出國報告（出國類別：進修）

英國倫敦大學國王學院精神醫療服務碩士學位進修報告

服務機關：行政院衛生署桃園療養院
姓名職稱：詹宏裕 高年精神科主任
派赴國家：英國
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摘要

本出國進修之目的在於前往英國倫敦國王學院的英文學習中心進修「學術英文」以及英國倫敦國王學院的精神醫療研究機構(Institute of Psychiatry)研習「精神健康服務以及族群研究」的碩士學位課程，學習相關的最新知識以及研究方法，並吸收英國最新的精神醫療服務相關研究成果。筆者利用一年的時間歷經五週的學術英文以及三個學期六大科目的學習，已經通過畢業審查，畢業總成績爲傑出(distinction)，預計 102 年 1 月正式獲得碩士學位。

老年人口的逐年增加，使得老年精神醫療的問題越來越重要，爲因應這個需求，筆者選定老年精神疾患作爲此次出國的學習主題，因此「學術英文」是以老年失智症認知改善藥物的費用以及療效評估的論文作爲期末報告，從學術英文學習到如何更正確的使用英文的文章架構、邏輯、文法、片語以及英語慣用寫法，而此論文獲得 A 的評量等級。在碩士的課程方面，學習了研究方法、研究倫理以及統計(Research Methods, Ethics and Statistics)這門必修的課程，這門課程學習到正確的研究方法和統計以及如何考慮研究倫理的可行性。另外學習了四門選修課程分別是「系統性回顧與統和分析」(Systematic review and meta-analysis)、「流行病學的統計方法」(Statistical methods of epidemiology)、「精神醫療服務研究：從理論到實務」(Mental Health Services Research: Theory to Practice）與「全球精神健康」(Global mental health)。這四門選修課程分別學習到如何全面性的搜尋研究論文、評估研究論文的品質以及如何對合乎品質的論文進行質性以及量性的彙整；更深入的統計原理以及應用，包含各類的廻歸模式以及重複測量的統計；在兼顧可行性、重要性以及可運用的研究資源下，如何進行臨床精神醫療服務的研究；以及在進行醫療服務以及研究時，須要考慮到當地的人文、宗教、政治、經濟、醫療以及人口分布等因素，去做最適合的規畫。在碩士論文方面，因爲過去一直注意到藥物對於老年失智症患者會出現死亡以及中風等重大的副作用，因此以長期使用抗精神病藥物的老年失智症患者進行隨機分配有對照組的停藥研

究，作爲碩士論文。論文彙整了所有過去的抗精神病藥物在老年失智症患者的停藥研究，並根據過去研究的限制以及缺點，訂定了新的研究主題方向。因爲不管必修科目、選修科目以及碩士論文大都是得到傑出的成績結果，因此最後畢業的結果，是以獲得傑出的等級畢業。

這次出國的學習心得，主要是學習到英國碩士課程的扎實以及研究資源的豐富性，課程內容非常重視學生的學習狀態，而且非常強調各種學問的基礎，不會有囫圇吞棗這種只求表面但不重視學生真正學習狀態的問題;而且學校中到處都是國際級的大師，可以來指導研究的進行以及討論，讓人收穫良多。

最後經過這一年的進修後，筆者有幾項建議提供長官們參考，對於「行政院衛生署及所屬醫院醫事人員出國進修計畫」的建議是建議設專人或委託專業機構協助出國申請，以改善部分通過衛生署核准出國進修的人員，最後未能順利出國完成學業的問題。另外對於台灣老年精神醫學的建議是需要提升老年精神病患的藥物以及非藥物介入治療的臨床實證研究，尤其是非藥物介入治療的臨床實證研究，來改善此一族群的身心健康。

最後感謝衛生署以及院內同仁的支持，特別是衛生署長官們的厚愛以及陳快樂院長的鼓勵與支持，讓筆者可以有這次豐富的出國學習機會。

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目的

行政院衛生署醫院管理委員會依據「行政院衛生署及所屬醫院醫事人員出國進修計畫」,自 96 年起甄選行政院衛生署行政院醫院管理委員會暨所屬醫院現職醫事人員，每年 2-8 名，薦送出國專題研究進修有關醫院管理、公共衛生及國際醫療衛生領域的碩士。筆者有幸於 98 年 11 月通過甄選，得以接受補助於民國 100 年出國進修一年。筆者自民國 83 年擔任桃園療養院醫師以來，就注意到老年精神醫療的特殊性以及重要性，老年人口的逐年增加，使得老年精神醫療的問題越來越重要。爲因應這個需求，自民國 93 年起，桃園療養院成立了專屬於老年精神病患的急性病房，而且於門診開立了專屬於老年精神病患的記憶門診，並且透過與社區老年安養中心的合作，來服務社區的老年精神病患。筆者透過臨床服務與教學，實際參與老年精神病患的服務，並有機會參與北區精神醫療網的老年精神病患服務計畫的執行，得以學習如何由公共衛生的角度，結合醫院、社區、社政與民間資源，建構老年精神病患的服務模式。然而，在工作的過程中常會發現，在執行某項醫療服務或社區計畫時，例如失智症病患出現精神症狀或問題行爲時，是否要使用精神科藥物治療時，本土的研究資料往往因爲缺乏資料、研究方法不良或無系統性的整理,而無法在實證的基礎上回答「此項方式是否有效」、「各種治療方式的優缺點如何」以及「成本效益」等問題。而英國倫敦國王學院（King's College London, KCL）的精神醫療研究機構（Institute of Psychiatry, IOP）所提供的精神醫療服務以及族群研究（Mental Health Services and Population Research）的相關課程,正好可以提供精神醫療臨床服務的研究方法與族群研究的實例與成果，讓使筆者有機會吸收其所長，思考回國後在台灣可行的方向。

本次出國進修，主要目的就是利用這一年的時間在 KCL 精進英文能力以及學習老年精神醫療服務的碩士課程，除了獲得碩士學位（Master of Science, MSc）外，更期待能學習相關的知識、研究方法以及整理技巧，進而運用在老年精神醫療的相關服務。

過程

準備期

筆者於 98 年承蒙陳快樂院長的支持與鼓勵，得知行政院衛生署有「行政院衛生署及所屬醫院醫事人員出國進修」的 5 年計劃，在民國 96 年到 100 年每年選派約 5 名所屬人員出國進修，因此決定著手進行出國進修的計畫，並且在規劃之初即以至少進修一年爲目標。由於本院陳快樂院長的指點與甫自英國歸國的謝迪忱醫師連繫，得知位於英國倫敦國王學院的精神醫學研究所（Institute of Psychiatry, IOP）爲精神醫學教學與研究鼎盛的學術重鎮，便以此爲出國的目標。而「行政院衛生署及所屬醫院醫事人員出國進修」的條件是要有英文檢定，並且要到衛生署口試。 而在衛生署口試審查時，審查的衛生署長官們主要就英文能力以及出國所學是否能應用在回國的工作上面加以了解以及建議，可見衛生署長官對此計畫的重視。

承蒙衛生署長官們同意此 98 年度出國進修計畫後，筆者原先計畫於民國 99 年就出國進修，但是因爲服務的醫院於民國 99 年進行醫院評鑑以及教學醫院評鑑，而筆者本身就是醫院評鑑的負責人，因此和本院陳快樂院長討論後，決定延後出國進修的時間到民國 100 年，也針對留學英國的英語能力測驗（IELTS 雅思）加以準備，而英國倫敦國王學院的精神醫學研究所入學的要求須要雅思 7 分或以上，而筆者在民國 100 年的雅思考試分數爲 6.5 分，雖然在 100 年 5 月收到倫敦國王學院的精神醫學研究所無條件入學通知（Unconditional Offer），但還是決定先於 100 年 7 月先到倫敦國王學院的英文學習中心進行 5 週的學術英文課程，學術英文的課程是相當緊湊的課程，上課的內容包含英文的發音、聽力、文法、相似字句以及反意字的運用、句型結構以及邏輯等，在學習的第二週就要完成一個 10 分鐘的學術英文演講，而在學習的第四週就要進行英文的聽力以及限時的作文測驗，而在第五週必須要完成一份英文的論文寫作。如果測驗的結果沒有達到

入學的標準就會被立刻退學，因此同學們都非常的緊張，深怕成績不好立刻就被退學而遣返回國。筆者因爲選定的研究主題是老年精神的研究，因此以老年失智症認知改善藥物的費用以及療效評估來作爲學術英文演講以及論文寫作的主題(如附件一)，最後於課程結束後的評量達到 A 的等級(等同於雅思 7 分或以上的成績)，順利取得入學的條件，之後再於 100 年 9 月開始一年老年精神醫療的學習。在此也感謝陳快樂院長與台大精神部高淑芬教授的推薦信，使得申請學校頗爲順利。而住宿方面選擇位於倫敦北區的地方，主要是因爲倫敦南區在民國 100 年 8 月發生暴動，爲了安全著想，因此不選擇學校所在的倫敦南區住宿。

學校簡介

IOP 位於倫敦南邊的丹麥山丘校區（Denmark Hill Campus），緊鄰世界知名的精神科醫院—莫斯理醫院（Maudsley Hospital），是一所授予碩士以上學位的精神醫學專門研究機構。它的部門眾多，從兒童到老人，從基因研究到社會精神醫學，從心理學到神經影像科學，可說是一所全方位的精神醫學研究重鎮。國內精神醫學界也有許多前輩先進與此機構保持研究上的合作關係（如鄭泰安教授），或是在此獲得博士學位（如中山醫學大學附設醫院精神科陳錦宏主任、北市聯合醫院社區精神科邱智強主任）。筆者上課時，都搭乘倫敦的紅色雙層巴士，慢慢由繁華熱鬧的倫敦北區經過市中心穿過泰晤士河，然後到達 IOP 所在的倫敦南區，彷彿進入另一個世界的區域，倫敦南區相當高比例的居民是黑人族群，相對比較落後。每次上課討論時，要舉出倫敦各區民眾社經地位最差之處，學校所在之處必定是其一。

課程內容

在 IOP 的課程共有三學期。第一個學期課程是必修課程，共 12 週，名稱是研究方法、研究倫理以及統計(Research Methods, Ethics and Statistics)，佔畢業成績的三分之一，以基本的流行病學方法與統計學方法爲主，課程內容也包括研究的倫理考量、醫學期刊以及醫學資訊的找尋方法。這門課程學習到正確的研究方法和

統計以及如何考慮研究倫理的可行性，雖然課程內容不算陌生，可是老師們南腔北調的英文，實在需要一段時間適應。幸好，他們的課程講義與指定書籍（IOP 爲此課程委由牛津出版社出版一本專書）都很有可讀性，彌補了上課時偶有鴨子聽雷的缺憾。期末的小考（不計分，算是模擬考）筆者得到 86 分傑出的成績（在英國，70 分以上就算傑出(distinction)，60 分以上算優良(merits)，50 分以上算通過(pass)，50 分以下就算需要重修）。

經過了一個聖誕與新年假期，同學們適應的差不多了，就開始進入緊湊的第二學期，第二學期一開始雖然都是選修課，可是經過課程的設計，讓人只能在許多有趣的課程中做一選擇，第二學期總共要選修 4 堂課，在前六週先進行其中的 2 堂，而在後六週再進行最後的 2 堂，中間間隔 2 週的時間讓同學來準備報告，而評分的方式都是約 2500 字的計劃或報告書。筆者在前六週選了「系統性回顧與統和分析」（Systematic review and meta-analysis）與「流行病學的統計方法」（Statistical methods of epidemiology）這兩門課。從「系統性回顧與統和分析」這門選修課程學習到如何全面性的搜尋研究論文，包含需要尋找的電子資料庫有哪些，例如 Pubmed、Medline、PsyInfo 、CINAHL 、Cochrane library 等，須要使用的關鍵字以及這些關鍵字的組合方式，也學習到如何評估研究論文的品質，例如可以使用考科藍團隊(Cochrane group)所發展出來的偏差嚴重度檢查表(risk of bias evaluation method)，來評估隨機分派有對照組的研究論文(randomized controlled trials, RCT)的各項品質，包括隨機分配表產生的方式(random sequence generation)、分配隱藏的方式(allocation concealment)、參與研究病患以及工作人員的盲性方式(blinding of participants and personnel)、結果評估的盲性方式(blinding of outcome assessment)、未完成評估資料的處理方式(incomplete outcome data)、選擇性報告內容(selective reporting)以及其他偏差等(other bias)，以及如何對合乎品質的論文進行質性以及量性的彙整，以及如何透過圖表以及統計方式來檢測是否有發表偏差(publication bias)的情形，「系統性回顧與統和分析」這項科

目雖然筆者只得了通過的等第(55 分)，可是卻可以學到如何對文獻作系統性的整理以及分析，相當有收穫（如附件二）。而由「流行病學的統計方法」這門選修課程學習到更深入的統計原理以及應用，包含常態分佈以及二項式分佈的理論以及第一型誤差(type I error or α)、第二型誤差(type II error or β)、統計檢力(statistical power)、p 值等定義，統計方法則學習到樣本數估計、t 檢定、卡方檢定、one sample proportional test、two sample proportional test、analysis of variance (ANOVA)、多層次分析(multi-level analysis)、各類的迴歸模式以及重複測量的統計；而「流行病學的統計方法」則是得到了傑出的等第(73 分)，從這個課程學到各種統計方法的概念以及 SPSS 統計軟體的使用，相當實用（附件三）。第二學期的後半則選修了本碩士課程最重要的「精神醫療服務研究：從理論到實務」（Mental Health Services Research: Theory to Practice）與「全球精神健康」（Global mental health）這兩個課程。「精神醫療服務研究：從理論到實務」這門課程主要是探討如何將實際的臨床服務模式，化成可以科學化評估成效的方式，來進行研究，因此這個課程非常強調如何在現實醫療環境下，來設計可行而且可以得到高證據力的研究，因此這類研究需要在兼顧可行性、重要性以及可運用的研究資源下，來進行臨床精神醫療服務的研究，另外在進行精神醫療服務以及研究時，須要考慮到當地的人文、宗教、政治、經濟、醫療以及人口分布等因素，去做最適合的規畫，而筆者就探討在台灣以醫療工作人員衛教的方式來降低老年失智症患者的抗精神病藥物不當使用來進行記劃書的撰寫（附件四），結果得到了優良但接近傑出的等第(69 分)。而「全球精神健康」這門課程則學習到各種階級的國家所面臨的精神健康的挑戰，可以了解如何因應各個國家地區的特殊需求，來制定適合的問題優先順序及介入方式，而筆者就以憂鬱症的文化及社會因素來加以探討，其全球的共通處以及差異處，以及如何用不同的角度來思考，來進行報告的撰寫（附件五），結果得到了傑出的等第(71 分)。因此這四科的期末成績有三科都是傑出或接近傑出的等第，只有一科是通過的等第，對於非英語母語的學生來說，算是相當不錯的成績。

度過復活節春假，第三學期首先要面對的就是五月底的「期末考」，考的就是第一學期的上課內容。只見同學們聚在一起做考古題的考前複習，大學聯考的記憶又浮上腦海，只是這一群人膚色語言大不相同，也算是特別的回憶了，而期末考的成績得到更高 88 分傑出的成績。期末考考完就和指導教授繼續討論畢業論文（dissertation）的撰寫。其實筆者於 100 年的 12 月就和指導教授 Sube Banerjee 討論以及選定畢業論文的題目，在經過完整的醫學文獻回顧後，以及考量研究可行性、科學證據重要性、在台灣可以獲得的研究資源等因素後，最後選定的畢業論文題目是「長期使用抗精神病藥物 quetiapine 的老年失智症患者進行隨機分配有安慰劑作爲對照組的停藥研究」計畫書，需要撰寫一萬字左右的內容，筆者於 100 年 12 月開始撰寫，之後每個月將撰寫的內容傳送給指導教授，因此平時就已經有充分的討論，所以最後指導教授只針對論文的英文用字作修改，對內容不只沒有意見而且非常讚賞，另外 Sube Banerjee 教授也建議筆者未來可以把論文的相關內容投稿到科學引用目錄(Science Citation Index, SCI)的醫學期刊，因而順利完成畢業論文（如附件六）。之後筆者於 101 年 9 月 14 日搭機離開倫敦，101 年 9 月 15 日回到台灣，到了 101 年 10 月 26 日接到了學校的電子郵件通知才知道，原來論文也得到了 79 分的傑出（distinction）成績，所以這一年最終是以總成績爲 78 分，傑出（distinction）的成績畢業，也算不辱台灣精神科醫師之名了。由於在英國的研究所多半以每年一月爲畢業季節，KCL 也不例外，所以，筆者雖已通過研究生畢業審查委員會（Postgraduate Board of Examiners in the Institute of Psychiatry）的審查，仍須等到 102 年 1 月以後才可領到正式的畢業證書。

心得與建議

心得

筆者有幸在進入職場十七年後，得以完全放下工作，出國進修，實在是相當幸運的一件事。除了可以精進專業知識外，還可以讓自己的視野更加的拓展，並且認識世界各國不同的同學，更是難得的經驗。

另外在 IOP 能夠受教於世界級大師的人物，如筆者的指導教授 Sube Banerjee，是世界級老年精神醫學的權威，尤其是老年精神藥理學的權威，英國政府甚至委託他本人進行全英國的抗精神病藥物的老年失智症患者使用調查，並作出具體的建議，並且得到英國政府的正面回應，投入大量經費來改善抗精神病藥物於老年失智症患者濫用的問題，可以看到一個致力於研究的學者如何發揮他的社會影響力，對整個國家健康政策做一個正確的導引，實在是一個典範。

另外英國對於人權以及精神病患的重視，也是相當讓人印象深刻之處。對於失智症患者，英國的文字敘述是 people with dementia(一個人伴隨有失智症)，強調一個人的特性，失智症只是他所得的一個疾病，而不會用 demented patient 來稱呼。另外失智症患者要參加醫療研究，需要有三份同意書，包括受試者同意書、家屬同意書以及家屬代表受試者同意書，來充份保障失智症病患的權益。

其他，如統計課程中，老師運用現成的研究原始資料（raw data），在電腦教室中讓大家一人一機的即時操作軟體，使人更能體會統計的奧妙之處，也是收穫良多的地方。還有英國傳統的導師制度，在第一學期中，導師以帶小組的方式每週討論當週的作業習題，實際解決學習的困難之處，也值得我們學習。更別說整個 IOP 支援的圖書館與網路資料查詢系統，真可說是一座寶庫。

建議

經過這一年的進修後，筆者有幾項建議提供長官們參考：

一、對「行政院衛生署及所屬醫院醫事人員出國進修計畫」的建議

建議設專人或委託專業機構協助出國申請，畢竟出國進修不是一件易事，從準備語言測驗到申請學校都有許多技巧，雖然作者歷經摸索期，並且多方請教前輩或相關機構，最後能幸運順利完成，但是如果能有專業人員協助，應該更能事半功倍，而且有些通過衛生署核准出國進修的人員，最後未能順利出國完成學業，也與此部分可能有關。

二、對台灣老年精神醫學的建議

由於各類老年精神問題十分常見，如失智症伴隨各類精神症狀、老年憂鬱症、老年失眠等等。但是各類精神科藥物在這些老年精神問題的使用，往往有其限制，因爲老年病患對於各類精神科藥物副作用往往非常敏感，臨床上常看到療效尚未出現但是副作用先出來，而且有可能是嚴重的副作用；因爲這個原因，英國對於老年精神病患的治療，投注相當高的人力以及經費在於藥物使用的臨床調查以及非藥物介入治療的臨床實證研究，因爲英國是相當重視人權的國家，因此病人安全是非常重要的議題，以失智症爲例，英國政府對於因爲過度使用抗精神病藥物於老年失智症患者，而產生不必要死亡以及腦血管疾患的問題相當重視，於 2009 年的委託調查報告發表後，立即進行相關的改善，包含醫師以及其他醫療專業人員的再教育，以及提高相關的人力，並且依照實證醫學的結果去制定相關的治療指引，讓抗精神病藥物於老年失智症患者的使用盛行率由過去的約 30%下降爲約目前的 10%，大大的降低抗精神病藥物於老年失智症患者所產生的死亡以及腦血管疾患的問題。建議衛生署也能考慮對於老年精神病患的藥物以及非藥物介入治療的臨床實證研究，也能逐年增加經費以及人力，來改善此一族群的身心健康。

誌謝

最後感謝院內同仁的支持，從陳快樂院長的鼓勵到所有醫療同仁辛苦的分擔工作、行政科室同仁在申請與經費核銷過程的指導、以及一般以及老年精神醫療團隊工作夥伴的體諒，讓筆者可以無憂無慮的重溫學生生活。也謝謝衛生署長官們的厚愛，讓筆者有機會獲得經費支援，到學費與生活費都很驚人的英國倫敦進修。

附件一「學術性英文課程」（Academic English course）課程報告

Anti-dementia medications for patients with Alzheimer's dementia: is it cost-effective?

Dementia is a mental illness which manifests itself through memory loss, self-care ability deterioration and many psychiatric symptoms such as delusion and depression (Seshadri, Beiser et al. 2011). Alzheimer's dementia is the highest subtype of dementia and more than 50% of dementia belongs to it (Brookmeyer, Evans et al. 2011). The prevalence of Alzheimer's dementia has risen sharply in the last decades due to the increase of the elderly population. The proportion of Alzheimer's dementia gradually elevates form 0.5-1 % in the age group of 60-64 y/o to 20-30% in the age group of ≧85y/o (Ferri, Prince et al. 2005). Some scholars (Brookmeyer, Johnson et al. 2007) estimated approximately 26.6 million people suffer from this disease all over the world. Furthermore, the global economic burden might achieve 422 billion USD in 2009 (Cappell, Herrmann et al. 2010). As a result, this disease is an important issue at present and in the future.

Alzheimer's dementia is recognized as an incurable disease. Therefore, some scholars have questioned the necessity of using anti-dementia medications in the treatment of Alzheimer's dementia (Kirby, Green et al. 2006; Loveman, Green et al. 2006). Nonetheless, many studies have demonstrated that these medications can improve the patients' memories and function and that it is cost-effective if all of the direct and indirect costs are counted and appropriate indicators to assess cost-effectiveness are used (Francois, Sintonen et al. 2004; Rive, Grishchenko et al. 2010). Another point is that different positions, including caregivers, insurance agents and the whole society, will result in different considerations of the costs and benefits (Murman, Von Eye et al. 2007). The purpose of this essay is to assess the cost-effectiveness of anti-dementia medications for the treatment of Alzheimer's dementia. It is clear that anti-dementia medications are cost-effective if the perspective of society is chosen and used an appropriate measuring indicator. The essay will begin by providing an overview of the anti-dementia medications. Then it will discuss the following issues including appropriate indicators to assess the effects of anti-dementia medications, the direct and indirect costs in anti-dementia treatment and the different viewpoints between caregivers, insurance agents and society. Finally, a conclusion to this topic will be drawn and some suggestions about further studies will be provided.

A group of medications, specifically anti-dementia medications, have been used to treat Alzheimer's dementia in the last three decades. Although there are variations in the price of these medications over the world, the cost of them is around 2-3 pounds per day on average. These medications can be seen as an economic burden, especially for the patients and their caregivers of developing countries (Zencir, Kuzu et al. 2005). It is concerned that the effectiveness of these medications worth the cost of them. As a consequence, the cost-effectiveness of these medications attracts much attention and becomes one the foci of geriatric psychiatry studies.

The most popular theory about the mechanisms of causing Alzheimer's dementia is the lack of acetylcholine and hyperactivity of glutamate in the brain (Palmer, Berger et al. 2007). The effects of anti-dementia medications (donepezil, rivastigmine, galantamine and memantine) may reverse the above problems and improve memory, cognitive function and psychiatric symptoms (Pepeu and Giovannini 2009). Moreover, anti-dementia medications could delay the progression of Alzheimer's dementia (ibid). Nonetheless, anti-dementia medications can only slow down but not stop the progression of Alzheimer's dementia (McAvinchey and Burns 2009). In addition, previous studies have been limited by short-duration of follow-up (up to three years at best (Courtney, Farrell et al. 2004)), inadequate study subjects (around 900 patients at most (Bullock, Touchon et al. 2005)) and not exploring some important issues (e.g., whether anti-dementia medications can prolong the life of patients or not (Cappell, Herrmann et al. 2010)). This indicates that many suggestions from past research are tentative. To summarize the above results, Alzheimer's dementia is an incurable disease at present, but these patients still can get benefit from the treatment of anti-dementia medications.

An argument in favor of not using anti-dementia medications in Alzheimer's dementia is that some studies showed the effect of these medications is limited (Courtney, Farrell et al. 2004; Green, Picot et al. 2005). Taking the study of Courtney et al. (2004) as an example, their results revealed that after a three-year follow-up, anti-dementia medications do not show remarkable differences with placebos in many aspects such as the proportion of nursing home admission (42 % vs 44 %), disability (58 % vs 59 %) and the severity of psychiatric symptoms. However, there are serious methodological flaws in the their study design, including too frequent medications washout during the study which leads to the patient's condition worsening, mixed Alzheimer's dementia with vascular dementia subjects whose response to medications are poor and high drop-out rates (48 % patients lose to follow after one year) which

impair the efficacy of medications. If researchers prevent these problems, the results of studies will be different (Winblad, Engedal et al. 2001). Many studies illustrate that anti-dementia medications are significantly better than placebos in terms of memory and cognitive function, nursing home admission, caregiver burden and the burden of whole society because they avoid the above drawbacks in study design (Homma, Imai et al. 2008; Ferris, Ihl et al. 2009). Consequently, it is very important to assess the design and quality of these studies to differentiate whether their results are trustful.

One of the controversial issues in using anti-dementia medications is the methods to calculate the cost of caregiver and social burden. Some studies only use direct expenditures as the method of calculation, such as the money spent on medicine, hospitalization, outpatient clinic visit and transportation. These studies have demonstrated that the use of anti-dementia medications does not significantly decrease the cost (Stewart, Phillips et al. 1998). Furthermore, Courtney et al.'s study (2004) showed that compared with placebos, the use of anti-dementia medications will increase the cost to roughly 498 pounds per patient per year. However, there are serious flaws in these studies because they do not take the indirect cost into consideration. The indirect cost means the services or activities that will benefit patients but cannot calculate the money directly, such as the time of caregiver spending on patients. Many researchers have suggested that the highest economic burden in Alzheimer's dementia is the indirect cost because the average time to care a patient with Alzheimer's dementia is around 8-16 hours per day (Miller, Rosenheck et al. 2011). Many studies have counted both the direct and indirect costs and their results showed anti-dementia medications are cost-effective, and can save approximately 1000 pounds per patient per year (Francois, Sintonen et al. 2004; Antonanzas, Rive et al. 2006). In summary, different cost measurement will lead to different results. Hence, appropriate methods to measure the cost of caregiver burden is essential.

While discussing the issue of cost-effectiveness, one of the important factors that need to be considered is the position on which the people stand. It depends on the role which is adopted, the insurance system of the nation, the perception of the general public toward this disease or the financial condition of the country. Some studies favor assessing the cost-effectiveness of medications from the perspective of insurance agents because they can decide the payment of medicine (Courtney, Farrell et al. 2004; Loveman, Green et al. 2006). Insurance agents need to consider not only the effectiveness of medications, but also the cost of them. The financial balance and obtaining necessary profits is one of their major concerns. This indicates that they

might only consider a part of direct cost; for example, whether the expenditure of medications will be offset by the decrease of clinic visits or hospitalization. The results of these studies have illustrated that anti-dementia medications are not cost-effective, either placebos are better than using medications or they have similar cost-effectiveness, due to their narrow scope of cost counting (Courtney, Farrell et al. 2004; Loveman, Green et al. 2006). As a consequence, the payment of anti-dementia medications in Alzheimer's dementia sets many limitations by the insurance agents. Even more, some insurance agents, including the national health insurance bureau of Taiwan for instance, use the method of pre-authorization to control the usage of these medications. Pre-authorization means doctors need to complete an application form and submit to an insurance agent. Because it is a time-consuming procedure, the motivation of prescribing these medications will fall significantly. Due to this reason, the perspective of insurance agents has been criticized that they tend to overlook the indirect cost which may lead to a higher burden to caregivers and the society.

In contrast to the perspective of insurance agent, some studies prefer to assess this problem from the perspective of caregiver (Feldman, Gauthier et al. 2001; Winblad, Kilander et al. 2006). These kinds of studies will count all of direct and indirect cost and their results frequently showed anti-dementia medications have excellent cost-effectiveness, and can save more than 1650 pounds per patient per year (ibid). However, these studies have been questioned by the inflation of indirect cost to get a positive result in the cost-effectiveness assessment. They list a variety of services which are needed to care for dementia patients, but some of these services are double-counted. For example, they estimate that caregivers spend 16 hours a day caring patients, but at the same time they also count the time spent on doctor clinic visits (Feldman, Gauthier et al. 2004). Furthermore, different studies have different results in the cost of caregiver's caring for patients and the differences can reach almost 3 times (Gustavsson, Jonsson et al. 2010). They cite the references which show the highest cost in caregiver loading to support their opinions. Therefore, the perspective of caregiver has been criticized by their tendency to inflate the indirect cost to underpin their contentions and to neglect the budget limitation of insurance agents.

Social perspective has the advantages of balancing the position of the perspective of insurance agents and caregivers. The studies which adopt this perspective maintain a relatively neutral attitude and design the studies by collecting an appropriate study population and outcome indicators. They include all related direct and indirect costs and estimate these costs by more reasonable methods. The results of social

perspective have illustrated satisfactory cost-effectiveness of anti-dementia medications, can save approximately 200-800 pounds per patient per year, but they are not as high as the results of caregiver's perspective (Lopez-Bastida, Hart et al. 2009; Getsios, Blume et al. 2010). This suggests that social perspective is a more suitable position and could be applied in this issue.

To sum up, the cost-effectiveness of anti-dementia medications is positive if the studies recruit the study subjects by appropriate inclusion and exclusion criteria, select suitable indicators to assess the effectiveness, consider both the direct and indirect cost and adopt the perspective of society. It is important to evaluate the study methods of each study carefully to differentiate whether their conclusions are reliable. The previous studies have some limitations and could be improved by longer follow-up period, larger study population and examining some unexplored important issues. In this way, the evidence of cost and effectiveness of the anti-dementia medications to treat Alzheimer's dementia will be complete and society can make a better decision on this topic.

References :

Antonanzas, F., B. Rive, et al. (2006). "Cost-effectiveness of memantine in community-based Alzheimer's disease patients: An adaptation in Spain." Eur J Health Econ **7**(2): 137-144.

Brookmeyer, R., D. A. Evans, et al. (2011). "National estimates of the prevalence of Alzheimer's disease in the United States." Alzheimers Dement **7**(1): 61-73.

Brookmeyer, R., E. Johnson, et al. (2007). "Forecasting the global burden of Alzheimer's disease." Alzheimers Dement **3**(3): 186-191.

Bullock, R., J. Touchon, et al. (2005). "Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period." Curr Med Res Opin **21**(8): 1317-1327.

Cappell, J., N. Herrmann, et al. (2010). "The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease." CNS Drugs **24**(11): 909-927.

Courtney, C., D. Farrell, et al. (2004). "Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial." Lancet **363**(9427): 2105-2115.

Feldman, H., S. Gauthier, et al. (2004). "Economic evaluation of donepezil in moderate to severe Alzheimer disease." Neurology **63**(4): 644-650.

Feldman, H., S. Gauthier, et al. (2001). "A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease." Neurology **57**(4): 613-620.

Ferri, C. P., M. Prince, et al. (2005). "Global prevalence of dementia: a Delphi consensus study." Lancet **366**(9503): 2112-2117.

Ferris, S., R. Ihl, et al. (2009). "Treatment effects of Memantine on language in moderate to severe Alzheimer's disease patients." Alzheimers Dement **5**(5): 369-374.

Francois, C., H. Sintonen, et al. (2004). "Cost effectiveness of memantine in moderately severe to severe Alzheimer's disease : a markov model in Finland." Clin Drug Investig **24**(7): 373-384.

Getsios, D., S. Blume, et al. (2010). "Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation." Pharmacoeconomics **28**(5): 411-427.

Green, C., J. Picot, et al. (2005). "Modelling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease." Pharmacoeconomics **23**(12): 1271-1282.

Gustavsson, A., L. Jonsson, et al. (2010). "Willingness-to-pay for reductions in care need: estimating the value of informal care in Alzheimer's disease." Int J Geriatr Psychiatry **25**(6): 622-632.

Homma, A., Y. Imai, et al. (2008). "Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial." Dement Geriatr Cogn Disord **25**(5): 399-407.

Kirby, J., C. Green, et al. (2006). "A systematic review of the clinical and cost-effectiveness of memantine in patients with moderately severe to severe Alzheimer's disease." Drugs Aging **23**(3): 227-240.

Lopez-Bastida, J., W. Hart, et al. (2009). "Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease." J Alzheimers Dis **16**(2): 399-407.

Loveman, E., C. Green, et al. (2006). "The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease." Health Technol Assess **10**(1): iii-iv, ix-xi, 1-160.

McAvinchey, K. and A. Burns (2009). "Alzheimer disease: Perceived efficacy of antidementia drug treatment." Nat Rev Neurol **5**(6): 302-303.

Miller, E. A., R. A. Rosenheck, et al. (2011). "Caregiver burden, health utilities, and institutional service use in Alzheimer's disease." Int J Geriatr Psychiatry. doi: 10.1002/gps.2730. [Epub ahead of print].

Murman, D. L., A. Von Eye, et al. (2007). "Evaluated need, costs of care, and payer perspective in degenerative dementia patients cared for in the United States." Alzheimer Dis Assoc Disord **21**(1): 39-48.

Palmer, K., A. K. Berger, et al. (2007). "Predictors of progression from mild cognitive impairment to Alzheimer disease." Neurology **68**(19): 1596-1602.

Pepeu, G. and M. G. Giovannini (2009). "Cholinesterase inhibitors and beyond." Curr Alzheimer Res **6**(2): 86-96.

Rive, B., M. Grishchenko, et al. (2010). "Cost effectiveness of memantine in Alzheimer's disease in the UK." J Med Econ **13**(2): 371-380.

Seshadri, S., A. Beiser, et al. (2011). "Operationalizing diagnostic criteria for Alzheimer's disease and other age-related cognitive impairment-Part 2." Alzheimers Dement **7**(1): 35-52.

Stewart, A., R. Phillips, et al. (1998). "Pharmacotherapy for people with Alzheimer's disease: a Markov-cycle evaluation of five years' therapy using donepezil." Int J Geriatr Psychiatry **13**(7): 445-453.

Winblad, B., K. Engedal, et al. (2001). "A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD." Neurology **57**(3): 489-495.

Winblad, B., L. Kilander, et al. (2006). "Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study." Lancet **367**(9516): 1057-1065.

Zencir, M., N. Kuzu, et al. (2005). "Cost of Alzheimer's disease in a developing country setting." Int J Geriatr Psychiatry **20**(7): 616-622.

附件二「系統性回顧與統和分析」（Systematic review and meta-analysis）課程報告

Antipsychotics discontinuation for Alzheimer's dementia patients with long-term antipsychotic treatment

Background

Description of the condition

Dementia is a disease with memory and other cognitive abilities deterioration which accompanies by daily functions impairment. Alzheimer's dementia is the highest subtype of dementia and the percentage is around 70% among all of the dementia (Lobo, Launer et al. 2000; Plassman, Langa et al. 2007; Kim, Park et al. 2011). The prevalence of Alzheimer's dementia is rising due to the increasing life expectancy of human. Many studies predict the prevalence will continue to soar and more than 1% by year 2050 (Cappell, Herrmann et al. 2010). Researchers estimate Alzheimer's dementia patients will reach 81 million in 2040 and will have 300% increased in the developing countries from 2001 to 2040 (Ferri, Prince et al. 2005). The burden of this disease to the world in 2009 is approximately 422 billion and increased by 34% compared to 2005 (Wimo, Winblad et al. 2010). This disease is a significant issue no matter now or in the following time.

Besides the amnesia and functional impairment, this disease also companies with behavioural or psychiatric symptoms (BPSD) such as delusion, disturbing behaviour and agitation. The prevalence of psychotic and agitated symptoms can reach 50% (Craig, Mirakhur et al. 2005). BPSD severely distressed to caregivers and constitute the major burden to the family and society (Allegri, Sarasola et al. 2006; Okura and Langa 2011). It is also the major contributing factor that leads to hospitalization or early institutionalization (Okura, Plassman et al. 2011).

Description of the intervention

Antipsychotic medications often used to manage BPSD while the non-pharamcological approaches are ineffective and the rates of antipsychotic prescription are up to 30-60% (Margallo-Lana, Swann et al. 2001; Rochon, Stukel et al. 2007). However, the effect size of antipsychotics in BPSD is only small (Ballard

and Waite 2006). Furthermore, many studies showed both conventional and atypical antipsychotics increased the risk of mortality (Schneider, Dagerman et al. 2005; Wang, Schneeweiss et al. 2005) and cerebrovascular adverse events (CVAs) (Kleijer, van Marum et al. 2009; Sacchetti, Turrina et al. 2010) in dementia population and the safety concerns among these medications have increased (Dorsey, Rabbani et al. 2010). Because of this, many experts emphasize that high antipsychotic prescription rates is an urgent safety issue and need to reduce immediately (Banerjee 2009). Therefore, whether the patients with Alzheimer's dementia can be smoothly discontinued the antipsychotic medications is a clinically important question.

How the intervention might work

Some studies focusing on antipsychotic withdrawal in Alzheimer's dementia population with long-term antipsychotic treatment. Their results demonstrated that the severity of BPSD did not have significant change in the antipsychotic discontinuation group, although around 30% patients increased the scores of neuropsychiatric inventory or behavioural worsening (Thapa, Meador et al. 1994; Bridges-Parlet, Knopman et al. 1997; Cohen-Mansfield, Lipson et al. 1999; van Reekum, Clarke et al. 2002; Ballard, Thomas et al. 2004; Ruths, Straand et al. 2004; Ballard, Lana et al. 2008; Bergh and Engedal 2008; Ballard, Hanney et al. 2009; Kleijer, van Marum et al. 2009). Furthermore, some research showed that patients with Alzheimer's dementia can gain benefits from antipsychotic discontinuation which include mortality risk reduction (Ballard, Hanney et al. 2009) cognitive function improvement (van Reekum, Clarke et al. 2002) and better affect expression (Thapa, Meador et al. 1994). Therefore, approximately two-thirds of patients can stop antipsychotic medications without BPSD exacerbation and prevent the potential side effects of these medications.

Why it is important to do this review

Many patients with Alzheimer's dementia suffer from the unnecessary side effects of antipsychotic medications because of no careful risk-benefit assessments toward these drugs. In fact, there are lots of scientific evidences suggested that a substantial proportion of patients with Alzheimer's dementia remain in stable mental condition and have better psychological or physical status after antipsychotic withdrawal. However, some studies addressed that some factors predict poor outcome of antipsychotic discontinuation such as higher baseline antipsychotic dosage, higher baseline NPI scores and use of benzodiazepines at baseline (Meador, Taylor et al. 1997; van Reekum, Clarke et al. 2002; Ballard, Thomas et al. 2004; Ballard, Lana et al. 2008; Ruths, Straand et al. 2008). Therefore, it is important to do a systematic review to summarize all of the related findings to evaluate the risk and benefit of

antipsychotic discontinuation in patients with Alzheimer's dementia and long-term antipsychotic treatment.

Objectives

To determine the effect of antipsychotic discontinuation among the Alzheimer's dementia patients with long-term antipsychotic treatment and will focus on the change of psychotic and agitated symptoms severity.

Methods

Criteria for considering studies for this review

Types of studies

Randomized, parallel-group, clinical controlled studies which are relevant to the study objectives. Double-blind or assessor-blind study design but not open-label study will include. Language limits to English.

Types of participants

Inclusion criteria include patients who are aged 50 years or more; both male and female; meet one of the following criteria for Alzheimer's dementia: DSM-IV or ICD-10 or NINCDS/ADRDA; are being prescribed antipsychotics for BPSD at least 3 months. Exclusion criteria are the follow-up period less than 4 weeks.

Type of interventions

Intervention target

The subjects of related studies are the Alzheimer's dementia patients with long-term antipsychotic treatment and aimed at the cessation of antipsychotic medications. Interventions only focused on non- Alzheimer's dementia or other psychotropic medications but not antipsychotics will be excluded. Furthermore, interventions only focused on staff education or administrative strategies to reduce the percentage of antipsychotic treatment but without BPSD severity assessment will also be excluded.

Definition of Antipsychotics

Both of the first- and second-generation antipsychotics are all included. The classification of antipsychotics (N05A) is according to the ATC (anatomical therapeutic chemical) index of WHO but not all of the N05A medications will be included. This is because some of the N05A medications do not use as antipsychotics in clinical practice such as lithium (N05AN). The antipsychotics will be included in this review see appendix 1.

The appropriate daily doses of Alzheimer's dementia are different from schizophrenia. Therefore, the definition of daily doses is according to Ballard et al's study (Ballard, Hanney et al. 2009) instead of defined daily doses of the WHO. Use risperidone as example, they define the daily antipsychotic dose as very low (0.5 mg/d), low (1 mg/d)

or high (2 mg/d) which is based on chlorpromazine equivalent dose (Ballard, Hanney et al. 2009).

Intervention type

Intervention group are the study subjects whose antipsychotic agents will be totally discontinued. The goal of antipsychotic withdrawal can be achieved by abrupt cessation or tapering no more than 4 weeks. Studies which allow the usage of antipsychotic agents to control BPSD symptoms will be excluded.

Control

Control group are the study subjects whose antipsychotic agents and dosage will be kept the same as their pre-study period.

Types of outcome measures

All of the outcome measures test for the differences between the intervention and control group.

Primary outcomes

1. The proportion of subjects who can successfully antipsychotic discontinuation but without BPSD worsening.
2. The change of the score of the BPSD severity from study baseline to endpoint.
3. The proportion of subjects who are dead or the occurrence CVAs.

Secondary outcomes

1. The change of the score of the cognitive function from study baseline to endpoint.
2. The change of the score of the quality of life from study baseline to endpoint.
3. The change of the score of the daily function from study baseline to endpoint.
4. The proportion of subjects who appeared adverse events.

Search methods for study identification

Electronic searches

All of the related electronic database will be searched including MEDLINE, EMBASE, PsycInfo, Cochrane Library, CINAHL, LILACS and ISI web of science. The ongoing trials or the completed trials but yet published will search related trial register database (appendix 2). The appendix 3 lists the search terms will be used in this review.

Searching other resources

1. Reference searching

   All of the references of the related papers will be manually searched to find additional articles. Those articles which are found by manual searching but not by electronic searching will be used as a method of sensitivity analysis of electronic searching.
2. Personal communication

We will contact the expert of this field to identify the undetected articles or ongoing studies. The criteria of the expert include all of the first or corresponding authors in the all retrieved papers or the authors who have been published review articles.

Data collection and analysis

Selection of studies

In the first stage, author B and C will act as two reviewers independently to review the title and abstract of all searching articles. These papers which are recognized by any one of the reviewers as relevant will search for the full text. In the second stage, all of the full text articles will be assessed by these two reviewers independently to decide whether these articles fulfill all of the criteria. The disagreement articles will be discussed by the two reviewers to get consensus. If the agreement still cannot achieve, author A will join the discussion to make the final decision.

Data extraction and management

Author B and C will extract data from all of the included articles independently by a data extraction form. The following items will be extracted: the name of the first author and the year of publication, number of study subjects, gender and age distribution, study setting, previous antipsychotics, methods of tapering antipsychotics, duration of follow-up, methods of randomization and allocation concealment, blinding methods, primary and secondary outcomes and their measurements, data analysis methods, and the data to evaluate the risk of bias. The methods of dealing with data extraction disagreement will be the same as study selection. We will contact the authors for missing data collection.

Assessment risk of bias

The internal validity of the included studies will assess by author B and C independently. They will use the Cochrane collaboration's tool for assessing risk of bias in randomized trials and items include random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data and selective reporting (Higgins, Altman et al. 2011). The missing data or inadequate description of the above items will contact the articles' authors. The process of management disagreement between author B and C will be the same as study selection.

Measures of treatment effect

1. Dichotomous data

We will use risk ratio (RR) with 95% confidence interval (CI) to calculate the relative

risk of intervention group compare to control group if the outcome measure is binary. This is because we can get the risk rate from both intervention and control group in a RCT.

2. Continuous data

We will calculate the mean differences (MD) with 95% CIs between intervention group and control group in the continuous outcome measures for all included studies. If a meta-analysis is appropriate, MD with 95% CIs will be used to calculate the outcome which was measured by the same scales and standardized mean differences (White and Thomas 2005) with 95% CIs will be used to standardize the different scales use in different studies, respectively. We will consult a statistician to deal with the data that are skewed or kurtotic distribution.

3. Time-to-event (survival) data

We will use hazard ratio (HR) with 95% CI to estimate the relative risk of intervention group compare to control group if the outcome measure is survival data. We will calculate the HR by Parmar's methods (Parmar, Torri et al. 1998) while the HR are not clearly reported but can be estimated from the paper's data. Authors will be contacted if the HR were not available or not be calculated.

Unit of analysis issues

1. Cluster trials

If the randomization unit of studies were cluster, we will examine whether the analytic method had dealt with the cluster effect. If the primary studies did not manage it, we will extract the related data and adjust for the clustering. The intraclass correlation coefficient (ICC, a method to predict the variability could be explain by the between cluster difference) will be used to adjust the cluster effect (Donner and Klar 2002). If ICC is not available, we will contact the authors. If this strategy does not succeed, the ICCs which were calculated from similar studies might be used. If all of the ICCs are obtainable and meta-analysis is appropriate, we will synthesize the data and weighting each study by inverse variance method.

2. Cross-over trials

The cross-over design will influence the outcome of interest of antipsychotic withdrawal. The subjects who are early or late antipsychotic discontinuation will have different impact on the BPSD symptoms and safety measures. Furthermore, carryover effect is difficult to estimate or exclude in a cross-over trial.

3. Multiple intervention groups

If there are more than one intervention group is appropriate to the definition of intervention type, we will perform additional comparisons with control group for all of the intervention groups. However, the sample size in the control group will be

divided proportionally by the number of intervention group. We will also combine the results of all of intervention groups to produce a single comparison if appropriate. If the additional intervention did not fulfill the criteria of intervention, it will not be reported.

Dealing with missing data

Except the duration of follow-up is over 2 years, studies which had more than 50% dropout rates will be excluded from data analysis due to poor data quality. We will perform intention-to-treat analysis as the primary analysis and compare with the results of completer analysis as the sensitivity analysis. We will use imputation method to deal with missing data. In case of binary outcome, we assume that the outcome of loss of follow-up is the same as negative outcome and will be imputed as negative event. Under the assumption of missing at random, we will use last observation carried forward (LOCF) method to impute the last available continuous data for all of the following missing continuous data. However, LOCF method is prone to bias if the missing data is informative (different reasons of lost follow-up have different outcomes). If data is available, we will compare the results of other imputation methods (e.g. the average of all participants with the same reason of dropout) with LOCF method as a sensitivity analysis.

Assessment of heterogeneity

The sources of heterogeneity are from different participants' characteristics (clinical heterogeneity) and/or study design (methodological heterogeneity). These two factors result in statistical heterogeneity. We will discuss the clinical and methodological heterogeneity if these issues arise.

We will check the statistical heterogeneity by visual examining the statistics and 95% CIs of all studies (forest plots). Then we will perform I^2 test and chi-squared (χ^2) test to determine the percentage of effect variability which is due to heterogeneity and whether it is statistical significance. The criteria of statistical heterogeneity is the value of I^2 test more than 50% (substantial) and χ^2 test show statistical significance (Higgins and Thompson 2002; Higgins, Thompson et al. 2003). If the statistical heterogeneity appears, we will inspect the heterogeneity by subgroup analysis and/or meta-regression.

Assessment of reporting biases

We will use the funnel plots to detect the publication bias while there were enough primary studies (more than 10) and not all studies with similar sample size. Begg's rank correlation test and Egger's linear regression test will be used to test the

statistical significance of reporting bias (Begg and Mazumdar 1994; Macaskill, Walter et al. 2001).

Data synthesis

If we can retrieve sufficient data, a meta-analysis will be performed. The choice of synthesizing method will depend on the statistical heterogeneity status of the primary studies. Fixed-effect model will be used while there was no substantially statistical heterogeneity and random-effect model will be used while substantially statistical heterogeneity existed. We will also compare the results of fixed-effect model and random-effect model as a sensitivity analysis.

While there were no sufficient data or prominent heterogeneity among the primary studies which makes meta-analysis is inappropriate, we will not do a meta-analysis. We will summarize the results of these studies and discuss the sources of heterogeneity or other related issues.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analysis-only primary outcomes

Subgroup analysis will be limited to below clinical heterogeneity to prevent type I error inflation.

a. Mild or severe BPSD symptoms at baseline
b. Low or high antipsychotic dose at baseline
c. First-generation or second generation antipsychotics at baseline
d. Outpatients or residents of long-term care facilities

2. Investigation of heterogeneity

We will check whether there were key-in errors at first. If all of the data enter correctly, we will remove the studies with results deviate from the majority of the studies to see whether the heterogeneity will disappear. If the status of the heterogeneity changes after this procedure, then we will discuss whether there were any characteristic differences of these deviated studies comparing to other studies.

Sensitivity analysis

Sensitivity analysis will be performed in the following situations.

1. The studies with clear randomization procedures description (e.g. computer generation by third party, permuted block randomization) versus not (e.g. only mentioned random allocation).
2. The ITT analysis versus completer analysis.
3. The use of ICC to adjust the cluster effect of cluster randomization studies versus not.
4. The studies with low risk of bias versus high risk of bias.

5. The differences between fixed-effect model and random-effect model in data synthesis.

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References

Allegri, R. F., D. Sarasola, et al. (2006). "Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease." Neuropsychiatr Dis Treat **2**(1): 105-110.

Ballard, C., M. L. Hanney, et al. (2009). "The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial." Lancet Neurol **8**(2): 151-157.

Ballard, C., M. M. Lana, et al. (2008). "A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial)." PLoS Med **5**(4): e76.

Ballard, C. and J. Waite (2006). "The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease." Cochrane Database Syst Rev(1): CD003476.

Ballard, C. G., A. Thomas, et al. (2004). "A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome." J Clin Psychiatry **65**(1): 114-119.

Banerjee, S. (2009). "The use of antipsychotic medication for people with dementia: Time for action." Department of Health.

Begg, C. B. and M. Mazumdar (1994). "Operating characteristics of a rank correlation test for publication bias." Biometrics **50**(4): 1088-1101.

Bergh, S. and K. Engedal (2008). "The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes: an open pilot study." Int J Geriatr Psychiatry **23**(8): 877-879.

Bridges-Parlet, S., D. Knopman, et al. (1997). "Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study." J Geriatr Psychiatry Neurol **10**(3): 119-126.

Cappell, J., N. Herrmann, et al. (2010). "The pharmacoeconomics of cognitive enhancers in moderate to severe Alzheimer's disease." CNS Drugs **24**(11): 909-927.

Cohen-Mansfield, J., S. Lipson, et al. (1999). "Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study." Arch

Intern Med **159**(15): 1733-1740.

Craig, D., A. Mirakhur, et al. (2005). "A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease." Am J Geriatr Psychiatry **13**(6): 460-468.

Donner, A. and N. Klar (2002). "Issues in the meta-analysis of cluster randomized trials." Stat Med **21**(19): 2971-2980.

Dorsey, E. R., A. Rabbani, et al. (2010). "Impact of FDA black box advisory on antipsychotic medication use." Arch Intern Med **170**(1): 96-103.

Ferri, C. P., M. Prince, et al. (2005). "Global prevalence of dementia: a Delphi consensus study." Lancet **366**(9503): 2112-2117.

Higgins, J. P., D. G. Altman, et al. (2011). "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials." BMJ **343**: d5928.

Higgins, J. P. and S. G. Thompson (2002). "Quantifying heterogeneity in a meta-analysis." Stat Med **21**(11): 1539-1558.

Higgins, J. P., S. G. Thompson, et al. (2003). "Measuring inconsistency in meta-analyses." BMJ **327**(7414): 557-560.

Kim, K. W., J. H. Park, et al. (2011). "A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea." J Alzheimers Dis **23**(2): 281-291.

Kleijer, B. C., R. J. van Marum, et al. (2009). "The course of behavioral problems in elderly nursing home patients with dementia when treated with antipsychotics." Int Psychogeriatr **21**(5): 931-940.

Kleijer, B. C., R. J. van Marum, et al. (2009). "Risk of cerebrovascular events in elderly users of antipsychotics." J Psychopharmacol **23**(8): 909-914.

Lobo, A., L. J. Launer, et al. (2000). "Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group." Neurology **54**(11 Suppl 5): S4-9.

Macaskill, P., S. D. Walter, et al. (2001). "A comparison of methods to detect publication bias in meta-analysis." Stat Med **20**(4): 641-654.

Margallo-Lana, M., A. Swann, et al. (2001). "Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments." Int J Geriatr Psychiatry **16**(1): 39-44.

Meador, K. G., J. A. Taylor, et al. (1997). "Predictors of antipsychotic withdrawal or dose reduction in a randomized controlled trial of provider education." J Am Geriatr Soc **45**(2): 207-210.

Okura, T. and K. M. Langa (2011). "Caregiver burden and neuropsychiatric symptoms in older adults with cognitive impairment: the Aging, Demographics, and Memory Study (ADAMS)." Alzheimer Dis Assoc Disord **25**(2): 116-121.

Okura, T., B. L. Plassman, et al. (2011). "Neuropsychiatric symptoms and the risk of institutionalization and death: the aging, demographics, and memory study." J Am Geriatr Soc **59**(3): 473-481.

Parmar, M. K., V. Torri, et al. (1998). "Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints." Stat Med **17**(24): 2815-2834.

Plassman, B. L., K. M. Langa, et al. (2007). "Prevalence of dementia in the United States: the aging, demographics, and memory study." Neuroepidemiology **29**(1-2): 125-132.

Rochon, P. A., T. A. Stukel, et al. (2007). "Variation in nursing home antipsychotic prescribing rates." Arch Intern Med **167**(7): 676-683.

Ruths, S., J. Straand, et al. (2008). "Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study--the Bergen District Nursing Home Study (BEDNURS)." Int J Geriatr Psychiatry **23**(9): 889-895.

Ruths, S., J. Straand, et al. (2004). "Effect of antipsychotic withdrawal on behavior and sleep/wake activity in nursing home residents with dementia: a randomized, placebo-controlled, double-blinded study. The Bergen District Nursing Home Study." J Am Geriatr Soc **52**(10): 1737-1743.

Sacchetti, E., C. Turrina, et al. (2010). "Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review." Drug Saf **33**(4): 273-288.

Schneider, L. S., K. S. Dagerman, et al. (2005). "Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials." JAMA **294**(15): 1934-1943.

Thapa, P. B., K. G. Meador, et al. (1994). "Effects of antipsychotic withdrawal in elderly nursing home residents." J Am Geriatr Soc **42**(3): 280-286.

van Reekum, R., D. Clarke, et al. (2002). "A randomized, placebo-controlled trial of the discontinuation of long-term antipsychotics in dementia." Int Psychogeriatr **14**(2): 197-210.

Wang, P. S., S. Schneeweiss, et al. (2005). "Risk of death in elderly users of conventional vs. atypical antipsychotic medications." N Engl J Med **353**(22): 2335-2341.

White, I. R. and J. Thomas (2005). "Standardized mean differences in individually-randomized and cluster-randomized trials, with applications to meta-analysis." Clin Trials **2**(2): 141-151.

Wimo, A., B. Winblad, et al. (2010). "The worldwide societal costs of dementia: Estimates for 2009." Alzheimers Dement **6**(2): 98-103.

Appendix 1: The included antipsychotics in this review classify by anatomical therapeutic classification (ATC)

N05A ANTIPSYCHOTICS

N05AA Phenothiazines with aliphatic side-chain

Chlorpromazine (N05AA01)

N05AB Phenothiazines with piperazine structure

Fluphenazine (N05AB02), perphenazine (N05AB03), trifluoperazine (N05AB06),

N05AC Phenothiazines with piperidine structure

Thioridazine (N05AC02), mesoridazine (N05AC03), pipotiazine (N05AC04)

N05AD Butyrophenone derivatives

Haloperidol (N05AD01), trifluperidol (N05AD02)

N05AE Indole derivatives

Molindone (N05AE02), sertindole (N05AE03), ziprasidone (N05AE04)

N05AF Thioxanthene derivatives

Flupentixol (N05AF01), clopentixol (N05AF02), chlorprothixene (N05AF03), zuclopentixol (N05AF05)

N05AG Diphenylbutylpiperidine derivatives

Pimozide (N05AG02)

N05AH Diazepines, oxazepines, thiazepines and oxepines

Loxapine (N05AH01), clozapine (N05AH02), olanzapine (N05AH03), quetiapine (N05AH04), arsenapine (N05AH05), clotiapine (N05AH06)

N05AL Benzamides

Sulpiride (N05AL01), remoxipride (N05AL04), amisulpride (N05AL05)

N05AX Other antipsychotics

Risperidone (N05AX08), zotepine (N05AX11), aripiprazole (N05AX12), paliperidone (N05AX13) and iloperidone (N05AX14)

Appendix 2: The trial register database which will be searched in this review

1. Cochrane trial registry
2. Clinical Trials Registry of American National Institute of Health (NIH)
3. Australian Clinical Trials Registry
4. International Standard Randomised Controlled Trial Number (ISRCTN) Register

5. Netherlands Trial Register
6. Japan's UMIN Clinical Trials Registry
7. WHO International Clinical Trial Registry Platform

Appendix 3: The search terms will be used in this review

1. Discontinuation: (discontinue* OR cessa* OR withdr* OR stop* OR end*)
2. Tapering: (taper* OR reduc* OR decreas*)
3. Antipsychotics: (antipsychotic* OR neuroleptic* or tranquilizer* OR individual name of all antipsychotics list in appendix 1)
4. Alzheimer's dementia: (Alzheimer* OR dement*)
5. Randomized controlled studies: (random* OR control* OR placebo)

The search will include both the MeSH terms and the free text. We will consult a librarian to combine all of these search terms appropriately.

附件三「流行病學的統計方法」（Statistical methods of epidemiology）課程報告

The analysis and interpretation for the data of European Union funded Study of Health and Retirement in Europe

Introduction

Old age people with depressive disorders need to face many adverse life situations such as cognitive and physical function impairment, life expectancy decrease due to various medical comorbidities and life quality deterioration.[1] Family members and the whole society also suffer from the burden of caring patients with old age depression.[2,3] Old age depression is a common disease spectrum and a recent meta-analysis demonstrated that the prevalence of major depressive disorder is 7.2% and the prevalence of other depressive disorders is 17.1% in this population.[4] The risk factors of old age depression include female gender, medical comorbidities, impaired cognition, disabilities, inadequate social relationship and previous depression history.[5] Therefore, the recognition, prevention and effective management for this disease is important at present and in the future.

There were only few studies focused on the prevalence and predictors of the old age depression which was based on international population with large enough sample size. Therefore, the precision of estimation and the external validity of these studies are better than the results of single country or single area. Euro-D scale study is one of them with serial important publications.[6,7] This study extracted part of the data from the Euro-D study and the variables include depression categorization by Euro-D scale, age, gender and marital status. It tries to explore the association between Euro-D defined depression and other three explanatory variables which include the main effect and the interactive effect of them.

Method

The population of this study was made up of 14 centres from 11 European countries. There were 16,383 subjects in this dataset and all of them were aged 50 years or older.

Outcome variable

The score of Euro-D scale was categorized into a binary data, case or non-case. The Euro-D scale consists of 12 items and is developed from 5 depression scales (GMS-AGECAT, SHORT-CARE, CES-D, ZSDS and CPRS).[7] The details of developmental process and the psychometric properties please refer to previous paper.[6,7]

Explanatory variables

The available explanatory variables in this study are the following three ones:

1. Age: a continuous variable; the unit is year and measure at the time of evaluation; will also categorize into four age group (50-59 y/o, 60-69 y/o, 70-79 y/o, 80 y/o or over) to detect whether the effect of age to depression is linear or not; and will categorize into two age group (50-64 y/o and 65 y/o or over) this is because the cutoff point of elderly population in most of studies is 65 y/o.
2. Gender: a binary categorical variable; male or female.
3. Marital status: a tertiary categorical variable; alone, co-habit and married; may be re-categorize into binary outcome by alone and not alone (the combination of the latter two) or married and not married (the combination of the former two). This is because some studies demonstrated that alone[8-10] is a risk factor of old age depression and married[11] is a protective factor of old age depression.

Statistical analysis

Since the outcome variable is a binary data, we used Pearson chi-square or Fisher's exact test to test for risk factors which are categorical variables (gender, marital status and age group). The Mantel-Haenszel method was used to measure the summary odds ratio (OR) of binary explanatory variables in stratified analysis. The unconditional logistic regression model was used to calculate the OR for the risk factor which is continuous variable (age) and for the risk factors which is more than two category (marital status and age group) by setting dummy variables. The unconditional logistic regression model will also be used to calculate the adjusted odds ratio of the main effect of each risk factor and their interactive effects. Because this is an exploratory study and no specific a-priori hypothesis, we used the forward stepwise method to choose the final model in the logistic regression. The criteria of model entry and model removal are 0.05 and 0.10 respectively. A p-value of less than 0.05 was considered significant. The data were analyzed by using the SPSS 18.0 (IBM, Chicago, Illinois).

Results

General description

The total subjects in this data are 16,383. Except age variable has no missing data, the number of missing data in the depression category, gender and marital status are 444 (2.7%), 4 (0.02%) and 17 (0.1%) respectively. We did not perform any special missing

data management due to the low proportion of them. We present the age variable as the median (63 years) and interquartile range of age (48-78 years) due to the distribution of age is not normal distribution (positive skewness). The proportions of depression case and male gender are 24.1% and 45.7% respectively. The proportions of the three marital status are 71.8% (married), 3.9% (cohabit) and 24.3% (alone).

Age effect

The depression cases show higher age than non-depression cases with statistical significance (Table 1). While we treated age as a continuous variable in a logistic regression model, the odds of depression would increase 2.3% for each additional year with statistical significance (Table 1). If we categorize the age into 4 age groups for every 10 years, the risk of depression is also rising in the higher age group and but the effect is like a curve but not linear (Figure 1). The age groups of 70-79 and 80-85 but not the age group of 60-69 has statistically significant higher risks compare to the age group of 50-59 (Table 1). Because many studies defined the old age as those who aged 65 years or over, one of the age grouping method is to categorize them as young old age group (50-64 years old) and old age group (65 years old and over). The prevalence of depression case in the young old age group and the old age group is 21.3% and 27.6% respectively. The old age group has statistically significant higher risk of depression than the young old age group (OR=1.407, 95% CI: 1.309-1.514, $p<0.001$).

If we stratified the whole population by the gender, the age effect of male is similar to female no matter how we treat the age as a continuous variable or 4 age groups (Table 2). The effect of age in the total population also does not have significant change comparing to the results of stratification by gender. If we treat age as 4 groups and put the gender and age & gender interaction term in the regression model, the interaction term is close to but not statistically significant ($p=0.07$). If we treated age as a binary data and stratified the whole population by the gender, the summary OR of old age group calculated by Mantel-Haenszel method (1.430, 95% CI: 1.328-1.540, $p<0.001$) was similar to the crude OR and the OR of male (1.427) and female (1.432) strata did not have significant difference (Breslow-Day test: $p=0.964$).

While we re-categorize the marital status into currently married and unmarried (cohabit and alone) and stratified the whole population by this new marital category. The age effect of the whole population still did not have significant change comparing to each stratum of marital status (Table 3). However, the risk of depression is slightly higher in the unmarried strata comparing to the married strata in all of the age group or treating age as a continuous variable. If we treat age as 4 groups and put the marital status and age & marital status interaction term in the regression model, the interaction term do not has statistical significance ($p=0.447$). The results of

classifying the marital status into alone or not alone (married or cohabit) were similar to married and unmarried category.

If we adjust the effect of age by the gender and marital status in a logistic regression model, the adjusted OR of age is similar to the crude OR and still has statistically significant.

Gender effect

Female has statistically significant higher risk of depression than male (Table 1). If we stratified the population into four age groups, the OR of female comparing to male is similar among the four age groups (50-59 y/o: 2.173, 60-69 y/o: 2.618, 70-79 y/o: 2.011, 80 y/o or over: 2.379). The Breslow-Day test showed the homogeneity assumption did not being rejected (p=0.07). The summary OR estimated by Mantel-Haenszel method was 2.279 (95% CI : 2.109~2.464, p<0.001), which is similar to the crude OR (2.290) of gender and slightly toward the null. The gender effect while we stratified the population into three groups by marital status is similar to the results of age group stratification. The Mantel-Haenszel method showed the p value of the Breslow-Day test is not significant (p=0.952) and the summary OR is 2.123 (95% CI : 1.963~2.297, p<0.001), which is similar to the crude OR of gender and slightly toward the null. If we treat marital status as 3 groups and put the gender and gender & marital status interaction term in the regression model, the interaction term do not reach statistically significant.

If we adjust the effect of gender by the age and marital status in a logistic regression model, the adjusted odds ratio of is similar to the crude odds ratio and still has statistically significant.

The effect of marital status

If we treat the marital status as a three-group categorical data and use the married people as the reference group in a logistic regression model, the overall effect of marital status has statistical significance and only the alone group has statistically significant higher depression risk than the married group (Table 1). If we stratified the whole population by gender, the marriage effect of male is similar to the female and both gender showed the overall effect of marital status has statistical significance and only the alone group has statistically significant higher depression risk than the married group (Table 4). If we adjust the effect of marital status by the gender and age group in a logistic regression model, the adjusted OR of marital status is similar to the crude OR and the overall effect of marital status still has statistically significant. If we treated the marital status as a binary data (married and unmarried or alone and not alone), the results were similar to the three-group categorical data analysis.

The final model

All of the three explanatory variables (four age groups, gender and three marital

groups) and their interaction terms (age group and gender interaction, age group and marital group interaction, gender and marital group interaction) were put into the logistic regression model and used forward stepwise method to select the variables. The results showed age group, gender, marital group and age & gender interaction term remained in the final model (Table 5). The existence and the level of statistical significance are similar to the single variable regression model. However, the age & sex interaction term changed from near to statistically significant (p=0.07) to become statistically significant (p=0.023) after adjusted all of the three explanatory variables. The adjusted ORs of each variable are also close to the crude OR. The Hosmer and Lemeshow test showed the goodness of fit for the model is adequate (Chi-squared=3.948, df=7, p=0.786). However, the variability explained by this model is low (Cox & Snell R square: 4.3%).

Discussion

The comparison of this dataset analysis with the results of Prince et al is complicated by five factors. First, this dataset do not have the centre variable. Second, the outcome variable of this dataset is binary and the outcome variable of the Prince et al's study is continuous. Third, the age range of this dataset is aged 50-85 years but the age range of the Prince et al's study is aged 65-85 years. Fourth, the grouping method of the marital status is different. This dataset categorized the marital status into three groups (married, cohabit, alone) but the Prince et al's study divided the marital status into four groups (never married, married, widowed, divorced or separated). Finally, the subject number of this dataset is 16,833 but the subject number of the Prince et al's study is 21,724. Therefore, the results may be not the same in all of the analysis due to the difference of the study population, outcome variable, explanatory variables and the method of analysis.

Age effect

This dataset showed the higher of the age, the higher of the risk of depression. This association is consistent in various analytic methods such as treating age as a continuous variable, categorize by age <65 y/o or age >64 y/o, or categorize into 4 age groups every 10 years. The effect of age on the risk of the depression is like a curve which was shown by the OR of the 4 age groups. The effect of the age did not have significant change after adjust the effects of other variables or interaction terms. These results are consistent with the findings of Prince et al's study.

However, there were two results not consistent with the Prince et al's study in the age effect. First, the age effect measured by 4 age groups in this analysis is like a curve but the effect measured by 5 age groups in Prince et al's study is close to linear. Second, the age and sex interaction term close to but did not reach statistical difference in this dataset (p=0.07) if only controlling the effect of age group and

gender. However, the gender effect is significantly modified by the age group (F=2.7, p=0.03) in their analysis.[6] The interpretation of these discrepancies is difficult due to the earlier mentioned differences in these two dataset.

Gender effect

Female demonstrated statistically significant higher depression risk than male. The effect of gender on the risk of the depression did not have significant change after adjust the effects of other variables or interaction terms. These results are consistent with the findings of Prince et al's study that female subjects had higher EURO-D score than male.[6]

The effect of marital status

This dataset illustrated that the married people had the lower risk of depression but not statistically significant comparing with the cohabited group and had statistically significant lower risk of depression comparing with the alone group. The effect of marital status on the risk of the depression did not have significant change after adjust the effects of other variables or interaction terms. Furthermore, there were no statistically significant interaction between the age/sex and marital status. The result is different from the finding of the Prince et al's study. Their results showed the never married and the married group had statistically significant lower risk of depression comparing with the widowed or separated group.[6] There was also significant marital status and gender interaction (F=10.6, p<0.001) in their analysis.[6] However, this difference is hard to make interpretation. The never married group in their analysis could be the alone group or cohabited group of this dataset. Therefore, we can only point out this inconsistency and cannot explore further.

Final model

The final model in this dataset included all of the three explanatory variables and the age & sex interaction term. Although the Hosmer-Lemeshow test illustrated the goodness of fit is acceptable in the logistic regression model, the variance could be explained by this model only 4.7%. This means many important predictors of depression may be not included in this dataset such as mental and physical conditions, social economic status and geographic area. The final model of the Prince et al's study included all of the four explanatory variables and four interaction terms. The comparison and interpretation of the model between these two findings are difficult due to the differences of the study population, outcome variable, explanatory variables and the method of analysis. The variance (15.8%) could be explained by the Prince et al's model is higher than this dataset.[6] This may be due to they had the centre variable in their data and their outcome is continuous variable.[6]

Limitations of this analysis

The interpretation of the results of this dataset analysis should be cautious and

consider the following limitations. First, this data set is from a cross-sectional survey. The causal relationship between the outcome variable and explanatory variable is not clear. Therefore, association rather than causality is a better way of description. Second, the cut-off point of Euro-D score to categorize the case or non-case of depression did not mention in this dataset. Thus, the appropriateness of the depression categorization cannot be assessed. Third, there were only three explanatory variables in this dataset and lack of many important confounders of depression. It is difficult to predict whether the results of this analysis will change after collecting and adjusting those potential confounders.

Implications of this analysis

Although the above mentioned limitations, there were very few large-scale, international, old age depression study before. The findings of this study could be recognized as a pilot work and the further studies with more sophisticated study design can carefully examine the effects of age, gender and marital status on old age depression in the future.

References:

1. Rodda J, Walker Z, Carter J. Depression in older adults. BMJ 2011;343:d5219.
2. Molyneux GJ, McCarthy GM, McEniff S, Cryan M, Conroy RM. Prevalence and predictors of carer burden and depression in carers of patients referred to an old age psychiatric service. Int Psychogeriatr 2008;20:1193-202.
3. Luppa M, Heinrich S, Matschinger H, et al. Direct costs associated with depression in old age in Germany. J Affect Disord 2008;105:195-204.
4. Luppa M, Sikorski C, Luck T, et al. Age- and gender-specific prevalence of depression in latest-life - Systematic review and meta-analysis. J Affect Disord 2010.
5. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. Acta Psychiatr Scand 2006;113:372-87.
6. Prince MJ, Beekman AT, Deeg DJ, et al. Depression symptoms in late life assessed using the EURO-D scale. Effect of age, gender and marital status in 14 European centres. Br J Psychiatry 1999;174:339-45.
7. Prince MJ, Reischies F, Beekman AT, et al. Development of the EURO-D scale--a European, Union initiative to compare symptoms of depression in 14 European centres. Br J Psychiatry 1999;174:330-8.
8. Alexandrino-Silva C, Alves TF, Tofoli LF, Wang YP, Andrade LH. Psychiatry: life events and social support in late life depression. Clinics (Sao Paulo) 2011;66:233-8.

9. Cheng ST, Fung HH, Chan AC. Living status and psychological well-being: social comparison as a moderator in later life. Aging Ment Health 2008;12:654-61.
10. Wilson K, Mottram P, Sixsmith A. Depressive symptoms in the very old living alone: prevalence, incidence and risk factors. Int J Geriatr Psychiatry 2007;22:361-6.
11. Barcelos-Ferreira R, Pinto JA, Jr., Nakano EY, Steffens DC, Litvoc J, Bottino CM. Clinically significant depressive symptoms and associated factors in community elderly subjects from Sao Paulo, Brazil. Am J Geriatr Psychiatry 2009;17:582-90.

Table 1: Demographic characteristics distribution of case and non-case

	Case N=3845	Non-case N=12094	MD or OR (95% CI)	P value
Age-year ± SD	65.4 ± 9.8	63.5 ± 8.9	1.9 (1.6 ~ 2.2)	<0.001[a]
Age-year			1.023 (1.019 ~1.027)	<0.001[b]
Age group-				<0.001[c]
50-59			1 (reference group)	---
60-69			1.001 (0.916 ~1.094)	0.986
70-79			1.391 (0.916 ~1.094)	<0.001
80 or over			2.229 (1.935 ~2.567)	<0.001
Gender- % of male	30.7%	50.4%	2.290 (2.120 ~ 2.474)	<0.001[c]
Marital status-				<0.001[c]
% of married	62.9%	74.6%	1 (reference group)	---
% of cohabit	3.6%	4.0%	1.063 (0.876 ~ 1.291)	0.534
% of alone	33.5%	21.3%	1.864 (1.720 ~ 2.021)	<0.001

Abbreviations: MD: mean difference, OR: odds ratio, SD: standard deviation

[a]Test by independent t-test.

[b]Test by logistic regression with age as continuous variable.

[c]Test by logistic regression with dummy variable management.

Table 2: The association between age and depression stratified by gender

Male	Case N=1181	Non-case N=6093	OR (95% CI)	P value
Age			1.024 (1.017 ~1.031)	<0.001[a]
Age group-				<0.001[b]
50-59	32.9%	36.9%	1 (reference group)	---
60-69	30.1%	37.2%	0.907 (0.777 ~1.059)	0.218
70-79	28.5%	21.3%	1.498 (1.275 ~1.760)	<0.001
80 or over	8.5%	4.6%	2.041 (1.586 ~2.626)	<0.001
Female	Case N=2664	Non-case N=6001	OR (95% CI)	P value
Age			1.023 (1.018 ~1.028)	<0.001[a]
Age group-				<0.001[b]
50-59	33.7%	39.7%	1 (reference group)	---
60-69	31.8%	34.3%	1.093 (0.978 ~1.221)	0.118
70-79	23.9%	20.3%	1.386 (1.225 ~1.567)	<0.001
80 or over	10.7%	5.6%	2.234 (1.875 ~2.662)	<0.001

Abbreviations: OR: odds ratio

[a]Test by logistic regression with age as continuous variable.

[b]Test by logistic regression with dummy variable management.

Table 3: The association between age and depression stratified by marital status (married or unmarried)

Married	Case N=2418	Non-case N=9027	OR (95% CI)	P value
Age- year			1.014 (1.009 ~1.019)	<0.001[a]
Age group-				<0.001[b]
50-59	38.1%	40.3%	1 (reference group)	---
60-69	33.7%	37.4%	0.952 (0.857 ~1.058)	0.362
70-79	22.4%	18.9%	1.251 (1.109 ~1.412)	<0.001
80 or over	5.8%	3.4%	1.799 (1.455 ~2.225)	<0.001
Unmarried	Case N=1427	Non-case N=3067	OR (95% CI)	P value
Age- year			1.025 (1.018 ~1.031)	<0.001[a]
Age group-				<0.001[b]
50-59	25.5%	32.4%	1 (reference group)	---
60-69	27.2%	31.0%	1.112 (0.940 ~1.316)	0.217
70-79	30.1%	26.3%	1.454 (1.229 ~1.719)	<0.001
80 or over	17.2%	10.3%	2.122 (1.727 ~2.606)	<0.001

Abbreviations: OR: odds ratio

[a]Test by logistic regression with age as continuous variable.

[b]Test by logistic regression with dummy variable management.

Table 4: The association between marital status and depression stratified by gender

Male	Case N=1181	Non-case N=6093	OR (95% CI)	P value
Marital status-				<0.001[a]
% of married	74.1%	81.2%	1 (reference group)	---
% of cohabit	4.5%	4.5%	1.098 (0.811 ~ 1.486)	0.545
% of alone	21.4%	14.3%	1.643 (1.404 ~ 1.923)	<0.001
Female	Case N=2664	Non-case N=6001	OR (95% CI)	P value
Marital status-				<0.001[a]
% of married	57.9%	68.0%	1 (reference group)	---
% of cohabit	3.2%	3.6%	1.057 (0.818 ~ 1.367)	0.671
% of alone	38.9%	28.5%	1.602 (1.454 ~ 1.765)	<0.001

Abbreviations: OR: odds ratio

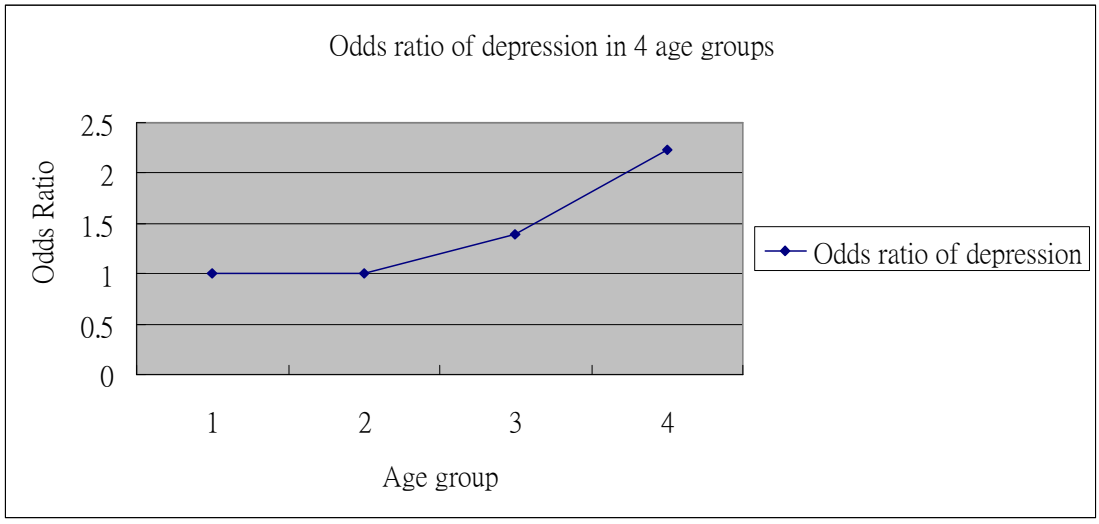
[a]Test by logistic regression with dummy variable management.

Table5: The adjusted ORs and 95% CI of the explanatory variables in the final regression model

Variable	df	Adjusted OR	95% CI	P value
Age group-	3			<0.001
50-59		1	---	---
60-69		0.920	0.787-1.074	0.291
70-79		1.495	1.272-1.757	<0.001
80 and over		1.978	1.536-2.547	<0.001
Sex	1	2.149	1.882-2.453	<0.001
Marital status-	2			<0.001
Married		1	---	---
Cohabit		1.097	0.901-1.336	0.356
Alone		1.472	1.351-1.605	<0.001
Age group & sex interaction	3			0.023
Model	9			<0.001
Cox & Snell R square: 4.3%				

Abbreviations: df: degrees of freedom, OR: odds ratio, CI: confidence interval.

Figure 1: The odds ratios of the four age groups



附件四「精神醫療服務研究：從理論到實務」（Mental Health Services Research: Theory to Practise）課程報告

A complex intervention which includes educational programs, skill promotion workshops, pharmacist prescription assessment, activity redesign and long-term staff support program in nursing homes to reduce the proportion of antipsychotic prescription for the dementia residents- a one-year, cluster randomized, parallel-group comparison, pilot study

Background:

The behavioural or psychiatric symptoms in dementia (BPSD) are popular and the lifetime prevalence is up to 50-90% (Parnetti, Amici et al. 2001). BPSD are distressful symptoms and constitute a large burden to their carers. Most of the treatment guidelines suggest non-pharmacological interventions as the first-line therapy such as comprehensive evaluations to find all of the reversible etiologies of BPSD, psychosocial intervention and environmental rearrangement (Corbett, Smith et al. 2012). The reason of putting pharmacological interventions in the lower priority is the severe side effects of these medications especially after long-term use in this vulnerable population. However, pharmacological interventions frequently used in front of non-pharmacological interventions in real life situation and which lead to patient safety concerns.

Among the pharmacological interventions, antipsychotics are the highest prescribed medication to mange BPSD, especially for the agitated or disturbing symptoms (Ballard, Corbett et al. 2009). Nonetheless, both conventional and atypical antipsychotics increase the risk of cerebrovascular events (CVAs) and mortality. A meta-analysis performed by the FDA in 2004 showed the mortality of dementia increased 60-70% at six months in the atypical antipsychotics group comparing to placebo (http://www.fda.gov/cder/drug/advisory/antipsychotics.htm). The mortality risk of conventional antipsychotics is even higher than atypical antipsychotics and the relative risk is 1.37 within 180 days (Wang, Schneeweiss et al. 2005). Another recent meta-analysis also showed the risk of CVAs is around 1.3-2.0 times in antipsychotics group compared to non-user group (Sacchetti, Turrina et al. 2010). Besides these side

effects, the efficacy of antipsychotics is low to improve BPSD. A large randomized controlled study (RCT) showed the efficacy of placebo is similar to all of the three comparison atypical antipsychotics (Schneider, Tariot et al. 2006). That is why antipsychotics should only be used in emergency situation or high risk of harm and the duration of prescription should be less than 12 weeks (Ballard and Corbett 2010).

Although the above evidences and the introduction of treatment guidelines, antipsychotics prescription rate in dementia are still high. A Canadian study showed the antipsychotic prescription rate even increased 20% from 2002 to 2007 in the dementia population (Valiyeva, Herrmann et al. 2008). The problems of high antipsychotic prescription are more severe in old-age long-term care facilities. Previous studies demonstrated that the antipsychotic prescription rate in nursing homes is from 25% in USA (Kamble, Chen et al. 2008), 32% in Canada (Rochon, Stukel et al. 2007) to 48% in UK (Fossey, Ballard et al. 2006). Therefore, many studies try to explore the reasons of high antipsychotic usage and perform lots of interventions to decrease the prescription rate in nursing homes.

The reasons for the high antipsychotic prescription in nursing homes include insufficient staff to perform time-consuming interventions, lack of information in the BPSD, inadequate knowledge in the risk and benefits of antipsychotics for BPSD, short of training in the non-pharmacological interventions, inadequate regular antipsychotics side effects monitoring and feedback system. Thus, many interventions have being studies in the way of RCT to explore their effectiveness to decrease psychotropic medications prescriptions. A recent systematic review of RCTs (Forsetlund, Eike et al. 2011) reported that these studies could be grouped as educational programs only (Kuske, Luck et al. 2009), educational programs plus interventional programs (Roberts, Stokes et al. 2001), pharmacist medication review (Crotty, Halbert et al. 2004), activity or recreational programs (Rovner, Steele et al. 1996), early BPSD detection program (Kotynia-English, McGowan et al. 2005), and introducing old-age specialist team (Cavalieri, Chopra et al. 1993). However, the effectiveness of these interventions is different because the differences in their methods, duration, intensity and quality of implementation, characteristics of nursing homes and the desire of the physicians and nursing home staff to change.

There are some drawbacks in previous studies. First, the characteristics of nursing homes are inadequately described. The effectiveness of the interventions is heavily contextual dependence and it is important to describe the background of these facilities. Second, the components and the details of the interventions are under

reported. Third, the fidelity of the intervention implementation has not being done or lack of information. Fourth, only few studies examined the effects of combined interventions through a multi-disciplinary approach. Fifth, most of the studies did not use appropriate methods to analyze cluster data. Therefore, it is difficult to determine how effectiveness of these interventions or make comparison. Due to these reasons, we plan to design a pilot study to improve them. We would like to evaluate whether a complex intervention which combines educational programs for nursing home staff, BPSD management skill promotion workshops, pharmacist prescription assessment and feedback, activity redesign and long-term staff support system is more effective than the usual care in decreasing the proportion of nursing home dementia residents with antipsychotic prescriptions.

Aims, objectives and hypothesis:

The aims of this pilot study are to assess the feasibility and to optimize the study design for the definitive RCT of a complex intervention to change the antipsychotic prescription rate in nursing homes. The objectives of this study are listed as below:

1. To assess the acceptability of the director and staff of nursing home, physicians, and dementia residents and their carers to participate this study and to be randomly assigned.
2. To collect the data of recruitment rate of nursing homes to determine the time schedule for the full-scale RCT.
3. To assess the appropriateness of the inclusion and exclusion criteria.
4. To examine the feasibility and implementation fidelity of each ingredient in the complex intervention.
5. To estimate the data of primary outcome for the sample size calculation in the future large RCT.
6. To evaluate the appropriateness of various outcome measures.

The primary hypothesis will be tested in the definitive RCT is ‘A cluster, randomized controlled study of a complex intervention which includes educational programs for nursing staff and nurse aides, BPSD management skill promotion workshops, pharmacist prescription assessment and feedback, activity redesign and long-term staff support program for the dementia residents in nursing homes are more effective than the usual care in reducing the proportion of antipsychotics usage after 1-year intervention.’

The secondary hypothesis will be tested in the definitive RCT include the complex intervention will be better than usual care in the general health status of nursing home residents, less new onset of CVAs or mortality, better knowledge, skills and

competence of staff in managing BPSD, less antipsychotics side effects, and reducing the average dosage of antipsychotics usage.

Methods:
This study will be performed in the nursing homes of Taiwan. The total duration of this study is 2-year which consists of ethical approval by the research ethics committee, getting research funding, study execution, data analysis, report making and results dissemination. All of the staff of the nursing homes, physicians, dementia residents and their carers needs to sign a study consent form after explanation the study purpose and procedures before the study implementation.

Eligibility criteria
The inclusion criteria of the nursing home include the dementia residents of nursing home are over 40 people, the antipsychotic prescription rate are over 30% among the physicians and the staff of the nursing homes agree to join this study. The exclusion criterion of the nursing home is not registered in the Taiwanese government. The inclusion criteria of the residents include people with dementia diagnosis and they and their carers agree to join this study. The exclusion criteria of the residents include people in unstable physical conditions and the age of the residents less than 50 years old.

Design
The participant flowchart see appendix 1. This study will be designed as a cluster RCT because the staff and residents in the same nursing home would be easily to share information. Therefore, contamination between the intervention and control group will occur in an individual randomization study. Another reason is that it is easier to perform the intervention to the whole nursing home.

Recruitment methods
The sampling frame of nursing homes will get from the public accessible website of Taiwanese Ministry of the Internal. All of the nursing homes which site on the north Taiwan will be screened because the working place of the study's principal investigator is over there. The study manager will mail the study information sheet to all of the nursing homes and then contact them to evaluate whether they fulfill the study criteria and their motivation to attend study. All of the eligible nursing home will be visited by the principal investigator to discuss the details of the study. Then all of the nursing homes which meet all of the study criteria and sign study consent form will be randomly selected by computer statistical software.

Randomization and blinding

The unit of randomization is nursing home. We will use block randomization with the block size is two to ensure that the balance number in both group. The computer generation randomization will be done by an independent statistician who will not have any connections with study personnel. The results of randomization will forward to the principal investigator and then principal investigator informs the intervention executors. This complex intervention is difficult to keep blinding to the staff and nursing homes residents. Therefore, we only blind the results of randomization to the data collectors. He/she and the staff of nursing homes will be asked not to discuss the results of randomization. We will ask the data collectors to guess the results of randomization to assess the success of rater-blinding in the study end.

Measurements:

Process measures

We will measure the context, intervention implementation and the experiences of nursing home staff as our process measurements. Context will include the antipsychotic prescription pattern of Taiwan, the proportion of private nursing home, the manpower, the BPSD training programs and the activity program in nursing home. Intervention implementation will include review the mechanism of each ingredient to reduce antipsychotic prescription, fidelity assessment for each intervention, and the worker diaries of intervention performers. A qualitative study to evaluate the experiences of nursing home staff will be done.

Outcome measures:

Primary outcome:

1. The proportion of nursing homes fulfills the study criteria and agrees to be random allocated.
2. The fidelity of the various interventions. The fidelity of the dementia lectures, workshops, activity redesign conferences and continuous support meetings will be assessed by the attendance rate of these interventions. The fidelity of the pharmacist assessment and feedback will be assessed by the response rate of nursing home physicians to pharmacist feedback.
3. The change of the proportion of the dementia residents receiving antipsychotics from baseline to 1-year follow-up. This outcome measure will be the primary outcome of the definitive RCT.

Secondary outcome: All of the following outcomes evaluate the change from study baseline to 1-year follow-up or study endpoint.

1. The mean dose of antipsychotics in the dementia residents.
2. The proportion of dementia residents receiving other psychotropic medications.
3. The change of the BPSD severity measure by Neuropsychiatric Inventory (Cummings, Mega et al. 1994).
4. The time to new onset stroke or death.
5. Antipsychotic side effects measure by Udvalg for Kliniske Undersogelser side effects rating scale (Lingjaerde, Ahlfors et al. 1987).
6. General health condition measure by a general health questionnaire (GHQ-12) (Goldberg, Gater et al. 1997).
7. BPSD knowledge measure by a dementia knowledge test (Hobday, Savik et al. 2010).
8. The competence of managing BPSD measure by a competency questionnaire (Gronroos and Perala 2008).

Baseline data collection:

1. Demographic data:
    A. Staff: the number of various staff, age, gender, education level, role in the facility, duration of working experiences.
    B. Residents: number of residents, age, gender, diagnosis of residents.
2. Antipsychotic prescription rate: It will be collected by prescription review.

Intervention

A complex intervention which consists of the following ingredients:

1. Educational programs for nurses and nurse aides: A geriatric psychiatrist will use standardized teaching materials which design by research team.
    A. Symptoms of dementia: 4 hours, 1 hour for each topic: cognitive symptoms of dementia, psychotic symptoms of dementia, agitated and disturbing symptoms of dementia, differential diagnosis with depression and delirium.
    B. Antipsychotics education: 4 hours, 1 hour for each topic: antipsychotic mechanism, antipsychotic classification, side effects of antipsychotics in dementia, effectiveness of antipsychotics in dementia.
2. Non-pharmacological intervention workshop for nurses and nurse aides:
    A. One-hour environmental arrangement by a senior nurse.
    B. One-hour cognitive training by a psychologist.
    C. One-hour recreational therapy by an occupational therapist.
    D. One-hour of managing difficult behaviours by a geriatric psychiatrist.
3. Pharmacist prescription assessment and feedback: 12 times, once per month
    A. Prescription assessment by a pharmacist for each dementia residents and feedback to the physicians and nursing staff by a print-out report. Pharmacist will

use a clinical medications review format (Lowe, Petty et al. 2000) to assess physician's prescription.

B. Pharmacist discuss with physicians about the feedback.

C. Physicians response to the feedback by ticking a box in the report either accepting or rejecting.

4. Activity redesign:

   Three-hour conference of occupational therapist, nurses and nurse aides discuss the activity schedule for each dementia residents in each month to determine whether schedule need to revise.

5. Continuous support:

   An old age psychiatrist visits the nursing home once per month to attend a two-hour conference to discuss with nurses and nurse aides about dementia care.

Control group

The nursing homes in the control group will keep their previous treatment model. The usual model only provides once per month physician visit and the evaluation time for each dementia resident is less than 10 minutes. All of the nursing homes are short of psychologists, social workers and occupational therapists.

Sample size justification

Four nursing homes in each group would not impose too much burden for this pilot study is also an appropriate number to test the acceptability and feasibility of randomization procedures and the appropriateness of various interventions. There are over 40 nursing homes in north Taiwan and we suppose around 50% of them fulfill all study criteria and agree to join study. Therefore, it would be easy to randomly select 8 from 20 nursing homes.

The antipsychotic prescription rate is approximately 55% for dementia in Taiwan (Chen and Chan 2010). Previous studies demonstrated the antipsychotic prescription rate would below 30% after intervention (Fossey, Ballard et al. 2006). Therefore, we suppose the antipsychotic prescription rate will drop 25% in intervention group and minimal decrease (5%) in control group. Under the condition of 5% significant level and 80% power, then we need at least 49 dementia residents in each group in individual randomization study. We adjust the cluster effect by the formula: [1+(N-1)× intraclass correlation coefficient (ICC)]. Previous studies suggest that the ICC can be assumed as 0.05 (Fossey, Ballard et al. 2006). We suppose the dementia residents who agree to attend this study in each cluster are 30. Thus, we need $49\times[1+(30-1)\times0.05] \fallingdotseq 121$ subjects in each group and that is close to 4 nursing homes. Therefore, 4 nursing homes in each group have the statistical power near 80%.

Statistical analysis

All of the nursing homes being randomized will be treated as intent-to-treat (ITT) cluster and as the unit of analysis. There are only 4 units in each group, it is inappropriate to analyze the data by the approximation assumptions of large sample (normal distribution and equal variance). Therefore, we will use weighted t-test method to do the comparison and the methods of weighting are according to resident number of the nursing home. It is because the assumption of large sample is more likely to fulfill under the situation of weighted analysis (Campbell, Donner et al. 2007). We also use non-parametric method as the sensitivity analysis. Cox regression analysis with bootstrap procedures to analyze correlated failure time in a cluster will be used to estimate the survival data (time to death or the time to CVAs) (Monaco, Cai et al. 2005). The treatment effect will be presented as the weighted means difference or hazard ratio and their 95% confidence interval, ICCs and p values. A 2-sided, p-value of less than 0.05 will be considered significant. The data were analyzed using the STATA 8.0.

References:

Ballard, C. and A. Corbett (2010). "Management of neuropsychiatric symptoms in people with dementia." CNS Drugs **24**(9): 729-739.

Ballard, C., A. Corbett, et al. (2009). "Management of agitation and aggression associated with Alzheimer's disease: controversies and possible solutions." Curr Opin Psychiatry **22**(6): 532-540.

Campbell, M. J., A. Donner, et al. (2007). "Developments in cluster randomized trials and Statistics in Medicine." Statistics in medicine **26**(1): 2-19.

Cavalieri, T. A., A. Chopra, et al. (1993). "Geriatric assessment teams in nursing homes: do they work?" J Am Osteopath Assoc **93**(12): 1269-1272.

Chen, J. J. and H. Y. Chan (2010). "A Cross-sectional Psychotropic Drugs Utilization Study for Patients with Dementia." 49th Annual meeting of Taiwanese Society of Psychiatry.

Corbett, A., J. Smith, et al. (2012). "Treatment of Behavioral and Psychological Symptoms of Alzheimer's Disease." Curr Treat Options Neurol.

Crotty, M., J. Halbert, et al. (2004). "An outreach geriatric medication advisory service in residential aged care: a randomised controlled trial of case conferencing." Age Ageing **33**(6): 612-617.

Cummings, J. L., M. Mega, et al. (1994). "The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia." Neurology

44(12): 2308-2314.

Forsetlund, L., M. C. Eike, et al. (2011). "Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials." BMC Geriatr **11**: 16.

Fossey, J., C. Ballard, et al. (2006). "Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial." BMJ **332**(7544): 756-761.

Goldberg, D. P., R. Gater, et al. (1997). "The validity of two versions of the GHQ in the WHO study of mental illness in general health care." Psychol Med **27**(1): 191-197.

Gronroos, E. and M. L. Perala (2008). "Self-reported competence of home nursing staff in Finland." Journal of advanced nursing **64**(1): 27-37.

Hobday, J. V., K. Savik, et al. (2010). "Feasibility of Internet training for care staff of residents with dementia: the CARES program." Journal of gerontological nursing **36**(4): 13-21.

Kamble, P., H. Chen, et al. (2008). "Antipsychotic drug use among elderly nursing home residents in the United States." Am J Geriatr Pharmacother **6**(4): 187-197.

Kotynia-English, R., H. McGowan, et al. (2005). "A randomized trial of early psychiatric intervention in residential care: impact on health outcomes." Int Psychogeriatr **17**(3): 475-485.

Kuske, B., T. Luck, et al. (2009). "Training in dementia care: a cluster-randomized controlled trial of a training program for nursing home staff in Germany." Int Psychogeriatr **21**(2): 295-308.

Lingjaerde, O., U. G. Ahlfors, et al. (1987). "The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients." Acta psychiatrica Scandinavica. Supplementum **334**: 1-100.

Lowe, C. J., D. R. Petty, et al. (2000). "Development of a method for clinical medication review by a pharmacist in general practice." Pharmacy world & science : PWS **22**(4): 121-126.

Monaco, J., J. Cai, et al. (2005). "Bootstrap analysis of multivariate failure time data." Statistics in medicine **24**(22): 3387-3400.

Parnetti, L., S. Amici, et al. (2001). "Pharmacological treatment of non-cognitive disturbances in dementia disorders." Mechanisms of ageing and development **122**(16): 2063-2069.

Roberts, M. S., J. A. Stokes, et al. (2001). "Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes." Br J Clin Pharmacol

51(3): 257-265.

Rochon, P. A., T. A. Stukel, et al. (2007). "Variation in nursing home antipsychotic prescribing rates." Arch Intern Med **167**(7): 676-683.

Rovner, B. W., C. D. Steele, et al. (1996). "A randomized trial of dementia care in nursing homes." J Am Geriatr Soc **44**(1): 7-13.

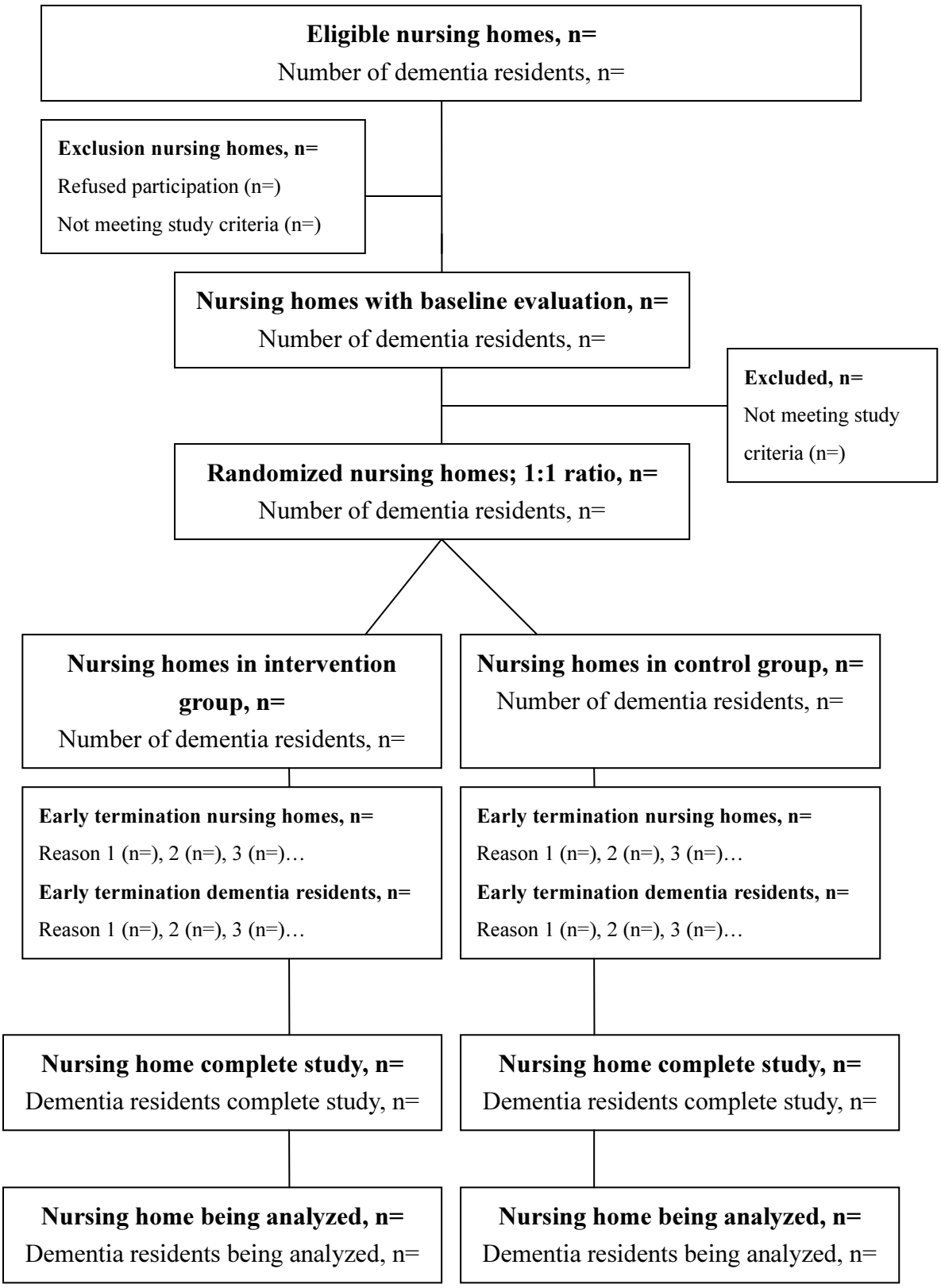
Sacchetti, E., C. Turrina, et al. (2010). "Cerebrovascular accidents in elderly people treated with antipsychotic drugs: a systematic review." Drug Saf **33**(4): 273-288.

Schneider, L. S., P. N. Tariot, et al. (2006). "Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease." N Engl J Med **355**(15): 1525-1538.

Valiyeva, E., N. Herrmann, et al. (2008). "Effect of regulatory warnings on antipsychotic prescription rates among elderly patients with dementia: a population-based time-series analysis." CMAJ **179**(5): 438-446.

Wang, P. S., S. Schneeweiss, et al. (2005). "Risk of death in elderly users of conventional vs. atypical antipsychotic medications." N Engl J Med **353**(22): 2335-2341.

Appendix 1. Summary of participant flowchart for this pilot study



附件五「全球精神健康」（Global mental health）課程報告

The critical evaluation to the phenomenon of medicalization of depression

Depression is a high prevalent syndrome and it is popular in different countries. Depression comprises lots of diagnosis in DSM-IV or ICD-10 system including unipolar (major) depressive disorder, dysthymia, adjustment disorder with depressed mood and bipolar disorder in depressive episode. The one-year prevalence of unipolar depressive disorder in the world is around 2.4% (World Health Organization 2004). One European study showed the one-year prevalence and lifetime prevalence of unipolar depression is 3.9% and 12.8% respectively (Alonso, Angermeyer et al. 2004). The prevalence of depression is various across different countries which was demonstrated by many cross-national studies. The Epidemiological Catchment Area study estimate the lifetime prevalence of unipolar depression and the results demonstrated that the range of prevalence is from 1.5% in Taiwan, 4.3% in Puerto Rico, 11.6% in New Zealand to 19% in Beirut (Weissman, Bland et al. 1996). The World Mental Health Survey Initiative study estimate the one-year prevalence of DSM-IV mood disorder (including unipolar disorder, dysthymia and bipolar disorder) also find the prevalence is low in Asia (Shanghai: 1.7%, Japan, 3.1%) and high in some Europe countries (France: 8.5%, Ukraine: 9.1%) and USA (9.6%) (Demyttenaere, Bruffaerts et al. 2004). These differences could be contributed to different demographic status, assessment instruments, diagnostic methods, sampling strategies and culture. Although there were variations in the prevalence of depression among different studies, all of the studies illustrated the prevalence of unipolar depression is more than 1% of the population all over the world.

Besides the high prevalence of depression, it is also a high burden disease to the society. The impact of depression comes from many aspects. The first is the symptoms of depression itself. Depression would make people suffering, decrease quality of life and impair the interpersonal functions and cognition. Depression's course is usually chronic and frequent relapse. The average course of each depressive episode is up to 1 year and the length of dysthymia is over 2 years (American Psychiatric Association 1994). The proportions of depressive subjects who did not receive treatment are high no matter in developed countries (50%) or developing

countries (85%) and this situation worsens the course of depression (Lepine and Briley 2011). The second is the increased mortality either directly through suicide or indirectly through rise the death rate of medical illness. The people with depression have over 20 times of risk to commit suicide and about twice of all cause mortality compare to people without depression (Osby, Brandt et al. 2001). For example, among the people with coronary heart disease, the adjusted odds ratio of mortality in depressed subjects over the non-depressed subjects is 2.6 after 2 years (Barth, Schumacher et al. 2004). The third is the disability due to depression. Many studies illustrated depression will reduce job productivity. In a 5-year longitudinal study, the people with depression have around 60% higher risk of unemployment compare to without depression (Whooley, Kiefe et al. 2002). A study collected data from employers demonstrated the depressed people have approximately 10 sick days in one year, which is higher than any other chronic diseases (Druss, Rosenheck et al. 2000). Another study also found depression is the only one of the chronic illness which would impair the concentration and productivity during the working period (Wang, Beck et al. 2004). That is no wonder that depression is a high burden disease and attracts attention from public health prospective.

According to the estimates of WHO, the burden of depression is huge to the society (World Health Organization 2004). Depression makes 98.7 million people in the state of moderate or severe disability and it is the third most common causes of disability. Disability adjusted life year (DALY) measure the loss of the full health multiply by year and WHO suggests that DALY is a favorable method because it considers both of the duration and the severity of disability. Unipolar depression is the third highest DALYs among all of the diseases and the DALYs of it are 65.5 millions, which occupy 4.3% of the total DALYs. Although the rank of DALYs of unipolar depression falls into the seventh in low-income countries, it rises to the first rank in the high- and middle-income countries. In consideration the gender issue, unipolar depression is the disease with highest DALYs in women in all of the income status. WHO also predicts the DALYs of unipolar depression in 2030 will reach 6.2% of the total DALYs and become the top rank of all diseases. Therefore, how to manage depression by cost-effectiveness methods to reduce the burden and use appropriate strategies in different areas to tailor to the local situations is a challenge for all of the countries.

To target the burden of depression in various regions, culture is a principal factor need to be considered. Prince et al. (1998) defined culture as " the totality of habits, ideas, beliefs, attitudes and values, as well as the behaviours that spring from them". From this definition, we can suppose that the way to experience low mood will be strongly

influenced by culture. Culture's influence to people's thinking and behaviours could be through three levels and interact between them. The first is the individual level and the individual differences due to their special temperament and personal experiences. The second is the group level and its occurrence is because of the unique history, language, religion, geography and politics of that area. The last one is the global level and it is the similar needs and behavioural patterns for the whole world. Therefore, even the medical diseases with universal biological markers can be found, people's beliefs about these diseases and help-seeking behaviours could be different. As most of the psychiatric illness, depression is a syndrome without definite diagnosis as medical diseases and psychiatric diagnosis depends heavily on people's subjective description. Therefore, the uniqueness of culture in the individual-level and group-level will strongly modify the way of perception and response to the low mood.

Some scholars hypothesized that the way of depression expression is different between the Western countries and non-Western countries (Lin 1982). Many researchers have noticed that Asian people are more focused on the somatic and cognitive component of depression and less connected to stressful life events (Chang, Hahm et al. 2008). For example, neurasthenia is a popular diagnosis in Mainland China and this term means the weakness of the nervous system (Parker, Gladstone et al. 2001). The symptoms of neurasthenia include exhaustion after minor efforts, weakness, tension, pains, sleep problems and dizziness. These symptoms are very similar to the somatic symptoms of depression or anxiety. There is strong stigma for people to admit mental illness in Chinese culture (Ryder and Chentsova-Dutton 2012). The communistic political background of the Mainland China also makes the mental illness unacceptable to the general publics. Mental illness would be interpreted as weakness or impureness of mind and what they need is thought correction rather than treatment. Furthermore, neurasthenia also can fit into the theory of traditional Chinese medicine. 'Chi' is a popular concept in Chinese medicine and it is a vital energy which can move around the body to maintain physical health. If Chi is not enough in central nervous system, then people's mind become weakness and will have the symptoms of neurasthenia. Therefore, Chinese people would focus on the somatic component to adapt to the Chinese cultural or political background. There are also different words to describe the situation of depression among different cultures. For instance, the popular words to express low mood in Chinese is 'lost-ambition', 'hard-to-pass' or 'hard-to-tolerate'…but not depression (Chan, Parker et al. 2007). If the assessors only use depression as the screening words, then many of depressed subjects will not be detected. Thus, some of the authors argue that the low prevalence of depression in Asian countries in previous studies is due to the diagnostic

framework of depression are grown from the Western societies and this concept are not familiar to other cultures (Ball, Siribaddana et al. 2010). Therefore, it is important to recognize the cultural differences in the understanding for depression. Then we can use appropriate language, concept and treatment to detect and manage depression in different countries to improve the outcome of this high burden disease.

As the previously mentioned, depression is a broad diagnostic term and it contains many diagnoses. It is inappropriate to consider all of the depressive categories having the same biological contribution in their etiology and over medicalization. May be some of the severe form of depression could be noted stronger biological basis such as unipolar depression. Severe depression has higher probabilities of genetic heritage, brain function change and metabolism abnormalities could be detected and some biological therapies have important roles in their treatment (Gelenberg 2010). Furthermore, many studies also showed unipolar depression has similar presentations in the core symptoms among different countries. For example, the prevalence of somatic symptoms in depression is up to 85% in the Western countries (Kirmayer, Robbins et al. 1993). Another international study demonstrated although the prevalence of depression is various among different countries, the proportions of somatic symptoms in depression are over 50% in all of the countries (Simon, VonKorff et al. 1999). These studies also reported 75-80% of the subjects would admit low mood and psychosocial stress if interviewers assessed this issue. Under such situations, etic approach could be used and recognize unipolar depression as a cross-culturally valid biomedical entity and set a standardized method to make diagnosis, treatment and international comparisons. However, researchers still need caution the cultural differences in the way of expressing depressive symptoms and tailored the detecting and treating methods for different countries.

Some of the depressive categories have important psychosocial contribution to their occurrence and do not have specific biological markers can be detected. Therefore, treating them as cross-nationally medical diseases is questionable. Bereavement is a strong depressive reaction to the death of beloved relatives. Although the symptoms of bereavement are similar to unipolar depression, most of the people will subside spontaneously within 2 months. Furthermore, some cultures have their unique bereavement response and might be misdiagnosed as psychotic disorder. Dysthmia is another arguing diagnostic category. Dysthymia was recognized as a personality disorder before but it was shifted to mood disorder since DSM-III in 1987. Dysthymia has the characteristics of chronic course and mild severity and these characters are often link to the diagnostic concept of personality disorder. American Psychiatric

Association had mentioned that the reasons of shifting dysthymia to mood disorder were the stronger genetic relationship between dysthymia and other mood disorder and some biological characteristics of dysthymia are similar to unipolar depression (Lima and Moncrieff 2000). However, many studies showed psychosocial factors and some personality pattern are important factors to maintain a person in long-term depression (Angst 1998; Garyfallos, Adamopoulou et al. 1999). Some expertise argued that the implicit reasons of shifting dysthymia to a mood disorder including expansion the territory of biological psychiatry and the medicalization of depression to enlarge the market of antidepressants (McPherson and Armstrong 2006). To sum up, although mild and short-term depression may have some similar depressive symptoms among different countries, their occurrence and categorization are modified by the psychological factors and social background, which are strongly influenced by culture. Therefore, the emic concept is an important tool to understand these depressive categories and formulate appropriate treatment plans to deal with them.

From the perspective of high prevalence and huge societal burden of depression, it should be a top priority for global health in the past, now and the future. While governments try to tackle this issue, they should pay attention to the cultural varieties and how do it influence to the perception of depression, symptoms presentations, help-seeking behaviours and affordable service plans. Both the etic and emic approach have their roles in understanding and providing help to the depressed subjects and complement to each other (Patel 2001). Hopefully, depression can be effectively managed under the comprehensive understanding and flexible use bio-psycho-social interventions to different types of depression. Then the burden of depression can be reduced substantially and can further improve the health condition of the world.

References:

Alonso, J., M. C. Angermeyer, et al. (2004). "Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project." Acta Psychiatr Scand Suppl(420): 21-27.

Angst, J. (1998). "Dysthymia and personality." Eur Psychiatry **13**(4): 188-197.

Association, A. P. (1994). "Diagnostic and Statistical Manual of Mental Disorders (4th ed). Washington DC: ." American Psychiatric Association.

Ball, H. A., S. H. Siribaddana, et al. (2010). "Epidemiology and symptomatology of depression in Sri Lanka: a cross-sectional population-based survey in Colombo District." Journal of affective disorders **123**(1-3): 188-196.

Barth, J., M. Schumacher, et al. (2004). "Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis." Psychosom Med **66**(6): 802-813.

Chan, B., G. Parker, et al. (2007). "Cross-cultural validation of the DMI-10 measure of state depression: the development of a Chinese language version." The Journal of nervous and mental disease **195**(1): 20-25.

Chang, S. M., B. J. Hahm, et al. (2008). "Cross-national difference in the prevalence of depression caused by the diagnostic threshold." J Affect Disord **106**(1-2): 159-167.

Demyttenaere, K., R. Bruffaerts, et al. (2004). "Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys." JAMA **291**(21): 2581-2590.

Druss, B. G., R. A. Rosenheck, et al. (2000). "Health and disability costs of depressive illness in a major U.S. corporation." Am J Psychiatry **157**(8): 1274-1278.

Garyfallos, G., A. Adamopoulou, et al. (1999). "Personality disorders in dysthymia and major depression." Acta Psychiatr Scand **99**(5): 332-340.

Gelenberg, A. J. (2010). "A review of the current guidelines for depression treatment." The Journal of clinical psychiatry **71**(7): e15.

Kirmayer, L. J., J. M. Robbins, et al. (1993). "Somatization and the recognition of depression and anxiety in primary care." Am J Psychiatry **150**(5): 734-741.

Lepine, J. P. and M. Briley (2011). "The increasing burden of depression." Neuropsychiatr Dis Treat **7**(Suppl 1): 3-7.

Lima, M. S. and J. Moncrieff (2000). "Drugs versus placebo for dysthymia." Cochrane Database Syst Rev(4): CD001130.

Lin, T. Y. (1982). "Culture and psychiatry: a Chinese perspective." Aust N Z J Psychiatry **16**(4): 235-245.

McPherson, S. and D. Armstrong (2006). "Social determinants of diagnostic labels in depression." Soc Sci Med **62**(1): 50-58.

Organization, W. H. (2004). "The global burden of disease: 2004 update. 2004 http://www.who.int/entity/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.".

Osby, U., L. Brandt, et al. (2001). "Excess mortality in bipolar and unipolar disorder in Sweden." Arch Gen Psychiatry **58**(9): 844-850.

Parker, G., G. Gladstone, et al. (2001). "Depression in the planet's largest ethnic group: the Chinese." Am J Psychiatry **158**(6): 857-864.

Patel, V. (2001). "Cultural factors and international epidemiology." Br Med Bull **57**: 33-45.

Ryder, A. G. and Y. E. Chentsova-Dutton (2012). "Depression in cultural context:

"Chinese somatization," revisited." The Psychiatric clinics of North America **35**(1): 15-36.

Simon, G. E., M. VonKorff, et al. (1999). "An international study of the relation between somatic symptoms and depression." N Engl J Med **341**(18): 1329-1335.

Wang, P. S., A. L. Beck, et al. (2004). "Effects of major depression on moment-in-time work performance." Am J Psychiatry **161**(10): 1885-1891.

Weissman, M. M., R. C. Bland, et al. (1996). "Cross-national epidemiology of major depression and bipolar disorder." JAMA **276**(4): 293-299.

Whooley, M. A., C. I. Kiefe, et al. (2002). "Depressive symptoms, unemployment, and loss of income: The CARDIA Study." Arch Intern Med **162**(22): 2614-2620.

附件六 期末論文

Withdraw study for patients with dementia on long-term quetiapine treatment: a multi-centre, randomized, double-blind, placebo controlled study

Background

The manifestations of dementia include decline in memory, cognitive function, and self-care. The three most common subtypes of dementia are Alzheimer's dementia, vascular dementia and Lewy body dementia (Jhoo et al., 2008). The risk factors for each kind of dementia are different but old age is the common to them all. Previous studies have shown the proportion of dementia to rise from 1-2% in people aged 61-69, to 5% in people aged 71-79 years and to over 30% in people aged 90 years or over (Plassman et al., 2007, Corrada et al., 2008, Ferri et al., 2005). The increase of elderly population in the last 3 decades means that the number of people with dementia has expanded sharply. Some scholars forecast that the number of people with Alzheimer's dementia will increase 4 times from 26.6 million in 2006 to 106.8 million in 2050 and which is equivalent to 1.17% prevalence in the world (Brookmeyer et al., 2007). They also predict that around 45% of people with Alzheimer's dementia will be in the late stage in 2050 and there will need to be huge resources to provide care (Brookmeyer et al., 2007). Another study estimates that in 2009 there were approximately 34.4 million people with dementia and the annual societal burden for dementia was 422 billion US dollars with 34% of the costs attributable to informal care (Wimo et al., 2010). The burden of dementia is especially large in high-income countries where it is the fourth leading causes of disease adjusted life years (DALYs) (World Health Organization, 2004). Therefore, the impact of this disease on the family, the health care sector and the world as a whole is large and growing. It is for this reason that dementia has become one of the major focuses of medical research and governmental policy.

Besides cognitive impairment and functional problems, behavioural and psychological symptoms in dementia (BPSD) are another major source of pressure. Patients with dementia frequently have psychiatric symptoms or behavioural

problems which include hallucinations, delusions, depression, anxiety, reverse sleep-awake cycle, stereotyped and disturbing behaviours, agitation or aggressive symptoms. The prevalence of BPSD is high and some studies have estimated that life time prevalence is close to 80% (Margallo-Lana et al., 2001). Most of the people with dementia have at least one of the BPSD and the highest prevalence symptoms are apathy (50.3 %), sleep problem (42.0%), irritability (28.8%), persecution (25.4%) and depression (20.5%) (Savva et al., 2009). BPSD is more stressful to the caregivers and community than the memory problems (Tan et al., 2005) and it can result in psychiatric ward admission or long-term institutionalisation (Tunis et al., 2002). Thus, the recognition and effective treatment of BPSD is an important issue and attracts the attention of researchers.

Strategies have been developed and evaluated to deal with BPSD including non-pharmacological and pharmacological interventions. Non-pharmacological management is the first line including detection and correction of any reversible factors which lead to BPSD (e.g. depression or other psychiatric illness, physical problems, medication side effects). Interventions include family and carer education, living setting rearrangement, cognitive stimulation, appropriate daily activities and personal interaction (Ballard and Corbett, 2010). If BPSD are still prominent after non-pharmacological interventions, then pharmacological interventions can be considered. Besides antipsychotics, many other psychotropic medications have been studied for their effectiveness for BPSD such as antidepressants (Seitz et al., 2011), valproate (Lonergan and Luxenberg, 2009), carbamazepine (Corbett et al., 2012) and cholinesterase inhibitors (Birks, 2006). The efficacy and safety of these medications for BPSD are inconclusive due to inadequate study statistical power and low quality in study design.

Antipsychotics are the most frequently used medications for BPSD, especially for psychotic symptoms, agitation and aggressive behaviours (Corbett et al., 2012). Antipsychotics are indicated for the treatment for psychotic disorders which include schizophrenia, schizoaffective disorder, schizophreniform disorder, psychotic disorder due to general medical conditions, substance induced psychotic disorder, psychotic disorder not otherwise specified, manic or mixed episode of bipolar disorder and major depressive disorder with psychotic features (Sadock and Sadock, 2007). Psychotic symptoms with agitation and aggression are a treatment indication for antipsychotic agents (Wilson et al., 2012). Therefore, it may be reasonable to consider antipsychotic medications as a treatment for people with dementia and psychotic symptoms or behavioural disturbances. Previous positron emission tomography (PET)

studies have shown the mechanism of psychotic symptoms is dopamine hyperactivity in the mesolimbic dopamine pathway of brain and the effects of dopamine are through the combination of dopamine with dopamine D2 receptors (Nord and Farde, 2011). PET studies have demonstrated that antipsychotic medications are dopamine D2 receptors antagonist and can reduce the effects of dopamine hyperactivity by blocking binding between dopamine and dopamine D2 receptors (Uchida et al., 2011). Antipsychotics are less likely to have the cumulative effects of benzodiazepines (Sylvestre et al., 2011) with less chance of falls, respiratory depression and sleep architecture disturbance compared to benzodiazepines (Huang et al., 2012, Wilson and Saukkonen, 2004, Dijk, 2010). Compared with mood stabilizers (e.g. lithium, carbamazapine, valproate), antipsychotics have lower probability of liver, kidney, skin allergic side effects and medication intoxication (Lange-Asschenfeldt et al., 2009, Musenga et al., 2009, Rej et al., 2012, Jankovic and Dostic, 2012). Furthermore, the newer atypical antipsychotics have less extrapyramidal side effects (EPS, including acute dystonia, akathisia, parkinsonism and tardive dyskinesia) than traditional antipsychotics (Rummel-Kluge et al., 2012, Lawlor, 2004) and people with dementia and BPSD are more sensitive to EPS than other psychotic disorders (Caligiuri et al., 2000). The mechanisms by which prescription of atypical antipsychotics result in less EPS include: serotonin 5HT-2A receptor antagonist effects which could increase dopamine secretion (Huttunen, 1995), more selectively act on mesolimbic than nigrostriatal dopamine pathway (Westerink, 2002), dopamine D2 receptors fast dissociation (Seeman, 2002), and dopamine D2 receptors partially agonistic effect (Lieberman, 2004). Due to the above reasons, antipsychotics are commonly used for BPSD across different countries (Rolland et al., 2012, Huber et al., 2012).

The rate of use of antipsychotic prescription to manage the BPSD is up to 30-60% (Rochon et al., 2007, Margallo-Lana et al., 2001). Many physicians and nurses believe that a substantial proportion of people with dementia and behavioual symptoms gain benefits from antipsychotic therapy and that only few people will have serious adverse events from these medications (Cornege-Blokland et al., 2012). However, systematic studies demonstrate that the effect size of antipsychotics in BPSD is low to moderate, at between 0.2 to 0.5 (Ballard and Waite, 2006). The CATIE-Alzheimer's dementia study, funded by the National Institute of Mental Health of USA government, reported that the effectiveness of three popular atypical antipsychotics (risperidone, olanzapine and quetiapine) for BPSD was not significantly different to that of placebo (Schneider et al., 2006b). Many studies have shown that both traditional and atypical antipsychotics increased the risk of mortality and cardiovascular adverse events in dementia population. The Food and Drug

Administration (FDA) of USA reported a meta-analysis of 17 randomized controlled trials (RCTs) of dementia population with behavioural disturbances in 2005 and found the hazard ratio of death in the atypical antipsychotics group was 1.6 to 1.7 times compared to placebo. The major causes of death were heart related problems or infection. The FDA issued a black box warning for atypical antipsychotics in the treatment of elderly patients with dementia with behavioural disturbances (*http:// www.fda.gov/ Drugs/ Drug Safety/ Postmarket Drug Safety Information for Patients and Providers/ Drug Safety Information for Heathcare Professionals/ Public Health Advisories/ ucm053171.htm*).

The hazard ratio of death in those taking atypical antipsychotics was 1.54 times compared to placebo in another meta-analysis which compiled the results of 15 good enough quality RCTs with study periods between 10 to 12 weeks (Schneider et al., 2005). Two historical cohort studies showed the risk of mortality of traditional antipsychotics was even higher than atypical antipsychotics after 180 days follow-up. Wang's study showed the relative risk of death was 1.37 times higher in traditional antipsychotic group compared with atypical antipsychotic group (Wang et al., 2005). Another study demonstrated that the hazard ratio of death was 1.23 times for community dwelling cohort and 1.27 times for long-term care cohort respectively in traditional antipsychotic group compared with atypical antipsychotic group (Gill et al., 2007). Due to the results of these two studies, the FDA also issued a black box warning to traditional antipsychotic medications in the treatment of elderly patients with dementia with behavioural disturbances in 2008 (*http:// www.fda.gov/ drugs/ drugsafety/ postmarket drugsafety information for patients and providers/ ucm124830.htm*).

Atypical antipsychotics were also noted to have around 2 times the rate of cerebrovascular events compared to placebo (1.9% vs 0.9%) in a meta-analysis (Schneider et al., 2006a). Concerns for the safety of antipsychotics in those with dementia have increased because of these emerging data. A report commissioned by the UK government estimated that there were around one hundred and eighty thousand people with dementia in the UK receiving antipsychotic treatment annually and this would lead to approximately one thousand eight hundred extra deaths and one thousand six hundred extra cerebrovascular events per year (Banerjee, 2009). Therefore, high antipsychotic prescription rates have emerged as an important and urgent patient safety issue.

Although the effectiveness of antipsychotics in BPSD is limited and antipsychotics have above mentioned adverse effects, there are no better pharmacological interventions than antipsychotics at present after considering all risks

and benefits. Therefore, many treatment guidelines suggest antipsychotics can use in short-term (less than 3 months) for psychotic or agitated symptoms of BPSD and need to closely monitor their effectiveness and side effects during the treatment period (Ballard and Corbett, 2010). If clinicians judge the necessity of continuous antipsychotic usage after 3 months of treatment, they must have clear indications for that and need to write down the reasons in medical document (OBRA, 1987). Although the existence of these guidelines, the antipsychotics prescription rates for BPSD are still high in many countries (Rochon et al., 2007, Margallo-Lana et al., 2001). For example, Banerjee's report demonstrated that antipsychotics prescription rates for BPSD in the UK were from 20% to 48% (Banerjee, 2009). He suggested the proportion on antipsychotic prescription can reduce two-thirds in the UK immediately to prevent unnecessary deaths and cerebrovascular events.

There are two kinds of approaches to explore the effects of reducing antipsychotic prescription. The first one is to study non-pharmacological interventions to determine their effectiveness in reducing antipsychotic prescription. The second is to investigate whether the severity of BPSD and the health condition of the people with dementia changes after antipsychotic tapering or direct discontinuation. Most non-pharmacological interventions focus on the residents of long-term care facilities such as nursing homes. One reason is because long-term care facilities have higher antipsychotic prescription than outpatient clinics (Huber et al., 2012, Rolland et al., 2012, Richter et al., 2012, Garcia-Gollarte et al., 2012, Shah et al., 2011, Azermai et al., 2011). Another reason is that it is easier in long-term care facilities than other settings to perform interventions and assess their outcomes. Forsetlund et al. performed a systematic review of 20 RCTs to assess the effects of different non-pharmacological interventions in reducing the prescription of psychotropic medications (Forsetlund et al., 2011). They categorized these interventions into the following groups:

- outreach educational interventions by a pharmacist to visit physicians (Crotty et al., 2004),
- educational conferences in the working places (Testad et al., 2010),
- educational conferences in the working places plus other interventions (Meador et al., 1997),
- prescription review by pharmacists (Patterson et al., 2010) and
- others such as activity rearrangement (Rovner et al., 1996).

The conclusion they drew was that most of the studies showed positive effects in

reducing psychotropic medication prescription but that the studies suffered from low or poor quality in study design or study reporting (Forsetlund et al., 2011). The most common quality problems were inadequate collection or reporting the characteristics of the long-term care facilities, under reporting of the details and the fidelity of the interventions and inadequate statistical power.

Another kind of study is the antipsychotic withdrawal study. There have been a number of antipsychotic discontinuation studies in those with dementia on long-term antipsychotic treatment in the last three decades. Many have suggested that the average severity of BPSD did not change significantly after antipsychotic withdrawal (Kleijer et al., 2009, Ballard et al., 2009, Bergh and Engedal, 2008, Ballard et al., 2008, Ballard et al., 2004, Cohen-Mansfield et al., 1999, Bridges-Parlet et al., 1997, Thapa et al., 1994), only a small proportion of study participants appeared NPI total score increasing or behavioural worsening (Ruths et al., 2004, van Reekum et al. 2002). However, a few studies showed the antipsychotic discontinuation group had statistically significant BPSD worsening (Devanand et al., 2011). Poor prognostic factors for antipsychotic withdrawal suggested include:

- higher baseline antipsychotic dosage (Ruths et al., 2008, van Reekum et al., 2002, Meador et al., 1997),
- higher baseline Neuropsychiatric Inventory (NPI) scores (Meador et al., 1997, Ballard et al., 2008, Ballard et al., 2004) or
- the use of benzodiazepines or antidepressants at baseline (Meador et al., 1997).

However, there are limitations in previous antipsychotic withdrawal studies. First, most of these studies focused on typical antipsychotics, or risperidone or olanzapine but not quetiapine, a popular atypical antipsychotic agent for BPSD (Kleijer et al., 2009, Ballard et al., 2009, Bergh and Engedal, 2008, Ballard et al., 2008, Ruths et al., 2004, Ballard et al., 2004, van Reekum et al., 2002, Cohen-Mansfield et al., 1999, Bridges-Parlet et al., 1997, Thapa et al., 1994). Second, most previous studies focused on people with dementia in care homes or other residential facilities, not outpatients. Therefore, the generalizability of these studies is limited to the residents of the long-term care facilities. Third, most of previous antipsychotic withdrawal studies assess the combined effects of several antipsychotic medications. Only two small pilot studies focused on the discontinuation of a specified antipsychotic medication, one (n=20) focused on haloperidol (Devanand et al., 2011) and another (n=36) focused on thioridazine (Findlay et al., 1989). Therefore, it is difficult to asses the unique

withdrawal effects of a specified antipsychotic medication or makes a comparison between different antipsychotics.

A summary of previous antipsychotic withdrawal RCTs and observational studies are presented in table 1 and table 2 respectively. The search strategy for antipsychotic withdrawal RCTs in people with dementia followed the systematic review protocol of the Cochrane Collaboration (Declercq, Petrovic et al. 2009). The key words and combinations in Medline used in the systematic review protocol are presented in appendix 1. Besides Medline, the following electronic databases were searched: The Cochrane Library, Embase, PsycInfo and Cinahl. The search strategies for other electronic databases were revised according to the rules of the electronic database. Eight hundred and twenty-three articles were identified in Medline by this search strategy and nine relevant RCTs were found. Two of the nine RCTs were the same study with different follow-up period and outcomes (Ballard et al., 2009, Ballard et al., 2008). Searching the other electronic databases and references of the nine trials identified one further relevant RCT (Findlay et al., 1989). Therefore, there are nine RCTs in table 1 in total.

Four observational studies were identified during the process of antipsychotic withdrawal RCTs searching (Shah, 2006, Kleijer et al., 2009, Bergh and Engedal, 2008, Thapa et al., 1994). One was excluded because the participants combined dementia and other psychiatric disorders and did not report the results separately (Shah, 2006). To find observational studies of antipsychotic withdrawal in dementia comprehensively, we used a similar search strategy (Declercq, Petrovic et al. 2009) with RCT changed to observational studies (e.g. cohort, prospective, case-control, retrospective, observational, non-randomized). The key words and combinations in Medline are presented in appendix 2. One hundred and twenty-five articles were identified by this search strategy in Medline. No further relevant observational studies were found. Searching other electronic databases and references of the nine trials and the four observational studies identified one further relevant observational study (Horwitz et al., 1995). Therefore, there are only four observational studies in table 2.

Table 1: Previous antipsychotics (AP) withdrawal randomized controlled studies

Author and year	Case number/ Setting/ Previous AP before Study (N)	Follow-up period	Outcome measure	Case number/ AP continuation group, Case number/ AP withdrawal group	Tapering speed	Primary results
Devanand et al. 2011	20/ Outpatient/ Haloperidol (20)	24 weeks	Psychotic and agitated symptoms worsening measured by the sum score of three BPRS items.	10/Haloperidol, 10/ Placebo	**4 mg/d at baseline:** 2 mg/d in the first week and then 1 mg/d in the second week **2-3 mg/d at baseline:** 1 mg/d for 2 weeks **0.5-1 mg/d at baseline:** abrupt stopping at baseline.	Proportion of subjects with more than 50% psychotic symptoms worsening: 40% in haloperidol group and 80% in placebo group. Statistically significant higher risk in placebo group.
Ballard et al. 2008 & 2009	165/ Residents of long-term care facilities/ Traditional AP or risperidone	**6 months outcomes**	BPSD severity change	83/ Traditional AP or risperidone, 82/ Placebo.	Abrupt stopping at baseline.	NPI score change from baseline to 6 months: Increase 1.3 points in AP continuation group and increase 4.5 points in placebo group. No statistically significant between-group difference.

		12 months outcomes	1. Mortality	83/ Traditional AP or risperidone, 82/ Placebo.		Survival rate: 74.7% in AP group and 79.3% in placebo. No statistically significant difference in survival rate.
			2. BPSD severity change	28/ Traditional AP or risperidone, 31/ Placebo. Only analyzed the data of study completers.		NPI score change from baseline to 12 months: Increase 1.4 points in AP group and increase 11.4 points in placebo group. Statistically significant higher NPI scores increase in placebo group.
		Extended outcomes (up to 54 months)	Mortality	83/ Traditional AP or risperidone, 82/ Placebo.		Placebo group had significantly higher mortality rate than AP group (log rank test: p=0.02, HR 0.58 (0.36-0.92)).
Ruths et al. 2008	55/ Residents of nursing homes/ Haloperidol or risperidone or olanzapine	4 weeks	NPI score change	28/Haloperidol or risperidone or olanzapine, 27/ Placebo.	Abrupt stopping at baseline.	Proportion of subjects with NPI score remained the same or decreased: 86% in AP group and 66% in placebo group. No statistically significant between-group difference.
Ruths et al. 2004	30/ Nursing homes/ Risperidone (22), olanzapine (4), haloperidol (4)	4 weeks	NPI-Q sum score change	15/Risperidone or olanzapine or haloperidol, 15/ Placebo.	Abrupt stopping at baseline.	Proportion of subjects with NPI-Q sum score remained stable or decreased: 87% in AP group and 73% in placebo group. No statistically significant between-group difference.

Ballard et al. 2004	100/ Residents of long-term care facilities/ Traditional AP or risperidone	3 months	NPI score change	54/ Traditional AP or risperidone, 45/ Placebo.	Abrupt stopping at baseline.	Proportion of subjects with NPI score remained the same or decreased: 91% in AP group and 87% in placebo group. No statistically significant between-group difference.
Van Reekum et al. 2002	33/ Residents of long-term care facilities/ Risperidone (12), olanzapine (3), traditional AP (19)	6 months	BEHAVE-AD score change	16/ Traditional AP or risperidone or olanzapine, 17/ Placebo.	Stop after 2 weeks tapering.	Proportion of subjects without study early withdrawal due to behavioural worsening: 81.2% in AP group and 76.5% in placebo group. No statistically significant between-group difference.
Cohen-Mansfield et al. 1999	58/ Residents of nursing homes/ Traditional AP (58)	6 weeks	BPRS score and CMAI score at study endpoint.	29/ Traditional AP or lorazepam, 29/ Placebo. A crossover trial.	Stop after 3 weeks tapering.	BPRS score at study endpoint: 2.32 in AP group and 2.12 in placebo group. No statistically significant between-group difference. CMAI score at study endpoint: 1.72 in AP group and 1.77 in placebo group. No statistically significant between-group difference.

Bridges-Parlet et al. 1997	36/ Residents of long-term care institute/ Haloperidol (21), thioridazine (9), thiothixene (3), other traditional AP (3).	4 weeks	Early study withdrawal due to agitation or aggression.	14/ Traditional AP, 22/ Placebo.	Abrupt stopping at baseline.	Proportion of subjects who can complete study without agitation: 100% in AP group and 91% in placebo group. No statistically significant between-group difference.
Findlay et al. 1989	36/ Long-stay psychogeriatic ward of a hospital/ Thioridazine (36).	4 weeks	CAS for cognitive function; SCAGS & LPRS for behavioural features.	18/ Thioridazine, 18/ placebo group.	Stop after 1 week tapering.	Total score changes from baseline to study endpoint: **CAS:** Increase 1.7 in placebo group and no change in AP group. **SCSGS:** Increase 1.1 in placebo group and increase 1.7 in AP group. **LPRS:** Increase 1.1 in placebo group and decrease 0.9 in AP group. No statistically significant between-group differences in all outcome measures.

Abbreviation: AP: antipsychotics, NA: not available, BPRS: Brief Psychiatric Rating Scale, NPI: Neuropsychiatric Inventory, NPI-Q: Neuropsychiatric Inventory Questionnaire, BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale, CMAI: Cohen-Mansfield Agitation Inventory, NHBPS: Nursing Home Behaviour Problem Scale, CAS: Cognitive Assessment Scale, SCAGS: Sandoz Clinical Assessment Geriatric Sale, LPRS: London Psychogeriatric Rating Scale.

Table 2: Previous antipsychotic withdrawal observational studies:

	Case number/ Setting/ Previous AP before Study (N)	Follow-up period	Outcome measure	Case number/ AP continuation, Case number/ AP withdrawal	Tapering speed	Primary Results
Kleijer et al. 2009	520/ Residents of nursing homes/ NA	6 months	CBP	All participants discontinued previous AP.	NA	Proportion of subjects with the same or lower CBP score: 68% at 3 months and 58% at 6 months.
Bergh et al. 2008	12/ Residents of nursing homes/ Risperidone (4), Olanzapine (5), Quetiapine (1), Traditional AP (2)	24 weeks	NPI	All participants discontinued previous AP.	One week tapering.	NPI score only mildly change from baseline to endpoint.
Horwitz et al. 1995	47/ Residents of nursing homes/ Traditional AP (47)	6 months	Resume antipsychotic or other psychotropic medications (treatment failure).	21/ AP discontinuation suggested by physicians (clinical judgment group), 26/ AP discontinuation without clinical judgment (empirical group).	Two weeks tapering. Tapered 50% in the first week and further 50% in the second week.	Treatment failure rate: Clinical judgment group: 4.8%, Empirical group: 50%. Empirical group had significantly higher treatment failure rate than clinical judgment group (Fisher's exact test: p=0.001).

Thapa et al. 1994	271/ Residents of nursing homes/ Traditional AP (271).	6 months	NHBPS for behaviour problem.	207/ Traditional AP group, 64/ AP discontinued group.	NA	NHBPS total score change from baseline to study endpoint: Decrease 0.17 ± 0.71 in placebo group and decrease 1.43 ± 0.71 in AP group. No statistically significant between-group difference.

Abbreviation: AP: antipsychotics, NA: not available, CBP: Challenging Behavior Profile, NPI: Neuropsychiatric Inventory.

Quetiapine is one of the atypical antipsychotics and it is popularly used in BPSD. It is the most popular antipsychotic prescription for people with dementia in Taiwan. Around 22% of the people in Taiwan with dementia receive quetiapine treatment (Chen and Chan, 2010). Compared with risperidone and olanzapine, previous studies have shown the efficacy of quetiapine is lower but safety is better than these two other atypical antipsychotics in the treatment of BPSD (Sultzer et al., 2008, Schneider et al., 2006b, Huybrechts et al., 2012). Furthermore, one study illustrated that quetiapine may decrease cognitive function compared with placebo after 26-week treatment (Ballard et al., 2005). According to the results of these studies, it seems reasonable to suppose that the response to quetiapine withdrawal may be different from the other atypical and traditional antipsychotics.

Taiwan has a population of 23 million people and 11% (2.5 million) of the total population are over 65 years of age (Department of Statistics, Ministry of the Interior. Statistical Yearbook of Interior. http: //www.moi.gov.tw/ stat/ english/ index. asp). According to previous epidemiological studies in Taiwan, the prevalence of dementia is between 1.7-4.3% in the elderly population (Fuh and Wang, 2008). Furthermore, around 60% of people with dementia have been reported to be receiving antipsychotic treatment in Taiwan (Chen and Chan, 2010). Therefore, the safety issue of antipsychotic usage is an important topic in Taiwan. Most previous Taiwanese studies have only focused on the efficacy of antipsychotics for BPSD (Yang et al., 2005, Lane et al., 2002). No studies have explored response to antipsychotic withdrawal. Here we propose a 24-week, randomized, double-blind, placebo controlled, parallel group study to compare quetiapine withdrawal with quetiapine continuation in people with dementia on long-term quetiapine treatment in Taiwan.

Aims, objectives and hypothesis

The primary aim of this study is to assess the proportion of participants who maintain the same or have a decrease in severity of BPSD in the quetiapine withdrawal group and quetiapine continuation group and to compare these groups in Taiwanese people with dementia on long-term (more than 3 months) quetiapine treatment in a 24-week, randomized, double-blind, placebo-controlled, parallel group study. The result of this can be used for sample size calculation in further related studies. The secondary aim of this study is to evaluate whether there are changes in severity of BPSD in a quetiapine withdrawal group compared with a quetiapine continuation group.
The following are the objectives of this study:

1. To compare BPSD severity in the quetiapine withdrawal group and quetiapine continuation group.

2. To compare mortality in the quetiapine withdrawal group and quetiapine continuation group.
3. To compare the incidence of new cerebrovascular events in the quetiapine withdrawal group and quetiapine continuation group.
4. To compare extrapyramidal syndrome severity in the quetiapine withdrawal group and quetiapine continuation group.
5. To compare depressive symptom severity in the quetiapine withdrawal group and quetiapine continuation group.
6. To compare activity limitation in the quetiapine withdrawal group and quetiapine continuation group.
7. To compare changes in quality of life between the quetiapine withdrawal group and quetiapine continuation group.
8. To compare changes in carer quality of life in the quetiapine withdrawal group and quetiapine continuation group.
9. To compare changes in carer burden in the quetiapine withdrawal group and quetiapine continuation group.
10. To compare changes in carer general health status in the quetiapine withdrawal group and quetiapine continuation group.

The primary hypothesis of this study is that the proportion of participants who remain the same or have a decrease in severity of BPSD as measured by the NPI from baseline to study endpoint in the quetiapine withdrawal group is equivalent to that in quetiapine continuation group.

The secondary hypotheses of this study include equivalence or better action in the quetiapine withdrawal group compared with the quetiapine continuation group in terms of mortality rate, rate of cerebrovascular events, antipsychotic-induced extrapyramidal syndrome severity, depressive symptom severity, cognitive function, activity limitation, general health status, quality of life of the people with dementia, quality of life of carers and carer burden.

Materials and Methods

Participants

Subjects will be recruited from 4 teaching hospitals in Taiwan including 2 mental hospitals (Taoyuan mental hospital and Jianan mental hospital) and 2 medical centers (National Taiwan university hospital and Cathay general hospital) from April 1, 2013 to September 30, 2014. All these hospitals have had recent experience in conducting clinical trials and have substantial numbers of patients with dementia.

The inclusion criteria of this study will be:

(i) age 60 years or more;
(ii) both male and female;
(iii) any treatment settings such as outpatients with community dwelling, inpatients of general hospital or mental hospital, or residents of long-term care facilities;
(iv) a carer who agrees to participate in the study;
(v) treatment with quetiapine for BPSD for at least 3 months;
(vi) probable or possible Alzheimer's disease using NINCDS/ADRDA (National Institute of Neurological Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association) criteria;
(vii) mini-mental status examination (MMSE) score less than 27; and
(viii) agree and have legal guardians who agree to join the study and provide written informed consent.

The patient information sheet, carer information sheet, patient consent form for patient, carer consent form for carer, and carer consent form for patient are presented in appendix 3 to 7 respectively. The template of these information sheets and consent forms are from Health Technology Assessment Study of Antidepressants for Depression in Dementia (HTA-SADD, http://www.hta.ac.uk/1508). Exclusion criteria include those with major systemic diseases in unstable condition and those with substance abuse or dependence in the last six months before the study. All eligible subjects will receive a psychiatric and physical assessment at the screening visit to determine whether they fulfill all of the study criteria.

The reasons for the inclusion criteria are: (i) including varied treatment settings to increase generalizability of the study; (ii) the need for a carer to participate in the study to provide reliable information and fulfill research ethical standards; (iii) antipsychotics for three months stipulated since that most treatment guidelines suggest antipsychotic medication should not be used for over 12 weeks (Ballard and Corbett, 2010, Banerjee, 2009); and (iv) MMSE score less than 27 is because the usual cut-off score of MMSE for dementia is equal to or less than 26 (Spering et al., 2012).

Randomization and blinding

Eligible subjects fulfilling the study criteria will be randomized to the quetiapine continuation group or a placebo control group with ratio 1:1. The method of randomization will be designed by an independent statistician using permuted block randomization with 6 participants in each block. The purpose of the block randomization

will be to maintain the balance of participant numbers in each study group. The block size of six is because it may be easy to guess the sequence of randomization if block size is small (e.g. 2 or 4). The random assignment will be stratified by hospital to prevent site difference in the study group distribution. The independent statistician will not contact study participants, study investigators and primary care staff to maintain concealment allocation and blinding during the study period. The results of the randomization will be put in envelopes which have the randomization number labeled on them. These envelopes will be sealed and kept in the office of the independent statistician. Both quetiapine and placebo will be over-encapsulated with identical appearance, color, smell and taste to hide the contents and keep blinding.

In situations of medical emergency where there is a need to know the results of random allocation to provide appropriate interventions for study participants, the code of the randomization can be broken. The data monitoring ethics committee (DEMC) also can request unblinding while they decide it is necessary to protect the safety of the study participants.

Dose of study medication

Subjects who are allocated to the quetiapine continuation group will use the quetiapine dose closest to their original quetiapine dose. There will be 3 fixed doses available 50, 100 and 200 mg/d. If the original quetiapine doses are in the category of low (less than 100 mg/day), moderate (100-200 mg/day) and high (more than 200 mg/day) at recruitment, the participants will receive fixed doses of 50, 100 and 200 mg/day quetiapine throughout the study period. The placebo control group will discontinue immediately or taper the dose of quetiapine from the study baseline depending on the original quetiapine dose. All quetiapine tapering will be completed within 2 weeks. If the original daily dose belongs to the low category, then quetiapine will discontinue immediately and use placebo from baseline. If the original daily dose is in the moderate category, quetiapine 100 mg/day will be used at baseline for 1 week and then taper to 50 mg/day in the next week and then discontinue and shift to placebo after 2 weeks of tapering. In the high category, quetiapine 200 mg/day will be used at baseline for 1 week and then taper to 100 mg/day in the next week and then discontinue and shift to placebo after 2 weeks of tapering. The time of the study medications consumption in both groups will be the same and will be once at 9 pm. This is because quetiapine has the effect of sedation and can help sleep. Drug compliance will be assessed by counting the medications left.

Prohibited and concomitant medications

Study participants will not be permitted to initiate any other antipsychotics, mood

stabilizers (lithium, valproate, carbamazepine or lamotrigine), antidepressants and dopamine agonists throughout the study period. If they are on these drugs at a stable dose for 3 months or more then they can be continued in the study period. Anticholinergic drugs, and propranolol can be prescribed if subjects appear EPS side effects during the study period. Hypnotics also can be prescribed if participants experience insomnia and the dose is no more than the equivalent dose of diazepam 10 mg/day (http://www. enzo.org.uk/ bzequiv.htm). Subjects can maintain the dosage of their cholinesterase inhibitors (rivastigmine, donepezil, galantamine) or memantine if these medications have been prescribed before study. No more than 4 mg/day of intramuscular lorazepam can be given to those who have agitation or exhibited aggressive behaviours.

Primary outcome

1. Short-term outcome: The proportion of participants who maintain the same or have a decrease in NPI total scores after 12 weeks follow-up compared with baseline. The reason to set 12 weeks as the short-term outcome for BPSD severity assessment is because there were studies which showed a substantial proportion of study participants would worsen BPSD within 3 months of antipsychotic discontinuations and comparators (Kleijer et al., 2009; Ballard et al., 2004).
2. Long-term outcome: The proportion of participants who maintain the same or have a decrease in NPI total scores after 24 weeks follow-up compared with baseline. The reason to set 24 weeks as the long-term outcome for BPSD severity assessment is because there were studies suggesting that most study participants would worsen BPSD within 24 weeks of antipsychotic discontinuation and comparators (Ballard et al., 2008, Devanand et al., 2011, Bergh and Engedal, 2008).

Secondary outcome

1. Short-term outcome: All short-term secondary outcomes will be assessed after 12 weeks follow-up or at study endpoint if participants dropout.
    a. The change in Neuropsychiatric inventory (NPI) total scores from baseline to study endpoint.
    b. The change in Mini-mental status examination (MMSE) total scores from baseline to study endpoint.
    c. The change in Bristol Activities of Daily Living Scale (BADLS) total scores from baseline to study endpoint.
    d. The change in Cornell Scale for Depression in Dementia (CDSS) total scores from baseline to study endpoint.
    e. The change in General Health Questionnaire (GHQ-12) total scores from baseline to study endpoint.
    f. The change in Zarit Inventory total scores from baseline to study endpoint.

g. The changes in Disease-specific Health Related Quality of Life (DEMQOL) total scores and DEMQOL-proxy total scores from baseline to study endpoint.
h. The changes in 5 domains of Extrapyramidal Symptom Rating Scale (ESRS) total scores: subjective domain, parkinsonism and akathisia domain, dystonia domain, dyskinesia domain, and each global impression item from baseline to study endpoint.
i. The score of Clinical Global Impression-Change (CGI-C) after 12 weeks follow-up or study endpoint if subjects dropout.
j. The number of new cerebrovascular events after 12 weeks follow-up.
k. The number of deaths after 12 weeks follow-up.

2. Long-term outcome: All short-term secondary outcomes will be included but the assessment time point will be 24 weeks or study endpoint if participants dropout.

Primary outcome measure

Neuropsychiatric inventory (NPI) (Cummings et al., 1994, Aalten et al., 2008): This assessment tool is for the evaluation of severity of psychiatric and behavioural symptoms in people with dementia. It consists of 12 items including delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night-time behaviour, and appetite/eating behaviour. The score of each item is calculated by the severity multiply the frequency of each symptoms. Total score is the sum of each item and the range is from 0 to 144. Higher score indicates more severe psychopathology.

Secondary outcome measures

1. ***Mini-mental status examination (MMSE) (Molloy et al., 1991):*** This assessment tool is for the evaluation of cognitive function in people with dementia. It consists of 6 domains including orientation, attention, memory, language, follow commands and visual-spatial function. Total score is the sum of each domain and the range is from 0 to 30. Higher score indicates better cognitive function.
2. ***Bristol Activities of Daily Living Scale (BADLS) (Bucks et al., 1996):*** This assessment tool is completed by caregivers to assess patient's ability to perform the activities of daily living. It consists of 20 items including food, eating, drink, drinking, dressing, hygiene, teeth, bath/shower, toilet/commode, transfers, mobility, orientation-time, orientation-space, communication, telephone, housework/gardening, shopping, finances, games/hobbies, and transport. Total score is the sum of each item (score range of each item: 0-3) and the range is from 0 to 60. Higher score indicates poorer function.
3. ***Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005):***

This assessment tool is for the evaluation of the EPS severity of antipsychotics. It consists of 5 domains including subjective assessment (7 items, score range of each item: 0-3, range of total score: 0-21), parkinsonism and akathisia (17 items, score range of each item: 0-6, range of total score: 0-102), dystonia (10 items, score range of each item: 0-6, range of total score: 0-60), dyskinesia (7 items, score range of each item: 0-6, range of total score: 0-42), and global impression (4 items, score range of each item: 0-8). Higher score indicates higher EPS severity.

4. ***Clinical Global Impression-Change (CGI-C) (Schneider et al., 1997):*** This assessment tool is for the evaluation of the change of dementia severity by the global impression of health-care providers. There is only 1 item in this scale with score range 1-7. The meaning of each score is 1 for very much improved, 2 for much improved, 3 for mild improved, 4 for no change, 5 for mild worsen, 6 for much worsen, and 7 for very much worsen.
5. ***Cornell Scale for Depression in Dementia (CDSS) (Alexopoulos et al., 1988):*** This assessment tool is done by both people with dementia and carers to assess the severity of depressive symptoms in people with dementia. It consists of 19 items in 5 domains including mood related signs (4 items in this domain: anxiety, sadness, lack of reactivity to pleasant events, irritability), behavioural disturbance (4 items in this domain: agitation, retardation, multiple physical complaints, loss of interest), physical signs (3 items in this domain: appetite loss, weight loss, lack of energy), cyclic function (4 items in this domain: diurnal variation of mood, difficulty falling asleep, multiple awakening during asleep, early morning awakenings), and ideational disturbance (4 items in this domain: suicide, poor self-esteem, pessimism, mood congruent delusion). Total score is the sum of each item (score range of each item: 0-2) and the range is from 0 to 38. Higher score indicates more severe depressive symptoms.
6. ***General Health Questionnaire (GHQ-12) (Goldberg et al., 1997):*** This assessment tool is completed by carers to assess their own general mental health status. It consists of 12 items including concentration, sleep, usefulness, decision-making, strain feeling, overcome difficulties, enjoy life, face problems, depression, lose confidence, worthlessness, and happy. Total score is the sum of each item (score range of each item: 0-3) and the range is from 0 to 36. Higher score indicates poorer general mental health status.
7. ***Zarit Inventory (Zarit, 2008):*** This assessment tool is performed by carers to assess their own burden from giving care to the people with dementia. It consists of 21 general items and 1 overall item. The 21 general items consist of demented participant ask more help than his/her need, do not have enough time for yourself, stress between caring and meeting other responsibilities, feel embarrassed over demented participant's behaviour, feel angry when you around demented participant, feel demented

participant affects your relationship with others, worry the future of demented participant, feel demented participant is dependent on you, feel strained when you are around demented participant, feel health has suffered because of demented participant, do not have privacy because of demented participant, social life has suffered because of demented participant, uncomfortable about having friends over because of demented participant, feel demented participant recognize that you are the only one she/he can depend on, feel you do not have enough money to care demented participant, feel you will be unable to take care of demented participant, feel you have lost control of your life, wish to leave the care of demented participant to others, feel uncertain about what to do about demented participant, feel you should be doing more for demented participant, and feel you could do a better job to care demented participant. Total score is the sum of all general items (score range of each item: 0-4) and the range is from 0 to 84. The score of overall item is from 0 to 4. Higher score indicates higher carer burden.

8. ***Disease-specific Health Related Quality of Life (DEMQOL) (Smith et al., 2007):*** DEMQOL is completed by people with dementia to evaluate their own quality of life. DEMQOL consists of 28 general items in 3 domains including feelings (13 items in this domain: cheerful, worried or anxious, enjoying life, frustrated, confident, full of energy, sad, lonely, distressed, lively, irritable, fed-up, things you want to do but cannot), memory (6 items in this domain: forgetting things happened recently, forgetting people, forgetting day, your thoughts being muddled, difficulty making decisions, poor concentration), everyday life (9 items in this domain: not having enough company, how you get on with people close to you, getting the affection that you want, people not listening to you, making yourself understood, getting help when you need it, getting to the toilet in time, how you feel in yourself, your health overall) and 1 overall item. Total score is the sum of each general item (score range of each item: 1-4) and the range is from 28 to 112. The score of the overall item is from 1 to 4. Higher score indicates better quality of life.
9. ***Disease-specific Health Related Quality of Life proxy (DEMQOL-proxy) (Smith et al., 2007):*** DEMQOL-proxy is done by their carer to assess how they feel the person with dementia would rate their own quality of life. DEMQOL-proxy consists of 31 general items in 3 domains including feelings (11 items in this domain: cheerful, worried or anxious, frustrated, full of energy, sad, content, distressed, lively, irritable, fed-up, he/she has things to look forward), memory (9 items in this domain: memory in general, forgetting things that happened a long time ago, forgetting things that happened recently, forgetting people's names, forgetting where he/she is, forgetting what day it is, his/her thoughts being muddled, difficulty making decisions, making him/herself understood), everyday life (11 items in this domain: keeping him/herself clean, keeping him/herself looking nice, getting what he/she wants from the shops,

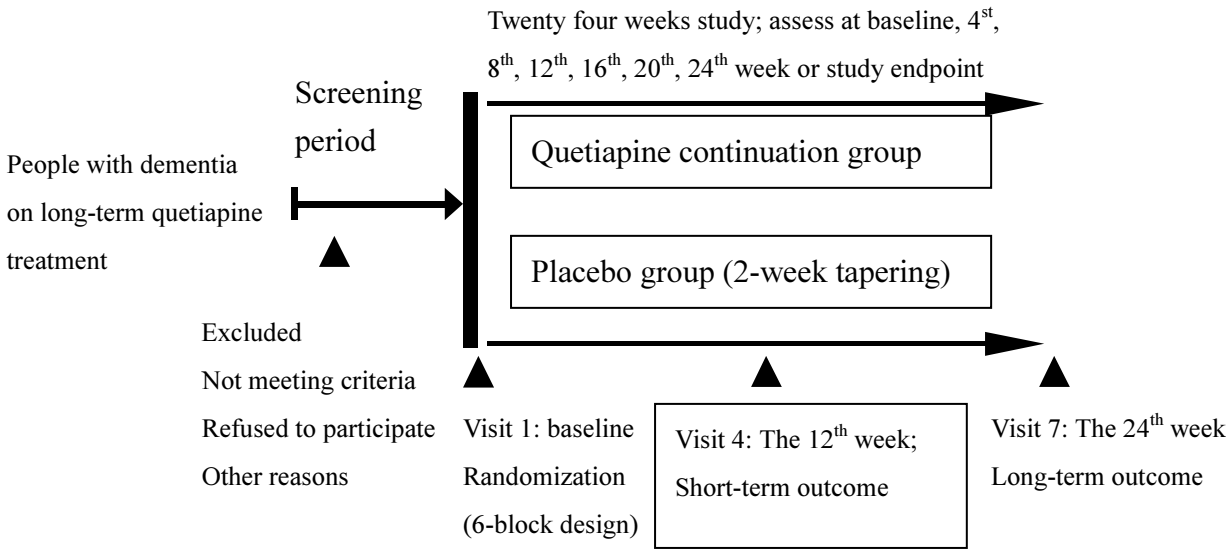
using money to pay for things, looking after his/her finances, things taking longer than they used to, getting in touch with people, not having enough company, not being able to help other people, not playing a useful part in things, his/her physical health) and 1 overall item. Total score is the sum of general item (score range of each item: 1-4) and the range is from 31 to 124. Higher score indicates better quality of life.

10. ***Death:*** Death of study participants will be confirmed by the death certificate.
11. ***Cerebrovascular events:*** New cerebrovascular events will be reported clinically and confirmed by report of brain imaging study.

Study diagram

The study diagram is presented in Figure 1. The diagram accords with the Consolidated Standards for Reporting of Trials (CONSORT) diagram.

Figure 1: Study diagram of quetiapine withdrawal study



Early termination from study

Study researchers will try to complete all assessments of the endpoint visit if participants withdraw from study early and they agree to do all of them. The following conditions are the criteria of study early termination:

1. People with dementia or their carers withdraw consent.
2. Serious adverse events happening for people with dementia such as death, life threatening situations, hospitalization, disability or permanent damage, required intervention to prevent permanent impairment, deliberate self harm, congenital anomaly or birth defect, and other severe adverse events.
3. BPSD severe worsening: The criteria of BPSD severe worsening include NPI total

score increase over 30% than baseline and the score of CGI-C is 6 (much worse) or 7 (very much worse). It accords with the protocol of Devanand et al's dementia antipsychotic withdrawal study (Devanand et al., 2012).

4. Major protocol violation: The situations of major protocol violation include: (i) participants use prohibited medications (ii) loss to follow-up (iii) poor drug adherence during study period (e.g. study medications consume less than 80% or more than 120% of prescription).

Reporting adverse events

All adverse events will be recorded in medical documents and transcribed to case report form. The reporting of adverse events will follow the Good Clinical Practice guidelines of Department of Health of Taiwan (http:// dohlaw.doh.gov.tw/ Chi/ FLAW/ FLAWDAT0201.asp). If death or life threatening situations occur during the study period, these events will be reported to National Reporting System of Adverse Drug Reactions in Taiwan (NRSADRT) within 7 days. Other serious adverse events will be reported to NRSADRT within 15 days. Non-serious adverse events will be compiled in a excel file and reported to NRSADRT every one month. These serious adverse events and non-serious adverse events will also be reported to the Research Ethics Committee of all participating hospitals concurrently.

Besides the differentiation of serious adverse events and non-serious adverse events, all adverse events will be categorized by their intensity (mild, moderate, severe), causality (not related, remote, possibly related, probably related, definitely related) and expectedness (expected and unexpected). The site principal investigator will evaluate all adverse events which happened in his/her study site and categorize them according to seriousness, intensity, causality and expectedness. The definition of seriousness, intensity, causality and expectedness of adverse events will follow the classification of NRSADRT (http:// dohlaw.doh.gov.tw/ Chi/ FLAW/ FLAWDAT0201.asp). We will follow all adverse events until their remission or until week 24.

The training of outcome assessors

Psychologists, psychiatric social workers or psychiatric nurses with at least 1 year of clinical experiences in mental health services will be recruited as study researchers to perform study rating scales at baseline and follow-up. The content and score anchoring methods of these rating scales will be printed out and compiled in a brochure. After the procedures of research staff recruitment, they will receive the following training sessions to qualify their abilities to perform these four rating scales (NPI, MMSE, ESRS, CDSS) of the study.

1. Lecture on rating scales: This training program consists of 12 hours training and will be finished in 2 days. The aim of this lecture series is to let study researchers familiarize these rating scales and ask questions. An old age psychiatrist who is experienced in using these rating scales will be the lecturer.
2. Rating exercise: This training program consists of 12 hours training and will be finished in 2 days. The aim of this exercise is to let study researchers have the chance to practice these rating scales and discussion. Four demented patients and his/her carers will be invited to make four interview videos. Each demented patient and his/her carer will be interviewed by an old age psychiatrist with these four rating scales approximately 2 hours in a video. Each video training program includes 2 hours rating practice and 1 hour discussion. An old age psychiatrist who is experienced in using these rating scales will host this training exercise.
3. Qualification of outcome assessors and inter-rater reliability assessment: This training program is a 6 hours program and will be finished in 1 day. The aim of this assessment is to evaluate the ability of each researcher to use the rating scales accurately and the degree of consistency among different researchers. Another two 2-hour interview videos will be made in advance. The consensus anchoring point for four rating scales in the two videos will be decided by three old age psychiatrists. Then all of the researchers will watch one video and finish their assessments independently in 3 hours and then submit the results of ratings immediately. Another 3 hours will be used to discuss the differences between the results of raters and the consensus anchoring point. The researchers with agreement below 50% in any one of rating scale will need to do another video assessment again until he/she has more than 50% agreement in that rating scale.

The Good Clinical Practice (GCP) training

According to the GCP guidelines of Taiwan (http:// dohlaw.doh.gov.tw/ Chi/ FLAW/ FLAWDAT0201.asp), chief investigator and principal investigator of clinical trial must have the certificate of at least 30 hours of GCP training with at least 9 hours of ethical training in the last 6 years. The other study researchers must have the certificate of at least 6 hours GCP training in the last 6 years. We will make sure whether all of the study personnel fulfill the above criteria. Study personnel who do not fulfill the above mentioned criteria will be asked to get the certificate before study initiation.

Study visit schedule

All study participants and their carers need to visit the study hospital on the scheduled time point to receive various assessments. The time of assessment will be within 3 days of the schedule. The schedule of the each assessment is presented in table 3.

Table 3: Outcome assessment schedule:

	Screen	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24 or study endpoint
Visit	1	2	3	4	5	6	7	8
NPI		*	*	*	*	*	*	*
MMSE	*	*	*	*	*	*	*	*
BADLS		*	*	*	*	*	*	*
CDSS		*	*	*	*	*	*	*
GHQ-12		*	*	*	*	*	*	*
Zarit		*	*	*	*	*	*	*
DEMQOL		*	*	*	*	*	*	*
DEMQOL-proxy		*	*	*	*	*	*	*
ESRS		*	*	*	*	*	*	*
CGI-C			*	*	*	*	*	*
Informed consent	*	*						*
Physical examination	*				*			*
Medical history	*							
Inclusion & exclusion criteria	*							
Demography data	*							
Monitor drugs adherence			*	*	*	*	*	*

Sample size calculation

Our hypothesis is that quetiapine withdrawal group will not have significant BPSD severity worsening and a substantial proportion of participants in the quetiapine withdrawal group will maintain the same mental status as quetiapine continuation group.

Therefore, the proportion of participants maintain the same or have a decrease in the NPI total score in quetiapine withdrawal group will be similar to that of quetiapine maintenance group (equivalent hypothesis testing) after 24 weeks follow-up. Because of the lack of quetiapine withdrawal study at the time of study design, we use the data of other antipsychotics withdrawal study to calculate sample size. Previous studies showed the average proportion of subjects maintain the same or have a decrease in BPSD severity is around 0.7 in the antipsychotic withdrawal group and is around 0.8 in the antipsychotic continuation group (Ballard et al., 2008, Ruths et al., 2008). Therefore, the expected difference between the quetiapine maintenance group and quetiapine withdrawal group is 0.1. We set the equivalence limit difference is 0.15. In situation of 0.05 statistical significant level, 80% power, this study need at least 74 participants. A 20 % dropout rate is expected throughout the study period, therefore this study need to recruit at least 94 intention-to-treat (ITT) participants in total.

Statistical methods

All participants who are randomly assigned will be included in the ITT analysis. If the ITT subjects withdraw from the study earlier than schedule, then the methods of missing data management will be according to the reasons of loss to follow-up. We will lose the information from the participants with loss to follow-up (incomplete cases) and may bias study results if we only analyze the data of study completers. Last observation carried forward (LOCF) methods will be employed to extend endpoint score if loss to follow-up is due to BPSD worsening, intolerable or severe adverse events, or other reasons of treatment failure. In these situations, we will get a conservative estimate because the data at the time point of treatment failure act as the source of imputation. If the reason of loss to follow-up is being considered as independent to the results of the primary outcome (e.g. change living place), the missing values will be recognized as right-censored data or independent censor.

The other reasons of loss to follow-up will use multiple imputation method to impute the missing data. Multiple imputation has the advantage of replacing missing values by possible values which consider the probability of data uncertainty. In general, RCTs have all of the observed data before the time point of early termination but have no data after early termination. This type of missing has been named as a ‘monotone missing data pattern’ (Lavori et al., 1995). Where there is a monotone missing data pattern, regression methods for parametric data which fulfill multivariate normality assumptions (Newgard and Haukoos, 2007). Propensity score methods can be used if the data do not fit normality assumption (Qu and Lipkovich, 2009). Multiple imputation methods are only use in the last resort because they are not always better than other missing data management strategies (White and Carlin, 2010). One of the blinded principal investigators will

categorize all of the incomplete cases into one of the three groups and inform the independent statistician about the results of categorization. Then the independent statistician can perform missing data management in accord with the results of categorization. The data of study completers will be used to perform per-protocol analysis. The results of per-protocol analysis will compare with that of ITT analysis as a sensitivity analysis.

For between group analysis, chi-squared or Fisher's exact tests and independent t-tests will be performed for categorical and continuous data respectively. The comparisons of changes in rating scales from baseline to study endpoints in the quetiapine continuation group and placebo control group will be tested by paired t-tests. A linear mixed model will be used for continuous variables that will be repeatedly measured. We will use Akaike's information criterion (AIC) to compare the log likelihood of different random effect structures (unstructured covariance matrix, first order autoregressive structure and compound symmetric structure) in the linear mixed model. The covariance structure with least AIC value will be chose as the random effect structure (Akaike, 1974). All continuous data will be checked for their degree of skewness and kurtosis to determine whether they fulfill normal distribution assumptions. If normal distribution assumptions are violated and transformations are not possible, then non-parametric methods (Mann Whitney U test or Wilcoxon signed rank test) will be used instead of independent t-tests or paired t-tests for continuous variables. Time to event data will be analyzed by Kaplan-Meier methods with log rank test to evaluate their statistical significance. Hazard ratios of survival data will be estimated by Cox regression analysis. All continuous data will be expressed as means and standard deviations if they meet the criteria of normal distribution. Median and interquartile range will be used if continuous data do not fit normal distribution assumptions. The level of statistically significant differences will be two-sided, $p<0.05$. The data will be analyzed by the version of SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

Anticipated study timeline

The time schedule for this study includes protocol discussion and confirmation, protocol submission to research ethical committee and application for research grant, study participants recruitment, assessment and follow-up, data management and analysis, study report completeness and submission to research ethical committee, trial sponsor and trial funder, and dissemination results of this study by submitting to peer-reviewed journal and reporting in Taiwanese and international academic conferences. The anticipated time schedule is presented in table 4.

Table 4: The anticipated time schedule of this study

	2012/ 09-12	2013/ 01-03	2013/04 ~2014/10	2014/ 10-12	2015/ 01-03	2015/ 04-06
Protocol discussion and confirmation	*					
Research committee evaluation and apply research grant		*				
Subjects recruitment and follow-up			*			
Data management and analysis				*		
Finished study report					*	
Dissemination by submitting to peer-reviewed journal or academic conferences						*

Ethics evaluation, research grant application and trial registration

This research protocol will be submitted to the Research Ethics Committee of all participating Taiwanese hospitals before study initiation. Research funding will be sought from the Department of Health and National Science Council of the Taiwanese government. After the completeness of ethical approval and research funding application, this research protocol will be registered to the clinical trial network of Taiwan (http:// www1.cde.org.tw/ct_taiwan/ index.htm) and the protocol registration system of National Health Institute of USA (http:// prsinfo.clinicaltrials.gov).

Trial Management Group (TMG)

A TMG will be organized to handle all the routine events related to the study. The

composition of the TMG will include the chief investigator as chair, all study investigators, trial statistician, trial manager and a consumer representative. The TMG will meet before the beginning of the trial and every three months thereafter.

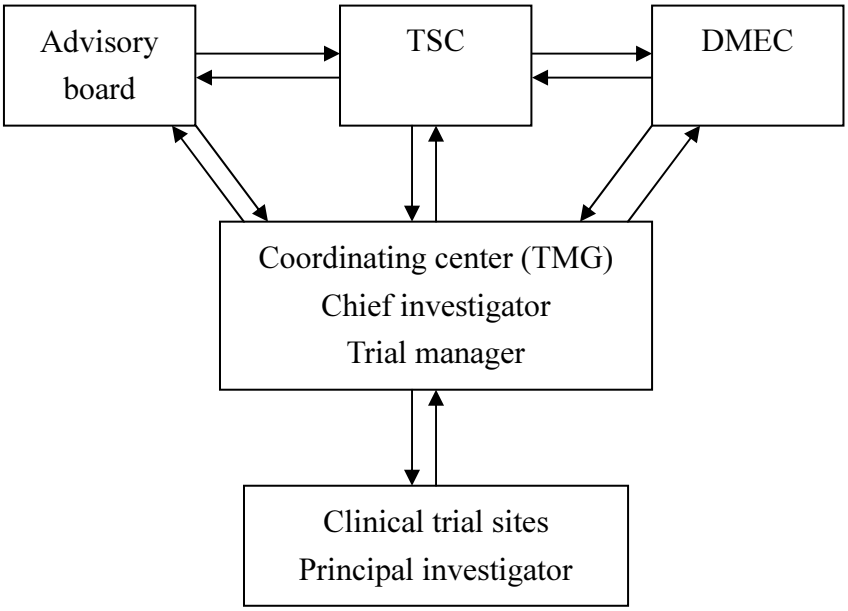
Data monitoring ethics committee (DMEC)

A DMEC will be organized to review unblinded safety data and efficacy data of this trial to protect the rights, well-being and safety of participants. The DMEC may also assess compliance to protocol and quality of data. The composition of the DMEC will include a senior old age psychiatrist as chair, a statistician with trial expertise, a consumer representative and two experienced researchers in the field of dementia. The members of the DMEC will be independent from the research team. The trial manager will collate and provide data to the DMEC. The DEMC will meet before the beginning of the trial and every six months thereafter. The DMEC template will generate a charter in accord with the DAMOCLES template (DAta MOnitoring Committees: Lessons, Ethics, Statistics) (DAMOCLES Group, 2005).

Trial steering committee (TSC)

The role of the TSC will be to provide overall supervision for the trial to ensure that the study is conducted according to the study protocol and GCP guidelines. The TSC will also focus on the progress of the trial, new information related to research question and the safety of trial participants. The composition of the TSC will include an independent chair, a principal investigator from the study team, a consumer representative and two other independent members. Representatives of the trial sponsor and trial funder will be invited to attend the TSC meetings. The TSC will meet before the beginning of this trial and every six months thereafter. The TSC will provide recommendations through the chair to the chief investigator, the trial sponsor and trial funder. The relationship between the research team, the DEMC and the TSC is presented in figure 2.

Figure 2: The relationship between the research team, the DEMC and the TSC.



Discussion

To the best of our knowledge, this will be the first RCT of quetiapine withdrawal in people with dementia. Some other aspects of the study design make it different from previous antipsychotic discontinuation trials and avoid the limitations of previous related studies. The results of this study would provide data to inform clinical practice and public health in people with dementia. This trial data will also be helpful in designing future antipsychotic withdrawal studies in terms of sample size estimation.

Most published studies investigate the withdrawal effects of mixed groups of antipsychotic medications. The results mix the responses to different antipsychotic withdrawal and make it difficult to know the response to a specific medication being withdrawn. Every antipsychotic medication has its own appropriate tapering speed, medication uptake schedule and the maintenance dose in the antipsychotic continuation group due to their different antipsychotic equivalent dose, different receptor profiles and pharmacokinetic properties. Therefore, a single antipsychotic medication design would be more specific and close to the real clinical situation of antipsychotic medication treatment and increase generalizability of the study. Furthermore, quetiapine is a popular medication among the antipsychotics for the people with BPSD but no published studies focus on it. This study will explore the effects of quetiapine withdrawal and should provide useful information for physicians' clinical decision-making.

The participants of most previous antipsychotic withdrawal studies were from Europe or the USA. Although these studies did not report their ethnic composition, it is likely that most of participants were not Asians. Previous psychopharmacological studies have shown different ethnicities may have different responses to antipsychotics compared with Caucasians, especially in terms of side effects (Lin et al., 1995, Lane et al., 1995, Frackiewicz et al., 1997, Matsuda et al., 1996, Citrome and Krakowski, 2009). We expect the majority of participants in this study would be of Han-Chinese ethnicity and so could provide the unique information of quetiapine withdrawal in Chinese or Asian population.

There are few inclusion/exclusion criteria in this study to improve the generalizability. Some of the published articles have many more inclusion/ exclusion criteria and the participants of them highly selected with limited external validity (Devanand et al., 2012). Many small trials (Devanand et al., 2011, Ruths et al., 2008, Ruths et al., 2004) did not perform sample size calculations to estimate their statistical power. They have high probability of inadequate power and type II error. Our study design is based on a power calculation to estimate the appropriate participant numbers for adequate statistical power.

Our study also comprehensively assesses multiple domains of dementia which include severity of BPSD, cognitive function, activity limitation, severity of depressive symptoms, side effects of antipsychotics, death and cerebrovascular events, quality of life of both patients and carers, general health status of carer and carer burden. There were no published articles evaluating the severity of depression for the people with dementia using appropriate rating scales in an antipsychotic withdrawal study. Depressive symptoms are common in people with dementia and can influence their behaviour. Therefore, depressive symptoms should be evaluated to differentiate from the psychotic or agitated symptoms of dementia. This study also uses two clinically meaningful time point to assess the short-term (12 weeks) and long-term (24 weeks) outcome. The Omnibus Budget Reconciliation Act of USA in 1987 (OBRA 87) asked physicians to describe their justification of antipsychotic prescription for people with dementia after 3 months treatment (http:// www. allhealth. org/ briefingmaterials/ obra87 summary -984.pdf). Previous studies also used 6 months to detect the mortality and cerebrovascular events risk difference between antipsychotic users and non-users (Schneider et al., 2005) or among different antipsychotics (Wang et al., 2005, Gill et al., 2005, Schneeweiss et al., 2007).

There are some limitations to this study which need to be considered. First, the generalizability of this study is limited to the people who meet all of the study inclusion and exclusion criteria and receive treatment in teaching hospitals. Furthermore, the majority of study participants are expected to be Han-Chinese ethnicity and the application

to other ethnicities needs further consideration. Second, the quetiapine dose of the quetiapine continuation group is similar to, but not necessarily the same as, their usual treatment dose for the convenience of study design. Therefore, it is likely that the BPSD of some of the participants in the quetiapine continuation group may be influenced by this small dose change. Third, the follow-up duration of this study is 24 weeks. Therefore, the results of this study cannot apply to people with dementia who have more than 24 weeks of quetiapine discontinuation. Fourth, this study does not perform laboratory examinations to prevent unnecessary burden to people with dementia and carer. Therefore, this study cannot provide information about the changes of any biochemical data before and after study.

This study has potentially important implications for clinical practice and public mental health even given the above mentioned limitations. The strengths in the study design include the focus on one commonly used drug, quetiapine, the Han-Chinese ethnicity of the majority of participants, comprehensive evaluation of domains of dementia, few inclusion and exclusion criteria to improve external validity, enough statistical power to detect primary outcome difference and clinically relevant short-term and long-term outcome assessments. Hopefully, this study can highlight the importance of single antipsychotics discontinuation studies for people with dementia on long-term antipsychotic treatment and stimulate other single antipsychotic discontinuation studies in the future. This study can provide meaningful information to help clinicians making clinical decisions and also help governments to plan their national strategy about antipsychotic usage for the people with dementia.

References

AKAIKE, H. 1974. A new look at the statistical model identification. *IEEE Trans,*19: 716-23.

AALTEN, P., VERHEY, F. R., BOZIKI, M., BRUGNOLO, A., BULLOCK, R., BYRNE, E. J., CAMUS, V., CAPUTO, M., COLLINS, D., DE DEYN, P. P., ELINA, K., FRISONI, G., HOLMES, C., HURT, C., MARRIOTT, A., MECOCCI, P., NOBILI, F., OUSSET, P. J., REYNISH, E., SALMON, E., TSOLAKI, M., VELLAS, B. & ROBERT, P. H. 2008. Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer Disease Consortium. Part II.

Dement Geriatr Cogn Disord, 25**,** 1-8.

ALEXOPOULOS, G. S., ABRAMS, R. C., YOUNG, R. C. & SHAMOIAN, C. A. 1988. Cornell Scale for Depression in Dementia. *Biol Psychiatry,* 23**,** 271-84.

AZERMAI, M., ELSEVIERS, M., PETROVIC, M., VAN BORTEL, L. & STICHELE, R. V. 2011. Assessment of antipsychotic prescribing in Belgian nursing homes. *International psychogeriatrics / IPA,* 23**,** 1240-8.

BALLARD, C. & CORBETT, A. 2010. Management of neuropsychiatric symptoms in people with dementia. *CNS Drugs,* 24**,** 729-39.

BALLARD, C., HANNEY, M. L., THEODOULOU, M., DOUGLAS, S., MCSHANE, R., KOSSAKOWSKI, K., GILL, R., JUSZCZAK, E., YU, L. M. & JACOBY, R. 2009. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol,* 8**,** 151-7.

BALLARD, C., LANA, M. M., THEODOULOU, M., DOUGLAS, S., MCSHANE, R., JACOBY, R., KOSSAKOWSKI, K., YU, L. M. & JUSZCZAK, E. 2008. A randomised, blinded, placebo-controlled trial in dementia patients continuing or stopping neuroleptics (the DART-AD trial). *PLoS Med,* 5**,** e76.

BALLARD, C., MARGALLO-LANA, M., JUSZCZAK, E., DOUGLAS, S., SWANN, A., THOMAS, A., O'BRIEN, J., EVERRATT, A., SADLER, S., MADDISON, C., LEE, L., BANNISTER, C., ELVISH, R. & JACOBY, R. 2005. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ,* 330**,** 874.

BALLARD, C. & WAITE, J. 2006. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst Rev***,** CD003476.

BALLARD, C. G., THOMAS, A., FOSSEY, J., LEE, L., JACOBY, R., LANA, M. M., BANNISTER, C., MCSHANE, R., SWANN, A., JUSZCZAK, E. & O'BRIEN, J. T. 2004. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. *J Clin Psychiatry,* 65**,** 114-9.

BANERJEE, S. 2009. The use of antipsychotic medication for people with dementia: Time for action. *Department of Health*.

BERGH, S. & ENGEDAL, K. 2008. The withdrawal of antipsychotics and antidepressants from patients with dementia and BPSD living in nursing homes: an open pilot study. *Int J Geriatr Psychiatry,* 23**,** 877-9.

BIRKS, J. 2006. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev***,** CD005593.

BRIDGES-PARLET, S., KNOPMAN, D. & STEFFES, S. 1997. Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double-blind, baseline-treatment-controlled pilot study. *J Geriatr Psychiatry*

Neurol, 10**,** 119-26.

BROOKMEYER, R., JOHNSON, E., ZIEGLER-GRAHAM, K. & ARRIGHI, H. M. 2007. Forecasting the global burden of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association,* 3**,** 186-91.

BUCKS, R. S., ASHWORTH, D. L., WILCOCK, G. K. & SIEGFRIED, K. 1996. Assessment of activities of daily living in dementia: development of the Bristol Activities of Daily Living Scale. *Age Ageing,* 25**,** 113-20.

CALIGIURI, M. R., JESTE, D. V. & LACRO, J. P. 2000. Antipsychotic-Induced movement disorders in the elderly: epidemiology and treatment recommendations. *Drugs & aging,* 17**,** 363-84.

CHEN, J. J. & CHAN, H. Y. 2010. A Cross-sectional Psychotropic Drugs Utilization Study for Patients with Dementia. *49th Annual meeting of Taiwanese Society of Psychiatry*.

CHOUINARD, G. & MARGOLESE, H. C. 2005. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophr Res,* 76**,** 247-65.

CITROME, L. & KRAKOWSKI, M. 2009. The impact of ethnicity on metabolic outcomes during treatment with antipsychotics: complexities abound. *The Journal of clinical psychiatry,* 70**,** 1608-9.

COHEN-MANSFIELD, J., LIPSON, S., WERNER, P., BILLIG, N., TAYLOR, L. & WOOSLEY, R. 1999. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. *Arch Intern Med,* 159**,** 1733-40.

CORBETT, A., SMITH, J., CREESE, B. & BALLARD, C. 2012. Treatment of Behavioral and Psychological Symptoms of Alzheimer's Disease. *Curr Treat Options Neurol*.

CORNEGE-BLOKLAND, E., KLEIJER, B. C., HERTOGH, C. M. & VAN MARUM, R. J. 2012. Reasons to prescribe antipsychotics for the behavioral symptoms of dementia: a survey in Dutch nursing homes among physicians, nurses, and family caregivers. *Journal of the American Medical Directors Association,* 13**,** 80 e1-6.

CORRADA, M. M., BROOKMEYER, R., BERLAU, D., PAGANINI-HILL, A. & KAWAS, C. H. 2008. Prevalence of dementia after age 90: results from the 90+ study. *Neurology,* 71**,** 337-43.

CROTTY, M., WHITEHEAD, C., ROWETT, D., HALBERT, J., WELLER, D., FINUCANE, P. & ESTERMAN, A. 2004. An outreach intervention to implement evidence based practice in residential care: a randomized controlled trial [ISRCTN67855475]. *BMC Health Serv Res,* 4**,** 6.

CUMMINGS, J. L., MEGA, M., GRAY, K., ROSENBERG-THOMPSON, S., CARUSI, D. A. & GORNBEIN, J. 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology,* 44**,** 2308-14.

DEVANAND, D. P., MINTZER, J., SCHULTZ, S., SULTZER, D., DE LA PENA, D., GUPTA, S., COLON, S., SCHIMMING, C., PELTON, G. H., ANDREWS, H. &

LEVIN, B. 2012. The antipsychotic discontinuation in Alzheimer disease trial: clinical rationale and study design. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry,* 20**,** 362-73.

DEVANAND, D. P., PELTON, G. H., CUNQUEIRO, K., SACKEIM, H. A. & MARDER, K. 2011. A 6-month, randomized, double-blind, placebo-controlled pilot discontinuation trial following response to haloperidol treatment of psychosis and agitation in Alzheimer's disease. *International journal of geriatric psychiatry,* 26**,** 937-43.

DIJK, D. J. 2010. Slow-wave sleep deficiency and enhancement: implications for insomnia and its management. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry,* 11 Suppl 1**,** 22-8.

DAMOCLES GROUP, D. S. 2005. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet,* 365**,** 711-22.

FERRI, C. P., PRINCE, M., BRAYNE, C., BRODATY, H., FRATIGLIONI, L., GANGULI, M., HALL, K., HASEGAWA, K., HENDRIE, H., HUANG, Y., JORM, A., MATHERS, C., MENEZES, P. R., RIMMER, E. & SCAZUFCA, M. 2005. Global prevalence of dementia: a Delphi consensus study. *Lancet,* 366**,** 2112-7.

FINDLAY, D. J., SHARMA, J., MCEWEN, J., BALLINGER, B. R., MACLENNAN, W. J. & MCHARG, A. M. 1989. Double-blind controlled withdrawal of thioridazine treatment in elederly female inpatients with senile dementia. *International Journal of Geriatric Psychiatry,* 4**,** 115-120.

FORSETLUND, L., EIKE, M. C., GJERBERG, E. & VIST, G. E. 2011. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. *BMC Geriatr,* 11**,** 16.

FRACKIEWICZ, E. J., SRAMEK, J. J., HERRERA, J. M., KURTZ, N. M. & CUTLER, N. R. 1997. Ethnicity and antipsychotic response. *The Annals of pharmacotherapy,* 31**,** 1360-9.

FUH, J. L. & WANG, S. J. 2008. Dementia in Taiwan: past, present, and future. *Acta Neurol Taiwan,* 17**,** 153-61.

GARCIA-GOLLARTE, F., BALERIOLA-JULVEZ, J., FERRERO-LOPEZ, I. & CRUZ-JENTOFT, A. J. 2012. Inappropriate drug prescription at nursing home admission. *Journal of the American Medical Directors Association,* 13**,** 83 e9-15.

GILL, S. S., BRONSKILL, S. E., NORMAND, S. L., ANDERSON, G. M., SYKORA, K., LAM, K., BELL, C. M., LEE, P. E., FISCHER, H. D., HERRMANN, N., GURWITZ, J. H. & ROCHON, P. A. 2007. Antipsychotic drug use and mortality in older adults with dementia. *Annals of internal medicine,* 146**,** 775-86.

GILL, S. S., ROCHON, P. A., HERRMANN, N., LEE, P. E., SYKORA, K., GUNRAJ, N., NORMAND, S. L., GURWITZ, J. H., MARRAS, C., WODCHIS, W. P. &

MAMDANI, M. 2005. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *BMJ,* 330**,** 445.

GOLDBERG, D. P., GATER, R., SARTORIUS, N., USTUN, T. B., PICCINELLI, M., GUREJE, O. & RUTTER, C. 1997. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. *Psychol Med,* 27**,** 191-7.

HORWITZ, G. J., TARIOT, P. N., MEAD, K. & COX, C. 1995. Discontinuation of antipsychotics in nursing home patients with dementia. *Am J Geriatr Psychiatry,* 3**,** 290-299.

HUANG, A. R., MALLET, L., ROCHEFORT, C. M., EGUALE, T., BUCKERIDGE, D. L. & TAMBLYN, R. 2012. Medication-related falls in the elderly: causative factors and preventive strategies. *Drugs & aging,* 29**,** 359-76.

HUBER, M., KOLZSCH, M., RAPP, M. A., WULFF, I., KALINOWSKI, S., BOLBRINKER, J., HOFMANN, W., SCHOLZE, J., DRAGER, D. & KREUTZ, R. 2012. Antipsychotic Drugs Predominate in Pharmacotherapy of Nursing Home Residents with Dementia. *Pharmacopsychiatry*.

HUTTUNEN, M. 1995. The evolution of the serotonin-dopamine antagonist concept. *Journal of clinical psychopharmacology,* 15**,** 4S-10S.

HUYBRECHTS, K. F., GERHARD, T., CRYSTAL, S., OLFSON, M., AVORN, J., LEVIN, R., LUCAS, J. A. & SCHNEEWEISS, S. 2012. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ,* 344**,** e977.

JANKOVIC, S. M. & DOSTIC, M. 2012. Choice of antiepileptic drugs for the elderly: possible drug interactions and adverse effects. *Expert opinion on drug metabolism & toxicology,* 8**,** 81-91.

JHOO, J. H., KIM, K. W., HUH, Y., LEE, S. B., PARK, J. H., LEE, J. J., CHOI, E. A., HAN, C., CHOO, I. H., YOUN, J. C., LEE, D. Y. & WOO, J. I. 2008. Prevalence of dementia and its subtypes in an elderly urban korean population: results from the Korean Longitudinal Study on Health And Aging (KLoSHA). *Dementia and geriatric cognitive disorders,* 26**,** 270-6.

KLEIJER, B. C., VAN MARUM, R. J., EGBERTS, A. C., JANSEN, P. A., FRIJTERS, D., HEERDINK, E. R. & RIBBE, M. 2009. The course of behavioral problems in elderly nursing home patients with dementia when treated with antipsychotics. *Int Psychogeriatr,* 21**,** 931-40.

LANE, H. Y., CHANG, Y. C., SU, M. H., CHIU, C. C., HUANG, M. C. & CHANG, W. H. 2002. Shifting from haloperidol to risperidone for behavioral disturbances in dementia: safety, response predictors, and mood effects. *J Clin Psychopharmacol,* 22**,** 4-10.

LANE, H. Y., LIN, H. N., HWU, H. G., JANN, M., HU, W. H. & CHANG, W. H. 1995. Haloperidol plasma concentrations in Taiwanese psychiatric patients. *Journal of*

the Formosan Medical Association = Taiwan yi zhi, 94**,** 671-8.

LANGE-ASSCHENFELDT, C., GROHMANN, R., LANGE-ASSCHENFELDT, B., ENGEL, R. R., RUTHER, E. & CORDES, J. 2009. Cutaneous adverse reactions to psychotropic drugs: data from a multicenter surveillance program. *The Journal of clinical psychiatry,* 70**,** 1258-65.

LAVORI, P. W., DAWSON, R. & SHERA, D. 1995. A multiple imputation strategy for clinical trials with truncation of patient data. *Statistics in medicine,* 14**,** 1913-25.

LAWLOR, B. A. 2004. Behavioral and psychological symptoms in dementia: the role of atypical antipsychotics. *The Journal of clinical psychiatry,* 65 Suppl 11**,** 5-10.

LIEBERMAN, J. A. 2004. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs,* 18**,** 251-67.

LIN, K. M., ANDERSON, D. & POLAND, R. E. 1995. Ethnicity and psychopharmacology. Bridging the gap. *The Psychiatric clinics of North America,* 18**,** 635-47.

LONERGAN, E. & LUXENBERG, J. 2009. Valproate preparations for agitation in dementia. *Cochrane Database Syst Rev***,** CD003945.

MARGALLO-LANA, M., SWANN, A., O'BRIEN, J., FAIRBAIRN, A., REICHELT, K., POTKINS, D., MYNT, P. & BALLARD, C. 2001. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *Int J Geriatr Psychiatry,* 16**,** 39-44.

MATSUDA, K. T., CHO, M. C., LIN, K. M., SMITH, M. W., YOUNG, A. S. & ADAMS, J. A. 1996. Clozapine dosage, serum levels, efficacy, and side-effect profiles: a comparison of Korean-American and Caucasian patients. *Psychopharmacology bulletin,* 32**,** 253-7.

MEADOR, K. G., TAYLOR, J. A., THAPA, P. B., FOUGHT, R. L. & RAY, W. A. 1997. Predictors of antipsychotic withdrawal or dose reduction in a randomized controlled trial of provider education. *J Am Geriatr Soc,* 45**,** 207-10.

MOLLOY, D. W., ALEMAYEHU, E. & ROBERTS, R. 1991. Reliability of a Standardized Mini-Mental State Examination compared with the traditional Mini-Mental State Examination. *Am J Psychiatry,* 148**,** 102-5.

MUSENGA, A., SARACINO, M. A., SANI, G. & RAGGI, M. A. 2009. Antipsychotic and antiepileptic drugs in bipolar disorder: the importance of therapeutic drug monitoring. *Current medicinal chemistry,* 16**,** 1463-81.

NEWGARD, C. D. & HAUKOOS, J. S. 2007. Advanced statistics: missing data in clinical research--part 2: multiple imputation. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine,* 14**,** 669-78.

NORD, M. & FARDE, L. 2011. Antipsychotic occupancy of dopamine receptors in schizophrenia. *CNS neuroscience & therapeutics,* 17**,** 97-103.

PATTERSON, S. M., HUGHES, C. M., CREALEY, G., CARDWELL, C. & LAPANE, K. L. 2010. An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern ireland (fleetwood northern ireland study). *J Am Geriatr Soc,* 58**,** 44-53.

PLASSMAN, B. L., LANGA, K. M., FISHER, G. G., HEERINGA, S. G., WEIR, D. R., OFSTEDAL, M. B., BURKE, J. R., HURD, M. D., POTTER, G. G., RODGERS, W. L., STEFFENS, D. C., WILLIS, R. J. & WALLACE, R. B. 2007. Prevalence of dementia in the United States: the aging, demographics, and memory study. *Neuroepidemiology,* 29**,** 125-32.

QU, Y. & LIPKOVICH, I. 2009. Propensity score estimation with missing values using a multiple imputation missingness pattern (MIMP) approach. *Statistics in medicine,* 28**,** 1402-14.

REJ, S., HERRMANN, N. & SHULMAN, K. 2012. The effects of lithium on renal function in older adults--a systematic review. *Journal of geriatric psychiatry and neurology,* 25**,** 51-61.

RICHTER, T., MANN, E., MEYER, G., HAASTERT, B. & KOPKE, S. 2012. Prevalence of psychotropic medication use among German and Austrian nursing home residents: a comparison of 3 cohorts. *Journal of the American Medical Directors Association,* 13**,** 187 e7-187 e13.

ROCHON, P. A., STUKEL, T. A., BRONSKILL, S. E., GOMES, T., SYKORA, K., WODCHIS, W. P., HILLMER, M., KOPP, A., GURWITZ, J. H. & ANDERSON, G. M. 2007. Variation in nursing home antipsychotic prescribing rates. *Arch Intern Med,* 167**,** 676-83.

ROLLAND, Y., ANDRIEU, S., CROCHARD, A., GONI, S., HEIN, C. & VELLAS, B. 2012. Psychotropic drug consumption at admission and discharge of nursing home residents. *Journal of the American Medical Directors Association,* 13**,** 407 e7-407 e12.

ROVNER, B. W., STEELE, C. D., SHMUELY, Y. & FOLSTEIN, M. F. 1996. A randomized trial of dementia care in nursing homes. *J Am Geriatr Soc,* 44**,** 7-13.

RUMMEL-KLUGE, C., KOMOSSA, K., SCHWARZ, S., HUNGER, H., SCHMID, F., KISSLING, W., DAVIS, J. M. & LEUCHT, S. 2012. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophrenia bulletin,* 38**,** 167-77.

RUTHS, S., STRAAND, J., NYGAARD, H. A. & AARSLAND, D. 2008. Stopping antipsychotic drug therapy in demented nursing home patients: a randomized, placebo-controlled study--the Bergen District Nursing Home Study (BEDNURS). *Int J Geriatr Psychiatry,* 23**,** 889-95.

RUTHS, S., STRAAND, J., NYGAARD, H. A., BJORVATN, B. & PALLESEN, S. 2004. Effect of antipsychotic withdrawal on behavior and sleep/wake activity in nursing

home residents with dementia: a randomized, placebo-controlled, double-blinded study. The Bergen District Nursing Home Study. *J Am Geriatr Soc,* 52**,** 1737-43.

SADOCK, B. J., SADOCK, V.A. 2007. Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry, 10th Edition.

SAVVA, G. M., ZACCAI, J., MATTHEWS, F. E., DAVIDSON, J. E., MCKEITH, I. & BRAYNE, C. 2009. Prevalence, correlates and course of behavioural and psychological symptoms of dementia in the population. *Br J Psychiatry,* 194**,** 212-9.

SCHNEEWEISS, S., SETOGUCHI, S., BROOKHART, A., DORMUTH, C. & WANG, P. S. 2007. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. *CMAJ,* 176**,** 627-32.

SCHNEIDER, L. S., DAGERMAN, K. & INSEL, P. S. 2006a. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. *Am J Geriatr Psychiatry,* 14**,** 191-210.

SCHNEIDER, L. S., DAGERMAN, K. S. & INSEL, P. 2005. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA,* 294**,** 1934-43.

SCHNEIDER, L. S., OLIN, J. T., DOODY, R. S., CLARK, C. M., MORRIS, J. C., REISBERG, B., SCHMITT, F. A., GRUNDMAN, M., THOMAS, R. G. & FERRIS, S. H. 1997. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord,* 11 Suppl 2**,** S22-32.

SCHNEIDER, L. S., TARIOT, P. N., DAGERMAN, K. S., DAVIS, S. M., HSIAO, J. K., ISMAIL, M. S., LEBOWITZ, B. D., LYKETSOS, C. G., RYAN, J. M., STROUP, T. S., SULTZER, D. L., WEINTRAUB, D. & LIEBERMAN, J. A. 2006b. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med,* 355**,** 1525-38.

SEEMAN, P. 2002. Atypical antipsychotics: mechanism of action. *Canadian journal of psychiatry. Revue canadienne de psychiatrie,* 47**,** 27-38.

SEITZ, D. P., ADUNURI, N., GILL, S. S., GRUNEIR, A., HERRMANN, N. & ROCHON, P. 2011. Antidepressants for agitation and psychosis in dementia. *Cochrane Database Syst Rev***,** CD008191.

SHAH, A. 2006. Can risperidone and olanzapine in elderly patients with dementia and other mental disorders be discontinued? *International journal of geriatric psychiatry,* 21**,** 140-6.

SHAH, S. M., CAREY, I. M., HARRIS, T., DEWILDE, S. & COOK, D. G. 2011. Antipsychotic prescribing to older people living in care homes and the community in England and Wales. *International journal of geriatric psychiatry,* 26**,** 423-34.

SMITH, S. C., LAMPING, D. L., BANERJEE, S., HARWOOD, R. H., FOLEY, B.,

SMITH, P., COOK, J. C., MURRAY, J., PRINCE, M., LEVIN, E., MANN, A. & KNAPP, M. 2007. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. *Psychol Med,* 37**,** 737-46.

SPERING, C. C., HOBSON, V., LUCAS, J. A., MENON, C. V., HALL, J. R. & O'BRYANT, S. E. 2012. Diagnostic Accuracy of the MMSE in Detecting Probable and Possible Alzheimer's Disease in Ethnically Diverse Highly Educated Individuals: An Analysis of the NACC Database. *The journals of gerontology. Series A, Biological sciences and medical sciences*.

SULTZER, D. L., DAVIS, S. M., TARIOT, P. N., DAGERMAN, K. S., LEBOWITZ, B. D., LYKETSOS, C. G., ROSENHECK, R. A., HSIAO, J. K., LIEBERMAN, J. A. & SCHNEIDER, L. S. 2008. Clinical symptom responses to atypical antipsychotic medications in Alzheimer's disease: phase 1 outcomes from the CATIE-AD effectiveness trial. *Am J Psychiatry,* 165**,** 844-54.

SYLVESTRE, M. P., ABRAHAMOWICZ, M., CAPEK, R. & TAMBLYN, R. 2011. Assessing the cumulative effects of exposure to selected benzodiazepines on the risk of fall-related injuries in the elderly. *International psychogeriatrics / IPA***,** 1-10.

TAN, L. L., WONG, H. B. & ALLEN, H. 2005. The impact of neuropsychiatric symptoms of dementia on distress in family and professional caregivers in Singapore. *Int Psychogeriatr,* 17**,** 253-63.

TESTAD, I., BALLARD, C., BRONNICK, K. & AARSLAND, D. 2010. The effect of staff training on agitation and use of restraint in nursing home residents with dementia: a single-blind, randomized controlled trial. *J Clin Psychiatry,* 71**,** 80-6.

THAPA, P. B., MEADOR, K. G., GIDEON, P., FOUGHT, R. L. & RAY, W. A. 1994. Effects of antipsychotic withdrawal in elderly nursing home residents. *J Am Geriatr Soc,* 42**,** 280-6.

TUNIS, S. L., EDELL, W. S., ADAMS, B. E. & KENNEDY, J. S. 2002. Characterizing behavioral and psychological symptoms of dementia (BPSD) among geropsychiatric inpatients. *J Am Med Dir Assoc,* 3**,** 146-51.

UCHIDA, H., TAKEUCHI, H., GRAFF-GUERRERO, A., SUZUKI, T., WATANABE, K. & MAMO, D. C. 2011. Dopamine D2 receptor occupancy and clinical effects: a systematic review and pooled analysis. *Journal of clinical psychopharmacology,* 31**,** 497-502.

VAN REEKUM, R., CLARKE, D., CONN, D., HERRMANN, N., ERYAVEC, G., COHEN, T. & OSTRANDER, L. 2002. A randomized, placebo-controlled trial of the discontinuation of long-term antipsychotics in dementia. *Int Psychogeriatr,* 14**,** 197-210.

WANG, P. S., SCHNEEWEISS, S., AVORN, J., FISCHER, M. A., MOGUN, H., SOLOMON, D. H. & BROOKHART, M. A. 2005. Risk of death in elderly users of

conventional vs. atypical antipsychotic medications. *N Engl J Med,* 353**,** 2335-41.

WESTERINK, B. H. 2002. Can antipsychotic drugs be classified by their effects on a particular group of dopamine neurons in the brain? *European journal of pharmacology,* 455**,** 1-18.

WHITE, I. R. & CARLIN, J. B. 2010. Bias and efficiency of multiple imputation compared with complete-case analysis for missing covariate values. *Statistics in medicine,* 29**,** 2920-31.

WILSON, K. C. & SAUKKONEN, J. J. 2004. Acute respiratory failure from abused substances. *Journal of intensive care medicine,* 19**,** 183-93.

WILSON, M. P., PEPPER, D., CURRIER, G. W., HOLLOMAN, G. H., JR. & FEIFEL, D. 2012. The psychopharmacology of agitation: consensus statement of the american association for emergency psychiatry project Beta psychopharmacology workgroup. *The western journal of emergency medicine,* 13**,** 26-34.

WIMO, A., WINBLAD, B. & JONSSON, L. 2010. The worldwide societal costs of dementia: Estimates for 2009. *Alzheimers Dement,* 6**,** 98-103.

WORLD HEALTH ORGANIZATION. 2004. The global burden of disease: 2004 update. 2004 http://www.who.int/entity/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.

YANG, C. H., TSAI, S. J. & HWANG, J. P. 2005. The efficacy and safety of quetiapine for treatment of geriatric psychosis. *J Psychopharmacol,* 19**,** 661-6.

ZARIT, S. H. 2008. Diagnosis and management of caregiver burden in dementia. *Handb Clin Neurol,* 89**,** 101-6.

Appendixes

Appendix 1: Search strategies for randomized controlled studies

Source searched	Platform	Search strategy
Medline	Ovid SP	1. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*) 2. Antipsychotic Agents: MESH 3. antipsychotic* 4. neuroleptic* 5. phenothiazines 6. butyrophenones 7. (risperidone or olanzapine or haloperidolor prothipendyl or methotrimeprazine or clopenthixol or flupenthixol or clothiapine or metylperon or droperidol or pipamperone or benperidol or bromperidol or fluspirilene or pimozide or penfluridol or sulpiride or veralipride or levosulpiride or sultopride or aripiprazole or clozapine or quetiapine or thioridazine) 8. #2 or #3 or #4 or #5 or #6 or #7 9. #1 and #8 10. Dementia: MESH 11. Dementia, Vascular: MESH 12. Dementia, Multi-Infarct: MESH 13. Delirium, Dementia, Amnestic, Cognitive Disorders: MESH 14. Alzheimer Disease: MESH 15. LewyBodyDisease: MESH 16. #10 or #11 or #12 or #13 or #14 or #15 17. dement*.mp. 18. Alzheimer*.mp. 19. (lewy* and bod*).mp. 20. deliri*.mp. 21. ((cognit* or memory* or mental*)and (decline* or impair* or los* or deteriorat*)).mp 22. (chronic and cerebrovascular).mp. 23. (“organic brain syndrome” or “organic brain disease”).mp 24. “supra nuclear palsy”.mp. 25. (cerebr* and deteriorate*).mp. 26. (cerebra* and insufficient*).mp.
		27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28. nursing homes: MESH

		29. intermediate care facilities: MESH 30. geriatric nursing: MESH 31. 28 or 29 or 30 32.16 or 27 or 31 33. 9 and 32 34. randomized controlled trial.pt. 35. controlled clinical trial.pt. 36. randomized.ab. 37. placebo.ab. 38. drug therapy.fs. 39. randomly.ab. 40. trial.ab. 41. groups.ab. 42. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 43. humans.sh. 44. 42 and 43 45. HIV*.ti. 46. 44 not 45 47. diabet*.ti. 48. 46 not 47 49. heart.ti. 50. 48 not 49 51. epilep*.ti. 52. 50 not 51 53. schizo*.ti. 54. 52 not 53 55. child*.ti. 56. 54 not 55 57. 33 and 56

Appendix 2: Search strategies for observational studies

Source searched	Platform	Search strategy
Medline	Ovid SP	1. (discontinu* or withdraw* or cessat* or reduce* or reducing or reduct* or taper* or stop*) 2. Antipsychotic Agents: MESH 3. antipsychotic* 4. neuroleptic* 5. phenothiazines 6. butyrophenones 7. (risperidone or olanzapine or haloperidolor prothipendyl or methotrimeprazine or clopenthixol or flupenthixol or clothiapine or metylperon or droperidol or pipamperone or benperidol or bromperidol or fluspirilene or pimozide or penfluridol or sulpiride or veralipride or levosulpiride or sultopride or aripiprazole or clozapine or quetiapine or thioridazine) 8. #2 or #3 or #4 or #5 or #6 or #7 9. #1 and #8 10. Dementia: MESH 11. Dementia, Vascular: MESH 12. Dementia, Multi-Infarct: MESH 13. Delirium, Dementia, Amnestic, Cognitive Disorders: MESH 14. Alzheimer Disease: MESH 15. LewyBodyDisease: MESH 16. #10 or #11 or #12 or #13 or #14 or #15 17. dement*.mp. 18. Alzheimer*.mp. 19. (lewy* and bod*).mp. 20. deliri*.mp. 21. ((cognit* or memory* or mental*)and (decline* or impair* or los* or deteriorat*)).mp 22. (chronic and cerebrovascular).mp. 23. (“organic brain syndrome” or “organic brain disease”).mp 24. “supra nuclear palsy”.mp. 25. (cerebr* and deteriorate*).mp. 26. (cerebra* and insufficient*).mp.
		27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 28. nursing homes: MESH 29. intermediate care facilities: MESH

		30. geriatric nursing: MESH 31. 28 or 29 or 30 32.16 or 27 or 31 33. 9 and 32 34. observational study.mp. 35. non randomi* study.mp. 36. observational.ab. 37. non randomi*.ab. 38. cohort.ab. 39. prospective.ab. 40. case-control.ab. 41. retrospective.ab. 42. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 43. humans.sh. 44. 42 and 43 45. HIV*.ti. 46. 44 not 45 47. diabet*.ti. 48. 46 not 47 49. heart.ti. 50. 48 not 49 51. epilep*.ti. 52. 50 not 51 53. schizo*.ti. 54. 52 not 53 55. child*.ti. 56. 54 not 55 57. 33 and 56

Appendix 3: Information sheet for patient

Patient Number: Carer Number:

Site Number: Initials of Site Principal Investigator:

PATIENT INFORMATION SHEET

Withdraw study for patients with dementia on long-term quetiapine treatment: a multi-centre, randomized, double-blind, placebo controlled study

We invite you to participate in a study. This information sheet is to explain the study and what will you do during the study if you decided to participate. It is important for you to understand the purpose of this study. Please read this information sheet carefully.

Section one tells you why this study is being done and what it will involve if you participate.
Section two provides you detailed information about this study.

If you are unclear to the information of this study, you can ask the research team members. You are free to discuss with others about the study. Please take your time to make your decision whether you would like to participate in this study.

Section one

What is this study?

We are trying to figure out the benefits and risks of quetiapine withdrawal in patients with dementia on more than 3 months of quetiapine treatment. Patients with dementia frequently have behavioural or psychiatric symptoms such as delusions, disturbing behaviours, agitation and aggressive symptoms. The non-pharmacological management usually is the first line in dealing with these symptoms. If these symptoms are still prominent after non-pharmacological interventions, then pharmacological interventions can consider and antipsychotics are the most popular medications for this situation. However, antipsychotics may increase the risks of mortality and cerebrovascular adverse events in dementia population. Therefore, most of guidelines suggest antipsychotics only use for short-term and need assess the benefits and risks of them regularly.

Quetiapine is one of the antipsychotics and popularly being prescribed for patients with dementia. Quetiapine acts on one of the chemicals, dopamine, in the brain, which tends to be high in people with dementia and psychotic symptoms. Previous studies have shown around two thirds of patients with dementia can withdraw from other antipsychotics successfully and get benefit from fewer adverse drug reactions. However, there were no studies to investigate the benefits and risks of quetiapine withdrawal. Therefore, it is an important issue to understand whether patients can get benefit from quetiapine withdrawal.

Why have I been chosen?

Your doctor believes that you are a patient with dementia on quetiapine treatment over 3 months that this study is sought for. With your permission, your doctor has referred you to this study.

Do I have to join?

No. It completely depends on you. No matter what is your decision, your current treatment and social benefits will not be affected. Even if you agree to participate, you can withdraw your consent at any moment during the study period and you do not need to provide any reason.

What will happen to me if I participate?

The study lasts for 6 months. We will usually make 7 visits to see you and your carer. The definition of carer is the person who knows you well and cares you (usually a close relative). The visits will take place at your treatment hospital, unless another venue is more convenient for you both. The researcher will spend about an hour with each of you during these visits. Every time when we visit you, the researcher will discuss with you about your conditions. Besides talking to you, the researcher will also discuss with your carer.

The first meeting will include an assessment of your mental status and your physical condition, made by a member of the research team. If you fulfill all of the study criteria, then the research team member will discuss with you whether you agree to participate in this study.

You will be allocated randomly to one of two groups – one group will uptake placebo and withdraw your previous quetiapine. The period of tapering will be up to 2 weeks which is

according to your previous quetaipine dose; another group will maintain your previous quetiapine treatment. The meaning of placebo is it looks like a real medicine but it does not contain the active ingredient of the medicine. Therefore, we can compare the effects of quetiapine withdrawal and quetiapine maintenance. The chance of being allocated to quetiapine withdrawal and quetiapine maintenance group will be equal.

We suppose that a substantial proportion of people with dementia on more than 3 months of quetiapine treatment can get benefit from quetiapine cessation. However, there were no clinical studies to support this hypothesis. Therefore, it is the research question that this study will investigate.

You will take one tablet in the night before your sleep through the whole 24-week study period. Both you and the research members will not know whether you are taking a placebo or a quetiapine tablet until the end of the trial, although your doctor can find out if he needed to know due to an emergency.

What are the possible benefits of taking part?

Although we suppose that a substantial proportion of people with dementia on more than 3 months of quetiapine treatment can get benefit from quetiapine cessation, we cannot promise that the study will help you. However, the information you provide us may help the people with dementia who also receive quetiapine treatment. It is possible that some patients get benefit from the different treatments of the study. The studies findings will help doctors to know which treatment is a better choice. Except the travel expenses, there will be no payment or reimbursements for participating in this study.

What are the potential disadvantages and risks of taking part?

Some of the people with dementia on long-term quetiapine treatment may appear their previous psychiatric or behavioural symptoms if they discontinue quetiapine treatment. Most of the people with symptoms worsening after quetiapine withdrawal can improve quickly while quetiapine restore. If you appear psychiatric symptoms or behavioural symptoms worsening during the study period, this should be discussed with the research team members.

It is possible that you may experience emotional distress during or after discussions with the research team members. While the discussion is focused on previous psychiatric or behavioural symptoms and memory, many people will fell upset. The research team members will support you if you are upset during the study visit. If further help is needed,

the research team members will contact the doctors or other healthy professionals who care for you.

What happens when the research study stops?

The doctor who cares you will discuss with you whether to keep your previous quetiapine treatment or not while the study terminates. The decision is usually according to your treatment response during the study period and which treatment group you are allocated.

What if there is a problem?

We will provide you a 24-hour telephone number if you participate in this study. The 24-hour telephone number will be used while you appear medical emergencies and your doctor should be informed the study medications you are receiving. You may be discontinued from this study and appropriate treatment will also provide you.

If you have any complaints about the study, please fell free to talk with the research team. There is more detailed information for complaints in Section 2.

What will happen to my answers?

All the information collected from you and your carer will only be used for this study. Code numbers will substitute for names or other personal details as the personal identifying method while we store and analyze the study data.

Whom do I contact for information or advice?

The person who has organized and is co-ordinating the study is Director Hung-Yu Chan at Taoyuan Mental Hospital.

The doctor who recruited you in the study is _____.
[insert local recruiting principal investigator name]

Section two

What if relevant new information becomes available?

It is possible that new information about the therapy which is under research becomes available during the study period. If it occurs, the research team members will discuss with

you whether you would like to continue in this research. If you decide to continue in this research, you will be asked to sign a new consent form. If you decide not to continue, we will arrange you back to your previous treatment setting. Besides your opinion, the research doctor might consider your best interests to let you discontinue from the study. He/she will tell you the reasons and let your medical care to continue. If this study is terminated due to other reasons, the research team members will tell you why and arrange your further care.

What will happen if I don't want to carry on with the study?

If you decide to withdraw from this study, we will arrange you back to your previous treatment environment. Your ordinary treatment and social benefits will not be affected by this decision. If you agree, we would like to use the data collected from you before your discontinuation. If you do not agree, the data collected to this point would be withdrawn.

What if there is a problem?

Complaints

If you have any concerns toward this study, we encourage you to talk with the research team. They will try their best to deal with your questions. The doctor who is responsible for you in the study is _____ and his/her contact telephone number is _____.

If you are still upset and decide to do a formal complaint, you can do this through the Research Ethics Committee of the study hospital. The staff responsible for the research ethics in your study hospital is _____ and his/her contact telephone number is _____.

Harm

If you are harmed during the study period and this is due to the negligence of the research team members, you will have compensation. All of the people who participates this study will be insured to protect their rights.

Will my taking part in this study be kept confidential?

We will keep all information which is collected from you confidentially. You can check the accuracy of the information from you and correct any errors. We will follow the

principle of Personal Data Protection Act 2010 of Taiwan to deal with your data.

Your medical documents and the data collected for the study will be looked at by authorized persons from the Department of Health and Taoyuan Mental Hospital. They may also be looked at by people representatives of regulatory authorities and by authorized people. All of them have a duty of confidentiality to you as a research participant. Any personally identifying information held at Taoyuan Mental Hospital for the purposes of the conduct of the study will be kept in a locked filing cabinet. They will only be assessed by the research team and will be destroyed at the study end.

Involvement of your primary care doctor

If you agree, your primary care doctor will be informed of your participation in the study. If appropriate, other medical staff not participated in this study but who are involved in your treatment will also be notified of your study participation.

What will happen to the results of the research study?

The results of this study will be reported to research sponsor and funder and submitted to medical journals for publication. Study participants will not be identified in any report or publication.

Who is organizing and funding the research?

The study is being organized by Taoyuan Mental Hospital. It is funded by _____ [depend on the results of grant application].

Who will review the study?

This study will be reviewed by the Research Ethics Committee of all participating study hospitals.

Thank you for taking the time to read this information sheet. You should keep this information sheet if you wish to take part in the study.

Appendix 4: Information sheet for carer

Patient Number: Carer Number:

Site Number: Initials of Site Principal Investigator:

CARER INFORMATION SHEET

Withdraw study for patients with dementia on long-term quetiapine treatment: a multi-centre, randomized, double-blind, placebo controlled study

We invite the person you care for to participate in a research project. If he/she participates, we will also collect information from you. It is important for you to understand the purpose of this study and what will you do during the study before you make your decision whether to participate in the study or not. Please read this information sheet carefully.

Section one tells you why this study is being done and what it will involve if you participate.
Section two provides you detailed information about this study.

If you are unclear to the information of this study, you can ask the research team members. You are free to discuss with others about the study. Please take your time to make your decision whether you would like to participate in this study.

Section one

What is this study?

We are trying to figure out the benefits and risks of quetiapine withdrawal in people with dementia on more than 3 months of quetiapine treatment. Patients with dementia frequently have behavioural or psychiatric symptoms such as delusions, disturbing behaviours, agitation and aggressive symptoms. The non-pharmacological management usually is the first line in dealing with these symptoms. If these symptoms are still prominent after non-pharmacological interventions, then pharmacological interventions can consider and antipsychotics are the most popular medications for this situation. However, antipsychotics may increase the risks of mortality and cerebrovascular adverse events in dementia population. Therefore, most of guidelines suggest antipsychotics only use for short-term and need assess the benefits and risks of them regularly.

Quetiapine is one of the antipsychotics and popularly being prescribed for people with dementia. Quetiapine acts on one of the chemicals, dopamine, in the brain, which tends to be high in people with dementia and psychotic symptoms. Previous studies have shown around two thirds of people with dementia can withdraw from other antipsychotics successfully and get benefit from fewer adverse drug reactions. However, there were no studies to investigate the benefits and risks of quetiapine withdrawal. Therefore, it is an important issue to understand whether patients can get benefit from quetiapine withdrawal.

Why has the person I look after been chosen?

The doctor who has cared the person you look after believes that he/she is a patient with dementia on quetiapine treatment over 3 months that this study is sought for. With your permission, the doctor has referred the person you look after to this study.

Do I have to join?

No. It completely depends on you both. No matter what is your decision, his/her current treatment and social benefits will not be affected. Even if you agree to participate, you can withdraw your consent at any moment during the study period and you do not need to provide any reason. If the person you look after is unable to decide his/her participation in the study because of his/her cognitive impairment, we will ask that you consent on his/her behalf.

What will happen to me if I participate?

The study lasts for 6 months. We will usually make 7 visits to see you both. The visits will take place at the treatment hospital of the person you look after, unless another venue is more convenient for you both. The researcher will spend about an hour with each of you during these visits.

The first meeting will include an assessment of his/her mental status and physical condition, made by a member of the research team. If the person you care for fulfill all of the study criteria, then the research team member will discuss with you both whether to participate in this study or not.

He/she will be allocated randomly to one of two groups – one group will uptake placebo and withdraw their previous quetiapine. The period of tapering is up to 2 weeks which is according to their previous quetaipine dose; another group will maintain their previous

quetiapine treatment. The meaning of placebo is it looks like a real medicine but it does not contain the active ingredient of the medicine. Therefore, we can compare the effects of quetiapine withdrawal and quetiapine maintenance. The chance of being allocated to quetiapine withdrawal and quetiapine maintenance group will be equal.

We suppose that a substantial proportion of patients with dementia on more than 3 months of quetiapine treatment can get benefit from quetiapine cessation. However, there were no clinical studies to support this hypothesis. Therefore, it is the research question that this study will investigate.

They will take one tablet in the night before their sleep through the whole 24-week study period. Both you and the research team members will not know whether you are taking a placebo or a quetiapine tablet until the end of the trial, although his/her doctor can find out if they needed to know due to an emergency.

What are the possible benefits of taking part?

Although we suppose that a substantial proportion of people with dementia on more than 3 months of quetiapine treatment can get benefit from quetiapine cessation, we cannot promise that the study will help the person for whom you care. However, the information they provide us may help the people with dementia who also receive quetiapine treatment. It is possible that some patients get benefit from the different treatments of the study. His/her participation will be invaluable for us to help others suffering from similar situations. The studies findings will help doctors to know which treatment is a better choice. Except the travel expenses, there will be no payment or reimbursements for participating in this study.

What are the potential disadvantages and risks of taking part?

Some of the people with dementia on long-term quetiapine treatment may appear their previous psychiatric or behavioural symptoms if they discontinue quetiapine treatment. Most of the people with symptoms worsening after quetiapine withdrawal can improve quickly while quetiapine restore. If the person for whom you care appears psychiatric symptoms or behavioural symptoms worsening during the study period, this should be discussed with the research team members.

It is possible that he/she may experience emotional distress during or after discussions with research team members. While the discussion is focused on previous psychiatric or behavioural symptoms and memory, many people will fell upset. Research team members

will support him/her if the person you look after are upset during the study visit. If further help is needed, the research team members will contact the doctors or other healthy professionals who care for him/her.

What happens when the research study stops?

The doctor who cares the person you look after will discuss with you both whether to keep his/her previous quetiapine treatment or not while the study terminates. The decision is usually according to his/her treatment response during the study period and which treatment group he/she is allocated.

What if there is a problem?

We will provide you a 24-hour telephone number if the person you look after participate in this study. The 24-hour telephone number will be used while he/she appear medical emergencies and his/her doctor should be informed the study medications he/she is receiving. He/she may be discontinued from this study and appropriate treatment will also provide him/her.

If you have any complaints about the study, please fell free to talk with the research team. There is more detailed information for complaints in Section 2.

What will happen to my answers?

All the information collected from you and the person you look after will only be used for this study. Code numbers will substitute for names or other personal details as the personal identifying method while we store and analyze the study data.

Whom do I contact for information or advice?

The person who has organized and is co-ordinating the study is Director Hung-Yu Chan at Taoyuan Mental Hospital.

The doctor who recruited you in the study is _____.
[insert local recruiting principal investigator name]

Section two

What if relevant new information becomes available?

It is possible that new information about the therapy which is under research becomes available during the study period. If it occurs, the research team members will discuss with you and the person you look after whether you both would like to continue in this research. If you decide to continue in this research, you both will be asked to sign a new consent form. If you both decide not to continue, we will arrange the person you look after back to his/her previous treatment setting. Besides your opinion, the research doctor might consider the best interests of the person you look after to let him/her discontinue from the study. The research doctor will tell you the reasons and let the care of the person you look after to continue. If this study is terminated due to other reasons, the research team members will tell you why and arrange the further care for the person you look after.

What will happen if I don't want to carry on with the study?

If you decide to withdraw from this study, we will arrange the person you look after back to his/her previous treatment environment. His/her ordinary treatment and social benefits will not be affected by this decision. If you agree, we would like to use the data collected from you before your discontinuation. If you do not agree, the data collected to this point would be withdrawn.

Complaints

If you have any concerns toward this study, we encourage you to talk with the research team. They will try their best to deal with your questions. The doctor who is responsible for you in the study is _____ and his/her contact telephone number is _____.

If you are still upset and decide to do a formal complaint, you can do this through the Research Ethics Committee of the study hospital. The staff responsible for the research ethics in your study hospital is _____ and his/her contact telephone number is _____.

Harm

If the person you look after is harmed during the study period and this is due to the negligence of the research team members, he/she will have compensation. All of the people who participates this study will be insured to protect their rights.

Will my taking part in this study be kept confidential?

We will keep all information which is collected from you and the person you look after confidentially. You can check the accuracy of the information from you and correct any errors. We will follow the principle of Personal Data Protection Act 2010 of Taiwan to deal with your data.

Your medical documents and the data collected for the study will be looked at by authorized persons from the Department of Health and Taoyuan Mental Hospital. They may also be looked at by people representatives of regulatory authorities and by authorized people. All of them have a duty of confidentiality to you as a research participant. Any personally identifying information held at Taoyuan Mental Hospital for the purposes of the conduct of the study will be kept in a locked filing cabinet. They will only be assessed by the research team and will be destroyed at the study end.

Involvement of the primary care doctor

If you agree, the primary care doctor of the people you care for will be informed of his/her participation in the study. If appropriate, other medical staff not participated in this study but who are involved in his/her treatment will also be notified of his/her study participation.

What will happen to the results of the research study?

The results of this study will be reported to research sponsor and funder and submitted to medical journals for publication. Study participants will not be identified in any report or publication.

Who is organizing and funding the research?

The study is being organized by Taoyuan Mental Hospital. It is funded by _____ [depend on the results of grant application].

Who will review the study?

This study will be reviewed by the Research Ethics Committee of all participating study hospitals.

Thank you for taking the time to read this information sheet. You should keep this information sheet if you wish to take part in the study.

Appendix 5: Patient consent form for patient participation

Patient Number: Carer Number:

Site Number: Initials of Site Principal Investigator:

PARTICIPATION CONSENT FORM FOR PATIENT

Title of Research: Withdraw study for patients with dementia on long-term quetiapine treatment

Please tick box

a.	I confirm that I have read and understand the patient information sheet (dated DDMMYYYY, version ___) for this study. I also confirm that I have been received a copy of the carer information sheet (dated DDMMYYYY, version ___). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
b.	I understand that my participation is voluntary and that I am free to withdraw from this study at any time, without giving any reason, without my medical care or legal rights being affected.	☐
c.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the Department of Health and Taoyuan Mental Hospital, or from related regulatory authorities, where it is relevant to my participation in this research. I give permission for these people to have access to my records.	☐
d.	I agree to my primary care doctor and other relevant professionals being informed of my participation.	☐

Name of patient _____

Signature _____ **Date** _____

Name of witness (if verbal consent only is possible) _____

Signature _____ **Date** _____

Researcher obtaining consent _____

Signature _____ Date _____

Appendix 6: Carer consent form for carer participation

Patient Number: Carer Number:

Site Number: Initials of Site Principal Investigator:

PARTICIPATION CONSENT FORM FOR CARER

Title of Research: Withdraw study for patients with dementia on long-term quetiapine treatment

Please tick box

a.	I confirm that I have read and understand the carer information sheet (dated DDMMYYYY, version ___) for this study. I also confirm that I have been received a copy of the patient information sheet (dated DDMMYYYY, version ___). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
b.	I understand that my participation is voluntary and that I am free to withdraw from this study at any time, without giving any reason, without my medical care or legal rights being affected.	☐
c.	I understand that relevant sections of any of medical notes of the person I care for and data collected from us both during the study, may be looked at by responsible individuals from the Department of Health and Taoyuan Mental Hospital, or from related regulatory authorities, where it is relevant to my taking part in this research. I give permission for these people to have access to information I have provided in these records for this study.	☐
d.	I agree to participate in this study.	☐

Name of carer _____

Signature _____ **Date** _____

Name of witness (if verbal consent only is possible) _____

Signature _____ **Date** _____

Researcher obtaining consent _____

Signature ____________________________________ Date ____________________

Appendix 7: Carer consent form for patient participation

Patient Number: Carer Number:

Site Number: Initials of Site Principal Investigator:

PARTICIPATION CONSENT FORM-CARER FOR PATIENT

Title of Research: Withdraw study for patients with dementia on long-term quetiapine treatment

Please tick box

a.	I confirm that I have read and understand the carer information sheet (dated DDMMYYYY, version ___) for this study. I also confirm that I have been received a copy of the patient information sheet (dated DDMMYYYY, version ___). I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
b.	I understand that the participation of the person I care for is voluntary and that he/she may be withdrawn from this study at any time, without giving any reason, without his/her medical care or legal rights being affected.	☐
c.	I understand that I have the authority to withdraw the person I care for from this study at any time, without giving any reason, without his/her medical care or legal rights being affected.	☐
d.	I understand that data collected during the study, and relevant sections of the medical notes of the person I care for, may be looked at by responsible individuals from the Department of Health and Taoyuan Mental Hospital, or from related regulatory authorities, where it is relevant to this research. I give permission for these people to have access to the appropriate records for this study.	☐
e.	I agree to the primary care doctor of the person I care for, and other relevant professional health care staff, being informed of his/her participation.	☐
f.	I agree to the person I care for participating in this study and have no reason to believe that he/she would not have wished to participate if he/she was able to make that decision.	☐

Name of carer _____

Relationship to patient _____

Signature _____ **Date** _____

Name of witness (if verbal consent only is possible) _____

Signature _____ **Date** _____

Researcher obtaining consent _____

Signature _____ **Date** _____