The Association Between High Nicotine Dependence and Severe Mental Illness May Be Consistent Across Countries

Jose de Leon, M.D.; Elisardo Becoña, Ph.D.; Manuel Gurpegui, M.D.; Ana Gonzalez-Pinto, M.D.; and Francisco J. Diaz, Ph.D.

Background: Studies all over the world suggest that severe mental illness, including schizophrenia and mood disorders, is associated with tobacco smoking. This study, combining samples from the United States and Spain, had 3 objectives: (1) to test the hypothesis that severely mentally ill patients who smoke are more likely to have a high nicotine dependence when compared with control smokers, (2) to compare frequencies of high nicotine dependence in controls in both countries, and (3) to compare frequencies of high nicotine dependence in severely mentally ill patients in both countries.

Method: Scores on the Fagerström Test for Nicotine Dependence (FTND) for 4 samples of current daily smokers were analyzed. The sample sizes of the U.S. and Spanish control groups were 129 and 646 subjects, respectively. The diagnoses for the U.S. patients were DSM-IV schizophrenia, 74% (89/120), and DSM-IV mood disorders, 26% (31/120). The diagnoses for the Spanish patients were DSM-IV schizophrenia, 87% (173/199), and DSM-III-R mood disorders, 13% (26/199). High nicotine dependence (FTND score ≥ 6) was the dependent variable in 5 logistic regression analyses.

Results: The main findings were that (1) severely mentally ill patients had significantly higher frequencies of high nicotine dependence than controls (odds ratio [OR] = 10.59, 95% CI = 7.31 to 15.34) even after controlling for gender, country, interaction between country and mental illness, and age; (2) U.S. controls had significantly higher frequencies of high nicotine dependence than Spanish controls (OR = 3.18, 95% CI = 2.02 to 5.00); and (3) U.S. and Spanish patients did not have significantly different frequencies of high nicotine dependence.

Conclusion: New studies, specially designed to test for transcultural differences in nicotine dependence, are needed to verify that nicotine dependence in severely mentally ill patients is consistently high and similar in different countries.

(J Clin Psychiatry 2002;63:812–816)

Received Oct. 3, 2001; accepted March 13, 2002. From the Mental Health Research Center at Eastern State Hospital, Lexington, Ky. (Drs. de Leon and Diaz); the Department of Clinical Psychology and Psychobiology, School of Psychology, University of Santiago de Compostela, Santiago de Compostela, Spain (Dr. Becoña); the Department of Psychiatry and Institute of Neurosciences, University of Granada, Granada, Spain (Dr. Gurpegui); and the Psychiatry Department, Santiago Apostol Hospital, Osakidetza Mental Health System, Vitoria, Spain (Dr. Gonzalez-Pinto).

Dr. Diaz is an Associate Instructor in Statistics at Universidad Nacional de Colombia. Dr. Diaz's salary was partly supported by a grant from the Kentucky Department of Mental Health and Mental Retardation to the Department of Psychiatry of the University of Kentucky through the University Collaboration Project (Dr. de Leon).

The authors have no affiliation or relationship with any organization that can be considered a conflict of interest.

Margaret T. Susce, R.N., M.L.T., helped with editing of this article. Please see original publications (references 1–3) for acknowledgments and a complete list of individuals who helped with data collection.

Corresponding author and reprints: Jose de Leon, M.D., Mental Health Research Center at Eastern State Hospital, 627 West Fourth St., Lexington, KY 40508 (e-mail: jdeleon@pop.uky.edu).

Studies from all over the world, including those done by our research group,[1–3] suggest that severe mental illness, including schizophrenia and mood disorders, is associated with tobacco smoking. The relationships of tobacco smoking in general and heavy tobacco smoking in particular, as well as high nicotine dependence, to severe mental illness have received study.

Tobacco Smoking and Severe Mental Illness

In a classic study, Hughes et al.[4] described that tobacco smoking was more frequent in psychiatric patients than in the general population. The association between smoking and mental illness may have become more obvious in the last few years in the United States, where less than one third of the population smoke and a portion of those cannot quit easily, particularly those with mental illnesses. Recently, Lasser et al.[5] estimated that almost half of U.S. smokers (41%) report having a mental illness in the past month.

It is well known that depression is associated with increased current smoking and decreased smoking cessation[6–8]; vulnerability to depression may be associated with vulnerability to smoking.[9] When bipolar patients were compared with a representative sample of the Spanish population, bipolar disorder increased the risk of being an

ever or current smoker by a factor of 2.[1] Other studies have replicated the finding of increased smoking in bipolar disorder in Israel[10] and the United States.[5]

The frequency of smoking is even higher in schizophrenia. Eight studies in outpatients and inpatients from all over the world, including 1007 schizophrenic patients and 969 patients with other severe mental illnesses, suggested that, on average, three quarters (78%) of the schizophrenic patients were current smokers versus 58% of the other patients.[11] In a Scottish study[12] that included 135 of the 168 schizophrenic individuals from that area, current smoking rates in schizophrenia and the general population were 53% and 28%, respectively. In a Canadian study[13] that included 106 schizophrenic patients from an outpatient clinic, current smoking rates in schizophrenia and the general population were 61% and 32%, respectively. Moreover, schizophrenia doubles the risk of being a current smoker when compared with other severe mental illnesses,[14] even after correcting for the association between smoking and antipsychotic treatment[11,14,15] and that between smoking and alcohol as well as drug abuse.[15] Alcohol and drug addiction also are associated with smoking.[16] Like major mood disorders, schizophrenia is also associated with a decreased number of quitters. However, schizophrenia may have a closer association with nicotine addiction[17] since schizophrenic patients show a higher rate of current and ever smoking than patients with mood disorders[2,10,18,19] and may specifically have greater risk of becoming daily smokers.[2] Since most schizophrenic patients start to smoke before the illness onset,[2,20,21] vulnerability to schizophrenia may be associated with a high vulnerability to start smoking.[2,20,22]

Heavy Tobacco Smoking and Severe Mental Illness

Fewer data support the idea that severe mental illness is also associated with heavy smoking (defined as consuming more than 20 or 30 cigarettes per day). A recent U.S. survey[5] found that the prevalence of heavy smoking was 10% in the population without mental illness and increased with the number of lifetime psychiatric diagnoses (up to 30% in those with 4 or more psychiatric diagnoses).

In Spanish bipolar patients, heavy smoking was increased by a factor of 4 (or factor of 12 when alcohol was controlled for) when compared with the general population.[1] Clinical experience has suggested that schizophrenia is particularly associated with heavy smoking among smokers.[23] General population studies do not explore heavy smoking well in schizophrenic patients, since schizophrenic patients are underrepresented in these studies.[24] The prevalence of heavy smoking among smokers with schizophrenia versus the general population was 68% versus 11% in a Scottish study[12] and 31% versus 11% in a Canadian study.[13] The comparison of heavy smoking between schizophrenia and other mental illnesses has provided inconsistent results.[11,14,15,25,26]

High Nicotine Dependence and Severe Mental Illness

The Fagerström Test for Nicotine Dependence (FTND) is the most widely used instrument to establish and quantify nicotine dependence and may help to predict the success at stopping smoking.[27] The FTND has 6 items (total score ranges from 0 to 10).[27] The number of cigarettes per day and the time of the first cigarette of the day are scored between 0 and 3 and may best reflect dependence.[28] Four other items (difficulty to refrain from smoking in forbidden places, the morning cigarette as the one most hated to give up, smoking more during the first hours after waking, and smoking if so ill that one must stay in bed) are scored 1 if present and 0 if absent. In spite of some psychometric problems,[28–31] the FTND continues to be the most widely used instrument to measure nicotine dependence.

In a review of several phone and mail surveys in 6 different countries,[32] mean FTND scores in smokers ranged between 3.0 and 4.3. It was suggested that countries such as the United States with a smaller proportion of smokers tend to have higher levels of nicotine dependence as measured by the FTND and that in such countries there is an overrepresentation of smokers that cannot quit easily because they have higher levels of dependence (the "hardening hypothesis").[33] Similar findings have been described using the DSM-IV definition of nicotine dependence.[34]

Few studies have used the FTND to measure nicotine dependence in severe mental illness. Three studies, using the FTND in current smokers, found no differences between schizophrenia and mood disorders.[2,10,18] In a sample of subjects seeking smoking cessation, depressed smokers had significantly higher mean FTND scores compared with nondepressed smokers (5.6 vs. 4.9).[35] Using the DSM-III-R definition of nicotine dependence, depression was also associated with nicotine dependence.[36,37]

Fagerström et al.[32] proposed that an FTND score of 6 or higher signifies high dependence. This cutoff point has not been well explored in the general or psychiatric populations. Most studies using the FTND (a MEDLINE search conducted in the summer of 2001 for all available years and including the terms *nicotine dependence* and *Fagerström* yielded more than 100 articles) focused on populations trying to quit smoking. The present study is a first attempt to explore the meaning of high nicotine dependence as an FTND score of 6 or higher in general and psychiatric populations in 2 different countries, the United States and Spain. Most of these samples have been published[1–3] or are in the process of being published (M. C. Aguilar, M.D.; M.G.; F.J.D.; et al., manuscript submitted). This article focuses on the dichotomous classification of current smokers as having or not having high nicotine dependence. This study had 3 objectives: (1) to test the hypothesis that severely mentally ill patients who smoke are more likely to have a high nicotine dependence when compared with control smokers, (2) to compare fre-

quencies of high nicotine dependence in U.S. and Spanish controls, and (3) to compare frequencies of high nicotine dependence in U.S. and Spanish severely mentally ill patients. Hypothesis testing and comparisons were performed correcting for possible effects of gender and age.

METHOD

Subjects

Four samples of current daily smokers who responded to the FTND were obtained by combining samples from several studies.[1–3] In all studies, subjects used the paper-and-pencil method to complete the FTND. The sample sizes were as follows: 129 U.S. controls, 646 Spanish controls, 120 U.S. psychiatric patients, and 199 Spanish psychiatric patients. The U.S. control sample was recruited using fliers in churches and community organizations and at the University of Kentucky and included volunteers who were not currently being treated for a psychiatric disorder.[2] The Spanish control sample was recruited after a systematic and representative sampling from the population over 16 years old in 21 cities or towns in a region of Spain. Streets were randomly selected and then the one hundredth house was selected and visited.[2] The U.S. psychiatric patients were recruited from among inpatients and outpatients seeking treatment in public health facilities in Lexington, Ky.[2] The diagnoses for the U.S. patients were DSM-IV schizophrenia, 74% (89/120), and DSM-IV mood disorders, 26% (31/120) (including major depression, 7% [8/120], and bipolar disorder, 19% [23/120]).[2] The Spanish psychiatric sample consisted of schizophrenic and bipolar patients; 87% (173/199) were schizophrenic (DSM-IV) and were recruited from outpatients seeking treatment at 2 Community Mental Health Centers and a rehabilitation program. The Spanish bipolar patients (DSM-III-R; 13% [26/199]) included the 26 smokers from the last 51 of all 148 bipolar patients identified in the state.[1]

Studies in different countries suggest no significant differences in nicotine dependence between patients with schizophrenia and mood disorders (see Introduction), justifying combining both populations of patients. The mean ± SD FTND scores were 3.9 ± 2.6 in U.S. controls, 2.9 ± 2.5 in Spanish controls, 6.3 ± 2.2 in U.S. patients, and 6.6 ± 2.4 in Spanish patients.

The above samples of smokers were part of larger samples that included smokers and nonsmokers. The prevalences of smoking were 25% in U.S. controls, 38% in Spanish controls, 73% in U.S. patients, and 66% in Spanish patients.

Variables and Statistics

High nicotine dependence was defined as an FTND score ≥ 6.[32] Five logistic regression analyses of high nicotine dependence were performed using the Statistical Package for Social Sciences.[38] In the first analysis, the association between mental illness and high nicotine dependence was analyzed using only the Spanish subjects. Two similar analyses were performed, one using only the U.S. subjects and the other using the total sample. The fourth analysis used only control subjects (Spanish and U.S. together) and assessed the association between country and high nicotine dependence. Finally, the fifth analysis used only patients (Spanish and U.S. together) and assessed the association between country and high nicotine dependence. Ninety-five percent CIs for odds ratios (ORs) were computed. The Hosmer-Lemeshow goodness-of-fit test was used to test the fitness of logistic models. All models fit well (a p value > .05 indicated a good fit).

To control for a possible effect of gender, the gender variable was additionally included as an independent variable in all logistic models. Statistical analyses were repeated by including an additional age variable. Since the age variable exhibited no significant effect and did not change conclusions, results for this variable are omitted.

RESULTS

The frequencies of high nicotine dependence were 17% (95% CI = 15% to 20%) for Spanish controls, 33% (25% to 42%) for U.S. controls, 71% (64% to 77%) for Spanish patients, and 63% (55% to 72%) for U.S. patients. These frequencies are not corrected for the association of high nicotine dependence with male gender.

In the logistic regression, Spanish patients were more likely to have high nicotine dependence when compared with Spanish controls (OR correcting for gender = 10.56, 95% CI = 7.29 to 15.31). Similarly, U.S. patients were more likely to have a high nicotine dependence when compared with U.S. controls (OR correcting for gender = 3.01, 95% CI = 1.75 to 5.16). When all samples were combined, patients were more likely to have high nicotine dependence when compared with controls (OR = 10.59, 95% CI = 7.31 to 15.34) after correcting for gender, country, interaction between country and mental illness, and age.

The frequency of high nicotine dependence in U.S. controls was significantly higher than that in Spanish controls (OR correcting for gender = 3.18, 95% CI = 2.02 to 5.00). However, the frequencies of high nicotine dependence in U.S. and Spanish patients were not significantly different from each other (OR correcting for gender = 0.78, 95% CI = 0.48 to 1.29).

DISCUSSION

The main findings were as follows: (1) severely mentally ill patients had significantly higher frequencies of high nicotine dependence than controls even after

controlling for gender, country, interaction between country and mental illness, and age; (2) U.S. controls had significantly higher frequencies of high nicotine dependence than Spanish controls; and (3) U.S. and Spanish patients did not have significantly different frequencies of high nicotine dependence.

Obviously, this study is limited because the samples were not collected for testing these hypotheses. High nicotine dependence was very strongly associated with severe mental illnesses (schizophrenia and mood disorders). This association was strong enough to be consistent across countries. Social pressure to quit in the United States appears to have produced significant differences in nicotine dependence between U.S. and Spanish controls. A portion of the more heavily dependent U.S. smoker population are unable to quit smoking.[32,33] The percentage of heavily dependent smokers increases from Spanish controls to U.S. controls and then to severely mentally ill patients of both countries.

As described in the Introduction, both schizophrenia and mood disorders are associated with smoking cessation difficulties. Both schizophrenia and mood disorders appear to increase the risk of becoming a smoker. Therefore, we believe that vulnerability to schizophrenia and mood disorders may increase vulnerability to daily smoking. Since most patients with schizophrenia and mood disorders start smoking daily before they are ill,[1,2,12,20,21] these illnesses cannot explain the high rates of daily smoking in the severely mentally ill. Our survival analyses in the U.S. sample[2] suggested that the differences in current smoking onset between controls and patients with mood disorders may be explained by differences in education levels. However, the differences between controls and schizophrenic patients persisted after controlling for education level and other demographic factors.[2] Thus, it is possible that the association between schizophrenia vulnerability and daily smoking onset may be stronger than the association between mood disorders vulnerability and daily smoking onset. However, proving this hypothesis may require large samples and complex statistical techniques.[2]

In the present article, we focus on nicotine dependence rather than on the onset of daily smoking. Nicotine dependence may be influenced by the brain changes associated with vulnerability to the mental illnesses (as daily smoking initiation is influenced), but may also be influenced by the brain changes associated with the illness itself. For the moment, it appears that brain changes associated with schizophrenia and mood disorders may share similar predisposition to high nicotine dependence.

New studies specifically designed to test for transcultural differences in nicotine dependence are needed to verify that nicotine dependence in severely mentally ill patients (schizophrenia and mood disorders) is consistently high and similar in different countries. Verification that nicotine dependence is so strongly associated with mental illnesses may provide clues to the common brain changes associated with mental illnesses and nicotine dependence.

REFERENCES

1. Gonzalez-Pinto A, Gutierrez M, Ezcurra J, et al. Tobacco smoking and bipolar disorder. J Clin Psychiatry 1998;59:225–228
2. de Leon J, Diaz FJ, Rogers T, et al. Initiation of daily smoking and nicotine dependence in schizophrenia and mood disorders. Schizophr Res 2002;56:47–54
3. Becoña E, Vázquez FL. The Fagerström Test for Nicotine Dependence in a Spanish sample. Psychol Rep 1998;83:1455–1458
4. Hughes JR, Hatsukamy DK, Mitchell JE, et al. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;43:993–997
5. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284:2606–2610
6. Glassman AH. Cigarette smoking: implications for psychiatric illness. Am J Psychiatry 1993;150:546–553
7. Glassman AH, Covey LS, Stetner F, et al. Smoking cessation and the course of major depression: a follow-up study. Lancet 2001;357: 1929–1932
8. Patten CA, Gillin JC, Golshan S, et al. Relationship of mood disturbance to cigarette smoking status among 252 patients with a current mood disorder. J Clin Psychiatry 2001,61:319–324
9. Kendler KS, Neale MC, MacLean CJ, et al. Smoking and major depression: a causal analysis. Arch Gen Psychiatry 1993;50:36–43
10. Itkin O, Nemets B, Einat H. Smoking habits in bipolar and schizophrenic outpatients in southern Israel. J Clin Psychiatry 2001;62:269–272
11. Llerena A, de la Rubia A, Peñas-Lledó EM, et al. Schizophrenia and tobacco smoking in a Spanish psychiatric hospital. Schizophr Res. In press
12. Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. Am J Psychiatry 1999;156:1751–1757
13. El-Guebaly N, Hodgins DC. Schizophrenia and substance abuse: prevalence issues. Can J Psychiatry 1992;37:704–710
14. de Leon J, Dadvand M, Canuso C, et al. Schizophrenia and smoking: an epidemiological survey in a state hospital. Am J Psychiatry 1995;152: 453–455
15. de Leon J, Tracy J, McCann E, et al. Schizophrenia and tobacco smoking: a replication study in another US psychiatric hospital. Schizophr Res 2002;56:55–65
16. Hughes JR. An overview of nicotine use disorders for alcohol/drug abuse clinicians. Am J Addict 1996;5:262–274
17. Dalack W, Healy D, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. Am J Psychiatry 1998;155:1490–1501
18. Diwan A, Castine M, Pomerlau C, et al. Different prevalence of cigarette smoking in patients with schizophrenia vs mood disorders. Schizophr Res 1998;33:113–118
19. de Leon J, Diaz FJ. Smoking in bipolar and schizophrenic patients [letter with reply]. J Clin Psychiatry 2002;63:368–369
20. de Leon J. Smoking and vulnerability for schizophrenia. Schizophr Bull 1996;22:405–409
21. McEvoy JP, Brown S. Smoking in first-episode patients with schizophrenia [letter]. Am J Psychiatry 1999;156:1120–1121
22. Freedman R, Coon H, Myles-Worsley M, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. Proc Natl Acad Sci U S A 1997;94:587–592
23. Lohr JB, Flynn K. Smoking and schizophrenia. Schizophr Res 1992;8: 93–102
24. Covey LS, Hughes DC, Glassman AH, et al. Ever-smoking, quitting, and psychiatric disorders: evidence from the Durham, North Carolina, epidemiological catchment area. Tob Control 1994;3:222–227
25. Olincy A, Young DA, Freedman R. Increased levels of nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. Biol Psychiatry 1997;42:1–5
26. Herrán A, de Santiago A, Sandoya M, et al. Determinants of smoking behavior in outpatients with schizophrenia. Schizophr Res 2000;41: 373–381
27. Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerström Test for

Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addict 1991;86:1119–1127
28. Kozlowski LT, Porter CQ, Orleans CT, et al. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HIS. Drug Alcohol Depend 1994;34:211–216
29. Pomerleau CS, Carton SM, Lutzke ML, et al. Reliability of the Fagerström Tolerance Questionnaire and the Fagerström Test for Nicotine Dependence. Addict Behav 1994;19:33–39
30. Payne TJ, Smith PO, McCracken LM, et al. Assessing nicotine dependence: a comparison of the Fagerström Tolerance Questionnaire (FTQ) with the Fagerström Test for Nicotine Dependence (FTND) in a clinical sample. Addict Behav 1994;19:307–317
31. Haddock CK, Lando H, Klesges RC, et al. A study of the psychometric and predictive properties of the Fagerström Test for Nicotine Dependence in a population of young smokers. Nicotine Tob Res 1999;1:59–66
32. Fagerström KO, Kunze M, Schoberberger R, et al. Nicotine dependence versus smoking prevalence: comparison among countries and categories of smokers. Tob Control 1996;5:52–56
33. Hughes JR. Distinguishing nicotine dependence from smoking: why it matters to tobacco control and psychiatry. Arch Gen Psychiatry 2001;58: 817–818
34. Breslau N, Johnson EO, Hiripi E, et al. Nicotine dependence in the United States: prevalence, trends and smoking persistence. Arch Gen Psychiatry 2001;58:810–816
35. Lerman C, Audrain J, Orleans CT, et al. Investigation of mechanisms linking depressed mood to nicotine dependence. Addict Behav 1996;21:9–19
36. Breslau N. Psychiatric comorbidity and nicotine dependence. Behav Genet 1995;25:95–101
37. Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. Arch Gen Psychiatry 1993;50:31–35
38. Norusis MJ. SPSS Professional Statistics 7.5. Chicago, Ill: SPSS Inc; 1997