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• 中文摘要	背景 精神分裂症是一種慢性化且使人喪失能力的疾病，每年的復發率爲 15-20%，其中約有一半以上的病人會進入慢性化的過程，患者的功能則會逐年下降，以台灣地區精神疾病流行病學研究資料顯示，則可以約略估算出台灣地區精神分裂症患者一年的經濟成本爲 180 億元，因此精神疾病是一個不容我們忽視的議題。 傳統抗精神病藥物可以改善正性症狀，但是對於負性症狀及認知功能的效果則有限，加上容易出現錐體外徑症狀，因此有新一代抗精神病藥物的發展。新一代抗精神病藥物同時作用於血清素及多巴胺接受器，不容易出現錐體外徑症狀，以及對於正性症狀、負性症狀及認知功能均有療效。Clozapine 屬於第二代抗精神病藥物之一，爲目前對於難治型精神分裂症之首選治療藥物，然而其所導致的副作用，特別是顆粒性白血球缺乏症，使其臨床應用受到侷限；此外有一部份的難治型精神分裂症對於 clozapine 亦缺乏療效，需要尋求其他的治療策略。以往對於此類病患的研究較少，且多侷限於小樣本數之開放性研究，評估工具也僅限於精神病症狀，因此並無法獲得肯定的結論。 針對此一藥物併用策略，本研究團隊已經進行前驅性研究，在開放性的臨床研究中，clozapine 100 mg/day 併用 fluvoxamine 50 mg/day 可以達到與 clozapine monotherpy (300 mg/day)相近的 clozapine 血中濃度，副作用方面兩組並無差異，在療效方面則呈現併用組優於單獨用藥組。雖然是屬於小樣本數之開放性研究，評估工具也較簡單，然而研究結果顯示此一藥物併用策略對於難治型精神分裂症患者的精神病症狀有改善，而且並不會導致藥物副作用的增加。我們的另一個研究結果則顯示併用 fluvoxamine 可以改善 clozapine 所導致之體重增加及新陳代謝異常。因此根據此前驅性研究所獲得之成果，設計一個大規模的雙盲性研究，本研究之基本假設爲對於難治型精神分裂症之療效及安全性，clozapine 併用 fluvoxamine 所產生的藥動學及藥效學之交互作用，會優於 clozapine monotherapy。 研究設計 本研究已經獲得人體試驗委員會通過，研究方法

是以爲期 3 年的時間，陸續收案 60 位難治型精神分裂症住院患者，隨機分爲兩組，雙盲地分別接受 clozapine monotherpy (300 mg/day)、與 clozapine 100 mg/day 併用 fluvoxamine 50 mg/day。臨床療效評估工具包括：活性與負性症狀量表(Positive And Negative Syndrome Scale; PANSS)，臨床整體評估(Clinical Global Impression; CGI)，以及住院病患護理觀察評估量表(Nurses' Observation Scale for Inpatient Evaluation; NOSIE)。藥物副作用則以 Extrapyramidal Symptom Rating Scale (ESRS)及 UKU Side Effect Rating Scale 評量。此外，亦會抽血測量血糖、血脂肪、胰島素、細胞激素、clozapine 及其代謝物之濃度。 預期結果 本研究除探討 clozapine monotherapy 與 clozapine 併用 fluvoxamine 兩種治療策略對於難治型精神分裂症之療效外，也將達成下列之研究成果： (1) clozapine 併用 fluvoxamine 之療效優於 clozapine monotherapy (2) clozapine 併用 fluvoxamine 之安全性及副作用優於 clozapine monotherapy (3) 對於個案體重變化及新陳代謝方面，clozapine 併用 fluvoxamine 優於 clozapine monotherapy (4) Clozapine 及其代謝物之穩定狀態血漿濃度可以部分解釋臨床療效及副作用之差異。 結果 本研究預計利用三年時間收案 60 位頑固型精神分裂症患者參與研究，目前本研究進行至第二年期末，由於計劃延至第一年 5 月才完成簽約手續，所以第一年研究較預定進度稍有延遲，共收案 15 人。第二年的計畫執行則已經趕上並超前預期進度，至 11 月底爲止，共收案 31 人。因此目前至第二年已經收案 46 人。 本研究爲三年期的雙盲性研究，目前只進行至第二年期末，結果尚無法解碼，因此尚無法提供相關研究成果。目前僅能提供受試者在基準點之相關研究資料。 46 位受試者中男性有 33 位，女性有 13 位。婚姻狀態爲 29 位單身，7 位已婚，7 位離婚，3 位喪偶。教育程度爲 10 位國小畢業，11 位國中畢業，22 位高中職畢業，3 位大專畢業。平均年齡爲 44.3 ± 10.3 歲，平均發病年齡爲 24.3 ± 8.6 歲。臨床診斷均爲精神分裂症。 最近使用的抗精神病藥物分別爲，haloperiodol 有 12 位，thioridazine 有 3 位，risperidone 有 13 位，quetiapine 有 6 位，olanzapine 有 11 位，ziprasidone 有 1 位。 身體健康檢查的資料爲平均身高 165.1 ± 8.9 公分，平均體重爲 72.1 ± 19.0 公斤，平均腰圍爲 93.2 ± 18.9 公分，平均臀圍爲 98.2 ± 8.4 公分。平均收縮壓爲 118.1 ± 20.1 mmHg，平均舒張壓爲 79.0 ± 12.0 mmHg。 臨床評估的結果爲 PANSS 的平均得分爲 65.7 ± 20.6，其中正性症狀平均得分爲 16.8 ± 7.7，負性症狀平均得分爲 20.6 ± 8.8，一般精神病理症狀平均得分爲 29.5 ± 9.5，嚴重度平均得分爲 3.5 ± 1.2。CGI severity scale 的平均得分爲 3.8 ± 0.8。在 Nurses' Observation Scale for Inpatient Evaluation (NOSIE)的平均得分 79.8 ± 17.5。 在情緒方面之評估結果，利用 Yale-Brown Obsessive Compulsive Scale (Y-BOCS)來評估強迫症相關症狀，Y-BOCS 平均得分爲 0.9 ± 4.7。利用 Young Mania Rating Scale (YMRS)來評估躁症相關症狀，YMRS 平均得分爲 0.7 ± 2.7。利用 Montgomery Åsberg Depression Rating Scale (MADRS)來評估憂鬱症相關症狀，MADRS 平均得分爲 3.7 ± 6.9。 在副作用的評估結果爲 Extrapyramidal Symptom Rating Scale (ESRS)的平均得分爲 8.1 ± 5.7，UKU Side Effect Rating Scale 平均得分爲 6.7 ± 5.1。 在實驗室檢驗的結果爲：空腹血糖平均值爲 95.2 ± 16.0 mg/dL，胰島素濃度平均值爲 13.1 ± 18.5 mU/L，C-peptide 平均值爲 4.0 ± 4.3 ng/mL，三酸甘油脂平均值爲 196.1 ± 154.6 mg/dL，HDL 平均值爲 42.4 ± 12.4 mg/dL，LDL 平均值爲 101.8 ± 35.9 mg/dL，膽固醇平均值爲 179.7 ± 37.8 mg/dL。利用 homeostasis model assessment (HOMA)來評估胰島素阻抗性，計算公式爲 HOMA-IR = fasting glucose [mmol/L] * fasting insulin [mU/L] /22.5，HOMA-IR 的平均值爲 3.1 ± 4.0。 在本研究相關經費支持下，我們於 97 年度有 3 篇 SCI 期刊論文及 1 篇學術會議論文發表，98 年度有 1 篇 SCI 期刊論文及 4 篇學術會議論文發表，並且還有 2 篇 SCI 期刊論文投稿中。請參考<98 年度計畫著作一覽表>。 結論 本研究爲

三年期的雙盲性研究，目前進行至第二年期末，結果尚無法解碼，因此尚無法提供相關研究成果。本研究之基本假設爲：對於難治型精神分裂症患者之療效及安全性，clozapine 併用 fluvoxamine 所產生的藥動學及藥效學之交互作用，會優於 clozapine monotherapy。依照我們之前開放性研究之結果，顯示此藥物併用策略具有較佳之療效，同時可以改善 clozapine 所導致之體重增加及新陳代謝異常。因此我們相信在本研究之隨機雙盲設計下能夠進一步釐清其效應。

- 英文摘要

Background Schizophrenia is one of the most severe mental illnesses. The prevalence of schizophrenia has been variously reported as ranging from 1 to 1.5 percent. More than 50% of patients can be described as having a poor outcome, with repeated hospitalizations, exacerbations of symptoms, episodes of major mood disorders, and suicide attempts. Schizophrenia is costly in medical care, treatment and rehabilitation, and reduced or lost productivity. Therefore, the development of effective treatment for schizophrenic patients is an important issue. The classical antipsychotic drugs are the dopamine receptor antagonists, which are effective in the treatment of schizophrenia, particularly of the positive symptoms. Even with treatment of typical antipsychotics, about 50% of schizophrenic patients lead severely debilitated lives. Second, the classical antipsychotic drugs are associated with annoying and serious adverse effects. Clozapine has been virtually the only psychopharmacological choice in patients with schizophrenia who either did not response to typical neuroleptics or experienced severe extrapyramidal side effects and consequently did not tolerate this medication. There are patients who do not respond to clozapine, and the need to treat these severely ill patients frequently compels clinicians to adopt therapeutic innovations that lack a sound empirical basis. One strategy is the combination of various other somatic treatments with clozapine. Recently, we conduct a preliminary open trial to evaluate the safety and efficacy of fluvoxamine coadministration with clozapine in refractory schizophrenic patients. The mean plasma clozapine levels obtained by clozapine 100 mg/day plus fluvoxamine 50 mg/day is close to that produced by 300-mg/day clozapine monotherapy in one of our previous studies. The combined treatment is well tolerated, and clinical improvement is observed in our patients. And the concomitant fluvoxamine could attenuate the clozapine-induced weight gain and metabolic disturbance. However, the effects of fluvoxamine on the safety and therapeutic efficacy of clozapine need to be further clarified in double-blind study. Methods This study is a three-year proposal. Sixty treatment-resistant schizophrenic inpatients will participate in this project. The subjects will be randomized to one of two parallel groups: clozapine monotherapy and clozapine plus fluvoxamine treatment. The double-blind active treatment will consist of two periods. The measures of clinical efficacy will be the Positive And Negative Syndrome Scale, Clinical Global Impression, and Nurses'Observation Scale for Inpatient Evaluation. The measures of side effects will be the Extrapyramidal Symptom Rating Scale and the UKU Side Effect Rating Scale. Fasting serum samples are collected to determine the lipid profile (total cholesterol, triglycerides, HDL, LDL, and VLDL), glucose level, insulin level, and leptin level. Plasma levels of clozapine, norclozapine, and clozapine N-oxide will be determined by high performance liquid chromatography with ultraviolet detection. The following results are expected: (1) In treatment-resistant schizophrenic patients, global antipsychotic effect of clozapine plus fluvoxamine treatment is superior to clozapine monotherapy. (2) Clozapine plus fluvoxamine treatment has less adverse effects than clozapine monotherapy.

(3) The effect of clozapine plus fluvoxamine treatment on body weight and metabolic disturbances is superior to clozapine monotherapy. (4) Steady-state plasma levels of clozapine and its metabolites account for a proportion of variance of clinical effects. Results During the first two years, we have recruited 46 refractory schizophrenic inpatients. All subjects were Taiwanese and 33 (72%) were men. The mean ± SD age was 44.3 ± 10.3 years. The mean ± SD age of onset was 24.3 ± 8.6 years. The last antipsychotic medication included haloperiodol (N = 12), thioridazine (N = 3), risperidone (N = 13), quetiapine (N = 6), olanzapine (N = 11), and ziprasidone (N = 1). The study is a double-blind, placebo-controlled design. We cannot provide any information during the trial period. Here we present the assessment results at the baseline evaluation. The mean ± SD height was 165.1 ± 8.9 cm. The mean ± SD weight was 72.1 ± 19.0 kg. The mean ± SD waist and hip circumference were 93.2 ± 18.9 cm and 98.2 ± 8.4 cm, respectively. The mean ± SD systolic and diastolic blood pressure were 118.1 ± 20.1 mmHg and 79.0 ± 12.0 mmHg, respectively. The mean ± SD PANSS total score, positive subscale score, negative subscale score, and general psychopathology subscale score were 65.7 ± 20.6, 16.8 ± 7.7, 20.6 ± 8.8, and 29.5 ± 9.5, respectively. The mean ± SD CGI severity score was 3.8 ± 0.8. The mean ± SD score of Nurses' Observation Scale for Inpatient Evaluation (NOSIE) was 79.8 ± 17.5. The mean ± SD score of Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was 0.9 ± 4.7. The mean ± SD score of Young Mania Rating Scale (YMRS) was 0.7 ± 2.7. The mean ± SD score of Montgomery Åsberg Depression Rating Scale (MADRS) was 3.7 ± 6.9. The mean ± SD score of Extrapyramidal Symptom Rating Scale (ESRS) was 8.1 ± 5.7. The mean ± SD score of UKU Side Effect Rating Scale was 6.7 ± 5.1. The mean ± SD fasting glucose level was 95.2 ± 16.0 mg/dL. The mean ± SD insulin and c-peptide levels were 13.1 ± 18.5 mU/L and 4.0 ± 4.3 ng/mL, respectively. The mean ± SD levels of triglycerides, HDL, LDL, and cholesterol were 196.1 ± 154.6 mg/dL, 42.4 ± 12.4 mg/dL, 101.8 ± 35.9 mg/dL, and 179.7 ± 37.8 mg/dL, respectively. Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR = fasting glucose [mmol/L] * fasting insulin [mU/L] /22.5). The mean ± SD HOMA-IR was 3.1 ± 4.0. Finally, three SCI journal articles and one conference article, supported by the NHRI grant, have been published in 2008. One SCI journal article and three conference articles have been published in 2009. Another two articles are submitted to SCI journal and under review. (please see References). Conclusion The study is a three-year proposal with a double-blind, placebo-controlled design. This is the year-end report of the second year. In our previous preliminary study result, the clozapine-fluvoxamine co-medication can provide more therapeutic efficacy and less metabolic adversity than clozapine monotherapy. Continuation of the double-blind comparison trial is warranted. This study will potentially refine the treatment of refractory schizophrenia.