出國進修研究報告

# 精 神 醫 學

服務機關：成大醫學院附設醫院
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出國地區：美 國

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主辦機關:

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關鍵詞: 精神病藥物臨床試驗,精神分裂症

內容摘要: 於89年8月至90年7月間至美國Duke University精神科從事研習抗精神病藥物臨床試驗及精神分裂症相關病理之研究。於其間現已完成5篇相關著作，及參加精神科臨床工作之研習及討論，並商討未來兩地共同合作研究的可行性，其相關主題爲探討hyperhidrosis(手汗症)之病人其精神疾病罹病率之研究。本次研習之建議爲：1.臨床藥物試驗是發展潛力極大的領域，跨國協同合作研究是很重要性且精神醫學訓練加強以神經科學知識爲基礎的方針是未來的主流。

本文電子檔已上傳至出國報告資訊網

**目的**：赴美研習抗精神病藥物臨床試驗及精神分裂症相關病理之研究。

**過程及心得**：

本人於89年8月至90年7月間至美國北卡羅萊納州杜克大學醫學院(North Carolina, Duke University)精神科從事研究進修之工作。杜克大學醫學院為美國前十名之醫學院，其精神科亦然，我選定以精神分裂症為主軸的研究。杜克大學精神分裂症的研究除了大學醫院本部外尚與州立醫院 John Umstead Hospital (JUH)合作從事抗精神病藥物及相關病理之研究，於 JUH 有個專屬藥物實驗的研究病房(其工作人員直屬 Duke University)，其住院病人均以接受臨床藥物研究為主，約 30 床，同時間進行多種藥物，不同階段之臨床藥物試驗。其主要探討的主題為(一)新一代抗精神病藥物的療效，(二)新一代抗精神病藥物不同劑型的療效，(三)nicotine(抽煙患者)對精神病理之影響，(四)nicotine 對患者認知功能之影響，(五)glutamate 及其相關藥劑對精神分裂症之療效等，主持該病房之醫師為 J.P. McEvoy(我的指導教授)。

我至 JUH 之工作重點為參與各項研究的資料收集、評估、整理之工作，並參與論文寫作之工作，其間計已完成下列五篇文章如下：

(1)Cassidy F, McEvoy JP, Yang YK, Wilson WH: Insight is Greater in Mixed than in Pure Manic Episodes of Bipolar I Disorder. J of Nervous and Mental Disease. 2001; 89:398-399.

(2)Cassidy F, McEvoy JP, Yang YK, Wilson WH: Smoking and psychosis in patients with bipolar disorder. Comprehensive Psychiatry (in press)

(3)Yang YK, McEvoy JP, Wilson WH, Levin ED, Rose JE: Reliabilities and intercorrelations of reported and objective measures of smoking in patients with schizophrenia. Schizophr Res (in press)

(4)Yang YK, McEvoy JP, Wilson WH: Benztropine and smoking in patients with schizophrenia. J of Clinical Psychiatry (submitted)

(5)Yang YK, Nelson L, Kamaraju L, McEvoy JP, Wilson WH:Nicotine decreases bradykinesia, rigidity, tremor in haloperidol-treated patients with schizophrenia. Neuropsychophamacolosy (submitted)

其他論文也正在寫作中，JUH 除了提供抗精神病藥物之研究外，尚提供老人精神醫學臨床見習之機會，除了參加其固定之個案討論會及病房迴診外，尚參加其以影像教學為主的 MRI reading conference。老人精神醫學的臨床工作，影像醫學的角色越來越重要，因此如何能熟悉並廣泛運用精神科的臨床用途是極為重要，MRI reading conference 舉行的方式為該段期間住院(老人精神科)病人，接受 MRI 檢查(於 Duke hospital)之片子，由其主治醫師說明病情，並進一步 MRI 影像判讀，之後由該科主任評論，最後再參考神經放射專科醫師之意見，這部份臨床的教育對我的臨床視野有很重大影響及提昇。

Duke 大學每週的專題演講是很具教育價值的，每週三上午均會邀請一位來至全美各地的知名學者，就其專長發表精闢的演說，對於從事臨床工作多年的我而言不諦是個很好的再教育。

除了研究工作，臨床討論會及專題演講之外，如何加強日後跨國性的研究合作，並提昇研究水準也是本次的重要工作之一。我試著將台灣目前研究的特色介紹給予杜克大學精神科相關的研究人員，並遊說跨國性計劃的可能性。Prof. J.R.T. Davidson 已同意申請一個研究計劃以探討 hyperhidrosis(手汗症)之病人其精神疾病罹病率之研究，並擬定若該項研究獲得經費支助(美國研究機構)則將該項研究將於台灣台南進行資料收集。此同時我們也將尋求相關主題的研究經費支助，並合作完成研究計劃(類似國科會之整合型計劃)，以便日後論文發表及臨床運用更具國際水準。

**建議：**

1.台灣正往生物科技發展，臨床藥物的研發是極為重要一環，而臨床藥物試驗雖屬生物技術開發之末端產業，但目前台灣臨床藥物試驗之環境相對藥物原料或新藥物的開發更成熟，且其具龐大的市場利基，值得各醫學中心發展及投入。

2.出國進修除研習新進技術、知識之外，如何推銷台灣研究上的利基，以此為跨國性協同研究的基礎，以加速研究及產業升級，是技術國際化的快速捷徑，在此過程中，研究者出國前基本研究能力的培養及本身研究方針的初步建立後才出國，是達到此目標的重要條件。

3.精神醫療除一般的社會、心理層面的探討外，如何以神經科學知識技術解釋行為變化的本質是當今技術的主流，台灣除研究上須再加強外，臨床的訓練如何加強這方面的涵養是極為重要的。

THE JOURNAL OF

# NERVOUS AND MENTAL DISEASE

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January 17, 2001

Joseph P. McEvoy, MD
John Umstead Hospital
1003 12th St.
Butner, NC 27509

Dear Dr. McEvoy:

Re: **BRIEF REPORT.** INSIGHT IS GREATER IN MIXED THAN IN PURE MANIC EPISODES OF BIPOLAR DISORDER.

We are pleased to tell you your manuscript has been accepted for publication in The Journal of Nervous and Mental Disease. Papers are accepted on the condition that the author(s) give the Editor the right to make revisions required to bring the manuscript into conformity with Journal style.

You will notice from the enclosed list that some additional information is needed before we can proceed with your paper. We hope to receive your response as promptly as possible so that we can schedule the paper for publication in a timely manner.

We will notify you when we have a firm publication date (there is currently a 6-month backlog). Our publisher will then send you galley proofs; please follow all instructions accompanying the proofs and correct and return them--within 48 hours of receipt--directly to the publisher as shown in their instructions. A reprint order blank will be sent to you along with the proofs. Please note that reprints are handled by the publisher, and are usually mailed within eight weeks of publication. If you expect to be away from your office for any extended period of time, please send us a forwarding address or arrange with one of your colleagues to read proof for you.

Thank you very much for offering us this paper and for your cooperation.

Sincerely,

Eugene B. Brody, MD

enc.

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THE JOURNAL OF NERVOUS AND MENTAL DISEASE

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# Brief Reports

## Insight is Greater in Mixed than in Pure Manic Episodes of Bipolar I Disorder

*" the correlation between truth and happiness is not invariably positive. " (Sackeim, 1998)*

Deficits in insight are common among patients in manic episodes of bipolar I disorder (Amador et al., 1994, Ghaemi et al., 1995, Michalakeas et al., 1994) However, none of the studies examining insight in patients with bipolar I disorder have addressed the issue of mixed episodes Depressed patients have consistently been found to have higher levels of insight than manic patients (Amador et al., 1994, Michalakeas et al., 1994, Peralta and Cuesta, 1998), and dimensional depression is inversely related to self-deception in both normal and clinically depressed populations (Kiersky, 1998, Sackeim, 1998) We measured insight in 53 newly admitted patients in mixed or pure manic episodes of bipolar I disorder

### Methods

*Patient Population.* Fifty-three newly admitted patients (26 men and 27 women) who met DSM-IV criteria (American Psychiatric Association, 1994) for mixed or pure manic episodes of bipolar I disorder provided signed informed consent to participate All had been noncompliant with prescribed medications prior to admission, 28 were assessed before resumption of treatment with antipsychotic and/or mood stabilizing drugs, and the remainder were assessed within 7 days of resuming treatment (on average, within 3 days) (Table 1)

*Assessments* DSM-IV criteria (American Psychiatric Association, 1984) for mixed or manic episodes were employed. The Insight and Treatment Attitudes Questionnaire (ITAQ), an 11-item scale addressing presence of mental disorder and need for hospitalization and pharmacotherapy (McEvoy et al., 1989), was used as the measure of insight. The Scale for Manic States (SMS), a 20-item scale designed to distinguish mixed versus pure manic episodes (Cassidy et al , 1998), was used to assess affective psychopathology Six items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution, and unusual thought content) from the Positive and Negative Syndromes Scale (PANNS, Kay, 1991) were used to assess psychotic psychopathology

*Analyses* Mixed and manic patients were compared on categorical variables, using chi-square analyses, and on continuous variables using *t*-tests Selected Pearson correlations were calculated. All tests were two-tailed

### Results

Eleven of these 53 patients met DSM-IV criteria for mixed episode, and 42 met criteria for pure manic episode The distributions of race (mixed 18% black, manic 29% black) or gender (mixed 64% female, manic 48% female) did not differ significantly The two groups did not differ significantly in age, length of illness, number of prior hospitalizations, or total score of the six PANSS items

Patients in mixed episodes had significantly higher ITAQ scores, and SMS factor 1 scores SMS factor 1 is the sum of the items depressed mood, anxiety, guilt, mood liability, and suicide The other SMS factors did not differ significantly across the two groups ITAQ scores were significantly correlated with SMS factor 1 scores ($r = .37$, $p = 006$), and significantly inversely correlated with the total scores of the six PANSS items ($r = 28$, $p = 045$)

### Discussion

Our finding of a weak inverse relationship between insight and psychotic psychopathology replicates the work of Michalakeas et al. (1994) in patients with mania. The PANSS items delusions ($r = -31$, $p = 022$) were most strongly inversely correlated with the ITAQ scores, with grandiosity ($r = -21$, NS) lagging behind. Thus, it is more general psychosis, not just mood-congruent grandiosity, that limits insight in these patients (Peralta and Cuesta, 1998)

Individual differences in the tendency to engage in self-deception (Fingarette, 1969) vary inversely with reports of depressed mood in the general population Optimistic, self-serving inaccuracies in self-knowledge, i e , favorable self-deception, may have adaptive function in mood regulation The gross failures of self-evaluation seen in manic patients may reflect " the release, over utilization, or rigidification of basic mood-regulatory operations," rather than a loss of judgment (Sackeim, 1998)

Depressed patients demonstrate diminished self-deception, seeing their flaws with painful clarity It is not clear whether self-deception protects against the development of depression, or the development of depression results in diminished capacity to self-deceive Patients in mixed episodes, who demonstrate both manic and depressive psychopathology, differ from patients in pure manic episodes in that they do not show gross failures of self-evaluation Future studies should examine whether the better insight these patients display translates into better compliance

### References

American Psychiatric Association (1994) *Diagnostic and statistical manual of disorders* (4th ed) Washington, DC Author
Amador XF, Flaumn, Andreasen NC, Strauss DH, Yale SA, Clark SC, Gorman JM (1994) Awareness of illness in schizophrenia and schizoaffective and mood disorders. *Arch Gen Psychiatry* 51 826–836
Cassidy F, Forest K, Murry E, Carroll BJ (1998) A factor analysis of the signs and symptoms of mania. *Arch Gen Psychiatry* 55 27–32
Fingarette H (1969) *Self-deception.* London. Routledge and Kegan Paul



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TABLE 1
*Characteristics of Patients in Mixed versus Pure Manic Episodes of Bipolar I Disorder (mean ± SD)*

| | Mixed ($N$ = 11) | Manic ($N$ = 42) | $t$ | $df$ | $p$ |
|---|---|---|---|---|---|
| Age (yr) | 45 ± 8 | 43 ± 10 | | | NS |
| Years since first hospitalization | 11 ± 8 | 10 ± 9 | | | NS |
| Number of hospitalizations | 8 ± 8 | 6 ± 7 | | | NS |
| ITAQ score | 14 ± 5 | 8 ± 7 | 2.60 | 51 | 012 |
| Total (6 PANSS Items) | 13 ± 5 | 14 ± 5 | | | NS |
| SMS total score | 36 ± 8 | 28 ± 9 | 1 87 | 51 | 067 |
| SMS factor 1 | 9 6 ± 3 8 | 1 5 ± 1 5 | 6 87 | 10 82[a] | < 001 |

[a] Corrected for unequal variances.

Ghaemi SN, Stoll AL, Pope HG (1995) Lack of insight in bipolar disorder The acute manic episode *J Nerv Ment Dis* 183 464–467.

Kay SR (1991) *Positive and negative syndromes in schizophrenia* New York: Brunner/Mazel.

Kiersky JE (1998) Insight, self-deception, and psychosis in mood disorders In SF Amador, AS David (Eds), *Insight and Psychosis* (pp 91–104) New York: Oxford University Press

McEvoy JP, Apperson LJ, Appelbaum PS, Ortlip P, Brecosky J, Hammill K, Geller JL, Roth L (1989) Insight in schizophrenia. Its relationship to acute psychopathology, *J Nerv Ment Dis* 177 43–47

Michalakeas A, Scouts C, Charalambous A, Peristeris A, Marinos V, Keraman E, Theologou A (1994) Insight in schizophrenia and mood disorders and its relation to psychopathology *Acta Psychiatr Scand* 90 46–49

Peralta V, Cuesta MJ (1998) Lack of insight in mood disorders *J Affect Disord* 46 55-68

Sackeim HA (1998) The meaning of insight. In XF Amador, AS David (Eds), *Insight and psychosis* (pp 3–11) New York: Oxford University Press.

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This study was supported by a NARSAD Independent Investigator Award to Dr McEvoy

# Comprehensive PSYCHIATRY

OFFICIAL JOURNAL OF THE AMERICAN PSYCHOPATHOLOGICAL ASSOCIATION



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February 13, 2001

Joseph P. McEvoy, M.D.
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1003 12th Street
Butner, NC 27509

Re: Smoking and Psychosis in Patients with Bipolar I Disorder (MS#2K111)

Dear Dr. McEvoy:

Your manuscript has been reviewed by ***Comprehensive*** **Psychiatry**. This is an important contribution to the field, and I am happy to let you know that it has been accepted for publication.

You will be hearing directly from our publisher, W.B. Saunders Company, regarding a copyright release and galleys of your manuscript.

Thank you for submitting your paper to ***Comprehensive*** **Psychiatry**.

Best wishes.

Sincerely yours,

David L. Dunner, M.D.
Editor

# SMOKING AND PSYCHOSIS

# IN PATIENTS WITH BIPOLAR I DISORDER

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Feb 6

ABSTRACT

We characterized 67 newly admitted patients in manic or mixed episodes of Bipolar I disorder on categorical and continuous measures of smoking and psychosis to test the hypothesis that patients who were smokers would be more likely to demonstrate psychotic features. Smoking did not associate with psychosis in any of our analyses

## INTRODUCTION

Patients with Major Depressive Disorder (MDD) smoke at significantly higher rates (49%) than the general population (25%).[1] Kendler et al[2] report that the association between MDD and smoking in women is best explained by a noncausal genetic model in which familial factors, probably genetic, predispose to both conditions.

Patients with Schizophrenia smoke at even higher prevalence rates (70-80%).[1,3] Abnormalities in nicotine receptors may predispose to both conditions. [4,5]

Patients with Bipolar I Disorder smoke at high prevalence rates (50-70%)[6,7] that are intermediate between those of MDD and Schizophrenia. We examined whether, among patients with Bipolar I Disorder, those who smoke would more frequently display psychotic features than those who do not smoke, reflecting a postulated factor that predisposed both to psychotic features and to smoking.

## METHODS

Patient Population: Sixty-seven patients (36 men, 31 women; 19 black, 48 white), newly admitted in manic or mixed episodes of Bipolar I Disorder,[8] provided signed informed consent to participate. All had been noncompliant with prescribed medications prior to admission; 33 were assessed before resumption of treatment with antipsychotic and/or mood stabilizing drugs and the remainder were assessed within 7 days of resuming treatment (on average, within 3 days).

Assessments: Current smoker/nonsmoker status was determined by chart review, patient interview, and ward observation. A Smoking History Form and the Fagerstrom Test for Nicotine Dependence[9] were administered to smokers. Smokers participated in 2-

hour free smoking sessions during which they could smoke as much as they liked; staff counted the number of cigarettes smoked, and measured expired carbon monoxide levels and serum nicotine and cotinine levels at the end of these sessions.

Six items from the Positive and Negative Syndromes Scale [10] and a Global Psychosis item (1=no psychotic features, 2=fleeting or questionable psychotic features, 3=mood congruent psychotic features, 4=mood incongruent psychotic features) were rated on every patient. Patients with Global Psychosis scores of 3 or 4 were considered psychotic.

Analyses: We contrasted the proportions of smokers and nonsmokers, with and without psychotic features, using a Chi square analysis, and contrasted smokers and nonsmokers on PANSS and Global Psychosis items using MANOVA, with post-hoc t-tests on the PANSS items. Selecting for smokers, we contrasted those with versus without psychotic features on continuous measures using t-tests. All tests were two-tailed.

## RESULTS

Thirty-eight (57%) of these patients smoked. Forty-three (64%) had psychotic features. The prevalence of psychotic features among smokers was 63%, and, among nonsmokers, 66% (N.S.). Smokers and nonsmokers did not differ significantly in their scores on any of the six PANSS items, or on the Global Psychosis item (Table 1)

When we selected only smokers, those with psychotic features had had significantly more prior hospitalizations than those without ($8 \pm 9$ versus $4 \pm 3$, $t=2.10$, $p=.044$). However, these two groups did not differ in age, duration of illness, number of years a smoker or packs per day smoked, Fagerstrom score, or 2-hour free smoking

measures (number of cigarettes smoked, expired CO levels, serum nicotine or cotinine levels).

## DISCUSSION

Our hypothesis that, among patients with Bipolar I Disorder, those who smoke would more frequently display psychotic features than those who do not smoke.

Acknowledgments: This study was supported by a NARSAD Independent Investigator Award to Dr. McEvoy.

Nicotine and cotinine assays were performed in the Clinical Pharmacology Laboratories, University of California-San Francisco (Neal L. Benowitz, MD).

REFERENCES


1. Hughes JR, Hatsukami DK, Mitchell J, Dahlgren L. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986; 143: 993-997.

2. Kendler LS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression. Arch-Gen Psychiatry 1993:50:36-43

3. deLeon J, Gadvand M, Cannso C, White AV, Stanilla JK, Simpson GM. Schizophrenia and smoking: An epidemiological Study in a state hospital. Am J Psychiatry 2995; 152: 453-455.

4. Leonard S, Adams C, Breese CR, Adler LE, Bickford P, Byerley W, et al. Nicotine receptor function in schizophrenia. Schiz Bull 1996;22:431-445.

5. McEvoy JP, Freudenreich O, Wilson, WH. Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry 1999; 46:125-129.

6. Diwan A, Castine M, Pomerlean CS, Meador-Woodouff JH, Dalack KGW. Differential prevalence of cigarette smoking in patients with schizophrenia no mood disorder. Schiz Bull 1998;33:113-118.

7. Gonzalez-Pinto A, Gutierrez M, Ezcurra J, Aizpuru F, Mosequera F, Lopez P, deLeon J. Tobacco smoking and bipolar disorder. J Clin Psychiatry 1998; 59:225-228.

8. Frances A, Pincus HA, First MB. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press, 1996

9. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire Br J of Addictions 1991, 86 1119-1127.

10. Kay SR. Positive and Negative Syndromes in Schizophrenia. New York, NY: Brunner/Mazel, 1991.

**Table 1**
**PANSS and Global Psychosis Items***

| | Smokers | Nonsmokers |
|---|---|---|
| P1. Delusions | 2.6 ± 1.4 | 3.3 ± 1.6 |
| P2. Conceptual disorganization | 2.2 ± 1.5 | 2.5 ± 1.3 |
| P3. Hallucinatory behavior | 1.4 ± 0.9 | 1.5 ± 1.1 |
| P5. Grandiosity | 3.0 ± 1.4 | 3.7 ± 1.6 |
| P6. Suspiciousness/persecution | 2.4 ± 1.3 | 2.8 ± 1 4 |
| G9. Unusual thought content | 1 5 ± 1.0 | 1.7 ± 1.3 |
| Global psychosis | 2.5 ± 1.3 | 2 8 ± 1.4 |

*All contrasts nonsignificant

# BENZTROPINE AND SMOKING IN PATIENTS WITH SCHIZOPHRENIA

Running title: Benztropine, smoking, and schizophrenia

Submitted as a brief report

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Two tables
No Figures

ABSTRACT: Attempts to understand the high prevalence rates for smoking among patients with schizophrenia must account for any effects from the drugs these patients are commonly treated with. We examined whether benztropine, an anticholinergic antiparkinson agent, affected the smoking behaviors of 46 patients with schizophrenia in 2-hour free smoking sessions. All 46 patients had an initial, 2-hour, free smoking session during which staff counted the number of cigarettes smoked and measured end-expiratory carbon monoxide levels. Before a second session, 37 patients received a total of 4 mg benztropine, and 9 patients did not receive benztropine. Smoking measures were highly reliable across the two sessions. There were no significant effects of benztropine or repeated testing.

Key words: Smoking, benztropine, anticholinergic, schizophrenia

## INTRODUCTION

Patients with schizophrenia smoke at much higher prevalence rates (70-90%) than the general population (25% in the U.S.A.) (Lasser et al, 2000), even at first episode prior to pharmacologic treatment or institutionalization (McEvoy and Brown, 1999). However, conventional neuroleptics (McEvoy et al, 1995) and the newer atypical antipsychotics (George et al, 2000) can affect these patients' smoking behaviors.

Anticholinergic antiparkinson drugs can block nicotine-induced seizures (Gao et al 1998), and muscarinic and nicotinic cholinergic receptors appear to interact in some neuronal circuits (Yeomans and Baptista, 1997). We examined whether routine clinical doses of the anticholinergic antiparkinson drug, benztropine, affected the smoking behaviors of patients with schizophrenia.

## MATERIALS AND METHODS

Patient population: Forty-six patients (34 men and 12 women) who met DSM-IV criteria for schizophrenia, and who smoked, provided signed informed consent to participate. Their mean (S.D.) age was 36(10) years (range 19-58 years). They had had 4.8 (5.5) prior hospitalizations (range 0-30), and it had been 9.5 (8.7) years since their first hospitalizations (range 0-30 years). All had been newly admitted in an acute psychotic exacerbation related to noncompliance with a prescribed antipsychotic or had never previously been treated. Their mean (S.D.) score on the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al, 1991) was 6.0(2 .0) with a range of 1-10.

Pharmacological procedures: All patients were initially treated with haloperidol alone, starting at 2 mg oral concentrate daily. This dose was adjusted at 2-3 day intervals until each patient's individual neuroleptic threshold (McEvoy et al, 1991) haloperidol dose was identified; the neuroleptic threshold is the lowest dose that produces a clinically detectable slight increase from baseline in bradykinesia-rigidity. While haloperidol doses remained fixed at neuroleptic threshold levels, patients underwent two 2 –hour free-smoking sessions (vide infra), 24 hours apart. Thirty-seven of the 46 patients took benztropine 2 mg the evening after completing the first free-smoking session, and

benztropine 2mg the next morning prior to the second free-smoking session. Nine of the 46 patients completed both the first and second free-smoking sessions while taking haloperidol alone (no benztropine).

Smoking measures: Inpatients at our hospital are permitted to smoke one cigarette per hour between the hours of 0700 and 2100 inclusive. Cigarettes are kept in the Nurses' Station and made available on the hour.

All patients participated in two 2-hour, free smoking sessions on our research wing (occurring after lunch from 1300-1500), during which they had free access to cigarettes, noncaffeinted sodas and snacks in a naturalistic environment where they could watch movies or regular television programming. Staff kept count of the number of cigarettes each patient smoked, and measured end-expiratory carbon monoxide (CO) levels at the beginning of each session and every 30 minutes throughout, up to 120 minutes (Vitalograph Breath CO Monitor, Lenexa, KS).

Statistical methods: The characteristics of the two patient groups were compared on continuous variables using t-tests, and on categorical variables using Chi-square tests. The potential effects of benztropine and repeated testing on the smoking measures were examined by repeated measures analyses of variance. The stability of the smoking measures was examined by Pearson correlation coefficients. All tests were two-tailed with alpha set at .05.

## RESULTS

The two groups did not differ significantly on any of the demographic or smoking history variables (Table 1)

There were no significant effects of benztropine or repeated testing on any of the smoking measures (Table 2).

Patient's scores on each of the smoking measures showed high levels of test-retest reliability across the two sessions: number of cigarettes ($r = .82$), CO baseline ($r = .70$), CO 120 minutes ($r = .79$), all p values $<.001$.

## DISCUSSION

Mecamylamine, an antagonist at nicotinic cholinergic receptors, blocks nicotine-induced seizures at doses ($ED_{50}$=0.1 mg/kg) equivalent to those used clinically in humans (Gao et al, 1998). Mecamylamine doses of 5-10 mg significantly increase smoking in patients with schizophrenia (Marx et al, 2000).

Although anticholinergic antiparkinson drugs, such as benztropine, block nicotine-induced seizures in mice (Gao et al, 1998) much higher doses are required ($ED_{50}$=7.4mg/kg) than would be equivalent to clinically used doses in humans.

Our results suggest that benztropine, at routine clinical doses, has no effect on smoking in patients with schizophrenia.

Table 1. CHARACTERISTICS OF THOSE PATIENS WHO DID VERSUS THOSE WHO DID NOT RECEIVE BENZTROPINE

| | Benztropine (n=37) | No benztropine (n=9) |
|---|---|---|
| Age | 37 (11) years | 33(8) years |
| Gender | 8 women, 29 men | 4 women, 5 men |
| Number of prior hospitalizations | 5(6) | 4(3) |
| Years since first hospitalization | 10(9) | 9(7) |
| FTND score | 6(2) | 6(3) |
| Years a smoker | 20(13) | 17(7) |

Table 2. SMOKING MEASURES OVER TWO FREE-SMOKING SESSIONS IN PATIENTS WHO DID VERSUS DID NOT RECEIVE BENZTROPINE

| | First Session | Second Session | |
|---|---|---|---|
| Number of cigarettes | 7.3(2.8) | benztropine (n=37) | 7.0(3.0) |
| | 8.6(4.1) | no benztropine (n=9) | 8.3(4.3) |
| CO Baseline (pm) | 20.9(10.1) | benztropine (n=37) | 19.7(9.3) |
| | 16.8(9.6) | no benztropine (n=9) | 16.0(8.7) |
| CO 120 minutes((pm) | 41.2(16.0) | benztropine (n=37) | 39.8(16.8) |
| | 42.9(17.6) | no benztropine (n=9) | 38.8(15.8) |

**REFERENCES**

Gao ZG, Liu BY, Cin WY, Li LJ, Fan QH, Liu CG (1998) Anti-nicotinic properties of anticholinergic antiparkinson drugs. Journal of Pharmacy and Pharmacology 50:1299-1305.

George TP, Ziedonis GM, Feingold A, Pepper WT, Satlerburg CA, Winkel J, Rounsaville BJ, Kosten TR (2000) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. American Journal of Psychiatry 157:1835-1842.

Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KP (1991) The Fagerstrom Test for Nicotine Dependence: A revision of the Fagerstrom Tolerance Questionnaire. British Journal of Addiction 86:1119-1127.

Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH (2000) Smoking and mental illness. Journal of the American Medical Association 284:2606-2610.

Marx CE, McIntosh E, Wilson WH, McEvoy JP (2000) Mecamylamine increases cigarette smoking in psychiatric patients. Journal of Clinical Psychopharmacology 20:706-707.

McEvoy JP, Brown S (1999) Smoking in first-episode patients with schizophrenia. American Journal of Psychiatry 156: 1120-1121

McEvoy JP, Freudenreich O, Levin E, Rose J (1995) Haloperidol increases smoking in patients with schizophrenia. Psychopharmacology (Berlin) 119:124-126.

McEvoy JP, Hogarty GE, Steingard S. (1991) Optimal doses of neuroleptic in acute schizophrenia. Archives of General Psychiatry 48:739-745.

Yeomans J, Baptista M (1997) Both nicotinic and muscarinic receptors in ventral tegmental area contribute to brain-stimulation reward. Pharmacology, Biochemistry and Behavior 57:915-921.

# Reliabilities and Intercorrelations of Reported and Objective Measures of Smoking in Patients with Schizophrenia

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# Reliabilities and Intercorrelations of Reported and Objective Measures of Smoking in Patients with Schizophrenia

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## ABSTRACT

**Background**: Patients with severe psychiatric illnesses are over-represented among persons who smoke. We examined the test-retest reliabilities of reported and objective measures of smoking, and the intercorrelations among these measures, in acutely psychotic patients with schizophrenia, in order to determine whether severe psychiatric illness affects the utility of these variables.

**Methods**: Fifty-seven acutely psychotic patients with schizophrenia participated. A brief smoking history and the Fagerstrom Test for Nicotine Dependence (FTND) were administered twice. Expired carbon monoxide levels, and serum nicotine and cotinine levels were obtained on repeated occasions after 2-hour free-smoking sessions.

**Results**: All measures demonstrated good test-retest reliability. Objective measures of smoking impact (expired carbon monoxide, nicotine, and cotinine levels) were consistently intercorrelated, and weakly correlated with the number of cigarettes smoked and the FTND scores.

**Conclusions**: In acutely psychotic patients with schizophrenia objective measures of smoking impact are reliable and coherently inter-related.

## INTRODUCTION

Data from the National Comorbidity Survey demonstrate that patients with mental illness are about twice as likely to smoke as other persons, and they consume approximately 44% of the cigarettes presently smoked in the United States (1). Patients with schizophrenia, in particular, have prevalence rates for smoking of 70-80% (2,3), even at first episode before the initiation of treatment (4), and they smoke more heavily than other smokers (5,6). We examined the test-retest reliabilities of reported and objective measures of smoking, and the intercorrelations among these measures, in newly admitted, acutely exacerbated patients with schizophrenia, prior to their treatment with antipsychotics, and again after antipsychotic treatment was initiated. We sought to determine whether standard measures of smoking, developed for use in general population samples, remain robust in severely ill psychiatric patients.

## METHODS

Patient Population: Forty men and seventeen women (20 black and 37 white) who met DSM-IV criteria for schizophrenia (7), and who smoked, provided signed informed consent to participate. Their mean ($\pm$ S.D.) age was 36 7 $\pm$ 10.5 years (range 19 to 58 years), it had been, on average, 10 4 $\pm$ 9.1 years since their first hospitalizations (range 0 to 30 years); they had had, on average 5.2 $\pm$ 5 8 prior hospitalizations (range 0 to 28). All were newly admitted to John Umstead Hospital for treatment of an acute psychotic exacerbation associated with failure to take their prescribed antipsychotic medications, or they had never previously been treated.

Pharmacologic Treatments. All patients had baseline assessments prior to the start of treatment. After baseline assessments were completed, treatment was begun with

oral haloperidol 2 mg daily. This dose was subsequently adjusted to a level at which a slight increase in Parkinsonian bradykinesia-rigidity was induced (the neuroleptic threshold), at which point pre-randomization assessments were completed. Patients were then randomly assigned to 28 days of double-blind treatment with either one-third their neuroleptic threshold doses, their neuroleptic threshold doses, or three times their neuroleptic threshold doses. Assessments were repeated at 14 and 28 days after randomization, or on the final day in trial for early terminations.

Smoking Measures: A three-question smoking history (age began smoking, number of years smoked, and average number of packs per day smoked in the preceding year) was administered twice, at least 24 hours apart, by the same rater, at baseline.

The Fagerstrom Test for Nicotine Dependence (FTND) (8) was administered twice, at least 24 hours apart, by the same rater, at prerandomization.

Each patient participated in two 2-hour (1300-1500) cigarette self-administration sessions on four occasions: at baseline (prior to haloperidol treatment), at prerandomization (when all patients were receiving neuroleptic threshold haloperidol doses), and 14 and 28 days after randomization. Patients came to our research area for these sessions, where they had free access to cigarettes, snacks, and noncaffienated sodas in a naturalistic environment. Research staff kept count of how many cigarettes each patient smoked at each session, and measured expired air carbon monoxide (CO) levels with a Breath CO Monitor (Vitalograph, Inc.) at the beginning of each session, and then every 30 minutes thereafter through 120 minutes. Blood was drawn from 44 of these patients for nicotine and cotinine levels at the end of only one of each of the paired cigarette self-

administration sessions. Assays were performed in the Clinical Pharmacology Laboratory of Dr. Neal Benowitz, University of California – San Francisco.

Routine Smoking Policies at John Umstead Hospital: Cigarette smoking is permitted at the rate of one cigarette/hour between the hours of 0700 and 2200 inclusive. All cigarettes are kept in the Nurses' Station on each ward, and these are distributed and lit on the hours by Nursing staff.

Statistical Procedures: Test-retest reliabilities of the individual measures were calculated as intraclass correlation coefficients (ICC). Relationships between measures were determined by Pearson product-moment correlations. All p-values reflect 2-tailed tests.

**RESULTS**

Smoking History. These patients began smoking, on average, at 17 ± 6 years of age; they had been smoking for 19 ± 12 years; and, they smoked 2.2 ± 1.2 packs per day. The ICCs for these patients' reports of the ages they began smoking, the number of years they had smoked, and the average number of packs per day the had smoked in the preceding year were .97, .99, and .92, respectively.

Fagerstrom Test for Nicotine Dependence These patients' mean FTND total score was 5.8 ± 2.4. The ICC for the FTND total score was .78.

Cigarette Self-Administration Sessions: At baseline assessments, these patients mean expired CO level was 17.2 ± 7.9 ppm at the beginning of the sessions; they smoked, on average, 6.4 ± 2.8 cigarettes during the 120 minute sessions, and their mean expired CO level at the end of the 120 minute sessions was 36.2 ± 13.1 ppm, mean

nicotine and cotinine levels at the end of the sessions were 36.2 ± 13.1 ng/ml and 289 ± 134 ng/ml, respectively.

The ICCs for the beginning CO levels across the four pairs of sessions (baseline, prerandomization, and 14 and 28 days post randomization) ranged from .74 to .84. The ICCs for the number of cigarettes smoked in each pair of sessions ranged from .88 to .92. The ICCs for the end CO levels (at the end of the 120 minute sessions) ranged from .82 to .91.

The ICCs for nicotine and cotinine levels drawn 14 days and 28 days after randomization (when patients were receiving fixed-dose haloperidol treatment) were .98 and .94, respectively.

Intercorrelations among the objective measures of smoking at baseline (medication free) and at pre-randomization (neuroleptic threshold, haloperidol treatment) are displayed in Table 1. Similar findings present at 14 and 28 days post-randomization are not displayed, but are available upon request from the authors. **(TABLE 1 APPROXIMATELY HERE).**

Neither the ages patients began smoking nor the total number of years they had smoked correlated (at $p<.05$) with any of the objective measures of smoking. The average number of packs per day smoked in the preceding year correlated with the number of cigarettes smoked in the cigarette self-administration sessions ($r=.37$, $p=.009$). The FTND total score was weakly correlated with beginning CO levels ($r=.31$, $p=.025$), the number of cigarettes smoked ($r=.39$, $p=.003$), end CO levels ($r=.38$, $p=.005$), and nicotine levels ($r=.37$, $p=.013$), but not with cotinine levels.

## DISCUSSION

All reported and objective measures of smoking showed good test-retest reliabilities, even in these acutely psychotic patients.

Objective measures of smoking impact (expired carbon monoxide, and nicotine and cotinine levels) showed consistent, moderately strong intercorrelations with each other. The numbers of cigarettes smoked were inconsistently and less strongly related among the objective measures.

The ages patients began smoking and the number of years they had smoked did not relate to any of the objective measures of smoking impact. FTND scores were only weakly associated with objective measures of smoking impact, as has been reported for smokers in general population samples(9,10).

Expired carbon monoxide levels, and nicotine and cotinine levels appear to be robust measures of smoking, even in acutely psychotic patients with schizophrenia

**Table 1. Intercorrelations Among Objective Measures of Smoking**

| | Begin Co | #Cigs | End CO | Nicotine |
|---|---|---|---|---|
| **BASELINE** | | | | |
| #Cigs | .02 | | | |
| End CO | .80** | .34* | | |
| Nicotine | .52** | .26 | .62** | |
| Cotinine | .57** | -.09 | .46* | .76** |
| **PRERANDOMIZATION** | | | | |
| #Cigs | .05 | | | |
| End CO | .73** | .29* | | |
| Nicotine | .54** | .37* | .72** | |
| Cotinine | .68** | .04 | .68** | .73** |

* $p<.05$

** $p<.001$

**REFERENCES**

1. Lasser, K., Boyd, J.W., Woolhandler, S., Himmelstein D.U., McCormick, D., Bor, D.H. 2000. Smoking and mental illness. Journal of the American Medical Association 284:2606-2610

2. Hughes, J.R., Hatsukami, D.K., Mitchell, J.E., Dahlgren, L.A., 1986. Prevalence of smoking among psychiatric outpatients. American Journal of Psychiatry 143:993-997.

3. De Leon, J., Davand, M., Canuso, C., White, A., Stanilla, J., Simpson, G. 1995. Schizophrenia and smoking: an epidemiological survey in a state hospital. American Journal of Psychiatry 152:453-455.

4. McEvoy, J.P., Brown, S. 1999. Smoking in first-episode patients with schizophrenia. American Journal of Psychiatry 156:1120-1121.

5. Olincy, A., Young, D.A., Freedman, R. 1997. Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biological Psychiatry 42:1-5.

6. Marx, C.E., McIntosh, E., Wilson, W.H., McEvoy, J.P. 2000. Mecamylamine increases smoking in psychiatric patients. Journal of Clinical Psychopharmacology 20:706-707.

7. Frances, A. Pincus, H.A., First, M.B., 1994. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition American Psychiatric Association, Washington, D.C.

8. Pomerleau, C.S., Carton, S.M., Lutzke, M.L., Flessland, K.A., Pomerleau, O.F. 1994. Reliability of the Fagerstrom Tolerance Questionnaire and the Fagerstrom Test for Nicotine Dependence. Addictive Behaviors 19:33-39.

9. Prokhorov A.V., deMoor, C., U.E., Hudmon, K.S., Koehly, L, Hu, S. 2000. Validation of the modified Fagerstrom Tolerance Questionnaire with salivary cotinine among adolescents. Addictive Behaviors 25:429-433.

10. Payne, T.J., Smith, P.O., McCracken, L.M., McSherry, W.C., Antony, M.M. 1994. Assessing nicotine dependence: A comparison of the Fagerstrom Tolerance Questionnaire (FTQ) with the Fagerstrom Test for Nicotine Dependence (FTND) in a clinical sample. Addictive Behaviors 19:307-317.