrics.com/documents/Cortisol_Kit_Insert.pdf*

Appendix 6

Venue Code: _____ Date: _____

Interventionist Skill Checklist of Intervention Protocol

Skills	Score*
Preparation	
1. Introduction, procedure explanation, hand preparation, client positioning	
Acupoint Identification	
2. Point 1	
3. Point 2	
4. Point 3	
5. Point 4	
6. Point 5	
General Techniques	
7. Light-strong-light principle	
8. Applying pressure time	
9. Sustainability of pressure	
10. Post-acupressure kneading	
11. Acupoint confirmation (eg. identification of the sore, numb, swollen, pain)	
Specific Techniques	
12. Point 1: specific techniques on applying pressure	
13. Point 2 & Point 3: specific techniques on applying pressure	
14. Point 4 & Point 5: specific techniques on applying pressure	
Post Intervention	
15. Advice to the client and the caregiver	

* 1=Very inappropriate, 2=Inappropriate, 3=Appropriate, 4=Very appropriate

Appendix 7

Venue Code: _____ Date: _____

Skill Checklist of Sham Protocol

Skills	Score*
Preparation	
1. Introduction, procedure explanation, hand preparation, client positioning	
Acupoint Identification	
2. Point A	
3. Point B	
4. Point C	
5. Point D	
6. Point E	
General Techniques	
7. Light-strong-light principle	
8. Applying pressure time	
9. Sustainability of pressure	
10. Post-acupressure kneading	
Specific Techniques	
11. Point A: specific techniques on applying pressure	
12. Point B & Point C: specific techniques on applying pressure	
13. Point D & Point E: specific techniques on applying pressure	
Post Intervention	
14. Advice to the client and the caregiver	

* 1=Very inappropriate, 2=Inappropriate, 3=Appropriate, 4=Very appropriate

Appendix 8.1

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「穴位按壓對治療老年癡呆症患者煩躁的成效」的研究計劃

本人關耀祖是香港理工大學護理學院的一名博士研究生。在香港理工大學護理學院賴錦玉教授的督導下，將進行一項研究。本研究已通過了香港理工大學人類實驗倫理委員會的審核（HSESC 參考編號：HSEARS20120920001）。

穴位按壓是源自中醫經絡學的一種非入侵性的治療。本研究的目的是要進一步探討穴位按壓對治療老年癡呆症患者在煩躁上的成效。在這項研究中使用的穴位治療細節（例如：選穴，手法），是由一個專家小組按中醫針灸學的原則及以往的臨床實證所編訂的。這項研究的穴位治療將會由一些受過訓練的研究員執行。在治療開始之前，研究員將會與您會談以取得您的一些基本資料(例如：年齡、性別、認知能力、健康狀況等）。在穴位按壓治療期間，研究員將會進行四次數據收集，分別在開始時、開始後兩星期、開始後四星期及開始後七星期。介時研究員將會收集您的唾液樣本，及咨詢在院舍的中的職員，以收集有關您的行為表現數據作研究分析。透過此項研究，我們希望可以對穴位按壓在老年癡呆症煩躁的治療上進一步了解，從而為老年癡呆症煩躁的情況提供更適切的治療。

在您同意參加本研究後，您將會被隨機安排到三個小組的其中一個。在第一個的「實驗小組」中，您將會接受理論上有效的穴位按壓。在第二個的「安慰小組」中，您將會接受理論上無效的穴位按壓。在第三個的「對照小組」中，您將不會接受任何的穴位按壓，但你仍會給予常規的照顧。為了增加研究的可信性，在研究進行期間，您將不會知道您所進的是哪一組。在最後一次的數據收集完成後，我們才會告訴您曾進的是哪一組。在研究完成後，如果您並沒有被安排到「實驗小組」中但您又想接受穴位按壓，我們將會提供一次免費的穴位按壓療程給您，以作補償。

當您接受穴位按壓治療時，你只需要放鬆躺臥在床上或坐在椅子上。在按壓身體穴位部位時，您可能會感到一些輕微的酸軟，這是正常的反應。這種治療在以往類似的研究中，並沒有引起明顯的不適。治療每天會進行兩次，每次的治療時間大概為 10 分鐘，整個療程為期兩星期。凡有關您的資料均會保密，及只會用作研究學術用途。只有研究小組的人才有權擷取您的資料。

在本研究進行的任何時候，您都享有充分的權利決定退出這項研究，而不會受到任何不正常的待遇或責任追究。整項研究將會在兩個月內完成。

如果您對本研究有任何不滿，請隨時與香港理工大學人事倫理委員會秘書親自或寫信聯絡(地址：香港理工大學人力資源辦公室 M1303 室轉交)。

Appendix 8.2

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學
護理學院
School of Nursing

香港 九龍 紅磡
Hung Hom, Kowloon, Hong Kong

如果您想獲得更多有關這項研究的資料，可以跟關耀祖先生（電話 2766-6546; 電郵 rick.kwan@ ）或賴錦玉教授（電話 2766-6544; 電郵 claudia.lai@ ）聯絡。

多謝您有興趣參加這項研究。

研究員

賴錦玉教授
關耀祖

日期: 2012 年 9 月 20 日

Appendix 9

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

參與研究同意書

「穴位按壓對治療老年癡呆症患者煩躁的成效」的研究計劃

本人 _____ 同意參加由理工大學護理學院舉辦的研究項目。

我理解此研究所獲得的資料可用於未來的研究和學術交流。然而我有權保護自己的隱私，我的個人資料將不能洩漏。

我對所附資料的有關步驟已經得到充分的解釋。我理解可能會出現的風險。我是自願參與這項研究。

我理解我有權在研究過程中提出問題，並在任何時候決定退出研究而不會受到任何不正的待遇或責任追究。

參加者姓名: _____

參加者簽署: _____

家屬姓名或監護人姓名（如需要）: _____

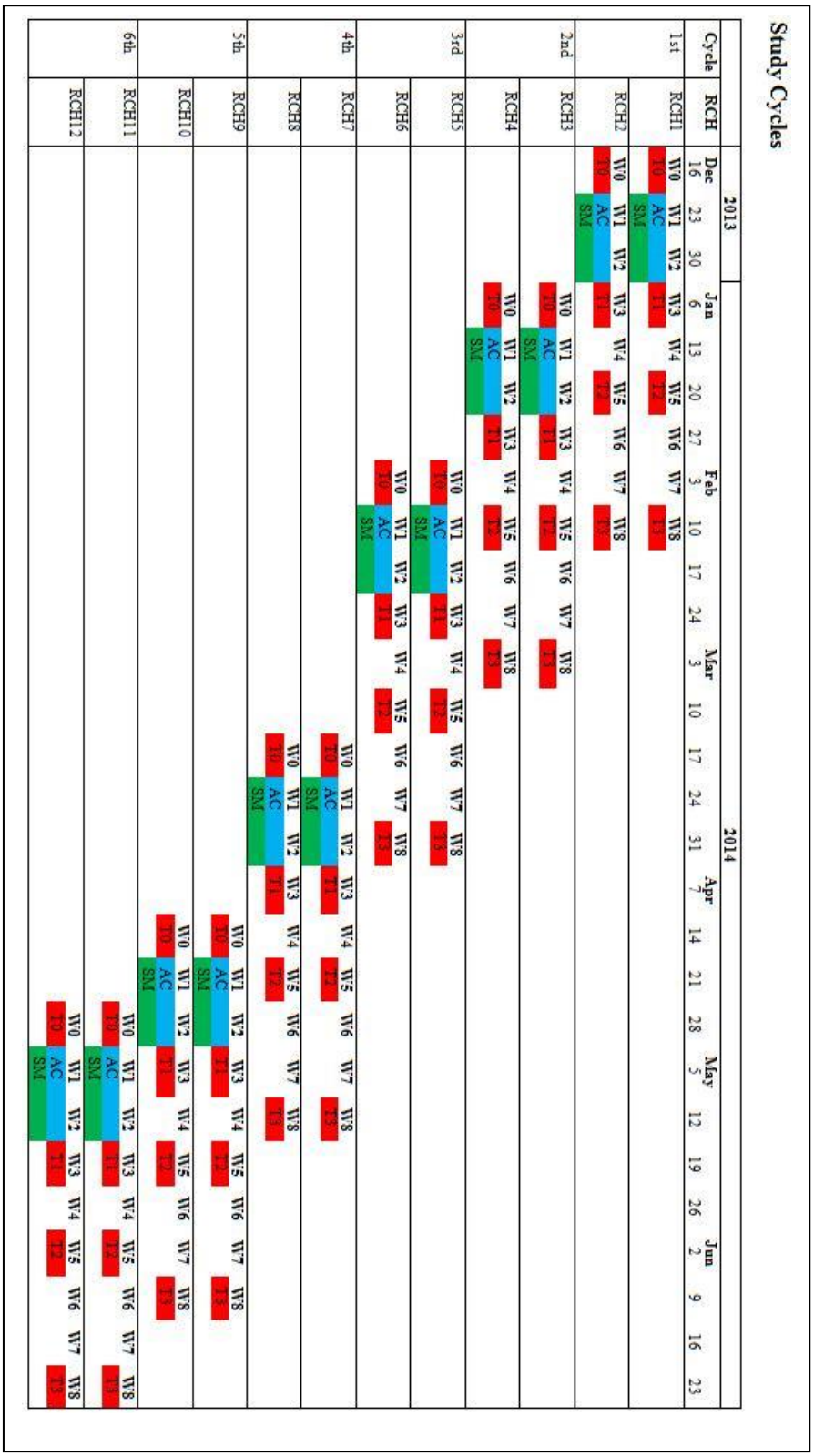
家屬或監護人簽名（如需要）: _____

研究人員姓名: _____

研究人員簽字: _____

日期: _____

Appendix 10


Study Cycles
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