

Given the results of this study and the knowledge gained from more than a decade of randomized trials of nonoxynol-9 as a vaginal microbicide, it is time to move on. Women at risk for STIs such as chlamydia and gonorrhea are often also at risk for HIV-1. In practical terms, a vaginal microbicide must have no risk of increasing HIV-1 incidence before it can be introduced as a microbicide for other STIs. Given its poor safety profile in frequent users, nonoxynol-9 is clearly not that product.

Despite more than 15 years of urgent appeals for an effective vaginal microbicide for prevention of HIV-1 and other STIs, few clinical trials of microbicides have been published. In contrast, several studies of mother-to-child transmission of HIV-1 have published results that have had a dramatic effect on reducing perinatal HIV-1 transmission rates. Whatever the reasons for this difference, during the past 5 years, while research on vaginal microbicides has inched forward, more than 10 million women worldwide have acquired HIV-1, the vast majority of whom live in the developing world.<sup>17</sup>

Although the message that nonoxynol-9 is not an effective vaginal microbicide is disappointing, it should not discourage further microbicide research. Clearly, there remains a need for an inexpensive, effective, female-controlled method for preventing STIs, and there may be many studies with negative results before one is found. Research on other vaginal microbicides, conducted by individual investigators as well as by research networks, should be encouraged.<sup>18</sup> The study by Roddy et al can serve as an example of a well-designed and executed trial that has moved the field of microbicide research another step forward.

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# Cannabis, Cognition, and Residual Confounding

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IN THIS ISSUE OF THE JOURNAL, SOLOWIJ AND COLLEAGUES<sup>1</sup> report a variety of neuropsychological deficits in long-term cannabis users who were tested a median of 17 hours after their last reported cannabis intake. Their findings of impairments in memory and attention are not surprising since several large and well-controlled studies have found similar deficits on neuropsychological tests administered to long-term cannabis users after 12 to 72 hours of

abstinence.<sup>2-5</sup> If these deficits are brief and reversible (ie, due to a residue of cannabinoids lingering in the brain or to withdrawal effects from abruptly stopping the drug), they might not be a serious threat. However, if these deficits are prolonged or irreversible (ie, due to neurotoxicity from years of cumulative cannabis exposure), they become a matter of grave concern. The findings of Solowij and colleagues fa-

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See also p 1123.

vor the latter possibility in that longer-term cannabis users in the study often showed significantly greater deficits than shorter-term users, and neuropsychological performance measures were often negatively correlated with lifetime duration of use. Furthermore, these correlations could not be explained by greater withdrawal symptoms or heavier recent cannabis consumption among the longer-term users. Solowij and colleagues<sup>1</sup> conclude that “our results confirm that cognitive impairments develop as a result of prolonged cannabis use . . . and [that] they worsen with increasing years of use.”

The findings reported by these leading researchers must be evaluated carefully. First, Solowij et al report only an association between lifetime duration of cannabis use and impairment at 17 hours since last cannabis use and therefore cannot extrapolate from this finding to infer whether impairment persists for longer periods. Second, the strength of the evidence for an association, even at the 17-hour mark, must be evaluated in context with other reports. Previous data from Solowij favor the possibility of persistent deficits associated with lifetime duration of cannabis exposure.<sup>6</sup> However, the weight of evidence from other studies seems tilted in the opposite direction. For example, a recent meta-analysis of neuropsychological studies of long-term marijuana users found no significant evidence for deficits in 7 of 8 neuropsychological ability areas and only a small effect size (ie, 0.23 SD units; 99% confidence interval, 0.03-0.43) for the remaining area of learning.<sup>7</sup> Another recent study<sup>5</sup> from our laboratory, published subsequent to this meta-analysis, found virtually no significant differences between 108 heavy cannabis users and 72 controls—screened to exclude those with current psychiatric disorders, medication use, or any history of significant use of other drugs or alcohol—on a battery of 10 neuropsychological tests after 28 days of supervised abstinence from the drug. In addition, no significant associations were found between the number of episodes of lifetime cannabis use and any of the test scores at day 28 even though the heavy users had smoked a median of about 15000 times over periods ranging from 10 to 33 years.<sup>5</sup> Further analysis of these data for associations between lifetime use and performance at day 0 and day 1 of abstinence revealed trends that were almost always in the same direction as those reported by Solowij et al,<sup>1</sup> but the effect sizes were much smaller (unpublished data).

We also analyzed the possible reasons for the difference between our study<sup>5</sup> and that of Solowij et al in the strength of association between duration of use and performance after 1 day of abstinence. The participants in the 2 studies reported very similar degrees of cannabis exposure, and the neuropsychological tests administered were generally similar or even identical. Both studies had similar sample sizes and thus similar statistical power. Therefore, the most likely remaining explanation would seem to be lack of comparability between the exposed and nonexposed groups within

one or both studies with respect to factors associated with the outcomes of interest (ie, residual confounding).

For example, cannabis users in the study by Solowij et al were seeking treatment for cannabis dependence, whereas controls were recruited from the general population by advertisement. Individuals seeking clinical treatment for cannabis dependence might exhibit higher levels of depression, anxiety, or attention-deficit/hyperactivity disorder than other cannabis users, and all of these psychiatric syndromes produce deficits on neuropsychological testing.<sup>8-10</sup> Some cannabis users seek treatment because they have gotten into trouble with the law and so might have higher levels of antisocial behavior than other users. Antisocial behavior is also linked to neuropsychological deficits.<sup>11</sup>

Although Solowij and colleagues excluded subjects with psychotic disorders or current drug or alcohol dependence (other than cannabis), subjects with depression, anxiety disorders, or other psychiatric conditions were not excluded. Also, subjects receiving prescription psychiatric medications, such as benzodiazepines or antidepressants, that can impair cognitive function were also not excluded.<sup>12,13</sup> In our study,<sup>5</sup> subjects exhibiting any current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* Axis I disorder (other than simple phobia or social phobia) or taking any psychoactive prescription medication were excluded. Thus, confounding factors associated with treatment seeking are possible explanations for the larger effect sizes in the study by Solowij et al. However, for this to be correct, cannabis users in the study by Solowij et al would have to have had more psychopathology or medication use than the controls, and the longer-term users, in turn must have had a higher prevalence of these features than the shorter-term users.

However, confounding can bias results in both directions. For instance, one might argue that excluding cannabis users with current psychiatric disorders or currently using medications would select in favor of unusually healthy long-term users who performed better on testing than the average of the overall population from which they were drawn. Moreover, cannabis use might cause or exacerbate anxiety or depressive disorders and hence be indirectly to blame for any neuropsychological impairment that these disorders create. This is a slightly different assertion, however, from the claim that cannabis impairs cognitive function directly.

Confounders associated with treatment seeking represent only 1 of the many problems that threaten naturalistic studies of substance abusers. Another is the problem of adjustment for premorbid differences between groups. Lacking a historical measure of cognitive function, which is based on testing subjects before they were first exposed to cannabis, leads to the question of whether current differences observed between groups are due to cannabis use or to some difference in premorbid cognitive ability for which adjustment was not made. By matching groups on measures of intellectual functioning that are relatively resilient to brain in-

jury, Solowij and colleagues have done their best to equalize the groups on premorbid cognitive abilities. But since the 33 controls were recruited at 1 site and the 102 cannabis users at 3 sites in different geographic settings, the possibility of residual confounding due to subtle sociodemographic differences between groups cannot be entirely dismissed.

Two of these sociodemographic differences in the group of longer-term cannabis users, namely the larger proportion of men and the significantly greater age of these subjects, are particularly important. Yet comparisons between the groups were performed without adjustment for sex, and some comparisons were also performed without adjustment for age, except in specific cases in which age correlated significantly with a particular outcome variable. However, it is hazardous to use significance testing instead of change-in-estimate criteria to exclude a potential confounding variable from adjustment. Such variables may still change the estimate of the effect considerably, even if they are not statistically significant, yielding residual confounding once again.<sup>14,15</sup> This is particularly worrisome with the age variable, because age differed to a significant degree between study groups and is also highly associated with cognitive function. For example, on the Rey Auditory Verbal Learning Test, where Solowij et al demonstrated the largest cannabis-associated deficits, both increased age and male sex have been shown to be associated with poorer performance,<sup>16</sup> but the effect sizes shown in Table 3 of the study were not adjusted for either age or sex.

Solowij and colleagues are aware of these limitations, and show (in Table 4 of their article) that even after adjusting for age (but not for sex), longer duration of cannabis use is associated with deficits on several key performance measures, although at a more modest level of significance. However, 47% of the long-term cannabis users also had a history of regular use of, dependence on, or treatment for alcohol or other drugs besides cannabis, introducing another possible confounder.

Given the minefield of possible confounding, should naturalistic studies of drug users be presumed untrustworthy or be abandoned entirely? As Solowij and colleagues point out, retrospective designs are the most efficient way to assess the long-term cognitive effects of cannabis consumption. Prospective designs would be extremely expensive, time-consuming, and in some cases unethical. Thus, despite all of their limitations, retrospective studies remain an important tool for answering these important questions.

In conclusion, currently available scientific evidence shows that almost certainly, some cognitive deficits persist for hours or days after acute intoxication with cannabis has subsided. The consensus across studies is strong enough to discount the likelihood that this finding can be explained by any combination of confounders. But whether these deficits increase with increasing years of cannabis exposure remains uncertain. On this question, the numerous potential confounding variables make it difficult to determine whether cognitive impairments are attributable to cannabis use or due to other factors. Even if lifetime duration of cannabis use is associated with greater impairment after 17 hours of abstinence, the data are insufficient to know whether greater impairment would be present a week or a month later. Despite the important contributions of this new study, we must still live with uncertainty.

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