Cigarette Smoking and Its Comorbidity

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Comorbidity is the existence of two conditions in the same individual at a greater frequency than would be expected by chance alone. The existence of such associations says nothing about the underlying cause of the comorbidity. Cigarette smoking in the United States has long been associated with an increased level of psychiatric symptomatology, but until recently this was not thought of in terms of specific diagnostic entities. Cigarette smokers were simply thought more likely to be "nervous" people than nonsmokers (Glassman 1993). However, it is important to realize that the appearance of comorbidity can be strongly influenced by social factors. If everybody smoked, there could be no association between smoking and any psychiatric condition.

In 1985, while testing a new drug for smoking cessation, Glassman and colleagues (1988) noted what they felt was an astounding lifetime rate of major depression among smokers coming to the clinic. Forty-two of 71 smokers (60 percent) had a history of major depression, while the best available data suggest lifetime rates for the general community of around 18 percent (Kessler et al. 1994). This threefold increase in the observed rate of major depression was even more dramatic than it might first appear because smokers coming to the clinic were screened to exclude individuals who were presently ill. Whereas community epidemiological data represent both individuals presently ill and those with only a past history of major depression, the clinic sample consisted only of smokers with a past history of depression. In retrospect, it is likely that the extraordinarily high rate of prior major depression observed by the researchers was an artifact of the particular academic population that they had happened to study.

The vast majority of the 71 smokers who participated in the study were either postdoctoral students or faculty at Columbia University, and most came from the medical school campus. This finding was undoubtedly related to the exceptionally high rate of major depression observed. Medical school faculty and their graduate students face considerably more social pressure to give up smoking than the general population. It would seem reasonable to assume that

in groups where awareness of the health risks increases and social pressure to stop smoking grows, those who can quit easily do so and those who remain smokers are individuals more vulnerable to nicotine.

Hughes and associates (1986) had earlier shown that patients coming to a medical center for treatment of a variety of psychiatric conditions, including depression, were more likely to be smokers than the general population. That seemed intuitively reasonable. However, once the strength of the association with a specific history of depression became apparent, it seemed worthwhile to determine whether a history of major depression influenced smoking cessation—and it did. Again, that patients presently depressed have more difficulty quitting than individuals not depressed seems obvious; however, the finding that a history of depression would still be associated with cessation failure, even when an individual had been euthymic for a considerable period of time, was not so obvious and required replication.

The first two replications both came from previously existing data sets. The St. Louis node of the Epidemiological Catchment Area (ECA) study contained both psychiatric diagnostic information and smoking history on over 3,200 randomly selected community residents (Glassman et al. 1990). Among those individuals with either no psychiatric illness or any psychiatric illness except major depression, 47 percent of the women and 68 percent of the men had at some time in their lives been regular smokers. By comparison, among those individuals with a history of major depression, 65 percent of the women and 80 percent of the men had been regular smokers. The increases among both men and women are highly significant, but the increased rate among the depressed women is particularly striking. The data on cessation also very much paralleled the data for the original small clinical sample. Thirty-one percent of those smokers with no history of any psychiatric history were able to stop smoking for more than 1 year, and 28 percent of those individuals with either no psychiatric history or no psychiatric history except major depression were able to quit. Among those with a lifetime history of major depression, less than 14 percent of smokers were able to stop and remain abstinent.

Similarly, data on 3,023 individuals from the National Health and Nutrition Examination Survey (N-HANES) also demonstrated an increased rate of smoking and a decreased rate of quitting associated with increasing levels of depression (Anda et al. 1990). The major difference between the ECA and the N-HANES data sets is that the

ECA instruments classified individuals by diagnosis, while N-HANES obtained only symptomatic measures of depression.

A subsequent community survey also produced by the Centers for Disease Control and Prevention was the Hispanic NHANES, which studied 3,337 individuals of Mexican origin and obtained both symptomatic and diagnostic measures of depression on this sample (R.F. Anda, personal communication, January 11, 1995). It is important to understand that this is an epidemiology survey that records lifetime rates of illness, and lifetime major depression involves both cases that are presently ill and cases of past illness. Presently ill cases will always show symptoms of depression as well as meeting diagnostic criteria. However, cases of past history may or may not presently have symptoms of depression. Both those individuals with symptoms but no diagnosis and those with a diagnosis but no symptoms showed higher rates of smoking than individuals with neither condition. However, individuals with both a diagnosis and symptoms of major depression showed the highest rates of smoking. Thus, there is now evidence that symptoms, as well as a diagnosis of major depression, are associated with cigarette smoking.

These data are somewhat more complex than is readily apparent. It might seem that symptoms of depression and major depression alone are approximately equal in their likelihood of being associated with cigarette smoking. However, it is probable that the cases of major depression in the major depression-only group will be less severe and less likely to be recurrent than those cases in the group with both major depression and present symptoms of depression. Recurrent major depression has regularly been shown to have higher levels of interepisode depressive symptomatology (Keller et al. 1983; Dalack et al. 1995) than single episode cases. Thus, it seems probable that the major depression-only group will contain a greater proportion of single episode cases of major depression. Cases of single episodes of major depression have already been shown in both clinical (Glassman et al. 1993) and epidemiological (Covey et al. 1994) research to be less strongly associated than recurrent major depression with cigarette smoking. As a result, it would seem likely that both individuals with symptoms of depression and individuals with a single episode of major depression are more likely to be smokers than individuals with no history of either condition. In addition, the association between smoking and depression will be strongest among those individuals with either recurrent major depression or major depression and high levels of chronic depressive symptoms. There is also evidence that a similar step function exists with the intensity of smoking. At least

among women, Kendler and associates (1993) have replicated the finding that heavier smoking is associated with an increasing likelihood of a lifetime history of major depression, and Breslau and associates (1993) have shown that this same association is greater in dependent than in nondependent smokers.

One of the issues not dealt with adequately in any of these three large data sets is the role of other psychiatric diagnoses. Breslau has examined 1,200 young adults (Breslau et al. 1991) and Kendler has data on 1,566 female twins (Kendler et al. 1993). Breslau replicates the previously observed associations between major depression and both smoking and smoking cessation. Kendler does not examine cessation, but does find a strong association between smoking and a lifetime diagnosis of major depression. However, these studies provide information that earlier data sets were not designed to address. As a major example, both Breslau and Kendler demonstrated that the relationship between major depression and smoking persists even after controlling for both alcohol and anxiety disorders. Both also showed that the association was most robust among heavier or more dependent smokers.

Beyond these observations, Kendler's study is uniquely valuable because it was done in twins. Community epidemiological surveys can identify an association; however, they allow no conclusion about the source or cause of an association. Cederloff and colleagues (1977) have shown that community surveys in twins allow inferences to be drawn about the source of an association. Ordinarily, twin pairs will be concordant for most behavioral characteristics. If there is an association between two characteristics, such as depression and smoking in the general population of twins, then the discordant dizygotic and monozygotic pairs, even though they are a minority of the pairs, are informative about the etiology of that association. If smoking damages the brain, for example, then the behavior (smoking) would be associated with depression. The increase in the odds ratio would be the same in the general population (of twins) and in both discordant monozygotic and dizygotic twins, and smoking would be associated with depression independent of zygocity. If, on the other hand, the association was based on familial or environmental factors, an association seen in the general population of twin pairs would not be found in either the discordant monozygotic or dizygotic twin pairs because they share those factors equally. If, however, the association was the result of genes, then no association would be seen in the monozygotic discordant twins because of their identical genes, but an intermediate association (a value between monozygotic discordant and

the general population in twins) could be expected among the dizygotic discordant pairs because they share only about half of their genes. The pattern seen with common or shared genes as the source of the association is precisely what Kendler observed (Kendler et al. 1993).

Breslau, using community epidemiological data obtained at two different points in time, made observations that are entirely consistent with Kendler's results (Breslau et al. 1993). Studying 1,200 young adults, examined initially and then again 18 months later, Breslau found that smokers who had no history of depression at the first examination were twice as likely to develop depression as were nonsmokers with no history of depression. Similarly, those individuals with a lifetime history of major depression who did not smoke at the first examination were twice as likely to become smokers as those individuals who did not smoke but who had no evidence of major depression at the first examination. This finding is exactly what the Kendler twin data would predict.

In addition to the available epidemiological data, the association between depression and both smoking and smoking cessation has also been replicated in several smoking cessation clinics (Glassman et al. 1988, 1993; Hall et al. 1992; Kinnunen et al. 1994). Thus, in the relatively few years since these associations with depression were first observed, they have been extensively replicated, and there is even fairly strong evidence that the association between smoking and lifetime major depression, at least in women, is based on common genes. One aspect of these data that is not clear is the relationship to gender.

The association between major depression and ever smoking has been seen in both men and women, but it appears to be stronger in women than men. Similarly, the association between major depression and smoking cessation has been demonstrated in both men and women, but when the relationship is not apparent, it most often has not been found in males. The same preponderance of positive observations among females exists in studies that focused on symptoms of depression rather than on a diagnosis of major depression (Frederick et al. 1988; Perez-Stable et al. 1990; Anda et al. 1990). The question of whether nicotine is a potentially more addicting substance among either women in general or among women at risk for depression may not be an answerable question. It could be that the genes common to smoking and depression exert an equal influence in males and females and that the apparent strength of the relationship in women is

merely an artifact of the increased frequency of depression in women. However, social factors clearly influence the likelihood of smoking and, until recently, men were much more likely to smoke because there was a higher social barrier to women smoking. The high rate of smoking, combined with the lower rate of depression in men, sets mathematical limits on the odds ratio for smoking in depression that are significantly less than for women. If the relative risk for smoking among depressed women were approximately 2, and 65 percent of men had a lifetime history of smoking, then more than 100 percent of the depressed men would smoke if the relative risk were also 2 among the men. Obviously, that is impossible. Even now that the rate of initiating smoking is essentially the same among men and women, it is not necessarily true that the relative proportion of genetic and social factors involved in initiating the behavior are the same in males as females. As a result, the association between smoking and major depression and the origin of that association need to be examined separately in men and women. What appears to be true is that the existence of major depression, and probably recurrent disease in particular, increases the likelihood of smoking behavior and decreases the odds of stopping that behavior. Because social factors can play a major role in these same behaviors, it will be easier to observe the effect of depression when social pressures tend to inhibit the initiation and encourage the cessation of smoking—a pattern that is probably true for most drugs of abuse.

In addition to the evidence linking smoking and smoking cessation failure to major depression, there is now considerable evidence that, in individuals with a history of major depression, successful smoking cessation can provoke the onset of severe depression. Most of the evidence to support this consists of case reports (Flanagan and Maany 1982; Glassman et al. 1993; Stage et al., in press). However, data have recently been published from a study in which 300 smokers, before attempting cessation, were given a psychiatric diagnostic examination (Glassman et al. 1993). One smoker among 153 individuals with no baseline evidence of psychiatric illness became so depressed during withdrawal from cigarettes that the therapist felt it necessary to recommend that the person return to smoking. In comparison, 6 smokers among 113 with a history of major depression became so depressed as to require the therapist to recommend resumption of smoking (odds ratio 8:5). These observations, among other things, constitute further evidence for a relationship between cigarette smoking and major depression.

Certainly depression and major depression are not the only psychiatric conditions that are comorbid with cigarette smoking. They are discussed here in detail because the detail is available. Chronic schizophrenic patients smoke at a rate that approaches 90 percent (Lohr and Flynn 1992; Goff et al. 1992), but, beyond the remarkable frequency of the behavior, little else is known about the relationship. No information is available on the relation to the phase of the illness, the type of symptom-atology, or the severity of the addiction. In fact, nothing is known about any details of the relationship between smoking cessation and schizophrenia. The other striking comorbidity is between cigarette smoking and other drug addictions, but again, almost nothing is known about these relationships except that they exist. It is rare to see an alcoholic who does not also smoke, yet almost nothing is known about the reasons behind this relationship. Some experts have speculated that because nicotine is a stimulant drug, it makes functioning easier or allows intake of higher levels of a basically depressant drug like alcohol. If there is some more fundamental basis, like the shared genes seen with smoking and depression, it is, again, unknown. It is important to know if smoking cessation is associated with increased craving for alcohol and/or alcoholic relapse in a way similar to its provoking depression in smokers with a history of depression, but, again, data are not available. The same questions arise with the other drugs of abuse, and the same lack of answers exists.

The association of specific psychiatric illness with various drugs of abuse is striking. In many ways it is easiest to examine nicotine, but the association is in no way less likely to occur or less important with any addicting drug. The basis of these associations may not be the same for different psychiatric conditions or for different drugs of abuse. However, careful study of such associations is likely to prove profoundly important to the basic understanding of either condition.

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