

**Applying the Bradford Hill Criteria for Causation to the Relationship
Between Marijuana Use and Suicidal Behavior**

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1. Demonstration of a strong association between the causative agent and the outcome (author's note: often termed "correlation", it is the first criteria required to be satisfied for causation): ✓

Among the largest effect sizes for increased risk of suicide attempt in marijuana users were found in two longitudinal studies of predominantly Caucasian youth, both of which adjusted for a variety of potentially confounding factors. One study combined 3 longitudinal data sets involving 6 to 9 assessments over a period of 15 years, finding a 6.9-fold increase in risk for subsequent suicide attempt in those using marijuana daily before age 17 (Silins et al., 2014). As well as adjusting for measures of depression and conduct disorder, along with a variety of demographics, the adjustment factors specific to other drug use included tobacco use, alcohol use and other illicit drug use. The second longitudinal study with a large effect size included two assessments and a follow-up time of 8 years (Clarke et al., 2014), and was notable in that it adjusted for a history of any mood disorder (including depression), in addition to familial/adolescent risk factors, alcohol use but not tobacco or other drug use, finding a 7.5-fold increase in risk for suicide attempt when the marijuana use commenced in the teen years. As the best predictor of completed suicide is suicide attempt (Nordstrom et al., 1995; Hawton et al., 2013), it would be expected that the increased risk would be fairly similar in magnitude for suicide attempt and completed suicides. Indeed, a 2013 study of predominantly Caucasian subjects found a 5.3-fold increased risk for completed suicide in those with a cannabis use disorder (Arendt et al., 2013). Although a variety of demographic and personal risk factors were adjusted for, other substance use was only available for the month before cannabis abuse treatment commenced.

2. Consistency of the findings across research sites and methodologies: ✓

A meta-analysis of a mix of longitudinal and case-control studies worldwide, some including a mix of ethnic groups (African ancestry, Hispanic ancestry) with a lower risk of suicide than Caucasians (Curtin et al., 2016), found an overall 2.2-fold increase in risk for suicide attempt in users of marijuana, a 3.2-fold increased risk of suicide attempt in heavy users, and a 2.6-fold increase in risk for completed suicides in ever users (Borges et al., 2016). The follow-up times in the longitudinal studies ranged from 1 year to 33 years, averaging somewhat less than 7 years. There have been only a few reports that failed to find an association, including a case-control (no follow-up) study of 9,268 Swiss adolescents (Gex et al., 1998). Given the study size, the lack of follow-up limited the sensitivity of the study, and the investigators found no association between suicide attempt and marijuana use after controlling for a variety of potentially confounding variables, including tobacco smoking. Because very many marijuana users during that general time period also began smoking tobacco if they were not already smokers (Patton et al, 2005), correcting for tobacco use would be expected to substantially reduce the effect size

of marijuana and therefore, could potentially explain the lack of association found depending on the study power. In a study of other mental health outcomes in 50087 Swedish conscripts by Zammit et al. (2002), 86% of the marijuana users also smoked cigarettes. In the same cohort, Price (2009) found that an unadjusted 1.6-fold increase in risk for completed suicide in the 33-year longitudinal study was eliminated after adjusting for confounding variables, including smoking of tobacco. Although the total study population was quite large, the small number of completed suicides expected in the cannabis-using group (likely <30), means statistical power may have been quite limited after adjustments for confounding variables. Suicide attempts are much more frequent and afford greater statistical power. A longitudinal study of suicide attempts by Rasic et al. (2013) in a cohort of 976 Canadian high school students over a two year period, found that marijuana users were more likely to be depressed after adjusting for other illicit drug use and alcohol (but apparently not tobacco), but were not significantly more likely to attempt suicide than nonusers. Notably, this study was underpowered to detect anything less than a 2.7-fold effect of marijuana on suicide attempt (a smaller increase in risk would certainly be of interest, particularly since the two year follow-up period was so short). The evidence for tobacco use confounding the association of marijuana with suicide risk is strong (Miller et al., 2011; Bohnert et al., 2014; Evins et al., 2017). Yet, after decades of tobacco prevention education, the use of tobacco by U.S. youth began to decline (Centers for Disease Control, 2020), as well as use by all age groups worldwide (WHO, 2019) while marijuana-only use has increased (Schauer and Peters, 2018) to the extent that it became easier for researchers to investigate marijuana-specific effects independent of cigarette use. In a recent case-control study (Kahn and Wilcox, 2020) of a large (59,079) ethnically mixed population of U.S. high school students, adjusting for a variety of factors as well as tobacco and alcohol use revealed that the impact of marijuana on suicide attempts was still significant, with an enhanced prevalence of suicide attempt of 2.6-fold for those who used marijuana 20 or more days per month and at that same rate of use, a 4.5-fold enhanced prevalence of suicide attempts requiring medical intervention. There was no follow-up in this study of incident marijuana use and suicidal behaviors over one year, and for the studies reviewed by Borges et al. (2016), the follow-up was on average shorter than the Silins et al. and Clarke et al. studies mentioned above showing higher impact. Kahn et al. also reported that marijuana use was generally equivalent to the impacts of tobacco and alcohol; however, this proportionality might not persist in a longitudinal study because the relative impact of each substance could theoretically change as more suicide attempters are registered over time in a cohort population.

3. Demonstration of specificity of the causative agent in terms of the outcomes it produces: N/A (see van Reekum et al., 2001)

This criterion may be applicable to outcomes from infectious organisms to a certain extent, but is considered not considered applicable to neuropsychiatry and neuropharmacology (van Reekum et al., 2001), where one drug can result in many different outcomes and conversely, many different drugs are associated with suicidal behavior, including tobacco products, alcohol (Kahn and Wilcox, 2020) and other recreational drugs of abuse (reviewed by Miller, 2018).

4. Demonstration of the appropriate temporal sequence so that the causative agent occurs prior to the outcome: +/-

More work needs to be done on the timing of marijuana use and suicide, although the existing data is strongly suggestive of an appropriate temporal sequence in some, but not all, studies. For this criterion, longitudinal studies are the most important. Of those identified with adequate assessment intervals and time frame, one (also described above) involved the analysis of 3 separate longitudinal studies combined, totaling 2675 predominantly Caucasian youth starting at age 16 for each study, with follow-up through age 30, as reported by Silins et al. (2014). Yearly assessments were conducted (with mental health data prior to age 16 acquired retrospectively), numerous potentially confounding variables were adjusted for, and for those youth who were using marijuana daily by the age of 17, the risk of suicide attempt over the ensuing years was found to be significantly increased (6.9-fold) as compared to controls. A subsequent meta-analysis of only longitudinal studies assessing marijuana use that commenced at ages less than 18 years (Gobbi et al., 2019), identified a significant 3.46-fold increase in risk for suicide attempt during young adulthood in those with no pre-existing suicidal behaviors, depression or anxiety. Not all of the included studies adjusted for other drugs of abuse, use of tobacco cigarettes, or psychosocial factors. A third longitudinal analysis found no significant impact of marijuana on suicide attempt (Agrawal et al., 2017), utilizing a database that assessed an ethnically mixed group of 3277 subjects (30% African American, 70% Caucasian) every two years over a period of 10 years, and encompassed a large age range at study inception, ages 12 to 22. Even early marijuana use (<15 yrs of age) was not significantly associated with subsequent suicide attempt; however, the study was underpowered to detect less than a 1.5-fold increase in risk. Intriguingly, a prior history of suicidal ideation was significantly protective for initiating marijuana use, while prior suicide attempts had no impact on initiating marijuana, though lack of statistical power would have influenced the latter result. Unlike the Silins et al. study, they did not investigate the effect of frequency of use on later suicide attempts. The study adjusted for race, but did not report a separate analysis for Caucasians alone. Yet, a recent data summary of case reports, with no statistical analysis, found that for 303 adults (aged 18 and over) with a self-reported history of marijuana use admitted over a 4 month period to the Emergency Department of an urban hospital, (Marco et al., 2020), 9% had experienced suicidal ideation in the past 30 days (whereas 2.4% has been reported as the one month prevalence in the adult population by Olsson et al., 1998, and 4.6% as the one month prevalence for teens, Turner et al., 2012), and most strikingly, of the 41% who had experienced lifetime suicidal ideation, the timing of their marijuana initiation preceded the onset of suicidal ideation in the vast majority of cases (91%). Of note, the majority did not perceive any harm associated with their use and therefore, were not attempting to excuse mental health problems by revealing marijuana use. Suicidal ideation, however, is not as strong a predictor of subsequent suicide as is a suicide attempt (McHugh et al., 2019; Nordstrom et al., 1995; Hawton et al., 2013). No statistical analysis nor correction for potentially confounding variables was carried out. The subjects were a fairly balanced mix of Caucasians and African Americans, with a small percentage of Hispanics and other groups. Rather than limiting the analysis to a direct effect of marijuana use on subsequent suicidal behavior, the effect of marijuana to trigger mental health disorders (major depression, bipolar disorder and schizophrenia; Miller, 2018) must be evaluated as an indirect mechanism leading to risk for suicide, because such disorders are associated with a much greater risk (7 to 21-fold) during the early stages of illness, even in the absence of marijuana use (Randall et al, 2014). Nussbaum et al. (2011) published a case report concerning a patient whose depression

surfaced after marijuana use began at age 18, eventually leading to polydrug use. In the weeks before the patient's suicide attempt, it was her marijuana use that doubled. For such indirect cases, the temporal sequence would nevertheless be satisfied. Finally, there is some evidence that marijuana can exert an acute effect to increase suicide risk in the short term, where the temporal sequence is more clear. In such cases, the acute effect of marijuana may be more similar to alcohol (Kaplan et al., 2013) than to tobacco (Kassel et al., 2007). Although rates of lifetime suicidal ideation or suicide attempts can be surprisingly high (e.g. Agrawal et al., 2017), the acute risk on any particular day for the general population remains very low; therefore, reports of a temporal sequence of events over a few days or on the same day, carry more meaning. Among marijuana using teens (68% Caucasian), use of marijuana on a particular day is reported to be a predictor of a suicide attempt on that day (Sellers et al., 2019). Lacking more extensive longitudinal research on the issue, case reports and anecdotal evidence can also offer some important insights. Suicidal ideation was observed in one out of fourteen subjects administered a liquid form of pure Δ^9 - THC (20 mg doses) over a period of 3 days in a clinical setting (Gorelick et al., 2011). Russo et al. (2015) observed the onset of suicidal ideation in a patient treating the spasticity of multiple sclerosis with a formulation containing Δ^9 - THC. Multiple sclerosis patients are already at higher risk for suicide, and a similar impact of Δ^9 - THC has been observed in other cases (Langford et al., 2013). Koppel et al. (2014) review reports of suicidal ideation following medical use of cannabinoids. Episodic marijuana use in a patient was found to result in acute suicidal ideation only during the periods of use (Raja and Azzoni, 2009), with a return to normalcy in the intervals of non-use. A Centers for Disease Control MMWR report attributes the intentional and fatal jump of a young college student from a hotel balcony to his recent consumption of a potent marijuana edible (Centers for Disease Control, July 24, 2015). The anecdotal report of a New York Times columnist (Dowd, 2014) describes overwhelming feelings of impending doom that lasted for hours after consumption of a potent marijuana candy bar during her 2014 visit to Colorado, and such feelings could be expected to lead to suicidal urges in those less able to mentally cope. Following Dowd's experience, a young, seemingly very well-adjusted college graduate visiting Keystone in 2016 to ski with his cousin, killed himself after consuming too many marijuana edibles, as reported by Michael Roberts in Westword (March 26, 2015). Roberts also covered the selfstabbing death of Daniel Juarez who was intoxicated from high levels of Δ^9 - THC in his system and the suicide of Brant Clark, which occurred a few weeks after he experienced a psychotic break from marijuana use (Roberts, May 19, 2015).

5. **5) Demonstration of a biological gradient, in which more of the causative agent leads to a poorer outcome: v**

Here, the studies looking at frequency of use show greatest impact with higher use rates (daily use most impactful, inferred from Silins et al., 2014; "heavy use" of greater impact than ever-use in a meta-analysis by Borges et al., 2016). Kahn and Wilcox (2020) provide a more fine-tuned investigation of the impact of frequency of use, investigating marijuana use rates of 1-2, 3-9, 10-19 and 20+ use days per month, and finding an enhanced prevalence of suicide attempt (as compared to nonusers) of 1.65, 2.11, 2.13 and 2.64-fold respectively. The corresponding figures for suicide attempt requiring medical intervention were 1.98, 2.52, 3.15 and 4.51-fold.

6. Demonstration of a biologic rationale, such that it makes sense that the suspected agent causes the outcome: ✓

Bloomfield et al. (2016) reviewed the overall experimental evidence that $\Delta 9$ - THC stimulates the dopaminergic reward system of the brain, and over time, depletes the integrity of the system leading to exhaustion of dopaminergic tone. As this reward system is important to deriving pleasure from everyday life, it is understandable that chronic use of THC may lead to a loss of interest in continuing to live. Several drugs of abuse act on the dopamine reward system (Blum et al., 2015).

7. Coherence of the findings, such that the causation argument is in agreement with what we already know: ✓

Suicide causation is almost always multifactorial (Pandey, 2013; Vijayakumar et al., 2016) and rarely associated with a single cause; therefore, this criterion is satisfied as it is consistent with what is known about other suspected causes, i.e. the impact of chronic marijuana use is thought to be exerted primarily in conjunction with other factors.

8. Experimental evidence: ✓

As stated above: "Suicidal ideation was observed in one out of fourteen subjects administered a liquid form of pure $\Delta 9$ - THC (20 mg doses) over a period of 3 days in a clinical setting (Gorelick et al., 2011). Subjects at already higher risk for suicide may similarly show a temporal relationship between suicidal ideation and administration of formulations containing $\Delta 9$ - THC (Langford et al., 2013). Koppel et al. (2014) review reports of suicidal ideation following medical use of cannabinoids."

9. Evidence from analogous conditions: N/A (see van Reekum et al, 2001)

For neuropsychiatric outcomes, parallels between related neuropsychiatric conditions is not a necessary finding because the response of the brain to different insults is so complex.

Conclusions: All but one (#4) of the seven relevant Bradford Hill criteria have been satisfied for the causal connection between marijuana use and the development of suicidal behavior. The evidence that an "appropriate temporal sequence" exists (outlined in criterion #4) is strongly suggestive though remains unconfirmed from an academic standpoint. Further study is required in the form of longitudinal studies that are prospective in nature. Adequate length of follow-up time and number of assessment intervals, ability to adjust effectively for poly-substance use with respect to timing of use, distinguishing acute from chronic effects, addressing ethnic diversity with respect to outcome and ensuring adequate statistical power should be incorporated in future research paradigms. Nevertheless, the weight of the evidence currently available should be regarded as strong enough to elicit widespread public health warnings about the suspected role of marijuana use in precipitating suicidal behaviors, since the mandate of the relevant authorities is to err on the side of protecting public health rather than to establish scientific certainty beyond a shadow of a doubt. This is particularly urgent in view of the continuing increase completed suicides in conjunction with rising marijuana use rates and more potent products, not only in specific states but across the nation as a whole (Miller et al., 2020).

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