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Table 6.3 Percentages with *Past Year Alcohol and/or Illicit Drug Dependence or Abuse* among Adults Aged 26 or Older, by Age at First Marijuana Use and Age Groups: 2000

Age in Years	Age of Marijuana Initiation in Years	Illicit Drug Dependence or Abuse	Alcohol or Illicit Drug Dependence or Abuse	Alcohol Dependence	Illicit Drug Dependence	Marijuana Dependence	Other Illicit Drug Dependence
Total	14 or younger	6.2	18.0	6.8	4.5	2.5	2.7
	15-17	2.2	9.5	3.6	1.4	0.7	0.9
	18-20	2.0	8.3	3.5	1.7	0.8	1.2
	21 or older	1.3	7.6	3.2	0.7	0.2	0.5
	Never used marijuana	0.2	2.1	0.9	0.1	0.0	0.1
26-34	14 or younger	7.7	19.2	6.7	5.7	3.3	3.2
	15-17	2.9	13.1	4.1	1.7	0.8	1.1
	18-20	1.8	11.4	4.3	1.3	0.9	0.5
	21 or older	3.0	13.7	4.0	0.7	0.6	0.1
	Never used marijuana	0.4	3.4	1.0	0.2	0.0	0.2
35-49	14 or younger	5.0	17.3	6.5	3.4	2.0	2.0
	15-17	1.7	7.8	3.5	1.4	0.7	0.8
	18-20	1.8	7.5	3.2	1.7	0.8	1.1
	21 or older	1.7	8.0	3.8	1.2	0.0	1.2
	Never used marijuana	0.2	2.6	1.4	0.1	0.0	0.1
50+	17 or younger	8.2	9.8	4.6	3.6	0.0	3.6
	18-20	2.8	7.2	3.4	2.1	0.4	2.1
	21 or older	0.6	5.7	2.7	0.4	0.2	0.2
	Never used marijuana	0.1	1.4	0.6	0.1	0.0	0.1

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Other illicit drug dependence indicates meeting the dependence criteria of at least one of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.4 Adjusted Odds Ratios of *Lifetime Use of Heroin, Cocaine, and Psychotherapeutics* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

Variables	Lifetime Heroin Use		Lifetime Cocaine Use		Lifetime Psychotherapeutic Use	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age at First Marijuana Use in Years						
14 or younger vs. 21 or older	15.45	(7.56 - 31.55)	7.95	(6.53 - 9.68)	5.25	(4.37 - 6.31)
15-17 vs. 21 or older	6.10	(2.95 - 12.58)	3.27	(2.76 - 3.87)	2.47	(2.09 - 2.92)
18-20 vs. 21 or older	3.53	(1.73 - 7.20)	1.88	(1.57 - 2.25	1.49	(1.24 - 1.78)
Age in Years						
26-34 vs. 50 or older	0.22	(0.13 - 0.38)	0.91	(0.73 - 1.12)	0.63	(0.51 - 0.77)
35-49 vs. 50 or older	0.53	(0.30 - 0.91)	1.41	(1.14 - 1.74)	0.93	(0.76 - 1.12)
Gender						
Male vs. female	1.61	(1.21 - 2.13)	1.33	(1.21 - 1.46)	1.04	(0.94 - 1.14)
Race/Ethnicity						
White vs. black	0.43	(0.29 - 0.64)	1.12	(0.93 - 1.34)	1.78	(1.48 - 2.13)
Hispanic vs. black	0.65	(0.38 - 1.12)	1.14	(0.88 - 1.48)	1.20	(0.92 - 1.58)
Other[1] vs. black	0.52	(0.23 - 1.16)	--	(-- - --)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.60	(0.38 - 0.95)	0.73	(0.45 - 1.19)
American Indian or Alaska Native vs. black	--	(-- - --)	1.82	(1.13 - 2.93)	2.85	(1.75 - 4.66)
More than one race vs. black	--	(-- - --)	1.19	(0.67 - 2.10)	1.57	(0.94 - 2.61)
Education						
Less than high school vs. at least some college	1.44	(0.96 - 2.17)	1.04	(0.88 - 1.21)	0.93	(0.79 - 1.10)
High school graduate vs. at least some college	1.03	(0.77 - 1.38)	0.90	(0.80 - 1.00)	0.91	(0.82 - 1.02)

-- Not available.

Note: Nonmedical use of any prescription-type psychotherapeutic indicates using pain relievers, tranquilizers, stimulants, or sedatives at least once. Indicated use does not include over-the-counter drugs.

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

Table 6.5 Adjusted Odds Ratios of *Past Year Use of Heroin, Cocaine, and Psychotherapeutics* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

Variables	Past Year Heroin Use		Past Year Cocaine Use		Past Year Psychotherapeutic Use	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age at First Marijuana Use in Years						
14 or younger vs. 21 or older	2.46	(0.54 - 11.28)	7.01	(3.60 - 13.66)	3.44	(2.37 - 5.00)
15-17 vs. 21 or older	0.91	(0.21 - 3.96)	3.81	(1.99 - 7.31)	1.67	(1.19 - 2.34)
18-20 vs. 21 or older	0.56	(0.10 - 3.09)	2.04	(1.02 - 4.09)	1.26	(0.85 - 1.87)
Age in Years						
26-34 vs. 50 or older	2.12	(0.23 - 19.96)	1.87	(0.83 - 4.23)	1.75	(1.04 - 2.93)
35-49 vs. 50 or older	6.04	(0.71 - 51.38)	1.19	(0.51 - 2.78)	1.33	(0.81 - 2.20)
Gender						
Male vs. female	0.60	(0.26 - 1.41)	1.35	(1.03 - 1.76)	0.76	(0.63 - 0.92)
Race/Ethnicity						
White vs. black	0.55	(0.20 - 1.52)	0.54	(0.39 - 0.76)	1.62	(1.18 - 2.24)
Hispanic vs. black	--	(-- - --)	0.74	(0.43 - 1.29)	1.86	(1.13 - 3.07)
Other[1] vs. black	1.51	(0.40 - 5.78)	--	(-- - --)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.23	(.07 - 0.76)	0.65	(0.27 - 1.55)
American Indian or Alaska Native vs. black	--	(-- - --)	1.56	(0.57 - 4.27)	3.23	(1.25 - 8.34)
More than one race vs. black	--	(-- - --)	0.81	(0.32 - 2.06)	0.99	(0.42 - 2.29)
Education						
Less than high school vs. at least some college	1.74	(0.60 - 5.03)	2.29	(1.54 - 3.40)	1.78	(1.33 - 2.39)
High school graduate vs. at least some college	0.93	(0.36 - 2.35)	1.28	(1.00 - 1.64)	1.10	(0.90 - 1.35)

-- Not available.

Note: For past year heroin use, three racial/ethnic categories were used: white, black; and Hispanic, American Indian/Alaska Native, Asian/Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Nonmedical use of any prescription-type psychotherapeutic indicates using pain relievers, tranquilizers, stimulants, or sedatives at least once. Indicated use does not include over-the-counter drugs.

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

CORRECTION

THE FOLLOWING DOCUMENT(S)
HAVE BEEN REFILMED TO
ASSURE LEGIBILITY OR PAGINATION

Table 6.4 Adjusted Odds Ratios of *Lifetime Use of Heroin, Cocaine, and Psychotherapeutics* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

	Lifetime Heroin Use		Lifetime Cocaine Use		Lifetime Psychotherapeutic Use	
Variables	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age at First Marijuana Use in Years						
14 or younger vs. 21 or older	15.45	(7.56 - 31.55)	7.95	(6.53 - 9.68)	5.25	(4.37 - 6.31)
15-17 vs. 21 or older	6.10	(2.95 - 12.58)	3.27	(2.76 - 3.87)	2.47	(2.09 - 2.92)
18-20 vs. 21 or older	3.53	(1.73 - 7.20)	1.88	(1.57 - 2.25)	1.49	(1.24 - 1.78)
Age in Years						
26-34 vs. 50 or older	0.22	(0.13 - 0.38)	0.91	(0.73 - 1.12)	0.63	(0.51 - 0.77)
35-49 vs. 50 or older	0.53	(0.30 - 0.91)	1.41	(1.14 - 1.74)	0.93	(0.76 - 1.12)
Gender						
Male vs. female	1.61	(1.21 - 2.13)	1.33	(1.21 - 1.46)	1.04	(0.94 - 1.14)
Race/Ethnicity						
White vs. black	0.43	(0.29 - 0.64)	1.12	(0.93 - 1.34)	1.78	(1.48 - 2.13)
Hispanic vs. black	0.65	(0.38 - 1.12)	1.14	(0.88 - 1.48)	1.20	(0.92 - 1.58)
Other[1] vs. black	0.52	(0.23 - 1.16)	--	(-- - --)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.60	(0.38 - 0.95)	0.73	(0.45 - 1.19)
American Indian or Alaska Native vs. black	--	(-- - --)	1.82	(1.13 - 2.93)	2.85	(1.75 - 4.66)
More than one race vs. black	--	(-- - --)	1.19	(0.67 - 2.10)	1.57	(0.94 - 2.61)
Education						
Less than high school vs. at least some college	1.44	(0.96 - 2.17)	1.04	(0.88 - 1.21)	0.93	(0.79 - 1.10)
High school graduate vs. at least some college	1.03	(0.77 - 1.38)	0.90	(0.80 - 1.00)	0.91	(0.82 - 1.02)

-- Not available.

Note: Nonmedical use of any prescription-type psychotherapeutic indicates using pain relievers, tranquilizers, stimulants, or sedatives at least once. Indicated use does not include over-the-counter drugs.

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000

Table 6.5 Adjusted Odds Ratios of *Past Year Use of Heroin, Cocaine, and Psychotherapeutics* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

Variables	Past Year Heroin Use		Past Year Cocaine Use		Past Year Psychotherapeutic Use	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age at First Marijuana Use in Years						
14 or younger vs. 21 or older	2.46	(0.54 - 11.28)	7.01	(3.60 - 13.66)	3.44	(2.37 - 5.00)
15-17 vs. 21 or older	0.91	(0.21 - 3.96)	3.81	(1.99 - 7.31)	1.67	(1.19 - 2.34)
18-20 vs. 21 or older	0.56	(0.10 - 3.09)	2.04	(1.02 - 4.09)	1.26	(0.85 - 1.87)
Age in Years						
26-34 vs. 50 or older	2.12	(0.23 - 19.96)	1.87	(0.83 - 4.23)	1.75	(1.04 - 2.93)
35-49 vs. 50 or older	6.04	(0.71 - 51.38)	1.19	(0.51 - 2.78)	1.33	(0.81 - 2.20)
Gender						
Male vs. female	0.60	(0.26 - 1.41)	1.35	(1.03 - 1.76)	0.76	(0.63 - 0.92)
Race/Ethnicity						
White vs. black	0.55	(0.20 - 1.52)	0.54	(0.39 - 0.76)	1.62	(1.18 - 2.24)
Hispanic vs. black	--	(-- - --)	0.74	(0.43 - 1.29)	1.86	(1.13 - 3.07)
Other[1] vs. black	1.51	(6.40 - 5.78)	--	(-- - --)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.23	(0.07 - 0.76)	0.65	(0.27 - 1.55)
American Indian or Alaska Native vs. black	--	(-- - --)	1.56	(0.57 - 4.27)	3.23	(1.25 - 8.34)
More than one race vs. black	--	(-- - --)	0.81	(0.32 - 2.06)	0.99	(0.42 - 2.29)
Education						
Less than high school vs. at least some college	1.74	(0.60 - 5.03)	2.29	(1.54 - 3.40)	1.78	(1.33 - 2.39)
High school graduate vs. at least some college	0.93	(0.36 - 2.35)	1.28	(1.00 - 1.64)	1.10	(0.90 - 1.35)

-- Not available.

Note: For past year heroin use, three racial/ethnic categories were used: white, black, and Hispanic. American Indian/Alaska Native, Asian/Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Nonmedical use of any prescription-type psychotherapeutic indicates using pain relievers, tranquilizers, stimulants, or sedatives at least once. Indicated use does not include over-the-counter drugs.

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

Table 6.6 Adjusted Odds Ratios of *Past Year Heavy Marijuana Use and Heavy Use of Other Illicit Drugs* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

	Heavy Marijuana Use		Heavy Use of Other Illicit Drugs	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.30	(2.43 - 11.56)	4.49	(2.56 - 7.87)
15-17 vs. 21 or older	1.36	(0.63 - 2.95)	2.12	(1.24 - 3.64)
18-20 vs. 21 or older	0.82	(0.32 - 2.13)	1.15	(0.62 - 2.11)
Age in Years				
26-34 vs. 50 or older	4.73	(1.33 - 16.83)	1.72	(0.83 - 3.55)
35-49 vs. 50 or older	2.31	(0.64 - 8.29)	1.52	(0.75 - 3.08)
Gender				
Male vs. female	2.12	(1.47 - 3.05)	1.11	(0.86 - 1.42)
Race/Ethnicity				
White vs. black	1.25	(0.77 - 2.02)	0.62	(0.42 - 0.91)
Hispanic vs. black	1.01	(0.53 - 1.95)	1.23	(0.69 - 2.18)
Other[1] vs. black	1.17	(0.45 - 3.01)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.54	(0.21 - 1.40)
American Indian or Alaska Native vs. black	--	(-- - --)	2.63	(1.06 - 6.54)
More than one race vs. black	--	(-- - --)	0.77	(0.26 - 2.29)
Education				
Less than high school vs. at least some college	2.43	(1.47 - 3.99)	2.99	(2.02 - 4.41)
High school graduate vs. at least some college	2.74	(1.24 - 2.43)	1.57	(1.15 - 2.13)

-- Not available.

Note: For heavy marijuana use, four racial/ethnic categories were used: white; black; Hispanic; and American Indian/Alaska Native, Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Heavy marijuana use refers to using marijuana on 300 or more days in the past year. Heavy use of other illicit drugs refers to using cocaine, hallucinogens, inhalants, heroin, or any prescription-type psychotherapeutic used nonmedically (i.e., pain relievers, sedatives, tranquilizers, or stimulants) on at least 50 days in the past year.

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

Table 6.7 Adjusted Odds Ratios of *Past Year Illicit Drug Dependence or Abuse and Alcohol or Illicit Drug Dependence or Abuse* among Lifetime Marijuana Users Aged 26 or Older: 2000

	Illicit Drug Dependence or Abuse		Alcohol or Illicit Drug Dependence or Abuse	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	4.74	(1.86 - 12.08)	1.90	(1.33 - 2.72)
15-17 vs. 21 or older	1.74	(0.69 - 4.36)	0.99	(0.71 - 1.37)
18-20 vs. 21 or older	1.51	(0.61 - 3.72)	0.94	(0.67 - 1.32)
Age in Years				
26-34 vs. 50 or older	1.31	(0.44 - 3.95)	2.20	(1.41 - 3.43)
35-49 vs. 50 or older	0.88	(0.31 - 2.52)	1.43	(0.92 - 2.22)
Gender				
Male vs. female	1.12	(0.72 - 1.74)	1.94	(1.56 - 2.42)
Race/Ethnicity				
White vs. black	0.52	(0.30 - 0.88)	0.93	(0.70 - 1.25)
Hispanic vs. black	0.89	(0.45 - 1.75)	0.95	(0.62 - 1.47)
Asian/Pacific Islander/Native Hawaiian vs. black	0.13	(0.03 - 0.63)	0.79	(0.27 - 2.28)
American Indian or Alaska Native vs. black	0.96	(0.26 - 3.46)	1.36	(0.59 - 3.13)
More than one race vs. black	3.01	(0.85 - 10.74)	1.59	(0.54 - 4.67)
Education				
Less than high school vs. at least some college	1.81	(1.05 - 3.13)	1.91	(1.42 - 2.56)
High school graduate vs. at least some college	0.75	(0.51 - 1.10)	1.32	(1.07 - 1.63)

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.8 Adjusted Odds Ratios of *Past Year Alcohol Dependence and Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older: 2000

	Alcohol Dependence		Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	1.64	(0.91 - 2.95)	6.19	(2.22 - 17.21)
15-17 vs. 21 or older	0.97	(0.57 - 1.65)	1.98	(0.74 - 5.27)
18-20 vs. 21 or older	1.02	(0.56 - 1.84)	2.29	(0.79 - 6.64)
Age in Years				
26-34 vs. 50 or older	1.51	(0.75 - 3.03)	1.20	(0.36 - 4.00)
35-49 vs. 50 or older	1.33	(0.67 - 2.64)	0.99	(0.30 - 3.30)
Gender				
Male vs. female	1.72	(1.23 - 2.41)	1.00	(0.61 - 1.64)
Race/Ethnicity				
White vs. black	0.83	(0.50 - 1.36)	0.49	(0.26 - 0.91)
Hispanic vs. black	0.67	(0.34 - 1.33)	0.57	(0.22 - 1.44)
Asian/Pacific Islander/Native Hawaiian vs. black	1.15	(0.23 - 5.64)	0.17	(0.03 - 0.87)
American Indian/Alaska Native vs. black	0.96	(0.23 - 3.99)	0.27	(0.08 - 0.95)
More than one race	0.81	(0.24 - 2.77)	1.09	(0.30 - 3.97)
Education				
Less than high school vs. at least some college	3.34	(2.21 - 5.07)	1.81	(0.90 - 3.62)
High school graduate vs. at least some college	1.62	(1.15 - 2.30)	0.69	(0.43 - 1.12)

Note: Illicit drug dependence indicates dependence on at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.9 Adjusted Odds Ratios of *Past Year Marijuana Dependence and Other Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older: 2000

Variables	Marijuana Dependence		Other Illicit Drug Dependence	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	9.77	(2.82 - 33.89)	5.67	(1.51 - 21.29)
15-17 vs. 21 or older	2.67	(0.76 - 9.38)	1.94	(0.56 - 6.74)
18-20 vs. 21 or older	2.98	(0.79 - 11.25)	2.52	(0.64 - 9.94)
Age in Years				
26-34 vs. 50 or older	2.47	(0.69 - 8.83)	0.76	(0.19 - 3.14)
35-49 vs. 50 or older	1.70	(0.46 - 6.27)	0.80	(0.19 - 3.33)
Gender				
Male vs. female	1.31	(0.71 - 2.40)	0.83	(0.44 - 1.56)
Race/Ethnicity				
White vs. black	0.52	(0.21 - 1.31)	0.53	(0.24 - 1.16)
Hispanic vs. black	--	(-- - --)	0.80	(0.27 - 2.35)
Other[1] vs. black	0.47	(0.12 - 1.77)	--	(-- - --)
Other[2] vs. black	--	(-- - --)	0.70	(0.20 - 2.50)
Education				
Less than high school vs. at least some college	0.95	(0.41 - 2.24)	2.98	(1.29 - 6.89)
High school graduate vs. at least some college	0.46	(0.23 - 0.92)	1.05	(0.59 - 1.88)

-- Not available.

Note: For marijuana dependence, three racial/ethnic categories were used: white; black; and Hispanic, American Indian/Alaska Native, Asian/Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race

[2] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.10 Percentages with *Past Year Alcohol and/or Illicit Drug Dependence or Abuse* among Past Year Marijuana Users Aged 26 or Older, by Age at First Marijuana Use: 2000

Age of Marijuana Initiation in Years	Illicit Drug Dependence or Abuse	Alcohol or Illicit Drug Dependence or Abuse	Alcohol Dependence	Illicit Drug Dependence	Marijuana Dependence	Other Illicit Drug Dependence
14 or younger	20.7	39.5	11.7	15.2	8.8	8.6
15-17	12.6	27.8	9.4	8.0	4.7	4.2
18-20	9.7	22.9	11.0	7.9	7.1	3.0
21 or older	7.5	16.7	5.4	3.4	2.1	1.3

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000

Table 6.11 Adjusted Odds Ratios of *Illicit Drug Dependence or Abuse and Alcohol or Illicit Drug Dependence or Abuse* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuana in the Past Year: 2000

	Illicit Drug Dependence or Abuse		Alcohol or Illicit Drug Dependence or Abuse	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.69	(2.12 - 15.28)	3.63	(1.86 - 7.06)
15-17 vs. 21 or older	2.94	(1.03 - 8.36)	2.17	(1.09 - 4.32)
18-20 vs. 21 or older	1.80	(0.71 - 4.59)	1.63	(0.88 - 3.01)
Age in Years				
26-34 vs. 50 or older	0.38	(0.13 - 1.09)	0.80	(0.32 - 1.97)
35-49 vs. 50 or older	0.37	(0.14 - 1.01)	0.76	(0.32 - 1.82)
Gender				
Male vs. female	0.89	(0.57 - 1.39)	1.16	(0.83 - 1.63)
Race/Ethnicity				
White vs. black	0.46	(0.26 - 0.80)	1.01	(0.64 - 1.59)
Hispanic vs. black	1.37	(0.59 - 3.19)	1.31	(0.65 - 2.64)
Other[1] vs. black	1.13	(0.49 - 2.62)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.23	(0.06 - 0.90)
American Indian/Alaska Native vs. black	--	(-- - --)	1.24	(0.38 - 4.04)
More than one race vs. black	--	(-- - --)	1.68	(0.56 - 5.06)
Education				
Less than high school vs. at least some college	1.02	(0.62 - 1.68)	1.44	(0.91 - 2.26)
High school graduate vs. at least some college	0.62	(0.40 - 0.98)	0.92	(0.63 - 1.34)

-- Not available.

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.12 Adjusted Odds Ratios of *Past Year Alcohol Dependence and Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuana in the Past Year: 2000

	Alcohol Dependence		Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	2.45	(0.79 - 7.63)	8.33	(2.99 - 23.19)
15-17 vs. 21 or older	2.09	(0.69 - 6.32)	3.68	(1.22 - 11.05)
18-20 vs. 21 or older	2.56	(0.94 - 6.95)	3.16	(1.06 - 9.44)
Age in Years				
26-34 vs. 50 or older	0.77	(0.17 - 3.49)	0.41	(0.14 - 1.19)
35-49 vs. 50 or older	0.86	(0.19 - 3.84)	0.45	(0.15 - 1.36)
Gender				
Male vs. female	1.16	(0.69 - 1.95)	0.81	(0.49 - 1.33)
Race/Ethnicity				
White vs. black	1.45	(0.58 - 3.62)	0.41	(0.23 - 0.75)
Hispanic vs. black	1.61	(0.56 - 4.65)	0.68	(0.24 - 1.92)
Other[1] vs. black	1.09	(0.22 - 5.33)	0.41	(0.11 - 1.54)
Education				
Less than high school vs. at least some college	2.94	(1.55 - 5.59)	0.90	(0.47 - 1.70)
High school graduate vs. at least some college	1.35	(0.76 - 2.41)	0.56	(0.32 - 1.00)

Note: Illicit drug dependence indicates dependence on at least one of the following: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.13 Adjusted Odds Ratios of *Past Year Marijuana Dependence and Other Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuan in the Past Year: 2000

	Marijuana Dependence		Other Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.05	(1.49 - 17.15)	17.03	(3.44 - 84.16)
15-17 vs. 21 or older	2.27	(0.63 - 8.15)	7.73	(1.41 - 42.32)
18-20 vs. 21 or older	3.55	(0.90 - 14.03)	3.97	(0.72 - 21.80)
Age in Years				
26-34 vs. 50 or older	1.05	(0.27 - 4.11)	0.19	(0.05 - 0.70)
35-49 vs. 50 or older	1.08	(0.26 - 4.53)	0.25	(0.06 - 1.07)
Gender				
Male vs. female	0.84	(0.45 - 1.57)	0.82	(0.41 - 1.65)
Race/Ethnicity				
White vs. black	0.62	(0.25 - 1.50)	0.38	(0.19 - 0.74)
Other[1] vs. black	0.58	(0.16 - 2.16)	0.83	(0.27 - 2.51)
Education				
Less than high school vs. at least some college	0.75	(0.33 - 1.72)	1.69	(0.71 - 4.00)
High school graduate vs. at least some college	0.42	(0.20 - 0.85)	0.99	(0.46 - 2.16)

Note: Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.6 Adjusted Odds Ratios of *Past Year Heavy Marijuana Use and Heavy Use of Other Illicit Drugs* among Lifetime Marijuana Users Aged 26 or Older: 1999 and 2000

	Heavy Marijuana Use		Heavy Use of Other Illicit Drugs	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.30	(2.43 - 11.56)	4.49	(2.56 - 7.87)
15-17 vs. 21 or older	1.36	(0.63 - 2.95)	2.12	(1.24 - 3.64)
18-20 vs. 21 or older	0.82	(0.32 - 2.13)	1.15	(0.62 - 2.11)
Age in Years				
26-34 vs. 50 or older	4.73	(1.33 - 16.83)	1.72	(0.83 - 3.55)
35-49 vs. 50 or older	2.31	(0.64 - 8.29)	1.52	(0.75 - 3.08)
Gender				
Male vs. female	2.12	(1.47 - 3.05)	1.11	(0.86 - 1.42)
Race/Ethnicity				
White vs. black	1.25	(0.77 - 2.02)	0.62	(0.42 - 0.91)
Hispanic vs. black	1.01	(0.53 - 1.95)	1.23	(0.69 - 2.18)
Other[1] vs. black	1.17	(0.45 - 3.01)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.54	(0.21 - 1.40)
American Indian or Alaska Native vs. black	--	(-- - --)	2.63	(1.06 - 6.54)
More than one race vs. black	--	(-- - --)	0.77	(0.26 - 2.29)
Education				
Less than high school vs. at least some college	2.43	(1.47 - 3.99)	2.99	(2.02 - 4.41)
High school graduate vs. at least some college	2.74	(1.24 - 2.43)	1.57	(1.15 - 2.13)

-- Not available.

Note: For heavy marijuana use, four racial/ethnic categories were used: white; black; Hispanic; and American Indian/Alaska Native, Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Heavy marijuana use refers to using marijuana on 300 or more days in the past year. Heavy use of other illicit drugs refers to using cocaine, hallucinogens, inhalants, heroin, or any prescription-type psychotherapeutic used nonmedically (i.e., pain relievers, sedatives, tranquilizers, or stimulants) on at least 50 days in the past year.

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 1999 and 2000.

Table 6.7 Adjusted Odds Ratios of *Past Year Illicit Drug Dependence or Abuse and Alcohol or Illicit Drug Dependence or Abuse* among Lifetime Marijuana Users Aged 26 or Older: 2000

	Illicit Drug Dependence or Abuse		Alcohol or Illicit Drug Dependence or Abuse	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	4.74	(1.86 - 12.08)	1.90	(1.33 - 2.72)
15-17 vs. 21 or older	1.74	(0.69 - 4.36)	0.99	(0.71 - 1.37)
18-20 vs. 21 or older	1.51	(0.61 - 3.72)	0.94	(0.67 - 1.32)
Age in Years				
26-34 vs. 50 or older	1.31	(0.44 - 3.95)	2.20	(1.41 - 3.43)
35-49 vs. 50 or older	0.88	(0.31 - 2.52)	1.43	(0.92 - 2.22)
Gender				
Male vs. female	1.12	(0.72 - 1.74)	1.94	(1.56 - 2.42)
Race/Ethnicity				
White vs. black	0.52	(0.30 - 0.88)	0.93	(0.70 - 1.25)
Hispanic vs. black	0.89	(0.45 - 1.75)	0.95	(0.62 - 1.47)
Asian/Pacific Islander/Native Hawaiian vs. black	0.13	(0.03 - 0.63)	0.79	(0.27 - 2.28)
American Indian or Alaska Native vs. black	0.96	(0.26 - 3.46)	1.36	(0.59 - 3.13)
More than one race vs. black	3.01	(0.85 - 10.74)	1.59	(0.54 - 4.67)
Education				
Less than high school vs. at least some college	1.81	(1.05 - 3.13)	1.91	(1.42 - 2.56)
High school graduate vs. at least some college	0.75	(0.51 - 1.10)	1.32	(1.07 - 1.63)

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.8 Adjusted Odds Ratios of *Past Year Alcohol Dependence and Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older: 2000

	Alcohol Dependence		Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	1.64	(0.91 - 2.95)	6.19	(2.22 - 17.21)
15-17 vs. 21 or older	0.97	(0.57 - 1.65)	1.98	(0.74 - 5.27)
18-20 vs. 21 or older	1.02	(0.56 - 1.84)	2.29	(0.79 - 6.64)
Age in Years				
26-34 vs. 50 or older	1.51	(0.75 - 3.03)	1.20	(0.36 - 4.00)
35-49 vs. 50 or older	1.33	(0.67 - 2.64)	0.99	(0.30 - 3.30)
Gender				
Male vs. female	1.72	(1.23 - 2.41)	1.00	(0.61 - 1.64)
Race/Ethnicity				
White vs. black	0.83	(0.50 - 1.36)	0.49	(0.26 - 0.91)
Hispanic vs. black	0.67	(0.34 - 1.33)	0.57	(0.22 - 1.44)
Asian/Pacific Islander/Native Hawaiian vs. black	1.15	(0.23 - 5.64)	0.17	(0.03 - 0.87)
American Indian/Alaska Native vs. black	0.96	(0.23 - 3.99)	0.27	(0.08 - 0.95)
More than one race	0.81	(0.24 - 2.77)	1.09	(0.30 - 3.97)
Education				
Less than high school vs. at least some college	3.34	(2.21 - 5.07)	1.81	(0.90 - 3.62)
High school graduate vs. at least some college	1.62	(1.15 - 2.30)	0.69	(0.43 - 1.12)

Note: Illicit drug dependence indicates dependence on at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.9 Adjusted Odds Ratios of *Past Year Marijuana Dependence and Other Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older: 2000

	Marijuana Dependence		Other Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	9.77	(2.82 - 33.89)	5.67	(1.51 - 21.29)
15-17 vs. 21 or older	2.67	(0.76 - 9.38)	1.94	(0.56 - 6.74)
18-20 vs. 21 or older	2.98	(0.79 - 11.25)	2.52	(0.64 - 9.94)
Age in Years				
26-34 vs. 50 or older	2.47	(0.69 - 8.83)	0.76	(0.19 - 3.14)
35-49 vs. 50 or older	1.70	(0.46 - 6.27)	0.80	(0.19 - 3.33)
Gender				
Male vs. female	1.31	(0.71 - 2.40)	0.83	(0.44 - 1.56)
Race/Ethnicity				
White vs. black	0.52	(0.21 - 1.31)	0.53	(0.24 - 1.16)
Hispanic vs. black	--	(-- - --)	0.80	(0.27 - 2.35)
Other[1] vs. black	0.47	(0.12 - 1.77)	--	(-- - --)
Other[2] vs. black	--	(-- - --)	0.70	(0.20 - 2.50)
Education				
Less than high school vs. at least some college	0.95	(0.41 - 2.24)	2.98	(1.29 - 6.89)
High school graduate vs. at least some college	0.46	(0.23 - 0.92)	1.05	(0.59 - 1.88)

-- Not available.

Note: For marijuana dependence, three racial/ethnic categories were used: white, black, and Hispanic, American Indian/Alaska Native, Asian/Pacific Islander/Native Hawaiian, and more than one race. Black was used as the reference group. Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

[2] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.10 Percentages with *Past Year Alcohol and/or Illicit Drug Dependence or Abuse* among Past Year Marijuana Users Aged 26 or Older, by Age at First Marijuana Use: 2000

Age of Marijuana Initiation in Years	Illicit Drug Dependence or Abuse	Alcohol or Illicit Drug Dependence or Abuse	Alcohol Dependence	Illicit Drug Dependence	Marijuana Dependence	Other Illicit Drug Dependence
14 or younger	20.7	39.5	11.7	15.2	8.8	8.6
15-17	12.6	27.8	9.4	8.0	4.7	4.2
18-20	9.7	22.9	11.0	7.9	7.1	3.0
21 or older	7.5	16.7	5.4	3.4	2.1	1.3

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.11 Adjusted Odds Ratios of *Illicit Drug Dependence or Abuse and Alcohol or Illicit Drug Dependence or Abuse* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuana in the Past Year: 2000

	Illicit Drug Dependence or Abuse		Alcohol or Illicit Drug Dependence or Abuse	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.69	(2.12 - 15.28)	3.63	(1.86 - 7.06)
15-17 vs. 21 or older	2.94	(1.03 - 8.36)	2.17	(1.09 - 4.32)
18-20 vs. 21 or older	1.80	(0.71 - 4.59)	1.63	(0.88 - 3.01)
Age in Years				
26-34 vs. 50 or older	0.38	(0.13 - 1.09)	0.80	(0.32 - 1.97)
35-49 vs. 50 or older	0.37	(0.14 - 1.01)	0.76	(0.32 - 1.82)
Gender				
Male vs. female	0.89	(0.57 - 1.39)	1.16	(0.83 - 1.63)
Race/Ethnicity				
White vs. black	0.46	(0.26 - 0.80)	1.01	(0.64 - 1.59)
Hispanic vs. black	1.37	(0.59 - 3.19)	1.31	(0.65 - 2.64)
Other[1] vs. black	1.13	(0.49 - 2.62)	--	(-- - --)
Asian/Pacific Islander/Native Hawaiian vs. black	--	(-- - --)	0.23	(0.06 - 0.90)
American Indian/Alaska Native vs. black	--	(-- - --)	1.24	(0.38 - 4.04)
More than one race vs. black	--	(-- - --)	1.68	(0.56 - 5.06)
Education				
Less than high school vs. at least some college	1.02	(0.62 - 1.68)	1.44	(0.94 - 2.26)
High school graduate vs. at least some college	0.62	(0.40 - 0.98)	0.92	(0.63 - 1.34)

-- Not available.

Note: Illicit drug dependence or abuse indicates dependence on or abuse of at least one of the following drugs: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence or abuse is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.12 Adjusted Odds Ratios of *Past Year Alcohol Dependence and Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuana in the Past Year: 2000

	Alcohol Dependence		Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	2.45	(0.79 - 7.63)	8.33	(2.99 - 23.19)
15-17 vs. 21 or older	2.09	(0.69 - 6.32)	3.68	(1.22 - 11.05)
18-20 vs. 21 or older	2.56	(0.94 - 6.95)	3.16	(1.06 - 9.44)
Age in Years				
26-34 vs. 50 or older	0.77	(0.17 - 3.49)	0.41	(0.14 - 1.19)
35-49 vs. 50 or older	0.86	(0.19 - 3.84)	0.45	(0.15 - 1.36)
Gender				
Male vs. female	1.16	(0.69 - 1.95)	0.81	(0.49 - 1.33)
Race/Ethnicity				
White vs. black	1.45	(0.58 - 3.62)	0.41	(0.23 - 0.75)
Hispanic vs. black	1.61	(0.56 - 4.65)	0.68	(0.24 - 1.92)
Other[1] vs. black	1.09	(0.22 - 5.33)	0.41	(0.11 - 1.54)
Education				
Less than high school vs. at least some college	2.94	(1.55 - 5.59)	0.90	(0.47 - 1.70)
High school graduate vs. at least some college	1.35	(0.76 - 2.41)	0.56	(0.32 - 1.00)

Note: Illicit drug dependence indicates dependence on at least one of the following: marijuana/hashish, cocaine (including crack), heroin, hallucinogens (including LSD and PCP), inhalants, or any prescription-type psychotherapeutic used nonmedically. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Table 6.13 Adjusted Odds Ratios of *Past Year Marijuana Dependence and Other Illicit Drug Dependence* among Lifetime Marijuana Users Aged 26 or Older Who Also Used Marijuana in the Past Year: 2000

	Marijuana Dependence		Other Illicit Drug Dependence	
Variables	**Odds Ratio**	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Age at First Marijuana Use in Years				
14 or younger vs. 21 or older	5.05	(1.49 - 17.15)	17.03	(3.44 - 84.16)
15-17 vs. 21 or older	2.27	(0.63 - 8.15)	7.73	(1.41 - 42.32)
18-20 vs. 21 or older	3.55	(0.90 - 14.03)	3.97	(0.72 - 21.80)
Age in Years				
26-34 vs. 50 or older	1.05	(0.27 - 4.11)	0.19	(0.05 - 0.70)
35-49 vs. 50 or older	1.08	(0.26 - 4.53)	0.25	(0.06 - 1.07)
Gender				
Male vs. female	0.84	(0.45 - 1.57)	0.82	(0.41 - 1.65)
Race/Ethnicity				
White vs. black	0.62	(0.25 - 1.50)	0.38	(0.19 - 0.74)
Other[1] vs. black	0.58	(0.16 - 2.16)	0.83	(0.27 - 2.51)
Education				
Less than high school vs. at least some college	0.75	(0.33 - 1.72)	1.69	(0.71 - 4.00)
High school graduate vs. at least some college	0.42	(0.20 - 0.85)	0.99	(0.46 - 2.16)

Note: Other illicit drug dependence indicates meeting the dependence criteria of one or more of the following drugs: cocaine, hallucinogens, inhalants, heroin, pain relievers, sedatives, tranquilizers, or stimulants. Dependence is based on the definition found in the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).

[1] Hispanic, Asian/Pacific Islander/Native Hawaiian, American Indian/Alaska Native, and more than one race.

Source: SAMHSA, Office of Applied Studies, National Household Survey on Drug Abuse, 2000.

Papers

Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people

Cecile Henquet, Lydia Krabbendam, Janneke Spauwen, Charles Kaplan, Roselind Lieb, Hans-Ulrich Wittchen, Jim van Os

Abstract

Objective To investigate the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during adolescence.

Design Analysis of prospective data from a population based sample. Assessment of substance use, predisposition for psychosis, and psychotic symptoms was based on standardised personal interviews at baseline and at follow up four years later.

Participants 2437 young people (aged 14 to 24 years) with and without predisposition for psychosis.

Main outcome measure Psychotic symptoms at follow up as a function of cannabis use and predisposition for psychosis at baseline.

Results After adjustment for age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at baseline, and use of other drugs, tobacco, and alcohol, cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow up four years later (adjusted odds ratio 1.67, 95% confidence interval 1.13 to 2.46). The effect of cannabis use was much stronger in those with any predisposition for psychosis at baseline (23.8% adjusted difference in risk, 95% confidence interval 7.9 to 39.7, P = 0.003) than in those without (5.6%, 0.4 to 10.8, P = 0.033). The risk difference in the "predisposition" group was significantly greater than the risk difference in the "no predisposition" group (test for interaction 18.2%, 1.6 to 34.8, P = 0.032). There was a dose-response relation with increasing frequency of cannabis use. Predisposition for psychosis at baseline did not significantly predict cannabis use four years later (adjusted odds ratio 1.42, 95% confidence interval 0.88 to 2.31).

Conclusion Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis.

Introduction

There is accumulating and converging evidence that cannabis use may be a risk factor for psychotic symptoms.[1-4] The possible causal nature of the association between cannabis and psychosis, however, is still a matter of debate, the main discussion revolving around the role of predisposition for psychosis and adjustment for confounders.[3 4] According to the self medication hypothesis,[5] individuals may start using cannabis because of predisposition for psychosis, rather than cannabis use causing expression of psychosis. To our knowledge, no prospective study to date has tested this hypothesis using information on predisposition for psychosis in relation to later cannabis use. Recent research, however, has suggested that rather than being the cause of cannabis use, such predisposition interacts synergistically with cannabis use. Two studies suggested that the joint effect of cannabis use and predisposition for psychosis on the emergence of psychotic symptoms was greater than the sum of their individual effects.[3 4]

We investigated prospectively whether cannabis use at baseline increases the risk of subsequent development of psychotic symptoms, whether any such increase in risk is higher in individuals with a predisposition for psychosis, and whether baseline expression predisposition increases the risk for subsequent use of cannabis. We adjusted for possible confounding factors in a large population-based sample of adolescents and young adults.

Methods

Sample

The study was part of the early developmental stages of psychopathology (EDSP) study,[6] in which data were collected on the prevalence, incidence, risk factors, comorbidity, and four year course of mental disorders in a random regional representative population sample of adolescents and young adults aged 14-24 years. The EDSP study is prospective, consisting of a baseline survey in 1995, an assessment of a subsample in 1996-7, and a four year follow up of the total sample in 1999.[7] The current analyses used the baseline and four year follow up data. The study sample was randomly drawn from the respective population registry offices of the city and each of the 29 counties of Munich. The base population were all those born between 1 June 1970 and 31 May 1981 who were registered as living in these areas as their primary place of residence and were German citizens. At baseline 3021 participants were interviewed face to face in their homes by using a computer assisted method (response rate 71%). An average of 42 months after the baseline investigations 2548 (response rate 84%) participants were successfully followed up. Of these, 90 participants did not want to respond to questions about illicit drug use at baseline or follow up, and data on the psychosis section of the Munich version of the international composite interview were incomplete for 21 participants. Our analyses were therefore of 2437 participants. To have 80% power to detect an odds ratio of 2.5 at the 5% level, given a base rate of psychotic experiences of 10% and a ratio of unexposed to exposed of 6:1,[8 9] we needed a sample size of 616. As around four times as many subjects are required for an inter-

action such as between cannabis use and predisposition for psychosis,[9] the sample size of 2437 was large enough.

Instruments

Participants were interviewed by trained psychologists using the Munich version of the composite international diagnostic interview (M-CIDI).[10] At baseline, they used the lifetime version of the interview. The interval version was used at follow up, which refers to the period of assessment between baseline and follow up. We assessed data on the psychosis (G) section only at follow up and these represent lifetime ratings. At baseline and at follow up, participants additionally completed the self report symptom checklist (SCL-90-R)[11] to screen for a broad range of psychopathological experiences including psychosis.

We used the "paranoid ideation" and "psychoticism" subscales of the symptom checklist to explore predisposition for psychosis at baseline and at follow up. Total scores of both subscales were added into a total score. Participants with total scores above the 90th centile were considered as having a predisposition for psychosis, both at baseline and at follow up.

We defined an outcome of psychosis as at least one (broad psychosis outcome) or at least two (narrow psychosis outcome) positive ratings on any of the 15 core psychosis items of the M-CIDI. We used the narrow outcome to exclude the possibility of spurious results due to false positive misclassification. None of these psychotic symptoms was due to acute effects of medication, drugs, or alcohol.

To assess symptoms of depression at baseline and follow up we calculated a mean score of the ratings on the 28 items of the depression section (E) of the M-CIDI. We divided this into two groups at the 90th centile, yielding a measure of significant symptoms at both baseline and follow up.

We assessed use of cannabis and other substances using the L-section of the M-CIDI. Individuals with lifetime cannabis use of five times or more at baseline were considered as exposed to cannabis. Cannabis exposure at baseline was defined as lifetime cannabis use of five times or more (any use) and frequency of use (use during the period of heaviest use: no use; less than once a month; three to four times a month, once to twice a week; three to four times a week; almost daily). Cannabis use at follow up was analysed as cannabis use of five times or more during the four years to follow up (any use at follow up). We combined psychostimulants, sedatives, opiates, cocaine, phencyclidine (PCP), and psychedelic drugs into a group of "other drugs." Lifetime tobacco use at baseline was defined as daily use during at least one month. Alcohol use at baseline was analysed as frequency of use during the past 12 months (no use; less than once a month; three to four times a month, once to twice a week; three to four times a week; almost daily).

Statistical analyses

Associations between any use of cannabis or frequency of use at baseline and psychotic symptoms at follow up were expressed as odds ratios from logistic regression models in Stata, release 8.0 (StataCorp, College Station, TX). All analyses were a priori adjusted for age, sex, socioeconomic status, urbanicity,[12] and experience of childhood trauma[13] as well as for predisposition for psychosis at baseline. To test whether the effect of cannabis on psychosis was independent of other drugs, tobacco, alcohol, and symptoms of depression at baseline and at follow up, we entered these variables in the model with any cannabis use at baseline. We also adjusted the effect of baseline cannabis on psychotic symptoms according to the M-CIDI at follow up for predisposition for psychosis at follow up.

The population attributable fraction was derived from the associations between any use of cannabis and psychotic symptoms according to the M-CIDI at follow up (adjusted for demographics and trauma during childhood) in the logistic regression models, both for the whole dataset and for the individuals with expression of baseline predisposition, using the aflogit procedure in Stata. This parameter gives a measure of the proportion of cases in participants with psychotic symptoms according to the M-CIDI at follow up that could have been prevented, assuming causality, had the exposure to cannabis been eliminated completely from the baseline population.

We calculated the interaction between predisposition for psychosis at baseline and any cannabis use (adjusted for demographics, childhood trauma, and predisposition at follow up) under an additive model rather than a multiplicative model because an additive model is more likely to yield information on the degree of synergism between causes—that is, the extent to which both causes depend on each other or coparticipate in disease causation.[14 15]

We investigated the self medication hypothesis by calculating the association between predisposition for psychosis at baseline and cannabis use at follow up, both for the whole dataset and for the individuals who had not used cannabis at baseline. We used sensitivity analyses to examine whether differential attrition in the sample as a whole (3021 at baseline, 2437 at follow up) could have biased the findings. This was done by multiple imputation of missing values of cannabis use at baseline, predisposition for psychosis at baseline, and psychotic symptoms according to the M-CIDI at follow up with the hotdeck command in Stata.

Results

We followed up 2437 participants, of which 1251 (51.3%) were men. The mean age was 18.8 years (SD 3.3 years) at baseline and 21.8 years (3.4 years) at follow up. At four year follow up the cumulative lifetime incidence of at least one psychotic symptom was 424 (17.4%), irrespective of severity and impairment probe criteria, and 174 (7.1%) participants reported two or more psychotic symptoms. At baseline 320 (13.1%) admitted to any use of cannabis (five times or more) and 361 (14.8 %) did so at follow up.

Any cannabis use at baseline increased the risk of psychotic symptoms according to the M-CIDI at follow up four years later in a dose-response fashion (tables 1-3), regardless of confounders, and with larger effect sizes for the narrowly defined psychosis outcome.

The effect of baseline cannabis use on the psychosis outcome according to the M-CIDI at follow up four years later was much stronger in those with predisposition for psychosis at baseline (23.8% adjusted difference in risk) than in those without (5.6% adjusted difference in risk, table 4). The population attributable fraction was 6.2% for the total group and more than twice as large (14.2%) for the group with predisposition for psychosis at baseline.

Predisposition for psychosis at baseline did not significantly predict cannabis use at follow up four years later (odds ratio 1.42, 95% confidence interval 0.94 to 2.15, for the whole sample and 1.42, 0.88 to 2.31, for the subgroup with no cannabis use at baseline).

Based on 1000 imputation sequences in which we stochastically imputed missing values of cannabis use at baseline and psychotic symptoms according to the M-CIDI at four year follow up in the whole sample, the estimated average additive interaction between predisposition for psychosis at baseline and cannabis

Table 1 Patterns of cannabis use at baseline and psychotic symptoms at follow up. Figures are numbers (percentages) of participants

Cannabis use at baseline	Any psychotic symptom at follow up		At least two psychotic symptoms at follow up	
	Yes (n=424)	No (n=2913)	Yes (n=174)	No (n=3223)
Any use (≥5 times)	82 (19.3)	230 (11.8)	44 (25.3)	276 (12.2)
Cumulative frequency*				
None	342 (80.7)	1775 (88.2)	130 (74.7)	1987 (87.8)
<1 times/month	13 (3.1)	66 (3.4)	5 (2.9)	77 (3.4)
1-4 times/month	18 (4.2)	62 (3.1)	10 (5.7)	70 (3.1)
2 times/week	17 (4.0)	42 (2.0)	7 (4.0)	52 (2.3)
3-4 times/week	12 (2.8)	21 (1.0)	8 (4.6)	25 (1.1)
Almost daily	22 (5.2)	46 (2.3)	14 (8.0)	54 (2.4)

Some percentages do not total 100 because of rounding

use at baseline remained significant (19.5% difference in risk, 95% confidence interval 0.5 to 38.6, P = 0.039).

Discussion

Exposure to cannabis during adolescence and young adulthood increases the risk of psychotic symptoms later in life. The findings confirm earlier suggestions that this association is stronger for individuals with predisposition for psychosis[3 9] and stronger for the more severe psychotic outcomes.[2 9] Frequent use of cannabis was associated with higher levels of risk in a dose-response fashion. Associations were independent of other variables known to increase the risk for psychosis. Also, the effect of cannabis remained significant after we corrected for baseline use of other drugs, tobacco, and alcohol. Finally, the data did not support the self medication hypothesis as baseline predisposition for psychosis did not significantly predict cannabis use at follow up.

Strengths and weaknesses

We examined psychotic symptoms according to the M-CIDI at follow up in a non-clinical sample. Symptoms were more prevalent than psychotic disorders defined according to the *Diagnostic and Statistic Manual of Mental Disorders*, fourth edition, but nevertheless have been shown to be on the same continuum of experiences as more severe states of psychosis, such as schizophrenia.[1 10] Established risk factors for schizophrenia, such as urbanicity and familial predisposition, also affect the occurrence of psychotic symptoms.[16 17] Our results confirm those from three previous studies that showed that exposure to cannabis plays a part not only in the expression of psychotic disorder but also in the emergence of less severe psychotic experiences.[2 9 10]

At baseline we used self reported psychotic experiences on the symptom checklist to determine predisposition for psychosis, whereas at follow up four years later we used the M-CIDI to determine psychosis outcome. In the group with predisposition for psychosis at baseline, any effect of cannabis can thus be interpreted as psychosis persisting from baseline to follow up (if we assume that the two measures of psychosis are identical), rather than an effect of transition from expression of predisposition at baseline to expression of overt symptoms at follow up. Although both explanations would be equally important, adjustment for the effect of the follow up equivalent of the baseline measure of predisposition for psychosis did not change the observed association between cannabis and psychotic symptoms according to the M-CIDI, indicating that the effect of cannabis can be interpreted as onset of clinical psychosis outside the continuity between the measure of predisposition for psychosis at baseline and follow up. In addition, cannabis also had a significant effect on psychotic symptoms in the group without predisposition for psychosis at baseline, albeit of smaller effect.

Synergistic interaction between cannabis and predisposition for psychosis

Findings from earlier research suggest biological plausibility, involving the endocannabinoid CB1 receptor system in close interaction with the dopamine neurotransmitter system. For example, delta-9-tetrahydrocannabinol (the major psychoactive component of cannabis) increases presynaptic dopamine efflux and utilisation in the prefrontal cortex in rats.[19] Increased concentrations of CB1 receptors were found in the dorsolateral prefrontal cortex of patients with schizophrenia,[20] and concentrations of anandamide (an endogenous cannabinoid that binds to the CB1 receptor) were found to be higher in the cerebrospinal fluid of these patients.[21] Furthermore, there is evidence from animal studies that puberty in rats is a vulnerable period with respect to the adverse effects of cannabinoids.[22] The long lasting behavioural disturbances observed in this animal study are consistent with impairments generally found in patients with schizophrenia, and the changes in these rats were reversed by the acute administration of the dopamine antagonist haloperidol.[22] Repeated exposure to cannabis may cause initial increases in synaptic dopamine and then lead to more prolonged changes in the endogenous cannabinoid systems. These changes might be most profound after exposure to cannabis during adolescence and in individuals with a pre-existing vulnerability to dysregulation of the cannabinoid system and related neurotransmission systems.

This work is part of the early developmental stages of psychopathology (EDSP) study. Principal investigators are Hans-Ulrich Wittchen and Roselind Lieb. Current or former staff members of the EDSP group include Kirsten von Sydow, Gabriele Lachner, Axel Perkonigg, Peter Schuster, Michael Höfler, Holger Sonntag, Esther Beloch, Martina Fuetsch, Elzbieta Garczynski, Alexandra Holly, Barbara Isensee, Chris Nelson, Hildegard

Table 2 Associations between any cannabis use at baseline and psychotic symptoms at follow up. Figures are odds ratios (95% confidence intervals)

Cannabis exposure at baseline	Any psychotic symptom				At least two psychotic symptoms
	Unadjusted	Adjusted*	Additional adjustment†	Additional adjustments‡	Adjusted*
Any use (≥5 times)	1.79 (1.36 to 2.36)	1.69 (1.26 to 2.25)	1.67 (1.13 to 2.46)	1.53 (1.13 to 2.07)	2.23 (1.52 to 3.29)

*Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at baseline.
†Also adjusted for other drug use, tobacco, and alcohol.
‡Also adjusted for predisposition for psychosis at follow up and depression at baseline and follow up.

Table 3 Associations between frequency of cannabis use at baseline and any psychotic symptoms. Figures are odds ratios (95% confidence intervals)

Cumulative frequency of cannabis use	Unadjusted	Adjusted*
None†	1	1
<1/month	1.01 (0.58 to 1.86)	0.99 (0.53 to 1.84)
1–4 times/month	1.58 (0.91 to 2.68)	1.50 (0.84 to 2.62)
1–2 times/week	2.28 (1.28 to 4.09)	1.95 (1.07 to 3.55)
3–6 times/week	3.07 (1.49 to 6.31)	2.44 (1.16 to 5.13)
Almost daily	2.97 (1.52 to 4.34)	2.23 (1.30 to 3.84)
Linear trend‡	1.24 (1.15 to 1.35)	1.20 (1.10 to 1.31)

*Adjusted for age, sex, socioeconomic, urbanicity, childhood trauma, and predisposition for psychosis at baseline.
†Reference category.
‡Increase in risk with one unit change in cannabis frequency.

What is already known on this topic

It is generally accepted that cannabis use is strongly associated with psychosis

We do not know whether the association is causal or whether those with a predisposition for psychosis are particularly at risk

What this study adds

Cannabis use in young people moderately increased the risk of developing psychotic symptoms

The risk for the onset of symptoms was much higher in young people with a predisposition for psychosis

Predisposition psychosis at baseline did not predict cannabis use at follow up, thus refuting the self medication hypothesis

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Contributors: H-UW and RL were the principal investigators of the study. CH analysed the data in collaboration with LK, JvO, and JS. CH drafted the paper. All authors contributed to subsequent drafts and the final version. JvO is guarantor for the paper. CK contributed to drafts of the paper and the final version.

Funding: The EDSP study is funded by grants of the German Ministry of Research, Education and Technology: 01EB9405/6 and 01EB9001/6 and the Deutsche Forschungsgemeinschaft (DFG). This paper is also part of NIH-grant "Longitudinal analysis of psychiatric risk factors for SUD" (RO1DA016977-01, PI: E. Costello, HU/Wittchen Co-PI).

Competing interests: None declared.

Ethical approval: The local ethics committee approved the study.

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(Accepted 27 September 2004)

doi: 10.1136/bmj.38267.664086.63

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Table 4 Interactions between any cannabis use and predisposition for psychosis

Cannabis use at baseline	No with psychosis outcome*	No without psychosis outcome*	Risk of psychotic symptoms at follow up	Difference in risk	
				Unadjusted	Adjusted† (95% CI)
No predisposition for psychosis at baseline					
None	294	1642	15%	6%	5.6% (0.4 to 10.8) P=0.033
Any (≥5 times)	56	216	21%		
Predisposition for psychosis at baseline‡					
None	47	133	26%	25%	23.8% (7.9 to 39.7) P=0.003
Any (≥5 times)	23	22	51%		

*Numbers total 2436 because of one missing value on predisposition for psychosis at baseline.
†Age, sex, socioeconomic status, urbanicity, childhood trauma, and predisposition for psychosis at follow up. Test for additive interaction: 18.2% adjusted difference in risk (95% confidence interval 1.8 to 34.8), P=0.032 (tests whether risk difference in "predisposition" group is significantly greater than risk difference in "no predisposition" group).
‡Total score ≥90th centile on "paranoid ideation" and "psychoticism" subscales of symptom checklist.

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Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study

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Abstract

Objectives An association between use of cannabis in adolescence and subsequent risk of schizophrenia was previously reported in a follow up of Swedish conscripts. Arguments were raised that this association may be due to use of drugs other than cannabis and that personality traits may have confounded results. We performed a further analysis of this cohort to address these uncertainties while extending the follow up period to identify additional cases.

Design Historical cohort study.

Setting 1969-70 survey of Swedish conscripts (>97% of the country's male population aged 18-20).

Participants 50 087 subjects: data were available on self reported use of cannabis and other drugs, and on several social and psychological characteristics.

Main outcome measures Admissions to hospital for ICD-8/9 schizophrenia and other psychoses, as determined by record linkage.

Results Cannabis was associated with an increased risk of developing schizophrenia in a dose dependent fashion both for subjects who had ever used cannabis (adjusted odds ratio for linear trend of increasing frequency 1.2, 95% confidence interval 1.1 to 1.4, $P<0.001$), and for subjects who had used only cannabis and no other drugs (adjusted odds ratio for linear trend 1.3, 1.1 to 1.5, $P<0.015$). The adjusted odds ratio for using cannabis >50 times was 6.7 (2.1 to 21.7) in the cannabis only group. Similar results were obtained when analysis was restricted to subjects developing schizophrenia after five years after conscription, to exclude prodromal cases.

Conclusions Cannabis use is associated with an increased risk of developing schizophrenia, consistent with a causal relation. This association is not explained by use of other psychoactive drugs or personality traits relating to social integration.

Introduction

The relation between cannabis use and subsequent onset of psychosis is complex.[1-3] Although it is clear that high doses of cannabis may lead to a short lived toxic psychosis, it is unclear whether cannabis increases the risk of psychotic illness persisting after abstinence from the drug. An association between self reported use of cannabis in adolescence and subsequent risk of schizophrenia was reported from a cohort study of Swedish conscripts,[4] which supports the view that cannabis might act as an independent risk factor for schizophrenia. Several uncertainties have, however, been raised regarding the interpretation of this result.

Firstly, the apparent effect of cannabis may be caused by other drugs (such as amphetamines) that are more likely to have been misused among cannabis users than among non-users.[5,6] Secondly, premorbid personality traits may have predisposed individuals both to developing schizophrenia and to using cannabis. Traits relating to social behaviour are likely to be particularly important in this respect. Thirdly, use of cannabis may have been secondary to the presence of schizophrenia, as a form of "self medication" for symptoms, despite failure to identify the disorder at the time of conscription.[7] Review of case histories of a small subsample from this cohort shows that the association was not due to use of other drugs and that use of cannabis preceded any mental illness,[8] but the causal pathways are difficult to disentangle and merit further study.

We are not aware of any other cohort studies that have investigated the association between drug use and subsequent risk of schizophrenia, and case-control studies are susceptible to recall bias. In this study we perform a further analysis of the Swedish conscript cohort to address some of the above concerns.[4] The follow up period is now 27 years (15 years in the original study) and covers almost the whole period of risk for schizophrenia.[9] Our improved understanding of risk factors for schizophrenia has also enabled us better to adjust for factors such as personality traits that potentially confound this relation.[10-13]

Methods

Subjects

The cohort consisted of 50 087 Swedish men conscripted for compulsory military training in 1969-1970. More than 98% (49 321) were 18-20 years of age. Only 2-3% of the male population were excused conscription because of severe mental or physical handicap. The conscription procedure included intelligence tests and non-anonymous self reported ques-

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bmj.com 2002;325:1199

tionnaires on family, social background, behaviour during adolescence, and substance use—including first drug used, drug most commonly used, frequency of use, and direct questions regarding use of a list of specified drugs. Details of the procedure and results of studies of its validity have been reported previously.[14]

All subjects underwent a structured interview conducted by a psychologist, and those reporting any psychiatric symptoms were interviewed by a psychiatrist and given a diagnosis according to ICD-8 (international classification of diseases, 8th revision) where applicable.[15] Thirty four cases of psychosis diagnosed at conscription were excluded from the study. Permission to use the anonymised database was granted by the Karolinska Institute research ethics committee and the Swedish data inspection board.

Follow up

The Swedish national hospital discharge register recorded about 70% of all psychiatric admissions in 1970, rising to 83% in 1973. Coverage was 97% in 1974-83, 95% in 1984-6, and has been virtually complete since 1987. The linkage reported here was from 1970 to 1996. The incomplete registration during some periods is unlikely to have affected the results. Misclassification of outcomes is likely to be low, given that over 90% of people with schizophrenia are admitted to hospital at some point during their illness.[16]

Patients were given clinical diagnoses according to the Nordic version of ICD-8 (ICD-9 from 1987). Outcomes investigated were schizophrenia (codes 295.00-295.99) and other psychoses (including affective and paranoid psychoses, codes 296.00-298.99). It is unlikely that cases diagnosed as schizophrenia in this cohort were either toxic psychoses induced by cannabis (or amphetamine) or acute, transient drug induced psychoses, given the restrictive tradition in Sweden regarding the diagnosis of schizophrenia.[17] Satisfactory validity of schizophrenia diagnoses in a small sample from this cohort has been observed,[8] and ICD-8 diagnoses from the register have shown high specificity with criteria for schizophrenia as defined in DSM-III (*Diagnostic and Statistical Manual of Mental Disorders*, third edition).[18]

Analysis

We used logistic regression to calculate odds ratios and 95% confidence intervals for developing schizophrenia in subjects who used cannabis compared with subjects with no history of drug use, both before and after adjustment for potential confounders. Odds ratios may be interpreted as rate ratios because schizophrenia is a rare outcome.[19] Although a few subjects died during follow up, analysis by using Cox regression made no difference to the results obtained by using logistic regression, which we therefore retained as the method of choice.

Previous research has found that psychiatric diagnosis at conscription, IQ score, personality variables concerned with interpersonal relationships, place of upbringing, paternal age, and cigarette smoking are all associated with schizophrenia.[9–11 20 21] We included these variables as potential confounders in the regression model. Disturbed behaviour in childhood, history of alcohol misuse, family history of psychiatric illness, financial situation of the family, and father's occupation were also considered to be potential confounders and included in the analysis. The variable relating to poor social integration as an aspect of personality was a summed score of questions regarding number of close friends, history of relationships with girlfriends, and individual sensitivity. We selected these questions after a factor analysis of over 40 questions relating to childhood and adolescent behaviour from one of the questionnaires. Only 3% of the sample had missing data for any of the questions.

Subjects were stratified into those receiving a diagnosis within five years of conscription (0-5 years) and those receiving a diagnosis after this time (>5 years) to investigate possible effects of a prodrome at the time of conscription.

Results

Out of the 50 053 subjects, 362 (0.71%, 95% confidence interval 0.65% to 0.80%) received a diagnosis of schizophrenia by 1996. Data on drug use, derived from all sources of information, were missing on 16 (4.4%) of subjects developing schizophrenia and on 1522 (3.1%) of non-cases ($P<0.2$).

Of 11 variables initially included as potential confounders, only five had any effect on the adjusted results. Table 1 shows a summary of these in relation to cannabis use. Adjusting for poor social integration made minimal difference to results but is also included in table 1. For the purposes of table 1 only we treated IQ score, poor social integration, and disturbed behaviour as dichotomous variables, using the 10th percentile as a cut-off point for coding.

Ever used cannabis

Altogether 5391 subjects (10.8% of the cohort) had ever used cannabis, and 73 of these (1.4%) developed schizophrenia. In 69 subjects who started using drugs before 1969, 19 (31%, 95% confidence interval 20% to 44%) of those developing schizophrenia had stopped using drugs before conscription, as opposed to 2810 (64%; 62% to 65%) of the 4418 who did not develop schizophrenia ($P<0.001$).

Table 1 Summary of confounders in relation to subjects' history of drug use at conscription. Values are numbers (percentages) of cohort sample

Subjects by type of drug use	Diagnosis of psychiatric illness on conscription*	Disturbed behaviour	Low IQ score	Brought up in city	Cigarette smoking	Poor social integration
Cannabis (n=5391)	1408 (27)	1582 (31)	297 (6)	2262 (43)	4582 (86)	130 (2.5)
Cannabis only (n=1648)	235 (15)	271 (17)	65 (4)	653 (40)	1331 (81)	34 (2.1)
Any drug (n=11 783)	2325 (20)	2557 (23)	1007 (9)	3358 (31)	8835 (80)	246 (2.3)
No drug (n=36 753)	2827 (8)	1681 (5)	3510 (10)	6759 (19)	19 229 (52)	841 (2.4)

Owing to missing data for each of the confounders, the percentages presented may not tally precisely with the numbers of subjects reported.
*Except psychosis or learning disability.

The crude and adjusted odds ratios with 95% confidence intervals for developing schizophrenia given a history of ever using cannabis are presented in tables 2, 3, and 4. The crude odds ratio for developing schizophrenia any time after conscription was 2.2 (1.7 to 2.8) and this association persisted, although reduced, after adjustment (adjusted odds ratio 1.5, 1.1 to 2.0).

We found a dose dependent relation between frequency of cannabis use and risk of schizophrenia, with an adjusted odds ratio for linear trend across the categories of frequency of cannabis use used in this study of 1.2 (1.1 to 1.4, $P<0.001$). The adjusted odds ratio for subjects with a history of heaviest use of cannabis (>50 occasions) was 3.1 (1.7 to 5.5).

The association between cannabis use and schizophrenia was greater in subjects admitted in the first five years after conscription (adjusted odds ratio 2.1, 1.2 to 3.7) compared with those admitted after five years (1.2, 0.8 to 1.8). Frequency of cannabis use was associated with schizophrenia in both the early onset group (adjusted odds ratio for linear trend 1.3, 1.1 to 1.6, $P<0.001$) and the later onset group (1.2, 1.1 to 1.3, $P<0.02$).

Cannabis only

Altogether 1648 subjects (3.3% of cohort, 3.1% to 3.5%) had used only cannabis, and 18 of these (1.1%, 0.6 to 1.7%) developed schizophrenia. Those who used only cannabis had an increased risk of schizophrenia compared with those who reported no drug use. The odds ratio before adjustment (1.9, 1.2 to 3.0) and afterwards (1.9, 1.1 to 3.1) was similar (table 5). We found a dose dependent relation for frequency of use, with an adjusted odds ratio for linear trend of 1.3 (1.0 to 1.7, $P<0.02$).

Stimulant use

We found an association between schizophrenia and stimulant use in the crude analysis (crude odds ratio 3.8, 2.7 to 5.4), but this became non-significant after adjustment for confounders (adjusted odds ratio 1.5, 0.9 to 2.4). Adjusting for frequency of cannabis use further reduced the association between stimulant use and risk of schizophrenia (adjusted odds ratio 1.1, 0.6 to 2.1). The association observed between schizophrenia and frequency of cannabis use was unchanged after adjustment for stimulant use.

Other psychoses

A total of 446 subjects were admitted with other psychoses. Subjects who had ever used cannabis had an increased risk of developing a psychosis other than schizophrenia (crude odds ratio 1.4, 1.1 to 1.9), but this effect was reduced after adjustment (adjusted odds ratio 1.1, 0.8 to 1.5). A similar pattern was observed for the association with cannabis frequency, with a linear trend odds ratio of 1.1 (1.0 to 1.2, $P<0.02$) before adjustment and of 1.0 (0.9 to 1.1, $P<0.85$) after adjustment.

For all the analyses, diagnosis on conscription, IQ score, and place of upbringing contributed most to confounding. Adjusting for the other potential confounders made virtually no difference to the final adjusted results.

Table 2 Crude and adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription in subjects who have ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5391	73 (1.4)	2.2 (1.7 to 2.8)	1.5 (1.1 to 2.0)
Frequency of use of cannabis (ever)				
None	36 429	215 (0.6)	1.0†	1.0†
Once	608	2 (0.3)	0.6 (0.1 to 2.2)	0.6 (0.1 to 2.3)
2-4 times	1380	8 (0.6)	1.0 (0.5 to 2.0)	0.9 (0.4 to 1.9)
5-10 times	806	9 (1.1)	1.9 (1.0 to 3.7)	1.4 (0.7 to 2.6)
11-50 times	689	13 (1.9)	3.2 (1.8 to 5.7)	2.2 (1.2 to 4.0)
>50 times	731	28 (3.8)	6.7 (4.5 to 10.0)	3.1 (1.7 to 5.5)
Linear trend for frequency of use	—	—	1.4 (1.3 to 1.5)	1.2 (1.1 to 1.4)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

Table 3 Crude and adjusted odds ratios with 95% confidence intervals (95% CI) for developing schizophrenia in years 0-5 after conscription in subjects who have ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5320	33 (0.6)	2.2 (1.7 to 2.8)	2.1 (1.2 to 3.7)
Frequency of use of cannabis (ever)				
None	36 429	47 (0.1)	1.0†	1.0†
Once	608	0	—	—
2-4 times	1380	2 (0.1)	1.1 (0.3 to 4.6)	1.0 (0.2 to 4.4)
5-10 times	806	4 (0.5)	3.9 (1.4 to 10.7)	2.6 (0.8 to 7.9)
11-50 times	689	4 (0.6)	4.5 (1.6 to 12.6)	2.8 (0.9 to 8.8)
>50 times	731	13 (1.8)	14.0 (7.5 to 26.0)	4.7 (1.8 to 12.4)
Linear trend for frequency of use	—	—	1.6 (1.4 to 1.8)	1.3 (1.1 to 1.6)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

Table 4 Crude and adjusted odds ratios with 95% confidence intervals (95% CI) for developing schizophrenia in years 5+ after conscription in subjects having ever used cannabis

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	5287	40 (0.8)	1.6 (1.1 to 2.2)	1.2 (0.8 to 1.8)
Frequency of use of cannabis (ever)				
None	36 382	168 (0.5)	1.0†	1.0†
Once	608	2 (0.3)	0.7 (0.2 to 2.9)	0.8 (0.2 to 3.2)
2-4 times	1378	6 (0.4)	0.9 (0.4 to 2.1)	0.9 (0.4 to 2.0)
5-10 times	802	5 (0.6)	1.4 (0.6 to 3.3)	1.0 (0.4 to 2.5)
11-50 times	685	9 (1.3)	2.9 (1.5 to 5.6)	2.1 (1.0 to 4.5)
>50 times	718	15 (2.1)	4.6 (2.7 to 7.8)	2.5 (1.2 to 5.1)
Linear trend for frequency of use	—	—	1.3 (1.2 to 1.4)	1.2 (1.0 to 1.3)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

Discussion

Self reported use of cannabis in early adulthood was associated with an increased risk of developing schizophrenia. Risk increased in a dose dependent manner with increasing frequency of cannabis use, and this relation remained when analysis was restricted to subjects who had used only cannabis and no other drugs before conscription. The largest risk was seen in subjects reporting use of cannabis on more than 50 occasions. We found no association between cannabis and other psychotic illnesses, which implies that cannabis has a rather specific association with an increased risk of schizophrenia.

Table 5 Adjusted odds ratios with 95% confidence intervals for developing schizophrenia any time after conscription for subjects taking cannabis only

Drug use	No of subjects	No (%) of subjects developing schizophrenia	Odds ratio (95% CI)	
			Crude	Adjusted*
Cannabis ever†	1635	18 (1.1)	1.9 (1.2 to 3.0)	1.9 (1.1 to 3.1)
Frequency of use of cannabis (ever)				
None	36 429	215 (0.6)	1.0‡	1.0‡
Once	245	0	—	—
2-4 times	499	5 (1.0)	1.7 (0.7 to 4.2)	1.9 (0.8 to 4.8)
5-10 times	255	3 (1.2)	2.0 (0.6 to 6.3)	1.7 (0.5 to 5.7)
11-50 times	176	1 (0.6)	1.0 (0.1 to 6.9)	0.8 (0.1 to 6.0)
>50 times	70	4 (5.7)	10.2 (3.7 to 28.3)	6.7 (2.1 to 21.7)
Linear trend for frequency of use	—	—	1.3 (1.1 to 1.6)	1.3 (1.0 to 1.5)

*Adjusted for diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, cigarette smoking, and place of upbringing.
†No drug use as baseline comparison.

The association between use of cannabis and schizophrenia was stronger in subjects who were first admitted within five years of conscription. One explanation is that subjects with a prodrome of schizophrenia at conscription may have increased their cannabis use, perhaps as a means of self medication.[3] But all subjects were screened at conscription, and we adjusted for other psychiatric problems recorded at that time. The relation with cannabis use was also observed in the later onset group, admitted more than five years after conscription. It seems more likely that the reduced association in the group with later onset is due to misclassification, as the number of people who discontinued cannabis use accumulated over time.[21]

Although adjustment for confounders substantially reduced the odds ratios, adjusting for poor social integration had only minimal effects. A similar effect was observed in the original study by Andreasson et al, who adjusted for the number of friends that the subjects reported having.[4] We used a more comprehensive measure of social integration as it is likely that on its own this question was not a strong measure of sociable personality traits. Personality traits are difficult to measure accurately, however, and residual confounding remains a possibility. The association between cannabis and schizophrenia persisted even after adjusting for use of alcohol, cigarettes, and other drugs, all of which are likely to be indicative of risk taking behaviour. This implies that a shared risk factor (be it biological, genetic, or through personality traits) for developing schizophrenia and for using psychoactive substances does not adequately explain the association observed.

We are limited in that we have only data regarding use of cannabis before conscription. But if the pattern of increased initiation and reduced cessation of drug use seen in the schizophrenia group persisted after the time of conscription, this would result in us underestimating the effect size of cannabis. Fewer subjects in this cohort claimed to have used cannabis and other illicit drugs compared with similar cohorts that used anonymous questionnaires.[23] The effect of under-reporting would again result in an underestimate of the true effect size. Non-response was similar for subjects developing schizophrenia and non-cases, although, as a further check, we repeated the analyses, having recoded non-responders as either users or non-users of cannabis. This made no difference when recoding was non-differential between cases and non-cases, but it increased the odds ratios substantially when recoding was differential.

What is already known about this topic

Use of cannabis has been associated with an increased risk of developing schizophrenia

Alternative explanations for this association include confounding by personality or by use of other drugs such as amphetamines, and use of cannabis as a form of self medication secondary to the disorder

What this study adds

Self reported cannabis use is associated with an increased risk of subsequently developing schizophrenia, consistent with a causal relation

This association is not explained by sociability personality traits, or by use of amphetamines or other drugs

Self medication with cannabis is an unlikely explanation for the association observed

It is possible that use of stimulants could explain the results if stimulants were able to induce a chronic psychotic illness, identical to schizophrenia. But we did not find an independent association between use of stimulants and schizophrenia, although power was reduced compared with other analyses. Although studies from the United States have found that initiation of amphetamine use peaks by age 18-20,[22] it is possible that initiation of stimulants after conscription was more likely in subjects who had previously used only cannabis. But the absence of an independent association with use of stimulants in our data implies that cannabis is potentially the more important agent.

These findings are in keeping with accumulating evidence that cannabis has detrimental effects on mental health in some people.[1] Molecular studies have shown that Δ^9-tetrahydrocannabinol, the active component of cannabis, increases release of dopamine in the mesolimbic pathway.[24] Given the suggested relation between increased mesolimbic dopamine and positive symptoms of schizophrenia,[25] such observations provide support for the hypothesis that cannabis may act as a risk factor for this disorder.

Use of cannabis use has increased substantially over the past few decades in the United Kingdom, and 50% of the population now report having used cannabis at least once.[26] If cannabis increases the risk of schizophrenia by 30%, as implied by these results, then 13% of cases of schizophrenia could be prevented if cannabis use was eliminated from the population, assuming that a causal relation between cannabis use and schizophrenia really exists. The overall weight of evidence is that occasional use of cannabis has few harmful effects overall,[1] and the drug is less likely to be used regularly and cause dependence than nicotine. Nevertheless, these results indicate a potentially serious risk to the mental health of people who use cannabis, particularly in the presence of other risk factors for schizophrenia. Such risks need to be considered in the current move to liberalise and possi-

bly legalise the use of cannabis in the United Kingdom and other countries.

We thank Hollie Thomas and Diane McCracken for their help and advice, and Jonas Sadigh for his help with data management.

Contributors: SZ contributed to the conception of the study, data analysis, and drafting of the manuscript. PA contributed to the conception and design of the study, and drafting of the manuscript. SA contributed to the conception and design of the study, and drafting of the manuscript. IL contributed to the design of the study and drafting of the manuscript. GL contributed to the conception of the study, data analysis, and drafting of the manuscript. SZ is the guarantor.

Funding: This research is funded from a clinical training fellowship grant awarded to SZ by the Medical Research Council, UK (grant no G84/5689).

Competing interests: None declared.

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(Accepted 12 September 2002)

Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study

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BMJ 2002;325;1199-
doi:10.1136/bmj.325.7374.1199

The British Journal of Psychiatry (2001) 178: 116-122

SUBSTANCE MISUSE PAPERS

Psychiatric effects of cannabis†

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Declaration of interest This review was commissioned and funded by the Department of Health, but the findings are those of the author alone.

† See editorial, p. 98, this issue.

ABSTRACT

Background Cannabis is commonly regarded as an innocuous drug and the prevalence of lifetime and regular use has increased in most developed countries. However, accumulative evidence highlights the risks of dependence and other adverse effects, particularly among people with pre-existing psychiatric disorders.

Aims To re-evaluate the adverse effects of cannabis in the general population and among vulnerable individuals, including those with serious psychiatric disorders.

Method A wide-ranging review of the topics related to these issues.

Results and conclusions An appreciable proportion of cannabis users report short-lived adverse effects, including psychotic states following heavy consumption, and regular users are at risk of dependence. People with major mental illnesses such as schizophrenia are especially vulnerable in that cannabis generally provokes relapse and aggravates existing symptoms. Health workers need to recognise, and respond to, the adverse effects of cannabis on mental health.

UNTOWARD MENTAL EFFECTS OF CANNABIS

The untoward mental effects of cannabis may be classified:

a. Psychological responses such as panic, anxiety, depression or psychosis. These effects may be described as 'toxic' in that they generally relate to excess consumption of the drug.
b. Effects of cannabis on pre-existing mental illness and cannabis as a risk-factor for mental illness.
c. Dependency or withdrawal effects.

The effects of cannabis on cognition are separately reviewed by Ashton (2001, this issue).

PSYCHOLOGICAL RESPONSES TO CANNABIS

There is good evidence that taking cannabis leads to acute adverse mental effects in a high proportion of regular users. Many of these effects are dose-related, but adverse symptoms may be aggravated by constitutional factors including youthfulness, personality attributes and vulnerability to serious mental illness.

Cannabis and mood change

The acute response to cannabis generally includes euphoria and feelings of detachment and relaxation. Adverse effects are not uncommon: these are generally short-lived, but may persist or recur with continued use of the drug.

From New Zealand, a sample of 1000 people aged 18-25 were asked to complete a self-administered questionnaire on cannabis use and related problems (Thomas, 1996). Those respondents who admitted using cannabis (38%) were asked about mental health consequences; of these, 22% reported panic attacks or anxiety. Women were twice as likely as men to report these symptoms. Troisi *et al* (1998) used urine tests on Italian draftees to identify 133 men who used only cannabis. All individuals with a pre-existing psychosis or severe personality disorder had been excluded. An adjustment disorder with depressed mood was found in 16%, major depression in 14%, and dysthymia in 10.5%. The severity of these symptoms was dose-related. No acute psychotic symptoms were reported. Reilly *et al* (1998) describe the adverse effects found among 268 cannabis users who had taken the drug for at least 10 years, and who continued to smoke about two refers a day. The most common adverse effects were feelings of anxiety, paranoia or depression (21%), tiredness and low motivation (21%).

Among individuals making serious attempts at suicide, 16.2% met criteria for cannabis misuse/dependence compared with 1.9% of controls — much of the highly significant association was thought to be due to independent variables including comorbidity, but it is suggested that cannabis misuse makes a direct contribution to the risk of serious self-harm, either directly or by aggravation of other mental disorders (Beautrais *et al*, 1999).

Cannabis and psychosis

Cannabis use can lead to a range of short-lived symptoms such as depersonalisation, derealisation, a feeling of loss of control, fear of dying, irrational panic and paranoid ideas (Thomas, 1993). For example, Thomas (1996) reported that, among cannabis users who responded to his survey, 15% identified psychotic symptoms such as hearing voices or having unwarranted feelings of persecution or risk of harm from others. Two small case studies have reported prolonged depersonalisation after

cessation of cannabis use (Szymanski, 1981; Keshaven & Lishman, 1986). 'Flashbacks' or the subsequent partial re-experience when drug-free of symptoms experienced during intoxication are rarely reported after cannabis use (Thomas, 1993).

The casual use of the term 'cannabis psychosis' in clinical psychiatric practice and in the scientific literature results in diagnostic imprecision and research of uncertain validity. Thornicroft (1990) reviews the possible associations between cannabis use and psychosis and suggests that common methodological failings are: (a) studies fail to adequately separate organic from functional psychotic reactions to cannabis; (b) they have insufficiently discriminated between psychotic symptoms and syndromes of a psychosis; and (c) they have not balanced the weight of evidence for and against the category of cannabis psychosis. Although there is good evidence for believing that cannabis use may in certain circumstances contribute to psychotic disorders, the connections are complex.

Hall *et al* (1994) suggest that the fundamental questions are: is there a cannabis psychosis, and does cannabis precipitate an underlying psychosis? In theory, cannabis use may precipitate a psychosis in the following ways.

a. Acute use of large doses of the drug may induce a toxic or organic psychosis with symptoms of confusion and hallucination, which remit on abstinence.
b. Cannabis use may lead to an acute functional psychosis, similar to an acute schizophreniform state and lacking the organic features of a toxic psychosis.
c. Cannabis use may lead to a chronic psychosis, which persists after abstinence.
d. Long-term cannabis use may lead to an organic psychosis which only partially remits after abstinence, leaving a residual deficit state, sometimes called an amotivational syndrome, which is thought to be analogous to the chronic organic brain syndrome seen after prolonged misuse of alcohol.
e. Cannabis use may be a risk-factor for serious mental illness such as schizophrenia.

Cannabis and toxic psychosis

Apart from single-case reports, the nature of cannabis-induced toxic psychosis is considered in the following studies, all of which are weakened by the lack of urine-testing to confirm the presence of cannabis and the absence of other drugs of misuse.

Talbott & Teague (1969) described 12 soldiers in Vietnam who, after their first admitted use of cannabis, showed dis-orientation, impaired memory, confusion, reduced attention span and disordered thinking with labile effect and hallucinations. These symptoms resolved within a week. Tennant & Groesbeck (1972) describe psychoses among 36 000 US servicemen stationed in Germany. Of the 5120 soldiers using cannabis at least three times a week, 720 presented with cannabis-related problems. The hashish available was potent, containing 5-10% tetrahydrocannabinol (THC). The authors identified 19 cases of a panic attack or short-lived toxic psychosis, which appeared after a single high dose of hashish, and a further 85 cases of toxic psychosis which appeared after the consumption of cannabis with other drugs. These acute states tended to resolve within 3 days.

From Calcutta, Chopra & Smith (1974) retrospectively identified 200 in-patients who showed serious psychiatric symptoms after taking cannabis. The most common symptoms in all patients were sudden onset of confusion, often associated with hallucinations and emotional lability. Disorientation, depersonalisation and paranoid symptoms were common. Many patients had taken a large dose of cannabis, which was followed by an intoxicated state for which they were subsequently amnesic. Among the 34% of patients without a previous history of psychiatric disorder, adverse symptoms lasted no more than a few days, followed by full recovery. A previous history of schizophrenia or personality disorder was associated with longer duration of adverse symptoms.

From Pakistan, Chaudry *et al* (1991) report on effects of *bhang*, a potent beverage made from an infusion of cannabis leaves and flowering tops. They identified 15 patients who having taken *bhang*, presented with a psychosis with symptoms of grandiosity, excitement, hostility, dis-orientation, hallucinations and thought disorder. Mental state was assessed systematically, using the Brief Psychiatric Rating Scale (BPRS) (Lukoff *et al*, 1986). The control group of 10 patients all used *bhang*, but less frequently than the study group.

This work suggests that cannabis, especially in high doses, can produce a toxic psychosis in individuals who have no history of severe mental illness. The main features are mild impairment of consciousness, distorted sense of passage of time, dream-like euphoria, progressing to fragmented thought processes and hallucinations, generally resolving within a week of abstinence (Lishman, 1998).

Cannabis and acute functional psychosis

A number of studies suggest that heavy cannabis use can lead to an acute functional illness, that is a state resembling the psychosis of acute schizophrenia without the amnesia and confusion of a toxic psychosis.

Tennant & Croesbeck (1972) identified 115 cases of schizophrenic reaction among the 720 regular users of cannabis; however, all but three had used cannabis with other drugs or alcohol. Thacore & Shukla (1976) compared 25 individuals with a putative diagnosis of 'cannabis psychosis of the paranoid type' with controls diagnosed with paranoid schizophrenia. Patients with cannabis psychosis showed more bizarre behaviour, violence, panicky affect, more insight and less evidence of thought disorder. They also showed a rapid response to neuroleptics with complete recovery. More robust in methodology is the work of Rottanburg *et al* (1982) in which 20 patients with psychosis and with high urinary cannabinoids were compared with 20 matched cannabis-free controls. Mental state was assessed using the Present State Examination (PSE) (Wing *et al*, 1974). The cannabis-positive patients had more symptoms of hypomania and agitation, less auditory hallucinations, flattening of affect, incoherent speech and hysteria than controls. Clouding of consciousness was absent in most cannabis patients. They also showed marked improvements in symptoms within a week, while the controls remained unwell despite receiving comparable antipsychotic drugs. The authors conclude that a high intake of cannabis may be related to a rapidly resolving psychosis with marked hypomanic features. However, 16 cannabis-positive psychotic patients left the study prematurely, which may bias the findings on the 20 who remained. Rapid resolution of symptoms is also reported by Carney *et al* (1984), who identified nine patients with cannabis-related psychotic episodes. Their differing symptomatology was described as

'schizophreniform, manic, delusional psychosis and confusion'.

More recently, Mathers & Ghodse (1992) carried out a prospective study of in-patients with psychotic symptoms and cannabis-positive urine. Blind to the urine test result, researchers applied the PSE on admission and again at 1 and 6 months. Concurrently admitted patients with psychosis but with drug-free urine analysis were controls. At 1 week the two groups differed significantly on only five PSE items: changed perception, thought insertion, non-verbal auditory hallucinations, delusions of control, and delusions of grandiose ability; this symptom cluster at 1 week was thought to be consistent with acute cannabis intoxication. These differences were minor at 1 month and absent at 6 months. Chronic cannabis-induced psychosis was not found. Caucasian patients were more likely to be depressed with depersonalisation and derealisation, while African-Caribbeans showed more culturally influenced delusions. However, these findings could not be replicated by McGuire *et al* (1994) who also used the PSE to assess the psychopathology of 23 patients with psychosis who were cannabis-positive on urinary screening, and 46 matched drug-free controls. Cases and controls were indistinguishable in terms of psychopathology, DSM-III diagnoses (American Psychiatric Association, 1980), onset of recent illness, the proportion of first admissions, ethnicity and socio-economic class, differing only in their histories of substance use.

Having compared groups of drug-misusing patients with psychosis of varying duration, Tsuang *et al* (1982) concluded that the shorter-duration disorders were drug-induced toxic psychoses, and the longer-lasting disorders represented the expression of functional psychiatric illness in vulnerable individuals. If corroborated, this suggests that the 'functional psychosis' related to cannabis use is best explained as a precipitated episode of an underlying functional illness.

Cannabis and chronic psychosis

Ghodse (1986) has suggested that regular heavy users of cannabis may suffer repeated short episodes of psychosis and effectively 'maintain' themselves in a chronic psychotic state. This is a possibility, but Hall *et al* (1994) note that it is difficult to distinguish between a chronic cannabis psychosis and the co-occurrence of an illness such as schizophrenia with continued cannabis use. There is however, no robust evidence that heavy cannabis use may lead to a psychotic illness which persists after abstinence (Thomas, 1993).

Cannabis and amotivational syndrome

It has been suggested that heavy cannabis use could lead to an 'amotivational syndrome' described as personality deterioration with loss of energy and drive to work (Tennant & Groesbeck, 1972). The supporting evidence largely comprises uncontrolled studies of long-term cannabis users in various cultures (Hall *et al*, 1994). It is probable that amotivational syndrome represents nothing more than ongoing intoxication in frequent users of the drug (Negrete *et al*, 1986) and the validity of this diagnosis remains uncertain (Hall *et al*, 1994).

Cannabis as risk-factor for serious mentall illness

Comorbidity rates

Cannabis use is associated with high rates of comorbidity for other psychiatric diagnoses. The Epidemiologic Catchment Area (ECA) survey (Regier *et al*, 1990) of 20 000 subjects in community and

institutional settings showed that 50.1% of individuals with cannabis dependence/misuse also met DSM-III criteria for one other non-drug or alcohol mental disorder. Among 133 Italian draftees, Troisi *et al* (1998) found that the prevalence of comorbidity was significantly related to the pattern of cannabis use: 69% of subjects with DSM-III-R cannabis dependence, 41% of those with cannabis abuse and 24% of occasional users reported at least one DSM-III-R Axis 1 psychiatric diagnosis. Most common were adjustment disorder with depressed mood (n=21), major depression (n=19) and dysthymia (n=14). The severity of symptoms also increased with degree of cannabis use. Psychotic symptoms were not found, but it should be noted all individuals with psychotic illness or severe personality disorder were not drafted.

There are high rates of drug misuse among people with mental illness. The ECA study (Regier *et al*, 1990) showed that the risk of meeting criteria for a substance misuse disorder was 4.6 times higher in those suffering from schizophrenia than in the general population. Schizophrenia was associated with a six-fold increase in risk of developing a drug use disorder, and cannabis was the most commonly misused drug. Menezes *et al* (1996) examined the prevalence of substance misuse problems among 171 patients with psychotic illness who had any contact with mental health treatment services in a south London area. Alcohol problems were more prevalent, but current use of one or more drugs was found in 35 subjects (20%); all but two said they used cannabis. Cantwell *et al* (1999) studied 168 subjects presenting with a first episode of psychosis and found 1-year prevalence rates of 19.5% for drug misuse, 11.7% for alcohol misuse, and cannabis was the most commonly misused substance. Given these findings, it is necessary to review the possible role of cannabis as a risk factor for functional illness and for the aggravation of symptoms.

Effects of cannabis on severe mental illness

Given that high doses of cannabis can cause a toxic psychosis, then it may be supposed it will aggravate the symptoms of schizophrenia. However, clinical experience suggests that some patients say that they take cannabis as a form of 'self-medication'. For example, Dixon *et al* (1990) interviewed 83 patients with schizophrenia or schizophreniform psychoses who reported that cannabis reduced anxiety and depression, led to increased suspiciousness and had varied effects on drive and hallucinations. Arndt *et al* (1992) investigated a cohort of 131 patients with schizophrenia and found that previous use of cannabis had no impact on current symptoms. Peralta & Cuesta (1992) reported that cannabis had no significant effect on positive symptoms of schizophrenia, but it did attenuate negative symptoms.

On the other hand, there are a few controlled studies that have tended to demonstrate that cannabis aggravates the severity of positive symptoms. Negrete *et al* (1986) described the history of confirmed cannabis use in 137 patients with schizophrenia in treatment. Subjects who were using cannabis over the 6-month observation period presented with significantly greater delusions and hallucinations, and made more use of psychiatric services. Similarly, Cleghorn *et al* (1991) found that drug-users with schizophrenia, among whom cannabis was the most heavily used drug, had a higher prevalence of hallucinations, delusions and other positive symptoms. This finding was replicated by Baigent *et al* (1995), who reported that among 53 in-patients with a dual diagnosis of substance misuse and schizophrenia, cannabis was the only drug that worsened positive symptoms.

Data from the ECA survey (Swanson *et al*, 1990) also casts some light on the possible effects of cannabis use disorder and violence. Subjects were asked about episodes of violence in the previous year (i.e. hitting a partner, bruising a child, fighting, using a weapon in a fight while drinking). Of the 191 respondents with cannabis abuse or dependence, 19.25% (risk ratio 9.4) had been violent compared with 12.69% (risk ratio 6.2) of those with schizophrenia or schizophreniform disorder and 24.57% (risk ratio 11.9) of those with alcohol abuse or dependence. Here, the risk is expressed relative to the 2.05% who were violent among those of the sample population who showed no psychiatric disorder. However, this does not amount to a causal correlation between cannabis co-morbidity and violence, given the possible role of intervening variables such as individual and social factors.

That cannabis consumption also has an adverse effect on the course of schizophrenia was noted by Negrete *et al* (1986) and confirmed in a prospective study by Linszman *et al* (1994). A cohort of newly admitted patients with schizophrenia were assessed monthly for a year, using the BPRS and self-reports of cannabis use. The cannabis-using group (n=24) experienced significantly more and earlier psychotic relapses and this effect was dose-related.

As Hall *et al* (1994) remark, these findings are a slender basis on which to draw conclusions about the effect of cannabis on schizophrenic symptoms. Until further prospective studies have been carried out, it would be prudent to regard cannabis as a vulnerability factor in relation to major mental illness and to caution at-risk individuals against using the drug.

Cannabis as risk factor for mental illness

There is no evidence that cannabis is a causal factor in schizophrenia and it is more relevant to consider whether the misuse of the drug constitutes a risk factor for this illness. Supporting evidence is found in a prospective study by Andreasson *et al* (1987) of 45 570 Swedish conscripts, of whom 9.4% had used cannabis and 1.7% were 'high consumers' having used more than 50 times. Fifteen-year follow-up data were drawn from national registers of deaths and psychiatric cases. Compared with non-users, the relative risk of schizophrenia was 2.4 in the group that reported use of cannabis at least once, rising to 6.0 among heavy users. Nearly half (430/730) of these high consumers had a psychiatric diagnosis other than psychosis on conscription; controlling for this reduced the relative risk to 2.9. The authors suggest that cannabis consumption is a 'life-event stressor' for individuals vulnerable to schizophrenia. Hall *et al* (1994) offer a number of alternative explanations. There is a large temporal gap between self-reported cannabis use on conscription and the development of schizophrenia over 15 years, and no data as to whether the cannabis use continued during this time. Drugs other than cannabis could have been taken at any time after conscription.

It should also be noted that as only 49 of the 274 conscripts with schizophrenia had ever tried cannabis, then this drug may only be relevant to a minority of cases. Furthermore, Jablensky *et al* (1992) demonstrate a striking uniformity in the incidence of schizophrenia in cultures with very different rates of cannabis consumption.

The possibility of a genetic explanation for the association between cannabis use and schizophrenia was raised by McGuire *et al* (1994). In this study, 23 patients with psychosis and with cannabis in their urine

were gender-matched with 46 drug-free controls with psychosis, and the lifetime risk of psychiatric disorder among all the first-degree relatives was ascertained. The cannabis-positive subjects had a significantly greater (7.1%) familial risk of schizophrenia than controls (0.7%), suggesting that the development or recurrence of acute psychosis in the context of cannabis use may be associated with a genetic predisposition to schizophrenia.

CANNABIS DEPENDENCE

Evidence for cannabis dependence

It had been believed that cannabis use did not lead to tolerance and that there was no withdrawal syndrome. However, since the mid-1970s, these views have been challenged by many experimental and observational studies. For example, Jones & Benowitz (1976) administered oral THC in doses of 70-210 mg/day to subjects for 30 days and noted a progressive loss of the subjective 'high'. This finding was replicated by Georgotas & Zeidenberg (1979), who gave an average daily dose of 210 mg THC to volunteers for a 4-week period — the subjects then "found that the marijuana was much weaker". Withdrawal signs were also found: during the first week of abstinence the subjects "became very irritable, uncooperative, resistant and at times hostile"; they also became hungry and experienced insomnia. These effects waned over 3 weeks. Cessation of smoked cannabis has also been shown to lead to withdrawal symptoms (Haney *et al*, 1999). The cannabis-withdrawal syndrome has now been unequivocally demonstrated and includes restlessness, anxiety, dysphoria, irritability, insomnia, anorexia, muscle tremor, increased reflexes and autonomic effects including changes in heart rate, blood pressure, sweating and diarrhoea. The syndrome may appear in about 10 hours, and peaks at about 48 hours (Mendelson *et al*, 1984).

The validity of cannabis dependence

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 1994) presents criteria for the diagnosis of psychoactive substance dependence, based largely on the concept of the dependence syndrome (Edwards *et al*, 1981). The key features of DSM-IV substance dependence are cognitive, behavioural and physiological symptoms, indicating that the individual continues to use the substance despite significant substance-related problems. The criteria include tolerance, a withdrawal syndrome, difficulty in controlling consumption and a pattern of use which leads to a reduction in other important activities. In an empirical study, Morgenstern *et al* (1994) found the DSM concept of cannabis dependence as least as valid as those for dependence on alcohol, opiates, stimulants and sedatives.

Prevalence and course of cannabis dependence

From ECA data, Anthony & Helzer (1991) showed that men had a higher prevalence (7.7%) of cannabis abuse or dependence than women (4.8%). This was largely due to the greater exposure to illicit drugs of men, since the prevalence of a diagnosis of abuse/dependence among those who had used cannabis more than five times was the same in men and women (21% and 19%, respectively). Extrapolating from these data, Hall *et al* (1994) suggest that about 17% of those who used cannabis more than five times would meet DSM-III criteria for dependence, and that for those who have ever used there is approximately a 1/10 risk.

From a New Zealand birth cohort of 1265 children, Fergusson & Horwood (2000) found that by the age of 21, nearly 70% had used cannabis and over 9% met DSM-IV criteria for cannabis dependence. Key predictors were male gender, ethnic minority status and measures of adolescent risk-taking behaviours, including cigarette smoking, conduct problems and a delinquent peer group.

Wiesbeck *et al* (1996) set out to determine the prevalence of the cannabis-withdrawal syndrome in people who had used the drug but who were not in treatment. In a cohort of 3611 individuals, 31% had taken the drug on more than 21 occasions in a year. Among these more frequent users, 16% met criteria for a cannabis-withdrawal syndrome — i.e. at least any one of the following: feeling nervous or irritable, insomnia, tremor, sweats, nausea, gastrointestinal disturbance or appetite change. These individuals had used the drug almost daily for an average of 70 months and even when use of alcohol and other drugs was considered, cannabis use was still significantly related to a self-report of a history of cannabis withdrawal.

Thomas (1996) found that 35% of cannabis users said that they could not stop when they wanted to, 24% continued to use despite problems attributed to the drug and 13% felt that they could not control their consumption. Restlessness or irritability if they could not use cannabis was reported by 20% of those surveyed. Interestingly, dependent users were no more likely to report panic or psychotic episodes than those classed as non-dependent. With regard to untoward social consequences, 14% of cannabis users agreed that the consumption of the drug had caused them to neglect activities previously considered important or enjoyable. These findings (Thomas, 1996) have to be qualified by the low overall response rate of 35%, the use of unvalidated criteria for cannabis dependence and by the lack of data on misuse of alcohol or other drugs among the sample.

Swift *et al* (1998) interviewed a sample from New South Wales of 243 long-term cannabis users who were smoking 3-4 times a week. A lifetime prevalence of 57% was found for both DSM-III-R and ICD-10 (World Health Organization, 1992) dependence, but only a quarter perceived that they had a cannabis problem.

VULNERABILITY TO ADVERSE EFFECTS OF CANNABIS

It has previously been emphasised that constitutional factors such as relative youthfulness, personality and misuse of other drugs, may act as vulnerability factors to the adverse mental effects of cannabis. Mental illness as a vulnerability factor has been reviewed in the previous section.

Adolescence

There are a number of reasons why adolescence may be regarded as a time of vulnerability for the adverse mental effects of cannabis. First, adolescents may experience emotional problems that cue cannabis use, and their relative youth may lead to an increased risk of adverse mental states on using the drug. Second, regular use of cannabis may interfere with learning and personal development. Last, early initiation of cannabis use may predict an increased risk of escalation in risk and progression to other drugs.

With regard to the possible impact of emotional problems, Newcombe & Bentler (1988) found a strong relationship between adolescent drug use and the experience of emotional distress, depression and lack of a sense of purpose in life. As to the prospect of adverse mental states on using high doses of cannabis, this review has demonstrated dose-related effects in adults and the younger user is not likely to be at any lesser risk. Crowley *et al* (1998) found that for adolescents with conduct problems, cannabis use was not benign in that misuse was associated with high rates of dependence and withdrawal.

The possible effects of cannabis consumption on the educational performance of adolescents are not easy to demonstrate in population studies (Hall *et al*, 1994). Newcombe & Bentler (1988), having controlled for the higher nonconformity and the lower academic potential among adolescent drug users, found only a modest negative link between drug use and college involvement. Schwartz *et al* (1989) found short-term memory impairment in 10 cannabis-dependent adolescents compared with matched controls. Test results tended to improve over 6 weeks, which suggested that the deficits observed were due to past cannabis use.

Polydrug use

A substantial number of young people in the community use a range of drugs which includes cannabis. Ramsay & Percy (1996) found that 4% of a group of 16- to 29-year-olds admitted using cannabis and other drugs in the past month, by contrast with 8% who had used only cannabis. Clinical observation suggests that cannabis users who also misuse other drugs or alcohol seem to experience more severe mental health problems than those who solely take cannabis, but there do not appear to be any substantial published studies on this issue. Polydrug use is a recognised concern in psychiatric populations: for example, Baigent *et al* (1995) found that 20% of their dual-diagnosis #patients misused more than one substance.

Personality

Given the heterogeneity of the population of cannabis users, it is not surprising that no single personality type or disorder is particular to users of that drug or, indeed, to users of any illicit drug (Allen & Frances, 1986). However, it is a matter of clinical observation that the use of cannabis by some individuals seems to be predisposed by traits such as social anxiety, anxiety or dysphoria. Such posited use as a form of self-medication to relieve unwanted affects or feelings was not corroborated in a study of cannabis-dependent individuals (Greene *et al*, 1993). There is good evidence for the comorbidity of drug misuse and some personality disorders. For example, Regier *et al* (1990) report that some form of substance abuse was identified in 83.6% of individuals with antisocial personality disorder (ASPD), with an odds ratio of 29.6. It should be appreciated that this very high rate arises because substance abuse is one of the major diagnostic criteria for ASPD; only 16% of individuals with ASPD did not have a history of substance abuse. The same study showed that the lifetime prevalence of ASPD in cannabis abuse or dependence was 14.7% with an odds ratio of 8.3. The interaction between ASPD and cannabis use is too complex to explore at length in this review, but it is probable that each disorder exacerbates the adverse effects of the other. See Dolan & Coid (1993) for a discussion of factors determining outcome in ASPD.

Implications for mental health care

How should mental health services respond to these findings? The key priorities are: (a) risk-management and care-planning have to be informed by a thorough substance-misuse assessment (Johns, 1997); (b) community and in-patient psychiatric services should develop policies on substance use which balance the treatment needs of individual patients with duties of care to other patients and to the general public; and (c) research is needed into treatment interventions for patients with mental illness and substance misuse problems.

Clinical Implications and Limitations

CLINICAL IMPLICATIONS

- **Among those who have ever taken cannabis, 1/10 are at risk of dependence.**
- **Heavy cannabis misuse leads to the risk of psychotic episodes, and aggravates the symptoms and course of schizophrenia.**
- **For any psychiatric patient, risk-management and care-planning is incomplete without a thorough assessment of substance misuse.**

LIMITATIONS

- **The available literature shows a preponderance of case reports and uncontrolled studies.**
- **Epidemiological findings from one setting cannot be assumed to generalise to other cultural groups.**
- **It is not easy to determine causal explanations from the studies cited.**

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April 24, 2002

Marijuana use often leads to depression

Those claiming that smoking marijuana brings medical relief for a long list of maladies, typically include depression in that list. A new study from the University of Pennsylvania Treatment Center indicates that "cannabis abuse is a risk factor for depressive symptoms rather than an effort to self-medicate depression."

The study, which included a large "randomly sampled adult population over a nearly 15 year period," found that those who used cannabis were "four times more likely" than those who didn't "to have depressive symptoms...in particular...more likely to have experienced suicidal ideation [thoughts] and anhedonia [inability to experience pleasure].

The author states that "The results [of the study] underscore the importance of cannabis abuse prevention rather than treatment.....Treating depression may reduce cannabis use in clinical populations, but depression did not necessarily lead these individuals to initiate cannabis use...Despite the limitations of the current study, the results suggest that the potentially serious consequences of cannabis abuse require further research."

"Cannabis Abuse as a Risk Factor for Depressive Symptoms"
Am J. Psychiatry, 158:12, December 2001
Bovasso

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Daily Telegraph, Sydney, Australia
August 26, 2002

Cannabis trebles mental illness risk

LONDON: Smoking cannabis can treble the risk of developing a mental illness, a new study has found.

In one of the biggest investigations into the long-term effects of the drug, scientists uncovered evidence proving marijuana is dangerous and can cause serious psychotic disorders in people with no history of mental illness.

The revelation will horrify thousands of people who either use the drug to ease a medical condition or are regular smokers, believing it harmless.

Results of the three-year study come just a month after Home Secretary David Blunkett announced plans to downgrade the drug so it is no longer an offence to possess small amounts.

The research by the University of Maastricht in the Netherlands appears to confirm anecdotal evidence.

It shows that people who smoke cannabis are nearly three times more likely to develop a psychotic disorder like hallucinations, paranoia, manic depression and schizophrenia. The risk increases with the amount smoked.

The Netherlands has one of the highest rates of cannabis use in the world because of its relaxed laws. But the three-year study is the first major study to examine the long-term dangers to mental health.

Experts said last night that the findings sound a warning bell for nations considering softening laws about the drugs usage.

Professor Robin Murray, from the Institute of Psychiatry in London, said services in some parts of the country are struggling to cope with the number of marijuana-related illnesses.

"I work in South London and 90 per cent of patients showing a first episode of psychosis also smoke cannabis. In fact, if theyre not taking cannabis, we think its strange, he said

The British Medical Association warned that the Dutch research - published in the American Journal of Epidemiology - could have serious implications if the British Government's proposal (to soften laws) leads to increased use of marijuana.

Dr Vivienne Nathanson, Head of Science and Ethics, said: "The Government needs to think about this incredibly carefully. This study shows that we do not know the long-term medical effects of cannabis".

The Dutch team tracked 4045 people from 1997 to the end of 1999, monitoring drug use and changes in mental health. At the beginning of the study, all the volunteers were mentally sound but by the end around 55 had been classed as suffering moderate to

severe psychosis. Almost a third of these used cannabis, while in the overall group only about seven per cent were regular users.

Professor Jim van Os, who led the study, estimates cannabis could already account for half of all new cases of psychosis. He said: "If you ask any doctor they will tell you this is a problem. And if people continue to use cannabis once they are psychotic it worsens their outcome because they become resistant to medication."

There are three more papers - from New Zealand, Sweden and Israel - coming out in the next few months which will all show the same results.

Why marijuana affects mental health is not clear but experts think it may be to do with how it affects the brains ability to deal with tetrahydrocannibol – a chemical found in the drug.

Another theory is that it switches on a gene that creates biochemical changes which can facilitate a psychotic experience.

According to Professor Murray, many cannabis users refuse to stop even when psychiatrists plead with them to give up. They make a recovery, go down the road to get some cannabis and an hour later they come back psychotic.

Mental health charity MIND said its helpline frequently takes calls from relatives of cannabis users worried about its effects.

The Royal College of Psychiatrists is reviewing its policy on the drug.

It is not the first time cannabis has been linked to mental illness. Two months ago, researchers at Okayama University in Japan discovered the first evidence that marijuana can cause genetic abnormalities associated with mental illness.

Scientists have warned for years that cannabis can trigger delusions and hallucinations similar to the symptoms found in schizophrenia. And past studies suggested that under 18-year-olds using the drug were six times more at risk of developing the condition in later life. # # #

Previous Top

Adolescent Depression and Suicide Risk
Association with Sex and Drug Behavior

Denise D. Hallfors, PhD, Martha W. Waller, MA, Carol A. Ford, MD, Carolyn T. Halpern, PhD, Paul H. Brodish, MSPH, Bonita Iritani, MA

Background: Depression is common among adolescents, and suicide is the third leading cause of death among 15- to 19-year-olds. Although both health problems have been associated with drug use and early sexual intercourse, the relationship has not been systematically studied in a nationally representative sample.

Methods: Sixteen patterns of combined sex and drug use behaviors were obtained using cluster analysis of responses to Wave I of the National Longitudinal Study of Adolescent Health conducted from September 1994 through December 1995. Bivariate and multivariate analyses tested correlations between behavior patterns and current depression, serious suicidal ideation, and previous suicide attempt, controlling for gender, race/ethnicity, Hispanic ethnicity, family structure, and parent education.

Results: Compared to youth who abstain from risk behaviors, involvement in any drinking, smoking, and/or sexual activity was associated with significantly increased odds of depression, suicidal ideation, and suicide attempts. Odds ratios were highest among youth who engaged in illegal drug use. There were few differences between boys and girls who abstain from sex and drug behaviors. Girls were less likely than boys to engage in high-risk behaviors, but those who did tended to be more vulnerable to depression, suicidal ideation, and suicide attempt.

Conclusions: Teens engaging in risk behaviors are at increased odds for depression, suicidal ideation, and suicide attempts. Although causal direction has not been established, involvement in any sex or drug use is cause for concern, and should be a clinical indication for mental health screening for girls; both boys and girls should be screened if engaging in any marijuana or illegal drug use.

(Am J Prev Med 2004;27(3):224–230)

Introduction

Suicide represents a significant and preventable loss of life. Among 15- to 19-year-olds, suicide is the third leading cause of death, accounting for approximately 2000 (or 12%) of the annual deaths in this age group.[1,2] Death rates from suicide among 15- to 19-year-olds doubled between 1960 and 2001, with reported rates peaking in 1990.[3] Reported rates for 2001 were 12.9 per 100,000 among males and 2.7 among females.[3] The lifetime prevalence of suicide attempts in this age group has been estimated to be 7.1% (10.1% for females and 3.8% for males).[4]

Data on adolescent suicide risk have generally been reported from either clinical population studies or from the Centers for Disease Control and Prevention's Youth Risk Behavior Survey (YRBS), which produces national estimates based on a biannual, school-based survey conducted in participating high schools. The 2001 YRBS[5] (n = 13,601) found that 28% of U.S. high school students reported severe depressive feelings, 19% had seriously considered attempting suicide, and 9% had attempted suicide at least once in the preceding year. Ninth, tenth, and eleventh graders (11%, 9%, and 8%, respectively) were significantly more likely than twelfth graders (5.5%) to have attempted suicide in the past year. Hispanic youth were significantly more likely to attempt suicide (12.1%) than blacks (8.8%) and whites (7.9%).

Girls were about twice as likely as boys to report severe depressive feelings, consider attempting suicide, or attempt suicide. Empirical studies have indicated that major depression is most highly correlated with suicide for girls (increasing the risk by up to 20-fold), followed by a previous suicide attempt. Among boys, a previous attempt is the most highly correlated factor (increasing the risk by over 30-fold), followed by de-

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0749-3797/04/$—see front matter
doi:10.1016/j.amepre.2004.06.001

pression, alcohol or drug abuse, and disruptive behavior.[4,6–9]

Depression, suicidal ideation, and suicide attempts have previously been linked to adolescent substance use and sexual activity.[10–16] Participation in these activities is widespread among teens.[5,17] In 2001, 45.6% of all high school students reported ever having had sexual intercourse, 33.9% reported current cigarette or other tobacco use, and nearly half (47.1%) had used alcohol in the previous 30 days.[5]

Knowledge about risk factors is important for diagnosing and treating adolescent depression and suicide risk.[18] An important clinical consideration is whether certain patterns of substance use and sexual behaviors are differentially associated with depression and suicide risk. Previous research on adolescent risk behaviors has shown that risk behaviors tend to cluster together rather than occur in isolation.[13,19–27] Cluster analytic methods can reveal the extent to which individuals participate in multiple risk behaviors.[28]

This paper examines the extent to which adolescent sex and drug behavior patterns are associated with depression, controlling for gender, age, race/ethnicity, Hispanic ethnicity, parental education, and family structure. The associations between behavior patterns and both suicidal ideation and attempt are also examined, adding depression as a control variable. Data were from Wave I of the National Longitudinal Study of Adolescent Health (Add Health).[29]

Although the YRBS is an important source of information about biennial trends, and both surveys measure adolescent depression, suicide risk, drug use, and sexual behavior, Add Health offers certain unique strengths. First, Wave-I data were carefully collected and weighted to provide a nationally representative sample of youth in grades 7 through 12; national YRBS data are representative of students in grades 9 through 12.[5] Second, Add Health collected sensitive data using an audio computer-assisted (ACASI) survey instrument, which maximizes confidentiality, improves veracity,[30] and reduces missing data.[31] Third, although both surveys measured the construct of depression, the YRBS included only a single "past 12-month" item, while Add Health questions were based on the 20-item Center for Epidemiological Studies-Depression Scale (CES-D). The present study built on the strengths of Add Health to contribute new information about patterns of adolescent sex and drug use and their association with important mental health problems.

Methods

Sample

Data were from the Wave-I in-home contractual data set of Add Health, a nationally representative probability sample of adolescents in grades 7 through 12 from 132 schools ($n = 18,924$) gathered from September 1994 through December 1995 and analyzed in November 2003. All students who had completed an in-school questionnaire or who were listed on a school roster were eligible for inclusion in the more in-depth follow-up interview, which was conducted in the home (see Bearman et al.[29] for additional detail). In-home questionnaires were administered via laptop computers and utilized ACASI technology to collect information on sensitive topics such as sexual activity and substance use. Informed assent by adolescents and parental consent were obtained for all participants.

Independent Measures

Sociodemographic measures. Gender was a self-reported dichotomous variable, with male as the referent. Chronological age in years was determined by subtracting the date of birth from the date of the interview, rounded to two decimal places. Race/ethnicity was based on respondent's self-report, categorized for multivariate analyses as two dichotomous variables: black and other (primarily Asian), with white as the referent. Hispanic ethnicity was based on the respondent's self-report of Hispanic origin and was a dichotomous variable, with non-Hispanic as the referent. Two different measures served as proxies for socioeconomic status (SES). Highest parental education was based on the adolescent's report of the highest education level attained by either the resident mother or father, with categories of less than high school (referent), high school graduate/General Educational Development (GED), some college, and college graduate or higher. Family structure was based on household roster information[32] and grouped into the following categories: two resident parents (referent), single mother, and other.

Cluster membership. K-means cluster analysis was used to group respondents into homogeneous profiles based on responses to 12 items concerning risk behavior. Similar to factor analysis, which groups variables together, cluster analysis groups individuals, based on the assumption that risk behaviors often occur together and interact with each other. By combining individuals with similar behavior patterns, cluster analysis allows for the interaction of all the variables (in the present case, up to 12-way interactions), resulting in a more parsimonious model and a more holistic way of considering youth behavior.[33,34]

Four clusters were defined a priori based on the complete absence of risk behavior (abstainers) or engagement in highly disunctive risk behaviors for HIV and other sexually transmitted diseases (IV drug users, sex for drugs or money, and males who have sex with males [MSM]). Since K-means analysis becomes unreliable with extreme observations, these less common behaviors were examined first. Next, using K-means cluster analysis to identify the modal risk patterns, all other participants were grouped into 12 clusters based on the following self-reported risk behaviors: cigarette use, alcohol consumption, binge drinking, marijuana use, other illicit drug use, sexual intercourse, condom use, number of sexual partners, and engaging in sex while under the influence of alcohol or drugs. The resulting 16 clusters accounted for almost 80% of the total variation in behavior patterns.

Table 2. Behavioral patterns defining clusters and cluster size (largest to smallest)

Cluster name	Patterns of sexual behavior and substance use	n	Weighted %*
Light substance dabblers	Infrequent or no current ATOD use None have had sexual intercourse	4559	25.20
Abstainers	Never engaged in any ATOD use None have had sexual intercourse	4292	23.41
Sex dabblers	All have had sexual intercourse Median number of partners=1 Low levels of ATOD use	3145	14.27
Drinkers	All report past-year alcohol use About 50% report binge drinking Infrequent or no illegal drug use None report sexual intercourse	1408	7.48
Smokers	All are daily cigarette smokers Infrequent use of alcohol or illegal drugs Majority have had sexual intercourse	1109	6.56
Alcohol and sex dabblers	All report occasional alcohol use and all have had sexual intercourse Low tobacco & illegal drug use	1068	5.30
Binge drinkers	All report frequent binge drinking Low cigarette, marijuana, and other drug use More than half binge one or more times/week About half have had sexual intercourse	856	4.44
Sex and drugs in combination	All have had sexual intercourse and all report alcohol or illegal drug use at most recent intercourse	602	3.38
Heavy dabblers	All report moderate levels of smoking, drinking, and binge drinking Half use marijuana; few use other illegal drugs Most (91%) have had sexual intercourse	541	3.27
Marijuana users	All use marijuana frequently; few use other illegal drugs Almost all drink alcohol Most smoke cigarettes Three quarters have had sexual intercourse	314	1.67
Multiple partners	All report ≥14 sex partners Moderate ATOD use	230	1.25
Sex for drugs or money	All report sex for drugs or money Most are moderate ATOD users Median sex partners=8	195	1.11
High marijuana and sex	All use marijuana frequently and all have had sexual intercourse All report AOD use at last intercourse Most report multiple partners (median=6)	198	1.09
Marijuana and other drugs	Most report heavy marijuana use and all report other illegal drug use Two thirds have had sexual intercourse One third report drug use during intercourse	107	0.68
IV drug users	All have injected drugs >80% have had sexual intercourse Median number of partners=4	100	0.56
MSM	All are males who have had sex with other males Most have had multiple partners (median=5) 40% have used marijuana in last 30 days Most are occasional drinkers 17% have had sex for drugs or money	82	0.37
Total		18,799	100.00

*Weighted percentage yielding national probability estimates for 7th- to 12th-grade youth.
AOD/ATOD, alcohol [tobacco] and other drugs; MSM, males having sex with males

drug use showed the highest proportions. After abstainers, the lowest proportions were in clusters with the lowest levels of legal drug use (light substance dabblers, drinkers) and those marked by sexual activity but relatively low drug use (sex dabblers, alcohol and sex dabblers). Multiple partners, smokers, heavy dabblers, and MSM clusters were at the midpoint, with proportions of affected individuals roughly four times that of abstainers. For girls, there was a dramatic rise in risk among light substance dabblers compared to abstainers (e.g., depression rose to 9.5% from 4.5%). For boys, there was a more modest difference between abstainers and light substance dabblers (depression rates were 3.6% and 5.6%, respectively). In most of the subse-

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other studies, females, Hispanics, and lower-SES adolescents are at elevated risk for depression. Controlling for sociodemographic characteristics, present analyses showed a dramatic relationship between sex and drug behaviors and multiple indicators of adolescent mental health. Compared to abstainers, membership in any of the risk clusters was associated with increased odds of depression, serious thoughts about suicide, and suicide attempts. Use of marijuana and other illegal drugs was associated with especially high risk.

The prevalence of current major depression (10.3%) in this study was lower than the prevalence of serious suicidal ideation (13.2%). This was not the case with YRBS data (28% and 19%, respectively), likely because of differences in the measurement of depression between the two surveys. The Add Health CES-D items tap current depressive symptoms, while the single YRBS item queries depressive symptoms over the past 12 months. Both surveys ask about serious suicidal ideation over the past 12 months.

Beyond the time-frame differences for depression assessment, there were other differences that likely contributed to the disparities between the two surveys in prevalence estimates of suicidal ideation and suicide attempt. The Add Health sample, for example, included 7th- and 8th-grade students; excluding these students, however, yielded only a modest increase (14.2%) in suicidal ideation. Given differences in sample construction, Add Health may provide a more representative sample of adolescents for that point in time. Examining the reasons for differences in the prevalence estimates of the two studies was beyond the scope of this paper. However, further examination is warranted, given the importance of the YRBS in documenting national prevalence and trends in adolescent depression and suicide risk.

Most YRBS reports do not control for sociodemographic characteristics. The present findings indicated that SES, as captured by parental education, does seem to have a strong independent association with depression, even after accounting for youth risk behaviors, with more education reducing the likelihood of depression by about half. Conversely, higher parental education was associated with an elevated relative risk of suicidal ideation, after controlling for depression. Further research is warranted to understand how SES may influence these two variables. Controlling for SES and risk behaviors may also explain why Hispanic ethnicity all but disappeared as an independent predictor of depression and suicide risk. Ethnicity was a significant predictor only in the depression regression model, with an OR of 1.19 that was much smaller than expected given the findings of previous studies, including those attempting to control for SES.[39]

The widely documented sex differences in depression that appear at puberty persisted in the regression models. However, descriptive analyses indicated little difference between abstaining boys and girls, and demonstrated variation in gender differences according to risk behavior pattern. Girls were less likely than boys to engage in high-risk behaviors, but those who did tended to be more vulnerable to depression, suicidal ideation, and suicide attempt. These findings indicate that further examination of the role of risk behavior in depression prevalence is warranted.

Although a small percentage of abstaining adolescents reported major depressive symptoms, risk was clearly elevated in association with substance use and sexual activity. Further, certain patterns of these behaviors identified adolescents who are at extremely high risk. These findings point to the need for longitudinal analyses in order to better address the causal ordering of risk behavior and depression, and to determine whether causal sequences differ by subgroup. There was some indication that substance use, such as cigarette smoking, led to depression rather than the reverse,[11,38] but there are other studies indicating that adolescents may become involved in risk taking in response to preexisting depression.[40,41] Determining the circumstances leading to these different developmental sequences will have important theoretical implications regarding etiology as well as important clinical and public health implications.

The present study findings have more immediate implications for preventive health care. Although many professional organizations recommend routine screening for depression and risk of suicide during adolescent health visits,[42] there is a lack of consensus regarding these recommendations. For example, based on a systematic review of the literature, the U.S. Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against routine screening of asymptomatic adolescents for depression[43] or risk of suicide.[44]

These results suggest that healthcare professionals who identify adolescent patients reporting sexual intercourse or drug use should strongly consider screening for depression and risk of suicide. Although most adolescents engaging in these behaviors will not be depressed or at risk of suicide, the odds of identifying adolescents with clinically important depression or risk for suicide are increased—sometimes quite substantially—among adolescents engaging in sex and drug use behaviors. Identifying mental health problems among adolescent patients who are engaging in sexual intercourse and/or drug use increases the likelihood that an appropriate management plan is developed. Management plans may need to address issues related to sexually transmitted infections, HIV, unintended pregnancy, drug use, injury prevention, and depression and/or suicide risk. It is particularly important not to miss opportunities to diagnose depression because effective treatments are available,[45–48] or to overlook suicide risk because suicide can be prevented.

What This Study Adds

Teens engaging in risk behaviors are at increased odds for depression, suicidal ideation, and suicide attempts.

This study uses cluster analysis to identify and estimate the prevalence of 16 separate patterns of sexual intercourse and drug use behaviors in a representative sample of U.S. adolescents.

Logistic regression findings demonstrate the strong, independent association between engagement in these behaviors and depression, suicidal ideation, and suicide attempts, after controlling for gender, age, race/ethnicity, Hispanic ethnicity, parental education, and family structure.

Further research is needed to better understand clustering patterns of sex behaviors, drug use, and mental health problems within a developmental context. Furthermore, it is important to identify the best ways to intervene when specific patterns are recognized. Until then, healthcare professionals should consider the pragmatic approach of screening all adolescent patients for sexual behaviors and drug use. Adolescents who report either—and especially adolescents reporting high-risk patterns of behaviors—should be screened for depression and risk of suicide.

We are grateful to Guang Guo, PhD, and Daniel Bauer, PhD, for their assistance with statistical methods. Funding for the study was from the National Institute of Drug Abuse (grant R01-DA14496; DDH, principal investigator). This research used data from Add Health, a program project designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris, and funded by the National Institute of Child Health and Human Development (grant P01-HD31921), with cooperative funding from 17 other agencies. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Persons interested in obtaining data files from Add Health should contact Add Health, Carolina Population Center, 123 W. Franklin Street, Chapel Hill NC 27516-2524, www.cpc.unc.edu/addhealth/contract.html.

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Cannabis use and mental health in young people: cohort study

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Abstract

Objective To determine whether cannabis use in adolescence predisposes to higher rates of depression and anxiety in young adulthood.

Design Seven wave cohort study over six years.

Setting 44 schools in the Australian state of Victoria.

Participants A statewide secondary school sample of 1601 students aged 14-15 followed for seven years.

Main outcome measure Interview measure of depression and anxiety (revised clinical interview schedule) at wave 7.

Results Some 60% of participants had used cannabis by the age of 20; 7% were daily users at that point. Daily use in young women was associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for intercurrent use of other substances (odds ratio 5.6, 95% confidence interval 2.6 to 12). Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (1.9, 1.1 to 3.3) after adjustment for potential baseline confounders. In contrast, depression and anxiety in teenagers predicted neither later weekly nor daily cannabis use.

Conclusions Frequent cannabis use in teenage girls predicts later depression and anxiety, with daily users carrying the highest risk. Given recent increasing levels of cannabis use, measures to reduce frequent and heavy recreational use seem warranted.

Introduction

After increases in cannabis use during the early 1990s, a majority of young people in the United Kingdom, United States, New Zealand, and Australia now use cannabis recreationally.[1 2] Despite the high prevalence of cannabis use, uncertainty persists about its physical and psychological consequences.[3]

Among the most prominent concerns have been putative links between use of cannabis and mental disorders. A large intake of cannabis seems able to trigger acute psychotic episodes and may worsen outcomes in established psychosis.[4 5] Associations with non-psychotic disorders have received less attention. Yet evidence for an association between cannabis use and depression and anxiety has grown.[6] Chronic daily users report high levels of anxiety, depression, fatigue, and their motivation is low.[7] In one recent survey of young adults, over a third reported symptoms of anxiety that were associated with cannabis use; young women reported these more commonly.[8] Cross sectional associations between cannabis use and depression and anxiety have now been reported in surveys in both adolescents and adults,[9 10] although not all studies have found an association in male participants.[11]

Questions remain about the level of association between cannabis use and depression and anxiety and about the mechanism underpinning the link. Pre-existing symptoms might raise the likelihood of cannabis use through a mechanism of self medication.[12] Alternatively, cannabis use may be more likely in people with a background of social adversity or particular characteristics—factors that might also raise risks for mental disorders. Cannabis may also carry a direct risk for depression and anxiety.

We examined the risks for later depression and anxiety associated with cannabis use in teenagers. Specifically, the study addressed three questions. Firstly, does cannabis use in adolescents predict the development of symptoms of depression and anxiety in young adults? Secondly, do symptoms of depression and anxiety in adolescence predict cannabis use in young adults? Thirdly, is any relation explained by factors such as family background or intercurrent use of other substances?

Methods

Sample

Between August 1992 and December 1998 we conducted a seven wave cohort study of adolescent health in the Australian state of Victoria. The cohort was defined in a two stage cluster sample, in which we selected two classes at random from each of 44 schools drawn from a stratified frame of government run, Catholic, and independent schools (total number of students 60 905). School retention rates to year nine in the year of sampling were 98%. One class from each school entered the cohort in the latter part of the ninth school year (wave 1) and the second class six months later, early in the 10th school year (wave 2). Participants were subsequently reviewed at six month intervals for the next two years (waves 3 to 6), with a final follow up (wave 7) at the age of 20-21, three years after the final school year in Victoria. In waves 1 to 6, participants self administered the questionnaire on laptop computers,[13] and those absent from school were followed up by tele-

Editorial by Rey and Tennant
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BMJ 2002;325:1195–8

phone. The seventh wave of data collection used computer assisted telephone interviews. All stages of the study were approved by the ethics committee of the Royal Children's Hospital.

From a total sample of 2032 students, 1947 (95.8%) participated at least once during the first six (adolescent) waves. In wave 7, 1601 young adults (79% of the initial sample or 82% of teenage participants) were interviewed between April and December 1998. Response rates are shown in figure 1. Reasons for non-completion at follow up were refusal (n=152), loss of contact (n=192), and death (n=2). We examined characteristics of non-completers in a logistic regression model. Male participants were over-represented (odds ratio 1.9, 95% confidence interval 1.5 to 2.4), as were parental divorce or separation (1.8, 1.4 to 2.5), and daily tobacco smoking at study inception (2.1, 1.5 to 2.9). Neither teenage depression and anxiety nor cannabis use were independently associated with loss to follow up. The mean age at wave 1 was 14.5 (SD 0.5) years; at wave 7 it was 20.7 (0.5) years. Of the 1601 participants in wave 7, 1130 (71%) still lived at home, 429 (27%) lived with others, and 42 (3%) lived alone. A total of 1345 (82%) had completed the final year of school; 1355 (85%) had started post-school study.

Measures

We used the computerised revised clinical interview schedule (CIS-R) to assess depression and anxiety at each wave.[14] The schedule provides data on the frequency, severity, persistence, and intrusiveness of 14 common psychiatric symptoms and has been widely used in population based surveys.[15] A total score of 12 or greater was taken to define a mixed state of depression and anxiety at a lower threshold than syndromes of major depression and anxiety disorder but one where clinical intervention would still be appropriate.[16]

We assessed cannabis use on the basis of self reported frequency of use in the previous six months in waves 1 to 6 and in the previous 12 months in wave 7. This allowed classification as never used, less than weekly use, at least weekly use, and daily use (defined as using on five or more days per week), and initiation after wave 6.

We assessed use of alcohol, tobacco, and other illicit drugs (including ecstasy, heroin, amphetamines, LSD, and steroids) on the basis of self reported frequency of use and with retrospective diaries over seven days for participants reporting recent drinking or smoking. Participants drinking on three or more days in the previous week were classified as frequent drinkers.

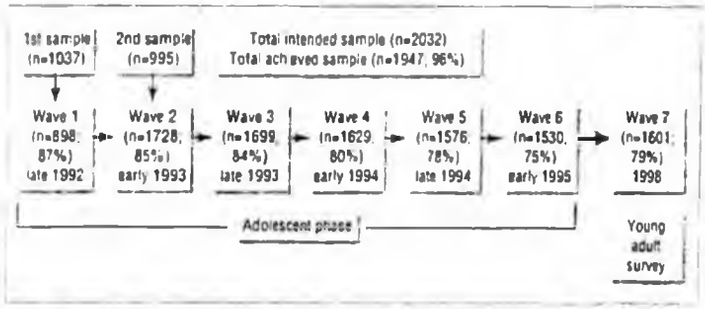

Fig 1 Participation rates of 2032 secondary school students in the Victorian adolescent health cohort study. The percentages in waves 2-7 are the proportions of the total intended sample for which complete data were collected

We assessed antisocial behaviour in waves 1 to 6 by using items from the self reported early delinquency scale that covered property damage, interpersonal violence, and theft.[17]

Analysis

We collected data at a developmental point when young people are difficult to trace because of high mobility. Although the response rate was high and attrition low, 70% of respondents missed at least one wave of data collection, which led to potential bias in summary measures of exposure to cannabis and mental health problems calculated from the six waves of data collection among adolescents. To circumvent this, we used multiple imputation with five complete datasets created by imputation under the multivariate mixed effects model of Schafer and Yucel, incorporating the covariates sex, age, rural or urban residence, and parental education (available for all participants).[18 19] These covariates were strongly associated with missingness, and the model incorporated a random effects structure to accommodate correlation within participants over time. We constructed principal measures by classifying participants according to whether they fell into categories of interest at least once during wave 1 to 6 (adolescence) and, separately, in wave 7 (young adulthood). Data analysis was performed with Stata 7. We modelled associations by univariate and multivariate logistic regression analyses and used Wald tests and related confidence intervals to assess statistical significance and precision.

Results

Altogether 71 male participants (9.7%, 95% confidence interval 7.5% to 12%) and 188 (22%, 19% to 25%) of female participants reported depression and anxiety as young adults (odds ratio 2.6, 1.9 to 3.5). Sixty six per cent (484/731) of male participants and 52% (448/859) of female participants reported using cannabis at some time (11 participants did not respond to this question), with three quarters starting use when they were teenagers. Twenty per cent (146; 17% to 22%) of male participants and 8% (69; 6% to 10%) of female participants were using cannabis at least weekly, with 10% (73; 8% to 12%) of young men and 4% (37; 3% to 6%) of young women using it daily.

Cannabis and depression in young adults

The prevalence of depression and anxiety increased with higher extents of cannabis use, but this pattern was clearest in female participants (table 1). We used logistic regression to analyse the level of association between depression and anxiety and cannabis use in young adults (table 2) after adjustment for concurrent substance use. We found a significant interaction between sex and daily cannabis use. In the adjusted model, young women who used cannabis daily had an over fivefold increase in the odds of depression and anxiety found in non-users.

Cannabis in adolescence and depression in young adults

We used logistic regression to examine the prediction of depression and anxiety in young adults by cannabis use in adolescence. In the univariate analysis a dose response was evident: daily use in female teenagers

Table 1 Prevalence of depression and anxiety according to cannabis use by sex in 1590 young adults in wave 7 (n=1601) of the Victorian adolescent health cohort study

Frequency of cannabis use in previous 12 months	Men			Women		
	No	% (95% CI)	Odds ratio* (95% CI)	No	% (95% CI)	Odds ratio* (95% CI)
None to <5 times ever	523	9 (6 to 11)	(1)	744	19 (17 to 22)	(1)
5 times ever to less than weekly	62	10 (2 to 17)	1.1 (0.46 to 2.8)	46	17 (6 to 29)	0.87 (0.40 to 1.9)
1 to 4 times per week	73	12 (5 to 20)	1.5 (0.70 to 3.2)	32	31 (14 to 48)	1.9 (0.87 to 4.1)
Daily	73	15 (7 to 23)	1.9 (0.93 to 3.8)	37	68 (52 to 83)	8.6 (4.2 to 18)

*Obtained from univariate logistic regression models.
11 (7 female) participants in wave 7 did not answer the questions about cannabis use
*Obtained from univariate logistic regression models.

predicted fourfold higher odds of later depression and anxiety (odds ratio 4.2, 1.6 to 11), weekly use a twofold elevation (2.3, 1.3 to 4.2). In the multivariate model we collapsed the top categories of cannabis use (table 3). The interaction between sex and weekly or more frequent use was significant. An almost twofold increase in risk for weekly or more frequent users who were female persisted after adjustment for potential confounders.

Depression in adolescence and cannabis in young adults

We considered whether depression and anxiety in adolescence predicted later cannabis use in young adulthood in two further logistic regression models, examining the predictions of weekly and daily use (table 4). After adjustment for adolescent cannabis use and other potential confounders, adolescent depression and anxiety predicted neither weekly nor daily use.

Discussion

Around 60% of the statewide secondary school sample had used cannabis recreationally by young adulthood; most participants first experimented while at secondary school. By young adulthood 7% were daily users and in young women this level of use was associated with over five times the odds of depression and anxiety found in non-users. In young women, weekly use as teenagers predicted a twofold increase in later depression and anxiety and daily use a fourfold increase. In contrast, depression in teenagers did not predict higher cannabis use.

Strengths

Earlier cohort studies had a limited capacity to address the key questions of this study. One study reported a prospective relation between cannabis use and later depression but started well after the risk period of onset for both.[20] Two important studies in adolescence examined either monthly cannabis use or use in the preceding year—doses that in the light of this study are unlikely to be associated with mental health problems.[21 22]

Our close to representative sample, high rates of participation, and frequent measures during participants' teenage years are strengths of this study. A telephone interview strategy was used in data collection in the last wave, and, although prevalence estimates may vary slightly as a result, it is unlikely to have caused a systematic bias in patterns of association. The use of multiple imputation minimised measurement biases arising from missing data during the teenage years, but we did not attempt to adjust for differential participation of young adults. Even though depression and anxiety in teenagers and cannabis use did not predict dropout from the study, the difference in non-responders on other factors (for example, sex or family structure) may have had some bearing on the specification of associations.

What the results might mean

Possible explanations for the high degree of depression and anxiety found in young women who used cannabis often include underlying characteristics that predispose to both anxiety and depression, self medication of pre-existing depressive symptoms, and an adverse effect of cannabis on mental health.[3] The association with cannabis use persisted after adjustment for concurrent use of alcohol, tobacco, and other illicit substances as well as indices of family disadvantage—findings consistent with a more direct relation. We considered self medication with cannabis

Table 2 Association between cannabis use in the previous 12 months and depression and anxiety in 1590 young adults in wave 7 (n=1601) of the Victorian adolescent health study, derived from a multivariate logistic model

Cannabis use	No	Adjusted odds ratio (95% CI)
None to <5 times in previous 12 months	1267	1
5 times ever to <weekly	108	0.80 (0.44 to 1.5)
1-4 times/week	105	1.1 (0.60 to 2.0)
Daily*		
Men	73	1.1 (0.55 to 2.6)
Women	37	5.6 (2.6 to 12)
Female sex in the absence of daily cannabis use	822	2.5 (1.8 to 3.4)

Odds ratios are adjusted for parental separation, parental education, current smoking, frequency of drinking, and use of other illicit drugs.
11 (7 female) participants did not answer the questions about cannabis use in wave 7.
*Wald test for interaction between daily cannabis use and sex: P=0.003.

Table 3 Association of cannabis use in teenagers with later depression and anxiety in 1601 young adults in wave 7 of the Victorian adolescent health cohort study

Measures in waves 1-6	No*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)†
Depression and anxiety (at least one wave)	744	6 (4.3 to 8.4)	5.1 (3.6 to 7.3)
Maximal cannabis use			
None	1083	1	1
<Weekly	332	1.5 (1.1 to 2.1)	1.4 (94 to 2.0)
>Weekly‡			
Male teenagers	108	0.62 (0.24 to 1.6)	0.47 (0.17 to 1.3)
Female teenagers	78	2.6 (1.6 to 4.3)	1.9 (1.1 to 3.3)
Female sex in the absence of >weekly cannabis use	788	2.3 (1.8 to 3.1)	1.6 (1.1 to 2.3)

*Numbers for adolescent cannabis use and depression and anxiety were estimated from five imputed datasets.
†Odds ratios by the highest frequency of cannabis use in teenagers (waves 1 to 6), obtained by using a multivariate logistic model, adjusted for teenagers' depression and anxiety, alcohol use, antisocial behaviour, parental separation, and parental education.
‡Wald test for interaction between more frequent than weekly cannabis use and sex: unadjusted P<0.001, adjusted P=0.011.

Table 4 Association of cannabis use in teenagers (waves 1-6) with later depression and anxiety in 1590 young adults in wave 7 (n=1601) of the Victorian adolescent health cohort study

Measures in waves 1 to 6	No*	Odds ratio (95% CI)†	
		>Weekly use	Daily use
Depression and anxiety at least one wave	739	1.2 (0.86 to 1.8)	1.3 (0.80 to 2.2)
Maximal cannabis use			
None	1074	1	1
<Weekly	330	3.7 (2.4 to 5.6)	3.1 (1.7 to 5.7)
>Weekly	185	15 (9.2 to 23)	15 (8.2 to 27)
Female sex	859	0.38 (0.26 to 0.54)	0.5 (0.29 to 0.77)

11 (7 female) participants in wave 7 did not answer the questions about cannabis use
*Numbers for adolescent cannabis use and depression and anxiety estimated from five imputed datasets
†Odds ratios obtained by using multivariable logistic models adjusted for teenagers' cannabis use, drinking frequency, parental separation and parental education

but found no prospective relation between depression and anxiety in adolescence and later frequent cannabis use, consistent with an earlier report.[11]

The persistence of associations in the multivariate models and the evidence for a prospective dose-response relation are consistent with a view that frequent use of cannabis in young people increases the risks of later depression and anxiety. Psychosocial mechanisms—for example, the adoption of a counter-cultural lifestyle—possibly underlie the association. Social consequences of frequent use include educational failure, dropout, unemployment, and crime—all factors that may lead to higher rates of mental disorders. Because risks seem confined largely to daily users, however, the question about a direct pharmacological effect remains. Cannabinoid receptors (CB1) are found widely in the central nervous system, with a distribution that is consistent with effects on a wide range of brain functions including memory, emotion, cognition, and movement.[20]

Cannabis use in young people remains a controversial area, and absence of good data has handicapped the development of rational public health policies.[3] These findings contribute to evidence that frequent cannabis use may have a deleterious effect on mental health beyond a risk for psychotic symptoms. Strategies to reduce frequent use of cannabis might reduce the level of mental disorders in young people.

Contributors: GCP was the principal investigator and prepared the manuscript. CC was the study coordinator and contributed to data analysis and manuscript preparation. JBC contributed to the data analysis and manuscript preparation. LD, ML, and WH contributed to the preparation of the manuscript. GCP is the guarantor.

Funding: National Health and Medical Research Council and Victorian Health Promotion Foundation.

Competing interests: None declared.

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What is already known on this topic

Frequent recreational use of cannabis has been linked to high rates of depression and anxiety in cross sectional surveys and studies of long term users

Why cannabis users have higher rates of depression and anxiety is uncertain

Previous longitudinal studies of cannabis use in youth have not analysed associations with frequent cannabis use

What this study adds

A strong association between daily use of cannabis and depression and anxiety in young women persists after adjustment for intercurrent use of other substances

Frequent cannabis use in teenage girls predicts later higher rates of depression and anxiety

Depression and anxiety in teenagers do not predict later cannabis use; self medication is therefore unlikely to be the reason for the association

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(Accepted 15 August 2002)

Endpiece

Surgical innovation

It is infinitely better to transplant a heart than to bury it so it can be devoured by worms.

Christiaan Barnard (1922-2001), who performed the first human heart transplant in 1967

Submitted by Max Edwards, surgical trainee, London

Cannabis use and mental health in young people: cohort study

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BMJ 2002;325;1195-1198
doi:10.1136/bmj.325.7374.1195

Adolescent Depression and Suicide Risk

Association with Sex and Drug Behavior

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Background: Depression is common among adolescents, and suicide is the third leading cause of death among 15- to 19-year-olds. Although both health problems have been associated with drug use and early sexual intercourse, the relationship has not been systematically studied in a nationally representative sample.

Methods: Sixteen patterns of combined sex and drug use behaviors were obtained using cluster analysis of responses to Wave I of the National Longitudinal Study of Adolescent Health conducted from September 1994 through December 1995. Bivariate and multivariate analyses tested correlations between behavior patterns and current depression, serious suicidal ideation, and previous suicide attempt, controlling for gender, race/ethnicity, Hispanic ethnicity, family structure, and parent education.

Results: Compared to youth who abstain from risk behaviors, involvement in any drinking, smoking, and/or sexual activity was associated with significantly increased odds of depression, suicidal ideation, and suicide attempts. Odds ratios were highest among youth who engaged in illegal drug use. There were few differences between boys and girls who abstain from sex and drug behaviors. Girls were less likely than boys to engage in high-risk behaviors, but those who did tended to be more vulnerable to depression, suicidal ideation, and suicide attempt.

Conclusions: Teens engaging in risk behaviors are at increased odds for depression, suicidal ideation, and suicide attempts. Although causal direction has not been established, involvement in any sex or drug use is cause for concern, and should be a clinical indication for mental health screening for girls; both boys and girls should be screened if engaging in any marijuana or illegal drug use.

(Am J Prev Med 2004;27(3):224–230)

Introduction

Suicide represents a significant and preventable loss of life. Among 15- to 19-year-olds, suicide is the third leading cause of death, accounting for approximately 2000 (or 12%) of the annual deaths in this age group.[1,2] Death rates from suicide among 15- to 19-year-olds doubled between 1960 and 2001, with reported rates peaking in 1990.[3] Reported rates for 2001 were 12.9 per 100,000 among males and 2.7 among females.[3] The lifetime prevalence of suicide attempts in this age group has been estimated to be 7.1% (10.1% for females and 3.8% for males).[4]

Data on adolescent suicide risk have generally been reported from either clinical population studies or from the Centers for Disease Control and Prevention's Youth Risk Behavior Survey (YRBS), which produces national estimates based on a biannual, school-based survey conducted in participating high schools. The 2001 YRBS[5] (n =13,601) found that 28% of U.S. high school students reported severe depressive feelings, 19% had seriously considered attempting suicide, and 9% had attempted suicide at least once in the preceding year. Ninth, tenth, and eleventh graders (11%, 9%, and 8%, respectively) were significantly more likely than twelfth graders (5.5%) to have attempted suicide in the past year. Hispanic youth were significantly more likely to attempt suicide (12.1%) than blacks (8.8%) and whites (7.9%).

Girls were about twice as likely as boys to report severe depressive feelings, consider attempting suicide, or attempt suicide. Empirical studies have indicated that major depression is most highly correlated with suicide for girls (increasing the risk by up to 20-fold), followed by a previous suicide attempt. Among boys, a previous attempt is the most highly correlated factor (increasing the risk by over 30-fold), followed by de-

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0749-3797/04/$–see front matter
doi:10.1016/j.amepre.2004.06.001

pression, alcohol or drug abuse, and disruptive behavior.[4,6–9]

Depression, suicidal ideation, and suicide attempts have previously been linked to adolescent substance use and sexual activity.[10–16] Participation in these activities is widespread among teens.[5,17] In 2001, 45.6% of all high school students reported ever having had sexual intercourse, 33.9% reported current cigarette or other tobacco use, and nearly half (47.1%) had used alcohol in the previous 30 days.[5]

Knowledge about risk factors is important for diagnosing and treating adolescent depression and suicide risk.[18] An important clinical consideration is whether certain patterns of substance use and sexual behaviors are differentially associated with depression and suicide risk. Previous research on adolescent risk behaviors has shown that risk behaviors tend to cluster together rather than occur in isolation.[15,19–27] Cluster analytic methods can reveal the extent to which individuals participate in multiple risk behaviors.[28]

This paper examines the extent to which adolescent sex and drug behavior patterns are associated with depression, controlling for gender, age, race/ethnicity, Hispanic ethnicity, parental education, and family structure. The associations between behavior patterns and both suicidal ideation and attempt are also examined, adding depression as a control variable. Data were from Wave I of the National Longitudinal Study of Adolescent Health (Add Health).[29]

Although the YRBS is an important source of information about biennial trends, and both surveys measure adolescent depression, suicide risk, drug use, and sexual behavior, Add Health offers certain unique strengths. First, Wave-I data were carefully collected and weighted to provide a nationally representative sample of youth in grades 7 through 12; national YRBS data are representative of students in grades 9 through 12.[5] Second, Add Health collected sensitive data using an audio computer-assisted (ACASI) survey instrument, which maximizes confidentiality, improves veracity,[30] and reduces missing data.[31] Third, although both surveys measured the construct of depression, the YRBS included only a single "past 12-month" item, while Add Health questions were based on the 20-item Center for Epidemiological Studies-Depression Scale (CES-D). The present study built on the strengths of Add Health to contribute new information about patterns of adolescent sex and drug use and their association with important mental health problems.

Methods

Sample

Data were from the Wave-I in-home contractual data set of Add Health, a nationally representative probability sample of adolescents in grades 7 through 12 from 132 schools (n = 18,924) gathered from September 1994 through December 1995 and analyzed in November 2003. All students who had completed an in-school questionnaire or who were listed on a school roster were eligible for inclusion in the more in-depth follow-up interview, which was conducted in the home (see Bearman et al.[29] for additional detail). In-home questionnaires were administered via laptop computers and utilized ACASI technology to collect information on sensitive topics such as sexual activity and substance use. Informed assent by adolescents and parental consent were obtained for all participants.

Independent Measures

Sociodemographic measures. Gender was a self-reported dichotomous variable, with male as the referent. Chronological age in years was determined by subtracting the date of birth from the date of the interview, rounded to two decimal places. Race/ethnicity was based on respondent's self-report, categorized for multivariate analyses as two dichotomous variables: black and other (primarily Asian), with white as the referent. Hispanic ethnicity was based on the respondent's self-report of Hispanic origin and was a dichotomous variable, with non-Hispanic as the referent. Two different measures served as proxies for socioeconomic status (SES). Highest parental education was based on the adolescent's report of the highest education level attained by either the resident mother or father, with categories of less than high school (referent), high school graduate/General Educational Development (GED), some college, and college graduate or higher. Family structure was based on household roster information[32] and grouped into the following categories: two resident parents (referent), single mother, and other.

Cluster membership. K-means cluster analysis was used to group respondents into homogeneous profiles based on responses to 12 items concerning risk behavior. Similar to factor analysis, which groups variables together, cluster analysis groups individuals, based on the assumption that risk behaviors often occur together and interact with each other. By combining individuals with similar behavior patterns, cluster analysis allows for the interaction of all the variables (in the present case, up to 12-way interactions), resulting in a more parsimonious model and a more holistic way of considering youth behavior.[33,34]

Four clusters were defined a priori based on the complete absence of risk behavior (abstainers) or engagement in highly distinctive risk behaviors for HIV and other sexually transmitted diseases (IV drug users, sex for drugs or money, and males who have sex with males [MSM]). Since K-means analysis becomes unreliable with extreme observations, these less common behaviors were examined first. Next, using K-means cluster analysis to identify the modal risk patterns, all other participants were grouped into 12 clusters based on the following self-reported risk behaviors: cigarette use, alcohol consumption, binge drinking, marijuana use, other illicit drug use, sexual intercourse, condom use, number of sexual partners, and engaging in sex while under the influence of alcohol or drugs. The resulting 16 clusters accounted for almost 80% of the total variation in behavior patterns.

Table 2. Behavioral patterns defining clusters and cluster size (largest to smallest)

Cluster name	Patterns of sexual behavior and substance use	*n*	Weighted %*
Light substance dabblers	Infrequent or no current ATOD use None have had sexual intercourse	4559	25.20
Abstainers	Never engaged in any ATOD use None have had sexual intercourse	4292	23.41
Sex dabblers	All have had sexual intercourse Median number of partners=1 Low levels of ATOD use	3148	14.27
Drinkers	All report past-year alcohol use About 50% report binge drinking Infrequent or no illegal drug use None report sexual intercourse	1403	7.48
Smokers	All are daily cigarette smokers Infrequent use of alcohol or illegal drugs Majority have had sexual intercourse	1109	6.58
Alcohol and sex dabblers	All report occasional alcohol use and all have had sexual intercourse Low tobacco & illegal drug use	1068	5.30
Binge drinkers	All report frequent binge drinking Low cigarette, marijuana, and other drug use More than half binge one or more times/week About half have had sexual intercourse	856	4.44
Sex and drugs in combination	All have had sexual intercourse and all report alcohol or illegal drug use at most recent intercourse	602	3.38
Heavy dabblers	All report moderate levels of smoking, drinking, and binge drinking Half use marijuana; few use other illegal drugs Most (91%) have had sexual intercourse	541	3.27
Marijuana users	All use marijuana frequently; few use other illegal drugs Almost all drink alcohol Most smoke cigarettes Three quarters have had sexual intercourse	314	1.67
Multiple partners	All report ≥14 sex partners Moderate ATOD use	230	1.25
Sex for drugs or money	All report sex for drugs or money Most are moderate ATOD users Median sex partners=3	195	1.11
High marijuana and sex	All use marijuana frequently and all have had sexual intercourse All report AOD use at last intercourse Most report multiple partners (median=6)	193	1.09
Marijuana and other drugs	Most report heavy marijuana use and all report other illegal drug use Two thirds have had sexual intercourse One third report drug use during intercourse	107	0.63
IV drug users	All have injected drugs >80% have had sexual intercourse Median number of partners=4	100	0.56
MSM	All are males who have had sex with other males Most have had multiple partners (median=5) 40% have used marijuana in last 30 days Most are occasional drinkers 17% have had sex for drugs or money	82	0.37
Total		18,799	100.00

*Weighted percentage yielding national probability estimates for 7th- to 12th-grade youth
AOD/ATOD, alcohol [tobacco] and other drugs; MSM, males having sex with males

drug use showed the highest proportions. After abstainers, the lowest proportions were in clusters with the lowest levels of legal drug use (light substance dabblers, drinkers) and those marked by sexual activity but relatively low drug use (sex dabblers, alcohol and sex dabblers). Multiple partners, smokers, heavy dabblers, and MSM clusters were at the midpoint, with proportions of affected individuals roughly four times that of abstainers. For girls, there was a dramatic rise in risk among light substance dabblers compared to abstainers (e.g., depression rose to 9.5% from 4.5%). For boys, there was a more modest difference between abstainers and light substance dabblers (depression rates were 3.6% and 5.6%, respectively). In most of the subse-

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other studies, females, Hispanics, and lower-SES adolescents are at elevated risk for depression. Controlling for sociodemographic characteristics, present analyses showed a dramatic relationship between sex and drug behaviors and multiple indicators of adolescent mental health. Compared to abstainers, membership in any of the risk clusters was associated with increased odds of depression, serious thoughts about suicide, and suicide attempts. Use of marijuana and other illegal drugs was associated with especially high risk.

The prevalence of current major depression (10.3%) in this study was lower than the prevalence of serious suicidal ideation (13.2%). This was not the case with YRBS data (28% and 19%, respectively), likely because of differences in the measurement of depression between the two surveys. The Add Health CES-D items tap current depressive symptoms, while the single YRBS item queries depressive symptoms over the past 12 months. Both surveys ask about serious suicidal ideation over the past 12 months.

Beyond the time-frame differences for depression assessment, there were other differences that likely contributed to the disparities between the two surveys in prevalence estimates of suicidal ideation and suicide attempt. The Add Health sample, for example, included 7th- and 8th-grade students; excluding these students, however, yielded only a modest increase (14.2%) in suicidal ideation. Given differences in sample construction, Add Health may provide a more representative sample of adolescents for that point in time. Examining the reasons for differences in the prevalence estimates of the two studies was beyond the scope of this paper. However, further examination is warranted, given the importance of the YRBS in documenting national prevalence and trends in adolescent depression and suicide risk.

Most YRBS reports do not control for sociodemographic characteristics. The present findings indicated that SES, as captured by parental education, does seem to have a strong independent association with depression, even after accounting for youth risk behaviors, with more education reducing the likelihood of depression by about half. Conversely, higher parental education was associated with an elevated relative risk of suicidal ideation, after controlling for depression. Further research is warranted to understand how SES may influence these two variables. Controlling for SES and risk behaviors may also explain why Hispanic ethnicity all but disappeared as an independent predictor of depression and suicide risk. Ethnicity was a significant predictor only in the depression regression model, with an OR of 1.19 that was much smaller than expected given the findings of previous studies, including those attempting to control for SES.[39]

The widely documented sex differences in depression that appear at puberty persisted in the regression models. However, descriptive analyses indicated little difference between abstaining boys and girls, and demonstrated variation in gender differences according to risk behavior pattern. Girls were less likely than boys to engage in high-risk behaviors, but those who did tended to be more vulnerable to depression, suicidal ideation, and suicide attempt. These findings indicate that further examination of the role of risk behavior in depression prevalence is warranted.

Although a small percentage of abstaining adolescents reported major depressive symptoms, risk was clearly elevated in association with substance use and sexual activity. Further, certain patterns of these behaviors identified adolescents who are at extremely high risk. These findings point to the need for longitudinal analyses in order to better address the causal ordering of risk behavior and depression, and to determine whether causal sequences differ by subgroup. There was some indication that substance use, such as cigarette smoking, led to depression rather than the reverse,[11,38] but there are other studies indicating that adolescents may become involved in risk taking in response to preexisting depression.[40,41] Determining the circumstances leading to these different developmental sequences will have important theoretical implications regarding etiology as well as important clinical and public health implications.

The present study findings have more immediate implications for preventive health care. Although many professional organizations recommend routine screening for depression and risk of suicide during adolescent health visits,[42] there is a lack of consensus regarding these recommendations. For example, based on a systematic review of the literature, the U.S. Preventive Services Task Force concluded that there is insufficient evidence to recommend for or against routine screening of asymptomatic adolescents for depression[43] or risk of suicide.[44]

These results suggest that healthcare professionals who identify adolescent patients reporting sexual intercourse or drug use should strongly consider screening for depression and risk of suicide. Although most adolescents engaging in these behaviors will not be depressed or at risk of suicide, the odds of identifying adolescents with clinically important depression or risk for suicide are increased—sometimes quite substantially—among adolescents engaging in sex and drug use behaviors. Identifying mental health problems among adolescent patients who are engaging in sexual intercourse and/or drug use increases the likelihood that an appropriate management plan is developed. Management plans may need to address issues related to sexually transmitted infections, HIV, unintended pregnancy, drug use, injury prevention, and depression and/or suicide risk. It is particulary important not to miss opportunities to diagnose depression because effective treatments are available,[45–48] or to overlook suicide risk because suicide can be prevented.

What This Study Adds . . .

Teens engaging in risk behaviors are at increased odds for depression, suicidal ideation, and suicide attempts.

This study uses cluster analysis to identify and estimate the prevalence of 16 separate patterns of sexual intercourse and drug use behaviors in a representative sample of U.S. adolescents.

Logistic regression findings demonstrate the strong, independent association between engagement in these behaviors and depression, suicidal ideation, and suicide attempts, after controlling for gender, age, race/ethnicity, Hispanic ethnicity, parental education, and family structure.

Further research is needed to better understand clustering patterns of sex behaviors, drug use, and mental health problems within a developmental context. Furthermore, it is important to identify the best ways to intervene when specific patterns are recognized. Until then, healthcare professionals should consider the pragmatic approach of screening all adolescent patients for sexual behaviors and drug use. Adolescents who report either—and especially adolescents reporting high-risk patterns of behaviors—should be screened for depression and risk of suicide.

We are grateful to Guang Guo, PhD, and Daniel Bauer, PhD, for their assistance with statistical methods. Funding for the study was from the National Institute of Drug Abuse (grant R01-DA14496; DDH, principal investigator). This research used data from Add Health, a program project designed by J. Richard Udry, Peter S. Bearman, and Kathleen Mullan Harris, and funded by the National Institute of Child Health and Human Development (grant P01-HD31921), with cooperative funding from 17 other agencies. Special acknowledgment is due Ronald R. Rindfuss and Barbara Entwisle for assistance in the original design. Persons interested in obtaining data files from Add Health should contact Add Health, Carolina Population Center, 123 W. Franklin Street, Chapel Hill NC 27516-2524, www.cpc.unc.edu/addhealth/contract.html.

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Cerebrovascular perfusion in marijuana users during a month of monitored abstinence

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Abstract—*Objective:* To determine possible effects of prolonged marijuana use on the cerebrovascular system during a month of monitored abstinence and to assess how the intensity of current use might have influenced cerebrovascular perfusion in these marijuana users. *Method:* The authors recorded blood flow velocity in the anterior and middle cerebral arteries using transcranial Doppler sonography in three groups of marijuana users who differed in the intensity of recent use (light: n = 11; moderate: n = 23; and heavy: n = 20) and in control subjects (n = 18) to assess the nature and duration of any potential abnormalities. Blood flow velocity was recorded within 3 days of admission and 28 to 30 days of monitored abstinence on an inpatient research unit in order to evaluate subacute effects of the drug and any abstinence-generated changes. *Results:* Pulsatility index, a measure of cerebrovascular resistance, and systolic velocity were significantly increased in the marijuana users vs control subjects. These increases persisted in the heavy marijuana users after a month of monitored abstinence. *Conclusions:* Chronic marijuana use is associated with increased cerebrovascular resistance through changes mediated, in part, in blood vessels or in the brain parenchyma. These findings might provide a partial explanation for the cognitive deficits observed in a similar group of marijuana users.

NEUROLOGY 2005;64:488–493

Marijuana is the most commonly used drug among young persons.[1] Prolonged effects of marijuana on the neurovasculature might be responsible, in part, for the reports of cognitive deficits observed in some of these users[2] because the acute administration of marijuana or delta-9-tetrahydrocannbinal (THC) causes increases in cerebral blood flow in marijuana users[3] and because reduced cerebral blood flow is observed in recently abstinent chronic marijuana users.[4] It remains to be determined whether the reported changes in cerebral blood flow might persist over an extended period of monitored abstinence, and whether the intensity of current marijuana use might influence the severity or duration of the perfusion deficits associated with use of the drug.

In order to address these issues further, three groups of marijuana users differing in the current intensity of use were tested with transcranial Doppler (TCD) sonography early and late during a month of monitored abstinence. Their data were contrasted with those of control subjects. In order to delineate possible effects of marijuana on cerebral vessels, we opted for TCD because TCD assessment is noninvasive, economical, and rapid.[5] Because TCD is a test that is easily available in clinical neurology settings, it allows for easy replication, unlike some of the more expensive imaging techniques.

Methods. *Subjects.* Fifty-four marijuana users (14 women, 40 men) and 18 control subjects (6 women, 12 men) were studied. Before undergoing blood flow velocity assessment by TCD, all volunteers had undergone medical, neurologic, psychological, and laboratory evaluations. Fourteen marijuana users also met criteria for a diagnosis of antisocial personality disorder and four met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV criteria for nicotine dependence.[6]

Exclusion criteria, which applied to all subjects, included 1) major medical and psychiatric illnesses including history of hypertension, 2) head injuries with loss of consciousness for greater than 5 minutes, 3) evidence of any neurologic abnormalities by history or examination, 4) HIV seropositivity, and 5) drug (e.g., cocaine, heroin) or excessive alcohol use by DSM-IV criteria for alcohol abuse or dependence. The research protocol was approved by the National Institute on Drug Abuse and Johns Hopkins Bayview Medical Center Institutional Review Boards for Human Research and was carried out in accordance the with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Demographic information and drug use history information were obtained from the Addiction Severity Index (ASI).[7] The metric, joints per week, was determined from the subjects' self-reported drug history. Since the number of marijuana joints per week ranged from 2 to 350, the 54 marijuana users were divided into three groups using the procedure described by Bolla et al.[4] Fifteen marijuana users in the present study were also in the Bolla study. In that procedure, a blunt (cigar-size marijuana smoking material) was equal to four joints (small diameter cigarette-size smoking material). The light group smoked 11.0 ± 3.5 joints per week (n = 11; range 2.2 to 15.0). The moderate group smoked the equivalent of 43.7 ± 16.4 joints per week (n = 23; range 17 to 70). The heavy group smoked the equivalent of 130.8 ± 73.0 joints per week (n = 20; range 78 to 350). Table 1 lists these measures for the control subjects and the three groups of marijuana users. The three groups of marijuana users did not differ in years of use. Other than alcohol, tobacco, and marijuana use reported in table 1, illicit drug use was not self-reported or observed in urine toxicologies obtained during the screening process. Subjects with drug use other than marijuana use were screened out of the present study. Subjects with a lifetime diagno-

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Received July 2, 2004. Accepted in final form October 14, 2004.
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Table 1 Demographic measures and drug history

Demographic measures	Control, n = 18, mean (SD)	Marijuana users		
		Light, n = 11, mean (SD)	Moderate, n = 23, mean (SD)	Heavy, n = 20, mean (SD)
Age, y	24.2 (3.2)	25.5 (6.3)	22.6 (4.9)	21.6 (2.8)
Education, y	13.0 (1.7)	12.2 (1.6)	11.7 (1.8)	11.2 (1.5*)
Shipley, IQ	102.5 (13.8)	96.8 (11.8)	95.7 (11.8)	97.0 (10.7)
Women, %	33.3	27.3	26.1	25.0
African Americans, %	88.9	81.8	78.3	100.0
Drug history measures				
Alcohol, d/30 d,† CV‡	0.6 (1.1)	3.4 (4.7)	3.7 (4.8)	6.2 (6.3*)
Alcohol, y§	1.2 (2.4)	1.4 (3.3)	3.4 (5.8)	2.5 (3.3)
Marijuana, d/30 d		15.9 (3.7)	24.5 (7.1)	29.2 (3.4)
Marijuana, y‖		5.6 (3.8)	7.2 (5.8)	6.1 (3.1)
Last use to early test, d		4.0 (1.5)	2.6 (1.9)	2.2 (0.9)
Median (range)		4 (2 to 7)	2 (1 to 10)	2 (1 to 4)
Cigarettes/day, CV	0.6 (1.5)	4.7 (5.3)	5.9 (5.8)	8.9 (9.2*)
Cigarettes, y	4.8 (11.0)	4.5 (4.9)	3.7 (4.2)	4.1 (2.6)

* $p < 0.05$ Alcohol days and cigarettes/day: heavy > control
† The number of days of substance use in the last 30 days from the ASI.
‡ Variable was used as a covariate in the analysis of blood flow velocity measures
§ Years of substance use calculated from ASI.
‖ The three groups of marijuana users did not differ on this measure [$F(2,50) = 0.40$, $p > 0.5$]

CV = covariate, ASI = Addiction Severity Index.

sis of alcohol abuse or dependence by DSM-IV criteria were also screened out of the study.

Procedures. TCD measurements were made within 72 hours of admission to our closed clinical research ward. A second measurement was made after 28 to 30 days of monitored abstinence on the research ward. Our closed research ward was assessable only to authorized staff and no visitors were permitted. Random urine samples were collected for urine toxicologies. The control subjects were tested once during an outpatient visit since it is difficult to recruit control subjects who would be willing to spend a month on a closed research ward and none of the measures were expected to change over this period.

Resting heart rate and blood pressure (BP) were measured in all subjects. Measurements were made within 72 hours of admission and at 28 to 30 days after admission to the clinical unit for the marijuana users. These cardiovascular measures were recorded on an outpatient visit for the control subjects as a comparison.

Blood flow velocity was determined using a temporal window (zygomatic arch) for four arteries: right and left middle (MCA) and right and left anterior (ACA) cerebral arteries using pulsed TCD sonography (Nicolet, Model TC2000). The evaluation of all four arteries took from 15 to 20 minutes. Mean velocity (Vm: cm/second), systolic velocity (Vs: cm/second), diastolic velocity (Vd: cm/second), and pulsatility index (PI = [Vs-Vd]/Vm) were determined for each artery. Any possible acute effects of nicotine on TCD measures were eliminated by testing subjects 20 minutes or longer after cigarette smoking. Caffeinated beverages were not allowed for 2 hours or more before the recording session. In one marijuana user, the 28-day TCD recording from the anterior cerebral arteries was not obtained due to recording difficulties. Thus, the evaluation of the effects of a month of monitored abstinence is based on 54 subjects for the MCA and 53 subjects for the ACA.

Statistical analysis. A group (three groups of marijuana users and control subjects) by sex analysis of variance (ANOVA) was used to test for differences in cardiovascular measures. An ANOVA with time (less than 72 hours vs 28 days) as well as dose groups (light, moderate, and heavy) between subject factor was used to determine if any of the cardiovascular measures were affected by the month of abstinence for the marijuana users.

An analysis of covariance (ANCOVA) was used on the blood flow velocity measures. A group (three groups of marijuana users and control subjects) by sex by side (right vs left) were the factors in each ANCOVA. The analysis compared the blood flow velocity data of the control subjects with that of the marijuana users collected early in abstinence. The covariates in ANCOVA were days of alcohol use in the last month and the cigarettes smoked per day since these variables differed across groups (see table 1). An ANCOVA with time (less than 72 hours vs 28 days) and side as well as the between-subject factor, dose group (light, moderate, and heavy), was used to determine if any of the blood flow velocity measures changed during the month of abstinence for the marijuana users. After each ANCOVA, post hoc tests were made using the Bonferroni procedure on the appropriate means. Statistical testing was performed with SPSS, version 11 (Chicago, IL).

Results. *Drug history and cardiovascular measures.* The drug history measures are reported in table 1. While the subject groups differed significantly by years of education [$F(3,64) = 3.67$, $p < 0.05$], there were no significant differences in Shipley estimates of IQ across groups. Cardiovascular measures are shown in table 2. Heart rate and systolic BP were similar for control and marijuana groups. Heart rate for the marijuana subjects tested at 28 to 30 days after admission was significantly greater than the values obtained within 72 hours of admission. No differences in systolic BP between the control and marijuana groups were observed. There were also no differences in systolic BP between the two test times for the marijuana groups. Diastolic BP for the marijuana users was significantly lower than that of the control subjects at the beginning of their inpatient stay. Diastolic BP did not differ

Table 2 Cardiovascular measures

Measure/time	Control	Marijuana users		
		Light	Moderate	Heavy
Heart rate, BPM				
<72 h	71.8 (6.9)	72.4 (10.0)	69.9 (10.7)	68.8 (12.5)
28–30 d		80.4* (9.6)	81.8* (9.4)	80.9* (10.6)
Systolic blood pressure, mm Hg				
<72 h	124.8 (11.5)	121.5 (14.4)	127.7 (15.0)	126.5 (15.0)
28–30 d		124.6 (6.2)	128.6 (15.6)	126.6 (12.0)
Diastolic blood pressure, mm Hg				
<72 h	75.8 (9.0)	68.3† (9.3)	69.3† (10.7)	70.0† (10.2)
28–30 d		69.1 (9.8)	71.8 (10.4)	68.6 (10.4)

Values are mean (SD).

* The means for the marijuana subjects tested at 28–30 days after admission is greater than the values obtained within 72 hours of admission [test time effect for marijuana groups: $F(1, 50) = 53.5$, $p < 0.001$]. Each early–late Bonferroni post hoc comparison was also significant at $p < 0.05$.

† The means of the diastolic blood pressure for the marijuana subjects tested within 72 hours after admission are lower than those of the control subjects [group effect for all groups: $F(3, 64) = 3.42$, $p < 0.05$] followed by post hoc comparisons ($p < 0.05$).

BPM = beats per minute.

among the three marijuana groups. There were no significant differences in diastolic BP throughout the stay of the marijuana users on the closed research unit.

TCD measures. No sex-related differences were observed in any of the TCD measures. There were no significant sex main effects or group by sex interactions in any of the MCA measures. There were no significant sex main effects or group by sex interactions in any of the ACA measures. In view of the lack of significant group by sex interactions in the analyses between the control subjects and marijuana users, sex was not considered in the analyses of the blood velocity values over time.

Vs and Vm for the MCA were higher for marijuana users in comparison to those for control subjects [Vs: $F(3,62) = 4.59$, $p < 0.002$; Vm: $F(3,62) = 3.14$, $p < 0.05$]. Vs and Vm did not differ among the marijuana groups (light, moderate, heavy). Figure 1A shows the means for the Vs measures for the control subjects and three marijuana groups. The results for Vm (not shown) were similar to Vs and Vd measures and were not significantly different in any of the groups. Figure 1B shows the means for the Vd measures for the control and three marijuana groups. The marijuana users also had higher PI values than the control subjects [$F(3,62) = 3.72$, $p < 0.02$]. PI did not differ among the marijuana groups (light, moderate, heavy). Figure 1C shows the means for PI for the control and marijuana groups.

Vs for the ACA was higher for marijuana users as compared to the control subjects [Vs: $F(3,62) = 5.68$, $p < 0.002$]. Vs values did not differ among the marijuana groups (light, moderate, heavy). Figure 2A shows the means for the Vs measures for the control subjects and three marijuana groups. Vd and Vm values were not significantly different among the groups. Figure 2B shows the means for the Vd measures for the control and three marijuana groups. The marijuana users also had higher PI values than the control subjects [$F(3,62) = 4.02$, $p < 0.01$], but PI did not differ among the marijuana groups (light, moderate, heavy). Figure 2C shows the plot of mean PI for the control and marijuana groups.

An ANCOVA with time and side and dose group (light, moderate, and heavy) was used to determine if any of the blood flow velocity measures changed during the month of abstinence for the marijuana users. For the MCA, the time by group interaction for Vs and PI was significant [Vs: $F(2,49) = 3.80$, $p < 0.05$; PI: $F(2,49) = 3.43$, $p < 0.05$]. This interaction indicated that there was a significant change over time for some of the marijuana groups. There was a significant decrease late in abstinence in Vs values for the light marijuana users compared to early abstinence (see figure 1A). A significant increase was observed for the heavy users late during the course of abstinence in comparison to the earlier time of testing (see figure 1A). PI for the light and moderate marijuana users decreased significantly from early to late abstinence (see figure 1C).

For the ACA, the time by marijuana group interaction was significant for Vs [$F(2,48) = 5.31$, $p < 0.01$], Vm [$F(2,48) = 3.35$, $p < 0.05$], and PI [$F(2,48) = 3.14$, $p < 0.05$]. Vs for the heavy marijuana users increased during the month of monitored abstinence (see figure 2B). PI values were reduced late in abstinence for the light marijuana users (see figure 2C).

Discussion. The main findings of the study are that, in comparison to control subjects, marijuana users show 1) elevated systolic and mean blood flow velocity in the MCA and ACA; 2) higher PI values in both the MCA and ACA; 3) no significant improvements in systolic velocity during a month of monitored abstinence; and 4) improvement in PI values only for the light and moderate marijuana users during the month of monitored abstinence. The present measurements, obtained during a month of observed abstinence from marijuana users, document poten-

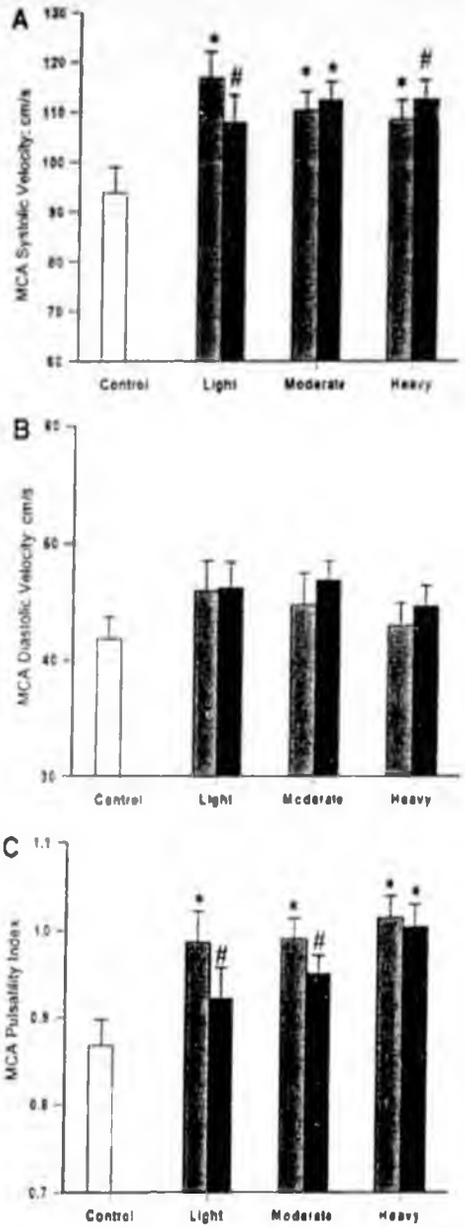

Figure 1. Mean systolic velocity is plotted for middle cerebral artery (A). Measurements were made within 72 hours of admission (gray bars) and after 28 days of monitored abstinence (black bars) for the marijuana users and at an outpatient test day for the control subjects (white bars). The error bar indicates the standard error. The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate significant decreases from early to late testing for the light group and increases from early to late testing for the heavy group. Mean diastolic velocity is plotted for the control subjects and the three marijuana groups for middle cerebral artery (B). No significant differences among the experimental groups were observed for diastolic velocity. Mean PI values are plotted for middle cerebral artery (C). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate a significant reduction in PI from early to late abstinence for the light and moderate groups.

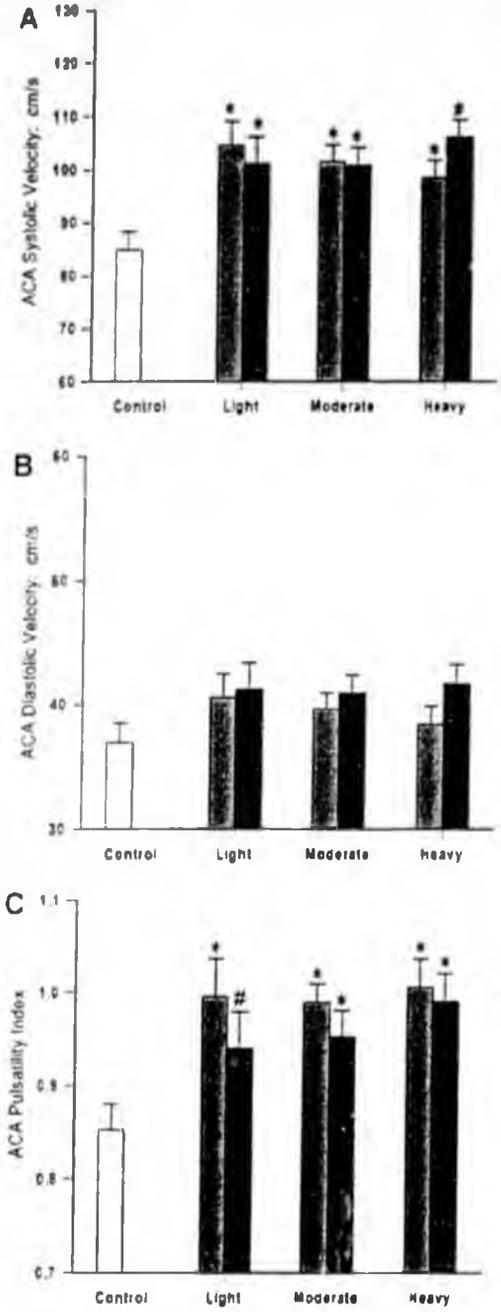

Figure 2. Mean systolic velocity is plotted for anterior cerebral artery (A). Recordings were made within 72 hours of admission (gray bars) and after 28 days of monitored abstinence (black bars) for the marijuana users and at an outpatient test day for the control subjects (white bars). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate significant increases from early to late testing for the heavy group. Mean diastolic velocity is plotted for the control subjects and the three marijuana groups for the anterior cerebral artery (B). No significant differences were observed among the experimental groups. Mean PI values are plotted for anterior cerebral artery (C). The asterisks indicate differences ($p < 0.05$) between the control and the marijuana groups at each test time using the Bonferroni procedure. The pound signs indicate a significant reduction in PI from early to late abstinence for the light group.

tially prolonged marijuana-mediated changes in vascular hemodynamics.

Reported increased cerebral blood flow velocities with increased PI observed in other patient populations are thought to be due to increased cerebrovascular resistance secondary to vasoconstriction of both small and large cortical vessels.[9] These changes might be secondary to increased cerebral perfusion pressure when vascular autoregulation is impaired.[9] Although caution must be taken when comparing different methods of assessing cerebral perfusion, the present study extends previous reports of marijuana-associated alterations in blood flow measured by SPECT,[10] PET,[4] or MRI.[11] For example, a study, using dynamic susceptibility contrast MRI, revealed significant increases in cerebral blood volume in marijuana users as compared to control subjects over a month of monitored abstinence.[11] Because increased blood volume has been reported to occur in areas of reduced perfusion,[12] it is possible that our present observations and those of others[11] might reflect similar distal perfusion deficits in marijuana patients. In contrast to the decreases observed during abstinence, acute administration of marijuana increases cerebral blood flow.[3] Taken together, those observations and ours are consistent with reports indicating that the acute effects of marijuana are opposite to those observed during withdrawal.[13]

The PI values of the marijuana users in the present study are higher than those of control subjects in this and other studies.[14] The marijuana users showed elevated PI values that are somewhat higher than those of patients with chronic hypertension[15] and diabetic patients[16] who show mean PI values ranging from 0.87 to 0.89. However, their PI values are lower than those reported for patients with multi-infarct dementia who have mean values of 1.20 to 1.27.[17] Given that the PI values from the present marijuana users fall between the ranges of less affected patients[15,16] and those patients with neurologic impairment,[17] we suggest that our findings might be secondary to abnormalities in small vessels because similar MCA PI values have been reported to reflect small-vessel diseases.[18]

Although we are suggesting that our observations are associated with marijuana use, it is also possible to suggest that they might be consequent to the concurrent use of other substances since cocaine users also show abnormalities in TCD indices.[19] This is probably not the case because the marijuana users in our study reported the use of no other substances except for alcohol and tobacco (see table 1). In fact, prospective subjects who reported other abuse of other substances or had urine tests positive for other substances were excluded from the study. Subjects with excessive use of alcohol were also screened out of this study. An analysis of covariance was also used in order to control for subjects with even modest use of these substances. These analyses revealed that neither alcohol nor tobacco use contributed to any of the differences in blood flow velocity observed between the control subjects and marijuana users. Furthermore, preliminary data from this laboratory have documented that chronic cigarette smoking does not alter PI.[20]

The changes in cerebrovascular flow observed in the present study might be related to the blood pressure differences between the control and marijuana groups. In the present study, systolic blood flow velocity was increased in marijuana users compared to control individuals. However, diastolic blood pressure was lower in the marijuana users, findings that are opposite of what might be expected if pressure and velocity were directly related. Furthermore, changes in cerebrovascular blood flow velocity appear to be related to blood pressure changes only when there is a loss of cerebral autoregulation.[9] It is more likely that the changes in blood pressure and blood flow velocity in the anterior and middle arteries might both be associated with withdrawal from the prolonged use of marijuana. In any case, the present observations suggest that more research is needed to study the effects of chronic marijuana use on cerebral and peripheral vascular systems.

A number of possible scenarios might be responsible for our present observations because of reported effects of the marijuana on the sympathetic and parasympathetic nervous systems. Specifically, marijuana administration is known to cause postural hypotension with dizziness as a result of drug-induced decreases in peripheral resistance.[21] These effects are thought to be mediated by CB1 receptors located on neurons and smooth muscle[22] and via stimulation of non-CB1 or non-CB2 receptors located on endothelial cells[23] which can also cause vasodilation.[24] This suggestion is consistent with our finding that the marijuana users in the present study had low resting diastolic blood pressure throughout the month of abstinence. The marijuana-associated cerebrovascular changes might be due to changes in the density of CB1 receptors in the brain and blood vessels as a result of the use of high doses of the drug. Chronic injections of THC have been shown to increase in the number of these receptors in the brain.[24] Therefore, it is possible that chronic intake of marijuana by drug users might affect cerebrovascular resistance through changes mediated in blood vessels or in the brain parenchyma.

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