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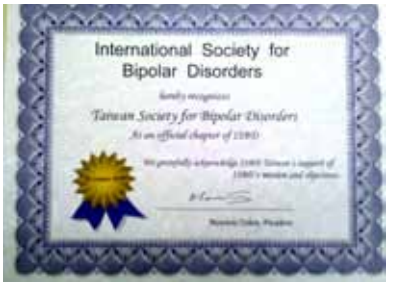
理事長的話

迎接生物精神醫學及神經藥理學的春天

有鑑於生物精神醫學及神經藥理學之快速發展，本學會因應世界潮流，於2010年1月16日成立了台灣第一個雙極性情感症(Bipolar Disorder)之小組。參加的成員均為本會之會員。同時在2010年8月14日接到ISBD(International Society of Bipolar Disorder)總部的來函恭賀台灣成為ISBD之家族成員。並給予ISBD Taiwan Chapter之證書。2010年8月28日在白秘書長之策劃下，聚集了13位會員，開始思考有關台灣Bipolar Disorder治療的專家Consensus。並根據病程，將朝3個治療phase(即急性躁期、急性憂鬱期及藥物治療維持期)之方向，進行研究。此研究主要是以世界生物精神醫學會(WFSBP)之治療指引為主要參考架構。訂定進度，期望在今年11月精神醫學會年會時有初步之訂稿。除了專家之意見外，我們也希望由實證醫學的角度找出目前台灣Bipolar Disorder藥物治療之現況。此方向可能要由健保資料庫及專家之實證經驗中去approach。完成後，再經專家們之討論，希望形成台灣Bipolar Disorder之治療指引之雛形。這是一個艱鉅的工程，盼本會會員全力支持。



● ISBD Taiwan Chapter 證書

世界生物精神醫學會(WFSBP)將於2011年5月29日至6月2日在歐洲捷克首都布拉格舉行年會，其abstract (poster)之deadline在今年12月15日。請各位會員踴躍參加，另WFSBP official雜誌The World J. of Biological Psychiatry之主編Kasper教授來函指出其impact factor在2009年上升至5.564，非常值得恭賀，也希望同仁能踴躍投稿。

亞洲神經精神藥理學會(AsCNP)主席Yamawaki教授積極與美國神經精神藥理學會聯繫，為了加強亞美之交流，今年AsCNP將派10位會員參加ACNP之年會，我國劉嘉逸主任及周元華主任將於今年12月中旬代表台灣赴美國佛羅里達州Miami市參加之。

雖然憂鬱症在2020年將是失能症中的第2名，在2030年預估將超過癌症及心臟疾病而成為第1名，然而在實證醫學的證據上，仍然無法超越，原因在於人腦本身及與其他器官的相聯繫卻是最難以解決的問題。如果說人們對於其他身體疾病之機轉已有相當的認識，然對精神疾病之了解卻還正在萌芽中。生物精神醫學在此關鍵時刻，扮演了更重要的角色，從基礎到臨床，從分子到器官至腦影像。本人深深期盼有志於生物精神醫學的同仁，無論基礎或臨床的專長，均能在一起合作，承先啟後創造未來。

理事長 蘇東平

文獻選讀及評論

Variation in the Risk of Suicide Attempts and Completed Suicides by Antidepressant Agent in Adults: A Propensity Score–Adjusted Analysis of 9 Years' Data

作者：Sebastian Schneeweiss, MD, ScD; Amanda R. Patrick, MS; Daniel H. Solomon, MD, MPH; Jyotsna Mehta, MS; Colin Dormuth, MA, MS, ScD; Matthew Miller, MD, ScD; Jennifer C. Lee, BS; Philip S. Wang, MD, DrPH

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背景： 近年來抗憂鬱劑廣泛的使用於憂鬱症的治療上，但是對於自殺意念及自殺行為是否產生降低的效果則尚無定論。在2004年10月美國FDA針對抗憂鬱劑使用提出警語，兒童及青少年接受抗憂鬱劑治療可能會增加自殺想法及行為之危險性。此一警語是經由meta-analysis結果顯示，兒童及青少年接受抗憂鬱劑治療出現自殺想法或行為是安慰劑組的兩倍（相關文章請見Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry. 2006;63(3):332-339）。2006年12月FDA近一步將警示範圍延伸到年輕成人。後續研究針對成人族群服用抗憂鬱劑與自殺進行分析，結果則顯示沒有增加自殺風險。

至於不同抗憂鬱劑間是否有差異性存在，目前各個研究的結果並無定論。曾有研究指出，與其他抗憂鬱劑比較，SSRI在使用的第一個月會增加自殺比率五倍；也有研究顯示SNRI有較高的自殺危險性。因此本研究嘗試針對各種抗憂鬱劑對於成人自殺的影響進行比較。

方法： 在1997年1月至2005年12月居住於加拿大英屬哥倫比亞18歲以上的居民，總人口數約為3百萬人，期間曾經接受過抗憂鬱劑治療而且有憂鬱症診斷者納入分析，主要預後指標是自殺死亡或因為自傷而住院。

結果： 研究期間共有287543人因為憂鬱症服用抗憂鬱劑，56.2%為女性。其中有69.4%在之前3年不曾接受過抗憂鬱劑治療。以抗憂鬱劑種類區分，SSRI佔65.5%，SNRI佔12.4%，TCA佔11.6%。

統計顯示自殺企圖及自殺死亡比率為6.06 per 1000 person-years，多數的自殺發生在開始使用抗憂鬱劑的前6個月。不同的SSRI及不同作用機制的抗憂鬱劑之間並沒有差異。

討論： 在FDA對於抗憂鬱劑與自殺之關連性提出警語後，陸續有許正反意見發表，本研究相對集中於探討不同抗憂鬱劑間的差異，結果顯示各種抗憂鬱劑間對於自殺沒有差異性，而且自殺容易發生於開始藥物治療的前六個月。至於抗憂鬱劑是否會增加自殺的危險性，則不在本研究的探討範圍。然而目前有研究證據顯示年紀較輕及有dual diagnosis的憂鬱症患者，是服用抗憂鬱劑導致自殺高危險群。相關文獻回顧請參考Möller HJ. Antidepressants: controversies about their efficacy in depression, their effect on suicidality and their place in a complex psychiatric treatment approach. World J Biol Psychiatry. 2009;10(3):180-95.

評論者

盧孟良，台北醫學大學醫學系精神學科副教授及萬芳醫院精神科主任。

本土研究及心得分享

探討精神分裂症患者的情緒管理與血清素2A接受體基因變異之關連性(Emotional management and 5-HT2A receptor gene variance in patients with schizophrenia)

作者：邱南英、許文郁、作者：羅紀萱,蔡果荃,廖俊惠, 王明鈺, 張倍禎, 莊慧君,藍先元

出處：Biological Psychology. 2010 Feb;83(2):79-83

摘要

背景：精神分裂症病患有明顯的社會認知功能缺損，特別是情緒管理能力，而目前已被指出部分是經由血清素系統調控。位於啟動子區域的血清素2A接受體基因(5-HT2AR)中的-1438 A/G基因多型性可調節血清素2A接受體的活動，且也被指出與情緒特質、憤怒及侵略相關行為有關。本研究欲探討5-HT2AR基因多型性是否與精神分裂症患者之社會認知功能中的情緒管理有關。

方法：研究個案為115位以抗精神病藥物理想劑量穩定症狀之慢性精神分裂症住院病患。所有個案皆經抽血並取得-1438 A/G基因多型性資料，且皆經過症狀評估量表、認知神經測量工具及Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) Version 2.0 的情緒管理向度評估。

結果：多元線性迴歸分析結果發現，A/G組之情緒管理表現明顯優於G/G組（p = 0.018），但與A/A組相較無異。進一步分析情緒管理的兩個分量表後發現，A/G組之情緒調控表現仍明顯優於G/G組 (p = 0.026)；而在與他人情緒往來表現上，A/G組亦優於G/G組 (p = 0.027)。

結論：本研究發現血清素2A接受體之–1438 A/G基因多型性在精神分裂症病患的社會認知功能中可能扮演重要角色，其中A/G組情緒調控表現明顯較G/G組佳，在與他人情緒往來表現亦然。

研究心得：本研究為為首篇探討精神分裂症患者的情緒管理與–1438 A/G基因多型性之關聯的研究，使用通過美國心理衛生和醫療研究機構(National Institute of Mental Health)推薦為評估情緒管理之唯一測量工具的Mayer–Salovey–Caruso Emotional Intelligence Test，嘗試釐清精神分裂症病人情緒管理的分子生物機制。但受限於本研究樣本數較小，未來希望可繼續擴大樣本數或延伸至其他族群，如從未用藥的個案、其他精神疾病診斷個案及健康受試者，以對情緒管理之生理機制有更全面性的了解。

作者：羅紀萱，成功大學行為醫學所碩士，現任成大醫院精神部臨床心理師

本土研究及心得分享

探於台灣一個精神科急性病房以肌肉注射olanzapine針劑、口服olanzapine口溶錠、口服risperidone內服液劑及肌肉注射haloperidol針劑比較處理急性激躁病人的療效和安全性 (Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan)

作者：邱南英、許文郁、黃斯聖、李柏賢

出處：J Clin Psychopharmacol. 2010 Jun;30(3):230-4.

摘要

背景：研究目的為在一個急性精神科病房比較以肌肉注射olanzapine針劑、肌肉注射haloperidol針劑、口服olanzapine口溶錠、口服risperidone內服液劑治療急性精神病激躁病人初24小時的療效與安全性。

方法：台灣中部一家醫學中心精神科急性病房的42位激躁精神病病人被納入研究。隨機分配成4組 (各組分別為肌肉注射10毫克的olanzapine針劑、口服10毫克的olanzapine口溶錠、口服3毫克的risperidone內服液劑、肌肉注射5毫克的haloperidol)，於處置後24小時內使用正性及負性症候群評估量表的躁動部分 (PANSS-EC) 和激躁-平靜評估量表 (Agitation-Calmness Evaluation Scale) 測量激躁的狀況，也使用臨床整體評估量表-嚴重度 (Clinical Global Impression-Severity, CGI-S) 評分。

結果：4個介入處置組於投藥治療後15、30、45、60、75和90分鐘在PANSS-EC總分有統計學上的顯著差異，治療早期的差異比較明顯。分析顯示使用口服olanzapine口溶錠組及肌肉注射olanzapine針劑組在PANSS-EC分數的改善於治療後15、30、45、60、75和90分鐘比接受肌肉注射haloperidol針劑組多。副作用方面均以嗜睡最常見，各組間沒有顯著差異。

結論：對於激躁不安的精神病患以肌肉注射olanzapine針劑、口服olanzapine口溶錠、口服risperidone內服液劑及肌肉注射haloperidol針劑治療均有療效，安全性無差異。肌肉注射olanzapine針劑和口服olanzapine口溶錠於治療的早期比肌肉注射haloperidol針劑有療效。

研究心得：精神病患的激躁不安是精神科急症，過去的處理均以注射方式處置常破壞醫病關係，病人的配合度常不好，引發後續的問題，同時注射藥物比較昂貴。此研究結果顯示口服藥物同樣有療效，且口服藥物甚至於治療初期療效比針劑注射好，較不會破壞醫病關係，也較經濟，治療處置時可考量使用。

作者：邱南英，財團法人彰化基督教醫院鹿東分院院長

本土研究及心得分享

Dextromethorphan 對電療效度的影響(Effects of dextromethorphan on ECT)

作者：李文貴、夏一新、張君威、羅時茂、諶立中

出處： Psychiatry and Clinical Neurosciences 2009; 63(1): 124-5

背景：Dextromethorphan is prescribed as an antitussive agent due to its cough-suppressant activity. It is also an N-methyl-D-aspartate (NMDA) antagonist. Animal studies have shown evidence that dextromethorphan can protect against NMDA-induced convulsions. However, there are no published reports regarding the effects of dextromethorphan on ECT in humans. We report a case of a chronic schizophrenic who took dextromethorphan because of the symptom of coughing during an ECT course and this agent remarkably influenced the therapeutic quality of the ECT.

個案報告: A 40-year-old male schizophrenic has been hospitalized in our chronic ward for more than 15 years. He has been continuously treated with clozapine 400 mg/day. However, additional ECTs are required each year when his psychosis gets exacerbated. On 19 April 2004 the patient was admitted to the acute ward because of acute exacerbation of psychotic symptoms. Bilateral ECT three times a week was arranged. The ECT procedure was performed based on the American Psychiatric Association’ s ECT Task Force.
On 21 April 2004 we administered his first ECT. The ECT device was Thymatron System IV. We used maximum sustained power (MSP) and postictal suppression index (PSI) as the ECT therapeutic markers. MSP is used to measure the highest average ictal amplitude, and the PSI reports the decrease percentage in ictal EEG amplitude immediately following seizure termination. These two indexes have been reported to be related to ECT clinical efficacy. The patient’ s concomitant medication was clozapine 400 mg per day. His initial four ECTs were performed smoothly. The MSPs of these four ECTs were all above 100000 uV2 (range: 102600 to 126430 uV2) and the PSIs of these four ECTs ranged from 95.7% to 99.4 %. However, the patient was given dextromethorphan (30mg) four times on 29 April 2004 because of the symptom of coughing. On the following day, we found that his fifth ECT MSP dropped down to 76598 uV2, his PSI was reduced to 95.2 %, and his seizure tonic and clonic motor responses were decreased. Therefore, we discontinued his dextromethorphan immediately. Interestingly, his sixth ECT MSP returned to 112510 uV2, his sixth PSI was normalized up to 99.2%, and his seizure motor intensity was restored. After we stopped dextromethorphan, the patient received four more ECTs. Each ECT response was adequate. The MSPs of the latter four ECTs were all above 100000 uV2 (range: 100620 to 123480 uV2), and the latter four PSIs ranged from 95.5% to 99.8%. His psychosis improved with the ECT.

結論：Our case suggests that dextromethorphan can influence the therapeutic quality of ECT, as indicated by the indexes of MSP and PSI, in schizophrenics. This is consistent with the findings from animal studies that dextromethorphan possesses an anticonvulsant effect. The mechanism underlying the anticonvulsant effect of dextromethorphan has been suggested to be its antagonizing effect on glutamate, which is an excitatory amino acid neurotransmitter and can lead to seizures. If we had not discontinued the patient’ s dextromethorphan, he might not have had the following adequate therapeutic seizures.

心得：Dextromethorphan (Medicon)具有NMDA antagonist之藥理機轉，會阻斷glutamate而造成痙攣閾值增加，表示Medicon為一具有抗痙攣作用之藥物，因此立即予以停用，以免降低誘導痙攣的效度。電療效度會受到諸多因素干擾，如操作流程、參數設定、合併用藥不當等，其中以「合併具有抗痙攣作用之內科藥物」最容易被精神科醫師忽略。

作者：李文貴，國軍北投醫院成人精神科主任

2010春季學術研討會精神分裂症藥物治療辯論

精神分裂症患者接受抗精神病藥物多重用藥之探討

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萬芳醫院精神科主任

在治療精神疾病患者時，併用多種同類或不同類的藥物是臨床上常使用的治療方式。Mojtabai等人分析美國1996年至2006年的用藥資料顯示(Mojtabai et al., 2010)，開立兩種或兩種以上藥物的比例由1996-1997年的42.6%增加到2005-2006年的59.8%，開立三種或三種以上藥物的比例由1996-1997年的16.9%增加到2005-2006年的33.2%，顯示多重用藥呈現逐年增加的趨勢。

目前治療精神分裂症以抗精神病藥物為主線藥物，同時抗精神病藥物單一用藥也是許多臨床治療指引所推薦的治療方式，但是仍然有一定比例的精神分裂症患者對於藥物治療反應不佳，因此臨床治療上便會嘗試採用多重用藥的治療策略。首先會針對兩個常混淆的名詞加以釐清，Combination是指同時給予兩種或兩種以上同類藥物，例如：SGA加上FGA；Augmentation則是指給予不同類的藥物，例如：抗精神病藥物加上情緒穩定劑。

臨床上治療精神分裂症患者時，如果遇到對於抗精神病藥物反應不佳的情形時，研究顯示有53%的病人會被換藥，27%會加上另一種抗精神病藥物，21%會加上一種非抗精神病藥物 (Kreyenbuhl et al., 2007)。

處方抗精神病藥物聯用治療的主要原因包括：

1.原本藥物療效不好，嘗試藉此改善療效

2.藉由調整改變神經傳導物質接受器的結合情形，達到加強治療效應

3.可以將原本的藥物劑量降低以減少副作用

4.治療者或病患的選擇

抗精神病藥物聯用治療常被質疑的部份包括，可能會增加藥物副作用、可能會存在藥物動力學及藥效學之交互作用、增加治療成本、及缺乏研究證據支持。而且併用第一代與第二代抗精神病藥物時，將會使第二代抗精神病藥物的“atypicality”喪失。雖然目前對於這些疑問還沒有結論，但是最近的meta-analysis結果顯示，在某些特殊的臨床狀態下，抗精神病藥物聯用治療的療效優於抗精神病藥物單一治療 (Correll et al., 2009)。同時抗精神病藥物聯用治療也不會增加代謝症候群的風險 (Correll et al., 2007)，不會影響心臟傳導(Ramos-Rios et al., 2009)，也部會增加死亡率 (Baandrup et al., 2010)。

同時還有兩個議題值得大家注意。第一個議題是服用抗精神病藥物聯用治療的患者多是屬於慢性化或嚴重病人，因此可能會接受較高劑量或長時間之治療，而導致出現較多副作用；同時也不容易觀察到症狀改善。第二個議題是，抗精神病藥物會影響許多不同的神經傳導物質接受器，因此雖然是抗精神病藥物單一治療，但是就接受器層面來看，也是另一種"聯用治療"。

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The debate for Mono- or Poly-pharmacy Treatment in Schizophrenia- Viewpoint from Mono-pharmacy

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Psychotropic medication polypharmacy is common in psychiatric settings and, in some patient groups, may have increased in recent years. In routine psychiatric practice, patients often receive psychiatric medication combinations that are not well supported by controlled clinical trials. One increasingly common combination is treatment with two concurrent antipsychotic medications. The review of clinical guidelines reveals that antipsychotics are essentially recommended in the monotherapy (1-3). Paradoxically, in clinical practice, concomitant use of antipsychotics is seen in 13–90% of patients (4). The higher numbers were reported in Japan (90%) and other East-Asian countries (45%) (5). In the US, antipsychotic combination rates used to vary between 13% in outpatient clinics and 50% in inpatients (6). An epidemiological study of 61257 Veteran Affairs patients showed that the prevalence of concomitant antipsychotic prescription was 20.0%, 13.1% and 9.5% when defined by a >30-, >60- or >90-day overlap, respectively (7). Another study found that, in a 1-year period, 57.7% of 796 patients were treated with a combination of antipsychotics for a prolonged period (>60-day overlap) (8). In this study, 74% of patients were being treated with both a first- and a second-generation agent, 18% were receiving two second-generation agents and 6% were receiving two first-generation agents. Recent large epidemiological studies have reported distinct trends of increased use of antipsychotic combination therapy (9); Clark et al. reported a quadrupling of the rate of antipsychotic combination use (from 5.7% to 24.3%) between 1995 and 1999, along with an increased use of second-generation agents (from 43% to 70%) over the same time period (10).

The potential hazards of combining antipsychotics include additional adverse effects (e.g. sedation, hypotension, anticholinergic toxicity, worsening metabolic profile), loss of advantages of second generation antipsychotics (e.g. increased risk oftardive dyskinesia when adding a first-generation agent and presence of metabolic adverse effects-the worse of both worlds), pharmacokinetic interactions and higher costs. Moreover, complex prescriptions decrease compliance; thus, exacerbating a clinical problem often encountered in patients with schizophrenia or other psychotic disorders.

Frequently, antipsychotic polypharmacy represents an attempt by the physician to achieve a greater or a faster therapeutic response (11). Many patients in routine care settings continue to experience significant symptoms while following usual treatment regimens (12). In other cases, antipsychotic polypharmacy may be the result of "getting stuck" in switching from 1 antipsychotic medication to another (4, 13). However, evidence supporting concomitant use of more than 1 antipsychotic medication is limited and this therapeutic option should be a last resort after all other options, including clozapine, have failed (14).

There is growing evidence regarding the increased adverse effects associated with combining antipsychotics. There are some epidemiological studies address safety concerns over antipsychotic

combination. Waddington et al. performed a prospective cohort study of 88 patients showed that prescription of more than one antipsychotic was associated with a 2.46 relative risk of reduced survival at 10 years (15). In a case-control study of 70 pairs of hospitalized patients, antipsychotic combined treatment was associated with a longer stay in hospital and a higher risk of adverse effects, while the clinical improvement scores were similar (16). There are some clinical studies address safety concerns over antipsychotic combination. For example, a double-blind controlled study of risperidone added to clozapine in refractory schizophrenia found a significantly greater increase in fasting blood glucose level in the combined-treatment group (17). Similarly, a small study of combined olanzapine-risperidone therapy in patients with schizophrenia who had not responded to sequential monotherapy found a significant increase in body weight, prolactin level, and total cholesterol level after an average of 10 weeks of concomitant treatment (18). These data call for more careful monitoring of metabolic parameters in patients taking more than 1 antipsychotic medication. Concerns have been also voiced about increased risk of QT prolongation in concomitant use of ziprasidone with low-potency conventional antipsychotic medications (eg, thioridazine), as well as worsening of psychosis when aripiprazole is added as a concomitant treatment (19).

Support for antipsychotic combination is largely confined to case reports and open-label trials rather than double-blind trials. In all of the randomized, double-blind, parallel-group study for antipsychotic combination, the support for this treatment strategy is limited. Clozapine and risperidone combination had three RCT studies (17, 20, 21). However, the data of these three studies showed controversial results. Only one study showed statistically significant greater reduction on both positive and negative symptoms of schizophrenia in clozapine and risperidone combination group (20). One clozapine and sulpiride combination study showed that clozapine and sulpiride combination group had greater psychotic symptoms and higher proportions of subjects met treatment responder criteria (22). However, this study was limited by only had 28 subjects, with 16 subjects in clozapine and sulpiride combination group and 12 subjects in clozapine and placebo combination group. One clozapine and aripiprazole combination study showed that there was no significant difference in the BPRS total score reduction between the clozapine and aripiprazole combination group and clozapine and placebo combination group (23). Only in the secondary analyses, improvement was significantly greater with aripiprazole treatment than with placebo for negative symptoms assessed by both the BPRS negative symptom sub-scale and the SANS total score but not for positive symptoms. One risperidone/quetiapine and aripiprazole combination study showed that risperidone/quetiapine and aripiprazole combination group did not have statistically significant greater reduction on both positive and negative symptoms of schizophrenia than risperidone/quetiapine and placebo combination group (24).

There are some clinical tips to reduce antipsychotic polypharmacy. First, physicians must optimize monotherapies prior to attempting polypharmacy. Too often monotherapies are tried for only 4–8 weeks, but the evidence suggests that it can take 16 weeks or longer for the majority of patients to improve symptoms by 30% and up to a year for some patients to improve by 60% (25, 26). Secondly, a pitfall to avoid is the common fallacy that improvement after adding drug B to drug A is because of

synergy between them. It is also possible that the improvement is because of drug B alone, and that drug A should be discontinued. It is even possible that the improvement is because of more time on drug A alone, and that drug B should be discontinued. Third, physicians must avoid "getting stuck" in switching from 1 antipsychotic medication to another due to forget to continue switching. Fourth, we can try whole department multi-faceted intervention to prevent antipsychotic polypharmacy. The multi-faceted intervention can include educational workbook, educational visit to consultants, and a reminder system on medication charts or computer reminder system to doctors and nurses (27).

The pervasive practice of antipsychotic combination treatment for patients with schizophrenia spectrum disorders is not supported by the EBM literature. We are not advancing that antipsychotic combination therapy should be banished from clinical practice. Indeed, a good clinical practice implies taking into account multiple complex variables while determining the best clinical algorithm that should be followed for a given patient. However, it could be argued that, in light of a relative lack of research-supported proof of efficacy, a treatment using the combination of antipsychotics should try carefully and periodically review the effectiveness and safety. We suggest that further trials should explore various antipsychotic combinations to address their effectiveness and safety issues.

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2010春季學術研討會精神分裂症藥物治療辯論

躁鬱症藥物治療辯論會：支持躁鬱症鬱期使用抗憂鬱劑治療

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99.4.17

針對躁鬱症鬱期是否該使用抗憂鬱劑治療，就實證醫學乃至臨床現況的觀點，本文支持「可使用抗憂鬱劑」。或許，此議題的真正論點不是討論「可不可以用」，而是該「如何使用」的問題。需要先行說明的是，討論此議題時，對「抗憂鬱劑」的重新定義，也為此議題重新開啟另一個對話空間，因為當抗精神病藥物或情緒穩定劑也具有抗憂鬱的作用時，究竟什麼才是「抗憂鬱劑」呢？有鑑於此，本文所討論的抗鬱劑，僅包含目前大家所熟悉的「抗憂鬱劑」，包括TCA,MAOI, SSRI, SNRI, NDRI, NaSSA等。

以下將從現行全球對躁鬱症鬱期的治療準則、躁鬱症鬱期使用抗憂鬱劑的好處與危險、躁鬱症與焦慮症的高共病性、以及在療效相對而言較差的躁鬱症鬱期的治療選擇等觀點，分別陳述之。Fountoulakis在2008年CINP的官方雜誌International Journal of Neuropsychopharmacology整理了目前對躁鬱症鬱期的治療準則，包括TMAP (Texas Medication Algorithm Project)、WFSBP (World Federation of Societies of Biological Psychiatry)、APA (American Psychiatric Association)、CANMET (Canadian Network for Mood and Anxiety Treatments)、NICE (the National Institute for Health and Clinical Excellence)，加上Malhi在2009年的文章中提及的RANZCP (The Royal Australian and New Zealand College of Psychiatrists)、BAP (The British Association for Psychopharmacology)，都一致指出，抗憂鬱劑可以作為躁鬱症鬱期的第一線使用藥物，並建議需合併抗躁症劑 (抗精神病藥物或情緒穩定劑)。而Arash 今年(2010)刊登在 Harvard Review of Psychiatry，對躁鬱症鬱期的治療流程，也為迄今為止的治療準則做了一個暫時的注解：首先，先確定是否有立即需電痙攣治療的適應症；其次考慮是否有精神病症狀需要使用抗精神病藥物；再來是若無使用情緒穩定劑，則可先考慮使用鋰鹽，若已使用情緒穩定劑，則建議調整原先情緒穩定劑劑量，或考慮加上或轉換至鋰鹽、quetiapine 或 lamotrigine；當無誘發躁症的危險性時，可考慮加上抗憂鬱劑。此外，對於快速週期型可能需要合併使用兩種以上情緒穩定劑，而對於難治型的病人，應考慮合併電痙攣治療及藥物治療。

Gijsman於2004年刊登於American Journal of Psychiatry的文章，對治療躁鬱症鬱期之12個randomized, controlled trials做了系統性的回顧，共有1088人納入分析，治療4到10週。有75%的病人同時合併使用情緒穩定劑或非典型抗精神病藥物，其結果顯示相較於安慰劑，抗憂鬱劑具有較佳之療效。Malhi於2009年的文章也認為，儘管好處並非十分明顯，然若考量急性期及預防復發期的治療，抗憂鬱藥物仍有其治療的價值。

相對於使用抗憂鬱藥物可以帶來的療效，使用抗憂鬱藥物時也不應使病人暴露於過高的風險。目前臨床上最擔憂的是使用抗憂鬱劑會誘發輕躁症、躁症或情緒快速循環。Post指出，在同時使用情緒穩定劑之下，10週的治療約有14%會轉換成輕躁症或躁症；而Sachs 2007年刊登於NEJM的研究指出，經過26週的治療，儘管抗憂鬱劑無明顯療效，但和大部分研究中的結果類似的是，使用抗憂鬱劑並不增加誘發輕躁症或情緒快速循環的可能，個案組與對照組相同，約僅有10%發生TEAS(treatment-emergent affective switch)。此外，不同病人的特性，不同藥物的特性也與TEAS有關：用於男性、第二型躁鬱症、無過往TEAS史者較安全；而誘發TEAS危險性，TCA 較其他抗憂鬱劑為高，venlafaxine較SSRI、bupropion為高。而Shi也在其病歷回顧的研究中特別提出，約8週左右出現情緒轉換的可能性較大，建議若使用抗憂鬱劑，不宜超過8週。簡言之，在合併使用抗躁症藥物下，使用抗憂鬱劑似乎不會帶來更多情緒轉換的風險，只要慎選病人及適合之藥物與使用的時間。

除了可能對憂鬱的療效與無過高的風險之外，若是使用抗憂鬱藥物可以帶來其他更多的好處，也可成為使用抗憂鬱藥物的其中一個理由。躁鬱症與焦慮症的高共病性則加強了此一論據。有24–79%躁鬱症的病人終生可能罹患一種以上的焦慮症 (Pini et al., 1997; Feske et al., 2000; McElroy et al., 2001; Freeman et al., 2002, Henry et al., 2003; Kessler et al.,2005; Otto et al., 2006; Simon et al., 2007)；加上共病焦慮症者具有較高之憂鬱症狀、酒精濫用、自殺意念、及對鋰鹽及抗痙攣藥物具有較差之反應 (Young et al., 1993; Frank et al., 2002; Feske et al., 2000; Henry et al.2003)，更加強了使用抗憂鬱藥物的合理性，因為對於複雜難治的疾病，不應輕易放棄任何一種治療選擇。

因此，本文建議躁鬱症鬱期可使用抗憂鬱藥物，只要Do the Right Thing,

and Do the Thing Right：Choose the right antidepressant, in the right combination, for the right patients, at the right timing, and for a right period of time，抗憂鬱藥物都應該是躁鬱症鬱期的治療選項之一。

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Antidepressant use in Bipolar depression

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雖然雙極性情感疾患方是由躁狂或者輕躁發作來定義，但實際上憂鬱期在疾病中所扮演的歷史角色可能更重要。憂鬱期比躁狂或者輕躁時期之平均發生頻率要高且持續時間也較長，且多數自殺事件在這時期發生。 延遲診斷以及不適當的治療將更進一步使預後惡化 (Thase 2005)。

第一型雙極性情感疾患之憂鬱時期，多數病患單獨使用情緒穩定藥物（carbamazapin、divalproex、lamotrigin、鋰或者非典型的抗精神病藥物）治療即可獲得良好之效果 (Yatham, Kennedy et al. 2009)。 且目前無臨床試驗結果支持於此階段單獨使用抗憂鬱藥物治療。 而急性時期抗憂鬱藥物合併情緒穩定藥物之使用則在單獨使用情緒穩定藥物治療反應不佳時才予考慮。但在先前一大規模之雙盲臨床藥物研究中顯示併用第一線抗憂鬱藥物雖不會增加轉為躁狂或者輕躁之風險但也不會改善治療反應 (Sachs, Nierenberg et al. 2007)。 而併用第二或第三線之抗憂鬱藥物則有增加轉為躁狂或者輕躁之風險 (Leverich, Altshuler et al. 2006)。 這風險與藥物種類以及服藥時間之長短有顯著之相關。 而此風險在憂鬱時期混合出現躁症症狀之病患更高，其發生之機會也與憂鬱期楊氏躁症量表之得分高低有顯著相關 (Schneck, Miklowitz et al. 2008; Frye, Helleman et al. 2009; Goldberg, Perlis et al. 2009)。重要的是，臨床上人們發現有極高比例之病患在雙極性情感疾患之憂鬱時期混合出現躁症（輕躁）症狀。而抗憂鬱藥物誘發躁狂或者輕躁之風險在第一型與第二型雙極性情感疾患又不相同 (Bond, Noronha et al. 2008)。文獻回顧顯示第二型雙極性情感疾患之風險介於第一型雙極性情感疾患與單極性之重度憂鬱症之間。

因此，情緒穩定藥物治療反應不佳之個案也應考慮合併人際與社會韻律療法、認知行為治療、穿顱磁刺激或電痙攣治療等非藥物治療方法以改善治療反應並減少合併合併抗憂鬱藥物誘發之情緒波動。 而併用抗憂鬱藥物之病患在緩解後需維持抗憂鬱藥物併用的時間仍不清楚，但在雙極性情感疾患之維持期亦不建議長期使用抗憂鬱藥物。 維持期單獨使用情緒穩定藥物即可有效降低未來憂鬱、躁狂或者輕躁發作之風險 (Licht 2010)。

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會員投稿

老年憂鬱症的病識感腦影像研究

高雄醫學大學附設醫院 精神科 陳正生

幾年來固守老年憂鬱症的研究，從最夯的血管性病因研究到認知功能變化的議題，也小有一些研究成果。一日，與隔壁辦公室的好友兼好同學與好同事的顏正芳醫師聊撰寫新的研究計畫，兩個人想著想著，要想出新研究的賣點。他有一系列的病識感研究，我有一些老年憂鬱症的病患照顧以及與醫學影像科醫師合作的經驗，兩個人一拍即合，計畫看看用MRI來研究老年憂鬱症的病識感，討論完自己心想真是crazy idea。臨床上建立病人對自己疾病的了解是看診重要的一部分，但總是會遇到「秀才遇到兵，有理說不清」的情境，沒經過brain storm，也沒想到要用腦影像的工具來研究「缺乏病識感」這個「兵」(有時更像「大軍」)。

天馬行空的crazy idea也要找落點的理論基礎。我們已經熟悉精神分裂症病識感的評估，現在要來找憂鬱症病識感的評估工具，還要找病識感在大腦裡的熱點。很幸運的找到一個針對情緒疾患的病識感評估量表Mood Disorder Insight Scale (MDIS)，MDIS包含了三個子問卷，分別是疾病的覺察、疾病歸因與對治療需要，每一項子問卷得滿分則定義為完整病識感，未滿分則定義為非完整病識感。文獻與我們之前的研究發現精神分裂症患者的病識感與執行功能(i.e. Wisconsin Card Sorting Test）相關，而且雖然腦影像的研究不多(這反而是我們研究的賣點之一)，但腦結構性的研究支持額葉體積較小與病識感相關。我們決定用這些間接證據，把region of interest (ROI)定在額葉。國科會青睞這個計畫後就開始上工了。

收案邀請老年人多做個MRI不是太難的事情，再加做個proton magnetic resonance spectroscopy (1H MRS)。1H MRS可以在in vivo的情況下，經過頻譜分析來測量大腦的一些生化代謝的濃度，1H MRS主要的化學物質有N-acetyl-L-aspartate (NAA)、creatine/phosphocreatine (Cr)、choline-containing compounds、及myo-inositol。NAA主要位在神經細胞內，可以當做健全神經元結構(structural integrity of the neuron)的指標；Cr是creatine kinase phosphate反應的產物，因為分散在大腦許多位置且濃度相當，常常被當作是一個參考值；Choline的濃度則是許多包含choline物質的總和，這些物質有free choline、phosphocholine、與glycerophosphocholine和少量的神經傳導物質acetylcholine；myo-inositol是phosphatidylinositol second messenger system的前驅物。
可能在大腦的額葉看到與病識感相關的發現嗎?不是那麼有信心。一年後有75名重度憂鬱症的老年人加入這個研究，在緩解期接受病識感評估與1H MRS。資料的分析又是要發揮抽絲剝繭、不屈不撓的精神，要能有橫看不到成嶺卻又能側看到成峰的功力，總算有一些新鮮的發現。ROI放置在左額葉，測得每個個案在左額葉的NAA、choline、and myo-inositol與Cr的比值。結果發現MDIS總分與左額葉NAA/Cr 相關(spearman rho=0.31; p<0.006)。MDIS-疾病歸因之病識感不完整者有較低的NAA/Cr (mean=1.27, SD=0.13 vs. mean= 1.37, SD=0.18; p<0.01)。此外，久病(病程較久)似乎對自己的憂鬱症能比較了解，但統計上只達邊緣性的相關(p=0.09)。研究結論支持額葉功能與病識感相關，尤其是與疾病歸因相關的病識感。前額葉較低濃度的NAA/tCr代表神經元的功能不足與病識感相關。

病識感不僅受到社會文化與心理的影響，腦部功能也來參一腳。當然影響因素可能更複雜，甚至這些社會文化、心理與腦部功能對病識感可能也有交互作用。但明確地把額葉神經元的功能好壞與病識感連結一起，實在也有小小的成就感。當然，研究結果總是要對臨床有些啟示，以後跟病人討論病識感，尤其怎麼解釋自己的疾病也要想到病人的額葉功能。小小的成果可以誘發更多的crazy idea，例如其他年齡的憂鬱症呢?精神分裂症與雙極性情感性疾病呢?進一步可以探討這個神經元功能可不可能經由某些藥物或非藥物的介入而有所改變?...好像又會有更多的研究題目，藉此拋磚引玉，呼朋引伴來探討這些題目。

PS: 此篇論文已被接受刊登

Chen CS, Kuo YT, Li CW, GC Liu, Ko CH, Lin HF, Yeh YC, Chang HC, Yen CF. Brain proton magnetic resonance spectroscopic study of insight among elders with late-life depression in remission. Journal of Affective Disorder. 2010 Jun 19. [Epub ahead of print]

● 第四屆第五次理監事會議

台灣生物精神醫學暨神經精神藥理學學會
99年秋季年會
Ceremony for Taiwan Chapter of International Society Bipolar disorder (ISBD)

時間：民國99年9月18日(六)
地點：台北榮總科技大樓1F會議室(立體停車場旁新建大樓)

時間	主題	主講者	主持人
08:30~09:00	報到及領取選票		
09:00~09:20	Opening remark	蘇東平 理事長	
09:20~10:20	Personalized, Quantitative, Evidence-Based Treatment for Bipolar Disorders---Potential to Change Practice	Prof. TA Ketter Director of Bipolar Disorders Clinic, Stanford University School of Medicine	蘇東平 理事長
10:20~10:30	休　息		
10:30~11:30	Stabilizing bipolar disorder: Clinical approach and biological understanding	Prof. Kyooseob Ha President of East Asian Bipolar Forum, Chairman of ISBD Asian Network for Bipolar Disorder	沈武典 教授
11:30~12:15	會員大會 (研究論文獎頒獎)		
12:15~01:45	午　餐		
01:45~02:45	TSBPN and JSBP Academic Exchange Program Award lecture 日本生物精神醫學會 交流講座得獎人演講	Dr. Fujimura, Yota : Decreased Neurokinin1 (Substance P) Receptor Binding in Panic Disorder Revealed by PET Dr. Akitoyo Hishimoto: A putative cis-acting polymorphism in the NOS1 gene is associated with schizophrenia and NOS1 immunoreactivity in the postmortem brain	劉嘉逸 主任
02:45~04:00	Taiwan Bipolar disorder consensus	陳益乾 主任、張景瑞 主任 蔡尚穎 教授	蘇東平 理事長
04:00~04:20	休　息 (理監事選舉開票)		
04:20~05:20	遺傳研究之倫理議題 (倫理學分)	雷文玫 教授	藍先元 教授
05:20~05:30	Closing remark	蘇東平 理事長	

International society of Bipolar disorder (ISBD) 在亞洲已有韓國、日本、中國、香港成立Bipolar chapter, 以進行各區之bipolar disorder 研究及教育並進行國際交流。本會已於2010年1月成立bipolar chapter，此次年會邀請美國Professor TA Ketter 及韓國Prof. Kyooseob Ha 兩位著名學者進行大會演講。Professor Ketter為國際知名之bipolar disorder大師，研究領域涵蓋病理影像MRI、MRS、PET、症狀診斷學及治療，今年並出版專書Handbook of Diagnosis and Treatment of Bipolar Disorders (American Psychiatric Pub Inc)。Prof. Kyooseob Ha為President of East Asian Bipolar Forum, Chairman of ISBD Asian Network for Bipolar Disorder，兩位大師之演講精彩可期。Taiwan chapter 已開始進行Taiwan Bipolar disorder consensus 之擬訂，下午將由Chairman蘇東平理事長主持及Vice- Chairman蔡尚穎教授進行台灣共識的初報，歡迎所有會員參與及提供意見。大會下午並有本會與日本生物精神醫學會交流講座得獎人演講，以促進國際交流。另倫理學分由陽明大學雷文玫教授針對會員所關注之遺傳研究之倫理法律相關研究規範進行精彩演講。本年度並將進行理監事改選，希望會員踴躍與會。

＊本活動申請台灣精神醫學、公務員學分及醫學倫理學分中。
學會網站: http://www.biopsychi.org.tw/index.html

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啟

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