Cannabis and the Gateway Effect

An extract from 'Cannabis: A General Survey of its Harmful Effects'. Mary Brett updated January 2017

The question as to whether cannabis "encourages" the use of other drugs has occupied the minds of researchers for the last 30 years or so. It is a very important one since if true, the use of cannabis would be much more dangerous than the effects of the cannabis use alone.

Tobacco and/or alcohol use in teenagers makes the use of other drugs more likely (Merrill et al, 1994) and the same is true of cannabis. A MORI poll in 1991 found that 50% of smokers had tried an illegal drug compared to only 2% of non-smokers and Califano (2003) concluded that young cigarette smokers were 14 times more likely to try pot. Cigarette smoking was discovered to be an important predictor of both the initiation and persistence of cannabis use. A report published in December 2006 by the Canadian Centre on Substance Abuse "Risks Associated with Tobacco Use in Youth Aged 15-19", an analysis of the data from the Canadian Addiction Survey, 2004, found that 91% of smoking youth reported using cannabis in the past year compared with 28.8% of non-smoking youth. And compared with 3.5% of non-smoking youth, 31% of smokers below 20 (including the 15 to 19 year olds) reported using cocaine, amphetamines, heroin, ecstasy or hallucinogens in the past year.

Professor Denise Kandel and her team in America have researched this subject for many years. Early in her work she found a series of graded steps that most of her subjects followed. There were four: 1.Beer and wine 2.Cigarettes and spirits 3. Marijuana 4. Other illegal drugs (Kandel, 1989).
The younger they started, the further they progressed and the more intense the abuse at any age the greater the risk of progression to the next stage. Of those who had used cannabis more than 1000 times, 90% moved on to other drugs. Between 100 and 1000 it was 79%, dropping to 51% between 10 and 100 times. Even 1 to 9 times usage saw 16% follow this path. Of non-users, only 6% eventually used drugs other than cannabis. (Kandel, 1986).

Among other researchers to discover a link between use of cannabis and use of other drugs are: Aas and Pederson, 1993, Von Sydow, et al 2001 and Brook, et al 1989 (The East Harlem Study of African-American and Puerto Rican 14 year old adolescents). In a large longitudinal study, 36% of a group of 27 to 29 year-olds were found to be dependent on both marijuana and cocaine (Newcomb, 1992). Kleber (1995) said that 60% of young Americans using marijuana before the age of 15 will use cocaine later in life, and those between 12 and 17 who use cannabis are 85 times more likely to use cocaine than non-smokers of the same age.

"The statistical association between the intensity of cannabis consumption and the likelihood of using hard drugs strengthens the case for assuming that there is a causal connection between cannabis smoking and progression to harder drugs, but it does not constitute proof of such a causal link…….. The general impression, then, has been that the imperative role of cannabis in the "stepping stone" model has resisted all attempts to prove it scientifically. On the other hand, a large body of circumstantial evidence has been gathered. It is found time and again that cannabis is a central component of the network of influencing factors that leads to the abuse of hard drugs" (Ramstrom, 2003).

To sum up, support for the gateway effect is as follows: 1. Marijuana users are many times more likely than non-users to progress to hard drug use. 2. Almost all who have used marijuana and hard drugs have used marijuana first (Yamaguchi and Kandel, 1984) 3. The greater the frequency of marijuana use, the greater the likelihood of using marijuana later.

Explanations for the gateway effect include the following:

1. Changes in brain chemistry that may make young people more susceptible.
2. Experiences with cannabis may encourage experimentation with other drugs.
3. Common factors in personality or background.
4. Cannabis use is illegal so supplies come from the illegal market, bringing exposure of young people to drug dealers.

Dr Patrick Dixon in his book The Truth About Drugs (1998), says, “Common sense tells us there is a link…….We know that once teenagers start smoking tobacco it is easier for them to cross the next step and smoke cannabis”. My pupils used to tell me, “Find a smoker and you will find a cannabis user”. The smoking technique has been learned. Dr Dixon also said, “……once someone starts using cannabis it is easier for them to try something else, and for the following reasons:

Desensitisation: “It was a big step at first, but cannabis didn’t kill me – actually I can’t see what all the fuss is about so why not try some other things?”

Targeting by dealer: “My mate offered me some free dope and also had some other stuff he was giving away so I tried both”

Knowledge of supply: “I was thinking about trying something else and I already knew who to ask”.

Drug-taking part of social life: “My friends do things together. We all smoke dope. Someone had something else so for a bit of a laugh we all tried it”

“It is dangerous nonsense therefore to suggest that cannabis use does not significantly increase the risk of a serious drug addiction later on” (Dixon, 1998).

Exactly the same sentiments were expressed to me by an ex-pupil, an ex-user. “Cannabis didn’t seem to have much effect and didn’t harm us so we looked for a bigger and better high. We tried more or less everything that was going except heroin”. (Crack cocaine was not around at the time).

The “personality and background predisposition hypothesis” was explored by Degenhardt and others in 2001. They looked at 201 15 to 16 year olds who had used cannabis at least 40 times. They found 3 “clusters” of heavy users. There was a small group with anti-social behaviour, another with low self-esteem and poor relationships with their parents and friends, the third group were “ordinary”. This last group were the least likely to use other illicit drugs.
Information from 44624 individuals of between 12 and 25 was gathered. These people did not seek out drugs but were “exposed” to the opportunity of taking them at a party or friend’s home. Users of tobacco and alcohol were more likely than non-users to have the opportunity to try marijuana and indeed were more likely to take it. Opportunities to try cocaine were associated with prior marijuana smoking. Among the young people who had a “cocaine opportunity”, those who had used marijuana were more likely to use cocaine than those with no previous history of using cannabis. They also found that by the age of 21, half the teenagers who had smoked marijuana had a chance to try a hallucinogenic drug, LSD, mescaline, PCP or mixed-stimulant-hallucinogens, compared to only 1 in 16 of non-users. Within one year of “exposure” two-thirds of the cannabis-users had tried it, but only 1 in 6 of those who had never smoked cannabis (Wagner and Anthony, 2002).

Two separate twin studies explored the “family environment/genetic influence”.

In 2003, Lynskey and others examined 311same-sex twins (identical and non-identical) in Australia. They were discordant for cannabis use before the age of 17. The twin using cannabis before 17 had odds of other drug use, alcohol dependence and drug use/dependence that were 2.1 to 5.2 times higher than their co-twin who was a non-user of cannabis prior to the age of 17. No significant differences were found between mono- and di-zygotic twins. Controlling for early alcohol or tobacco use, parental conflict/separation, childhood sex abuse, conduct disorder, major depression and social anxiety had negligible effects of the outcome. So common environmental and genetic influences seemed not to be predisposition factors. Association with different peers and the social contexts in which cannabis was used may have some bearing on the results.

2004 Agrawal et al looked at twins. They concluded: Early cannabis use is strongly associated with other illicit drug use and abuse/dependence. The relationship arises largely due to correlated genetic and environmental influences with persisting evidence for some causal influences.

In 2006 Lynskey, again with a team, conducted research into twins this time of Dutch nationality, 219 same-sex pairs, discordant for cannabis use before 18 were used. Covariants were adjusted. The rates of lifetime party drug use, use of hard drugs, but not regular cannabis use, were significantly higher `in

the pre-18 using twin. Again this suggested that the progression seen is not explained by common familial risk factors, genetic or environmental. Different friends or social experiences obviously could play a part.

Professor David Fergusson and his teams have conducted a long-term longitudinal study in New Zealand, The Christchurch Health and Development Study. It has followed 1265 children from birth in the middle of 1977. They have been regularly assessed till the age of 21 with an 80% follow-up (Fergusson et al, 1997, 2000, 2002).

At the age of 18, the associations for the "gateway question" did not appear to be very strong when all other factors were taken into account. However at 21, more data were available and methods of analysis were more advanced. For young 14 to 15 year old heavy consumers a very strong association existed even after controlling for other suspected or known causal factors. It was the first time such a strong connection had been seen (Fergusson et al, 2002). By the age of 21 nearly 70% of the cohort had used cannabis and 26% other drugs. In all but 3 cases, cannabis use came first. Those using cannabis on 750 occasions/year had hazards of other illicit drug use 59.2 times higher than non-users. After adjustments for co-variants, childhood, family and adolescent lifestyle factors, the association was still remarkably strong. Fergusson points out that, "…findings support the view that cannabis may act as a gateway drug that encourages other forms of illicit drug use. Nonetheless the possibility remains that the association is non-causal and reflects factors that were not adequately controlled in the analysis".

In April 2006 Ferguson updated his results. The sequence of events he said could suggest a cause and effect relationship where the use of cannabis encourages the use of other illicit drugs. He points out that it has often been suggested that associations between cannabis and other illicit drug use arise from common factors that predispose young people to using cannabis and other drugs. However, he says, this study applied complex statistical methods and controls and still found a clear tendency for those using cannabis to have higher rates of usage of other illegal drugs. It was most evident for regular users and more marked in adolescents than young adults.

Looking for a neurophysiological explanation rather than a psychosocial mechanism, the phenomenon of sensitisation, an "inverse tolerance effect" was suggested as long ago as 1999 by Torngren. This is the process by which an addictive substance increases a person's sensitivity to the exhilarating effects of that substance. This process exists in humans and has been shown in animals. Exposure to one substance e.g. cannabis, should be able to make a person more sensitive to another substance like heroin (cross-sensitisation). At the moment, he said, this remains hypothetical reasoning.

Professor Heather Ashton, Emeritus Professor of Clinical Psychopharmacology at The University of Newcastle-on-Tyne, puts forward mechanisms for the association which may favour a causal role for cannabis. They are:
1. Tolerance to the "high" leading users to seek more potent drugs.
2. Withdrawal symptoms being alleviated by the use of other drugs.
3. Interaction of cannabinoids with the endogenous opioid systems which have been shown in animals to increase the rewarding properties of opioids such as heroin.

(Ashton 2002)

Professor Robin Murray of The Institute of Psychiatry in London commented (The Daily Telegraph 18/06/05), " Clearly it needs to be replicated but there is already evidence that, in animals, cannabis and amphetamine show cross-tolerance. So that rodents given THC, the active ingredient of cannabis, show greater effects when given amphetamine".

A 2006 paper by Maldonado, Valverde and Berrendero has shown that the endocannabinoid system (neurotransmitters mimicked by THC) is involved in the common neurobiological mechanism underlying drug addiction in three ways.

1. The system participates in the primary rewarding effects of nicotine, alcohol, opioids and cannabinoids through the release of endocannabinoids in one part of the brain (the ventral tegmental area).
2. Endocannabinoids are also involved with motivation to seek drugs through a dopamine-independent mechanism (this has been demonstrated for psychostimulants and opioids).

3. The common mechanisms responsible for relapse into drug-taking behaviour also include the participation of endocannabinoids. This is done by mediation of the motivational effects of drug-related stimuli in the environment and exposure to drugs.

Professor Yasmin Hurd (2006) warns that the human brain is not fully developed till around the age of 25. Chronic periodic use of cannabis can interfere with the development of rat brains. She says, "The developing brain is definitely more sensitive". After training rats to self-administer heroin by pushing a lever, rats exposed to THC took more heroin than those not previously exposed to it. They were more sensitive to lower concentrations of heroin and took more in response to stress. Her conclusion reads: The current findings support the gateway hypothesis demonstrating that adolescence cannabis exposure has an enduring impact on hedonic processing resulting in enhanced opiate intake, possibly as a consequence of alterations in limbic opioid neuronal populations".

The December 2006 edition of Alcoholism: Clinical and Experimental Research carried an article about smoking among adolescents and an increased risk of developing alcohol-use disorders. Results indicate that smoking "primes" the brain for subsequent addiction to alcohol and possibly other drugs. Almost 75,000 adolescents and young adults were randomly selected for the study by Grucza and Chen. Typically teenage smokers had a 50% higher risk of developing an alcohol-use disorder (a range of problems including alcohol abuse and alcohol dependency). Grucza said, " Addictive drugs all act on a part of the brain that is described as the central reward circuitry. Once this system is exposed to one drug, the brain may become more sensitive to the effects of other drugs, as demonstrated by a number of rodent studies. Our results are in line with an emerging literature that shows adolescence may be a unique window of vulnerability for addiction".

In February 2007 a Swedish paper by Ellgren set out "to determine whether cannabis exposure during periods of active brain development alters reward-related behaviour and neurobiology for psycho-stimulant and opioid drugs by the use of animal models". Results did not support the cannabis gateway hypothesis in relation to subsequent psycho-stimulant use but did support it in relation to opioids. The typical pattern of intermittent use by adolescents was mimicked and discrete opioid-related alterations were revealed in brain regions highly implicated in reward and hedonic processing. This was coupled to increased heroin intake in a self-administration paradigm, and increased morphine conditioned place preference, indicating altered sensitivity to the reinforcing properties of opioids. In the limbic region, there were pronounced alterations in endocannabinoid levels in cognitive brain areas even though alterations were also apparent in reward-related regions. Pre-natal exposure induced discrete opioid-related alterations within brain regions highly implicated in reward and hedonic processing.

They concluded, "Taken together, this thesis presents neurobiological support for the cannabis gateway hypothesis in terms of adult opiate, but not amphetamine abuse, with underlying long-term disturbances of discrete opioid-related systems within limbic brain regions".

In the light of all the evidence, it is obvious that every effort must be made to try to prevent vulnerable children from ever starting to use cannabis, not least because of the potential damage done by cannabis itself.

October 23 2007 brought a report from The National Center on Addiction and Substance Abuse at Columbia University. (CASA), "Tobacco: The Smoking Gun". They found that "Compared to 12 to 17 year olds that don't smoke, those who do are more than 5 times likelier to drink and 13 times likelier to use tobacco than non-smokers. Those who begin smoking at age 12 or younger: More than three times likelier to binge drink; nearly 15 times likelier to smoke marijuana and nearly 7 times likelier to use other illegal drugs such as heroin and cocaine". The nicotine poses a significant danger of chemical and structural changes in the developing brain. This can make a teenager more susceptible to alcohol and other drug addiction and mental illness.

A paper by Patton et al in 2007 found in a 10-year 8-wave cohort study of 1943 Victorian children, originally 14 to 15, that heavy (daily) teenage cannabis users tend to continue selectively with cannabis use. "Considering their poor young adult outcomes, regular adolescent users appear to be on a problematic trajectory."

In 2008 (April) Fergusson et al updated their findings from The Christchurch Longitudinal Study. Their results showed that "Illicit drug use and abuse/dependence from ages 16 to 25 were significantly

associated with a range of parental adjustment measures; exposure to abuse in childhood; individual factors; and measures of childhood and early adolescent adjustment. Analyses…suggested that parental illicit drug use, gender, novelty-seeking and childhood conduct disorder predicted later illicit drug use and abuse/dependence. Further analysis revealed that these pathways to illicit drug use and abuse/dependence were mediated via cannabis use, affiliation with substance-using peers, and alcohol use during ages 16-25". In their conclusion they said, "the use of cannabis in late adolescence and early adulthood emerged as the strongest risk factor for later involvement in other illicit drug use".

2010 June 2010 Melberg et al (Norwegian researchers) tested the "gateway" hypothesis. 'The model they chose suggests two distinct groups; a smaller group of "troubled" youths for whom there is a statistically significant gateway effect that more than doubles the hazard of starting to use hard drugs, and a larger faction of youths for whom previous cannabis use has less impact'.

2010 A study from Australia by Degenhardt et al found that occasional cannabis use in adolescence predicts later drug use and educational problems. Nearly 2000 secondary school pupils were followed from 14.9 to 24 years of age. Those who continued cannabis use into early adulthood had higher risks of later adult alcohol and tobacco dependency and illicit drug use, as well as being less likely to complete a post secondary qualification.

2011 (July) Swift et al found that quitting cannabis in your twenties cuts progression to other drugs. Use of cannabis declines among Australians throughout their twenties but those who are still using are more likely to be weekly users or even more frequent. They have an increased risk compared with occasional users. Weekly users – risk of other illicit drugs – 2 to 3 times, daily – 6 times as likely to smoke tobacco and less likely to give up all others except cocaine. Nearly 2000 Victorian secondary school pupils followed for 13 years, from 1992. Six, six monthly intervals, then 20-21, 24-25, and 29. While overall decrease (age 20 – 58% to only 29% at 29) in cannabis use in young adults, number of those who use weekly/daily almost doubled. Among non-users, use of amphetamines, cocaine or ecstasy virtually non'existent.

2011 November Levine et al looked at nicotine as a gateway drug. Epidemiological evidence has pointed to the fact that most illicit drug users report use of tobacco or alcohol prior to illicit drug use. The aim was to discover a possible biological mechanism by which nicotine exposure increases the vulnerability of people to illicit drug use. Mice exposed to nicotine in their drinking water for at least 7 days, showed an increased response to cocaine. The nicotine changes the DNA structure, re-programmes the expression pattern of specific genes especially the FosB gene that has been related to addiction and so ultimately alters the behavioural response to cocaine. The 2003 Nat Epidemiological Study of Alcohol-related consequences was examined. The rate of cocaine dependence was higher among cocaine users who smoked prior to cocaine use than those who tried cocaine first before smoking. 'Now that we have a mouse model of the actions of nicotine as a gateway drug, this will allow us to explore the molecular mechanisms by which alcohol and marijuana might act as gateway drugs' said Kandel, 'in particular if f there is a single common mechanism'.

2012 Mayet looked at the influence of cannabis use patterns on the probability of subsequent initiation with other illicit substances among French adolescents. 29,393 teenagers were studied. All possible pathways were modelled from initial abstinence to cannabis initiation, daily cannabis use and OID (other illicit drugs) initiation. The model was adjusted for tobacco and alcohol use. The risk for OID initiation was 21 times more with experimenters, 124 times higher among daily users than non-users. Tobacco and alcohol were associated with a greater risk of moving on to cannabis.

2012 September. Agrawal looked at 3797 sets of twins in Australia and siblings between 21 and 46 to find out whether cigarette smokers were at increased likelihood of early opportunity to use cannabis and early onset of cannabis use. They found that regular users were more likely to report an earlier opportunity to use cannabis and early onset of cannabis use. Conclusion: These findings indicate that the well-known overlap in cannabis and cigarette smoking behaviours may evolve as early opportunity to use and extend through the course of the substance use trajectory.

2013 Fiellin found that 'previous alcohol, cigarette and marijuana use were each associated with current abuse of prescription opiods in 18-25 year old men, but only marijuana use was associated with subsequent use of prescription opioids in young women'.

2013 Palamar . Data was obtained from over 29,000 high school seniors who took part in the 'Monitoring The Future' Survey. He found that youths who smoked cigarettes or used more than one hard drug were consistently less critical of other drug use. The lifetime use of alcohol had no impact on peoples' attitudes. Those who used only marijuana were less judgemental of further using of such so-called socially acceptable drugs such as LSD, amphetamines and ecstasy. They did not approve of crack, cocaine or heroin. Females and religious people had much less approval of drug use. Youths from more advantaged socio-economic backgrounds with highly educated parents and those who live in urban areas were much less disapproving of the so-called 'less-dangerous' drugs.
Black students are less disapproving of powdered cocaine, crack and ecstasy. They use this type of drug less than white people. This could be influenced by their strong religion and higher rates of arrest and incarceration than whites which may act as a deterrent.

2014 Tzilos et al investigated co-occurring drug use among marijuana users. 1075 'emerging adults' were studied. Daily marijuana use was associated with a significant increase in the expected odds of opiate, cocaine, stimulant, hallucinogen, inhalant and tobacco use. They may be vulnerable to additional negative consequences associated with poly-substance use.

2014 Secades-Villa et al looked at the 'gateway' effect of cannabis. 6624 participants who had used cannabis before any other drug (Wave 1 of The National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Lifetime cumulative probability estimates that 44.7% of individuals with lifetime cannabis use progressed to other illicit drugs at some time in their lives. There was an increased risk of progression amongst those with mental illness disorders.

2015 Szutorisz et al found that rats, whose parents had been exposed as adolescents to the main psychoactive ingredient in marijuana (THC) sought heroin more vigorously than the offspring of unexposed animals. This suggests that a parent's history of drug abuse, even preconception, may affect a child's brain function and behaviour. It was thought that these alterations in the THC-exposed rats' offspring may be due to epigenetic factors.

2015 May, Badiani et al looked at tobacco and cannabis use for evidence of reciprocal causal relationships, using date from the Christchurch Health and Development Study (CHDS). Significant associations between the extent of cannabis use and tobacco smoking and vice versa, after controlling for non-observed fixed confounding factors and for a number of time-dynamic covariate factors (major depression, alcohol use disorder, anxiety disorder, stressful life events, deviant peer affiliations) were found. Furthermore, increasing levels of tobacco smoking were associated with increasing cannabis use and vice versa over time. The results lend support to the notion of both of 'gateway' and 'reverse gateway' effects. That is, the association between tobacco and cannabis use arises from a reciprocal feedback loop involving simultaneous causation between tobacco use disorder and cannabis use disorder.

2016 Weinberger et al found that marijuana users were 5 times more likely to develop an alcohol use disorder, alcohol abuse or dependency. The researchers analyzed data from 27,461 adults enrolled in the National Epidemiologic Survey on Alcohol and Related Conditions who first used marijuana at a time when they had no lifetime history of alcohol use disorders. The population was assessed at two time points. Adults who had used marijuana at the first assessment and again over the following three years (23 percent) were five times more likely to develop an alcohol use problem, compared with those who had not used marijuana (5 percent). Adult problem drinkers who did not use cannabis were significantly more likely to be in recovery from alcohol use disorders three years later.

2016 Blanco et al looked at cannabis use and the risk of psychiatric disorders. Respondents in the US aged 18 or over, mean age 45.1 years, were interviewed 3 years apart. Cannabis use in 'wave 1' (2001-2) reported by 1279 respondents, was significantly associated with substance use disorders in 'wave 2' (2004-5). Any substance use disorder OR (Odds Ratio) 6.2, any alcohol use disorder OR 2.7, any cannabis use disorder OR 9.5, any other drug use disorder OR 2.6 and nicotine dependence OR 1.7. No

mood disorder OR1.1 or anxiety disorder OR 0.9. Cannabis use is associated with an increase for several substance use disorders.

2016 Osborne analysed information from more than 11,000 children (10-18) from 10 American cities. They were asked whether they had used prescription opioids in the last 30 days and whether they had ever used cannabis. About 29% said they had used cannabis at some point in their lives, but among the 524 participants who had used prescription opioids in the last 30 days, nearly 80% had used cannabis. Among those who had used non-prescription opioids, about 88% had used cannabis compared to 61% who had had it prescribed. Teens reporting opioid use as well as alcohol and tobacco were much more likely to have used cannabis. The opioid users using alcohol were nearly 10 times more likely to have used cannabis, and those who currently smoked tobacco were 24 times more likely to have used cannabis. More males were at risk than females.

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