• 計畫中文名稱	頑固型精神分裂症之治療策略:Clozapine 與 fluvoxamine 之藥物交互作用		
• 計畫英文名稱	Treatment Strategy for Refractory Schizophrenia: Drug Interaction between Clozapine and Fluvoxamine		
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• 研究人員	盧孟良,黃名琪,陳俊興		
• 中文關鍵字	精神分裂症；藥物治療；clozapine；fluvoxamine；；；；		
• 英文關鍵字	；；；；；；；		
• 中文摘要	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。
• 英文摘要	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.