# Cannabis and Mental Illness (Psychosis/schizophrenia) and Brain Damage

## An extract from Cannabis: A General Survey of its Harmful Effects
## Mary Brett updated June 2019

Cannabis – some very old papers:

Let's take a look at what physicians from a time untainted by politics, drug morality, or profit motive had to say about cannabis risks:

"In large doses it will produce hallucinations, which, in some, are of merriment and in others of a violent nature, even tendency to crime… Its habitual use will cause insanity"

*Materia Medica and Clinical Therapeutics*, by Fred Petersen, published in 1905
The most common effect, however, is the development of insanities which have been known for many years… Chronic mania and dementia represent terminal stages"

*A Textbook of Materia Medica, Pharmacology and Therapeutics*, by George F. Butler, published in 1908
"Repeated use of the drug produces mental weakness and [mental] impotence, the result of over-stimulation."

*A Compend of Materia Medica, Therapeutics, Prescription Writing: With Especial Reference to the Physiological Actions of Drugs*, by Samuel O.L. Potter, published in 1890
"Sometimes the delirium induced by hemp causes the individual to do deeds of violence, but does not act upon all alike… The after-effects are those of depression."

*Materia Medica and Therapeutics for Physicians and Students*, by John Biddle, published in 1895
"Hallucinations occur, but they are not usually agreeable; they are often painful and are replaced by stupor… Not unfrequently the excitement takes the form of a furious delirium, in which acts of violence are committed – whence the name 'haschaschins,' or assassins, applied to the unfortunate hashish-eater who, under the influence of the drug, commits murder… Dilatation of the pupil, and disorders of vision, which contribute to the hallucinations by distortions of external objects, are produced by hemp"

*A Practical Treatise on Materia Medica and Therapeutics*, by Roberts Bartholow, published in 1893
"There is often a disposition to laugh, sing, shout, or dance, or to do some other extravagant act; but, in other instances, the excitement betrays itself in a quarrelsome temper or deeds of violence… Occasionally, a species of intoxication is induced, with hallucinations or complete delirium… Among those who use it habitually, it is said ultimately to impair the mental faculties"

*A Treatise on Therapeutics, and Pharmacology, or Materia Medica*, by George B. Wood, published in 1868

The first paper to link cannabis and psychosis was published in 1845 by Moreau de la Tour, a French psychiatrist: https://www.preventteendruguse.org/
https://archive.org/details/duhachischetdela00more/page/n6

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Although I welcomed the comments about cannabis made by Tony Blair just before the election, and his recognition of the dangers it poses, I was angered to hear him say to John Humphrys on the Today programme (May 4th 2005), in reference to the down-classification debacle, "It was worth seeing what happened". Was this just some huge experiment conducted primarily on our vulnerable young people? How many of them would, prior to down-classification, ever have been tempted to try the drug but given the "green light" by this government, now find themselves with a psychiatric problem, perhaps for life. We shall never know.

There is much talk about whether cannabis actually *causes* psychosis or schizophrenia. There are 2 points about this argument.

Firstly, to quote from the Report of an ARF (Addiction Research Foundation)/WHO scientific meeting in Toronto as long ago as 1981 on adverse health and behavioural consequences of cannabis use. “It is instructive to make comparisons with the study of effects of other drugs, such as tobacco or alcohol. With these drugs, “risk-factors” have been freely identified, although full causality has not yet been established. Nevertheless such risk-factors deserve and receive serious attention with respect to the latter drugs. It is puzzling that the same reasoning is not often applied to cannabis”. …. “To provide rigid proof of causality in such investigations is logically and theoretically impossible, and to demand it is unreasonable”.

And in March 2006, Harrison Pope, a professor of psychiatry at Harvard Medical School, said that in most aspects of science, the only way to answer a question once and for all is to do a randomized, controlled trial of 100 people or more. But since giving people marijuana in a clinical setting poses a rather formidable dilemma he and other psychiatrists must fall back on messy methodology.

Secondly, there is ample undisputed evidence that cannabis exacerbates the course of schizophrenia and triggers it at an earlier age than would have been the case. It also causes a toxic psychosis recognized as a diagnostic unit in the DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders.

When you have young people suffering from a psychiatric illness, that would never have manifested itself if he or she had not taken the drug, then cannabis is certainly a contributing factor, whether or not they may have had a genetic predisposition. As new studies emerge, the evidence that cannabis may actually *cause* schizophrenia becomes ever stronger, see the most recent in the updated section at the end of the chapter.

Robin Murray and John Witton of The Institute of Psychiatry, London, in their paper, “Reefer madness revisited: cannabis and psychosis” March 2004, said, “The public health message is clear. Some cases of psychotic disorder could be prevented by discouraging cannabis use, particularly among psychologically vulnerable youths, with the youngest cannabis users most at risk…..action is needed to avoid a further burden on already over-stretched mental health services”.

When BSE became a problem, in spite of the fact that the government had no real idea how the disease was transmitted, beef-on-the-bone was banned. “We must err on the side of caution”, said a spokesman at the time. Indeed we must. Why were they so incautious in the case of cannabis classification?

It is ironic that the USA whose drug tsar John Walters’ strong prevention messages are seeing a consistent year-by-year drop in drug use, invited a British scientist, Professor Neil McKeganey, Professor of Drug Misuse Research, Glasgow University, to speak at a conference on May 3rd 2005, when our previous Home Secretary, David Blunkett, before down-classification, consistently refused to see a group of 6 eminent British scientists, all experts in the field of drugs.

In 2004 I was asked to speak to a group of parents, all of whom had children who were psychotic or schizophrenic. All the youngsters had previously used cannabis. There was no doubt whatsoever in the minds of these parents what had caused their children to become ill. They were incensed that no one had ever warned them of the dangers of this harmful drug. They kept me talking and answering questions for 3 hours. I think it was one of the most emotional and disturbing evenings I have ever spent.

There has been a 22% increase in the number of hospital admissions of cannabis users with mental illness since down-classification in the UK. In the year April 2003-04, the number of admissions was 710, up from 580 in each of the two previous years. In the same period, admissions caused by the abuse of other drugs including heroin and alcohol fell. The exception was cocaine which rose by 16%. I thought that one of the reasons for down-grading cannabis was to free up police time to combat the harder drugs. On April 25th 2008, in answer to a parliamentaruy question from Graham Brady MP, updated figures for admiision to hospitals with mental illness were given. In 2003/4 40,763 people in England were admitted for primary or secondary diagnoses of schizophrenia, in 2006/7 it was 45,955, an increase of 12.7%. For psychosis, the increase was 20.8%, from 176,776 to 213,624. Since 2001, the year in which the intention to downclassify was suggested, the figures for schizophrenia have risen by 24% and those for psychosis by 42%.

On January 23rd 2005, The Herald (Scotland) reported that numbers of hospital discharges after treatment for cannabis-related problems had more than trebled in The Lothians and doubled in the Greater Glasgow Health Board Area. According to police figures, the number of under-16s at the end of 2004 charged with supply or possession of drugs had risen by 13%. Some were only 10 years old.

Professor Peter Jones of Cambridge University, one of Britain's leading psychiatrists and an expert in schizophrenia, addressing an Institute of Psychiatry (London) Conference on 28th November 2005 said, "Cannabis is a huge issue for psychiatric services at this moment. I work in a first-contact schizophrenia service and it might as well be a Cannabis Dependency Unit". He warned that children of 10 or 11 who start smoking the drug could be trebling their risk of schizophrenia. He said that 80% of first episode psychiatric disorders, schizophrenia or schizophrenia-like illnesses occurred in either heavy users of cannabis or cannabis dependents. " I think this is an iceberg effect", he said, "If you were able to measure the toll on GCSE results, A level results, training and social development, we would have a much bigger number of deleterious effects".

Professor Robin Murray of the Institute of Psychiatry in London, who has done so much to draw attention to the links between cannabis and mental illness, took part in a Radio 4 You and Yours programme on 30th December 2004. When asked if he would say that cannabis is one of the biggest problems facing psychiatric wards, replied, "I've been saying it for some time. It's worse now, it's *very* difficult to convince patients that cannabis is causing their problems. They say that's not what the *government* says. Their general understanding is that it is safe".

He ended the programme by saying that Mental Health Services are overwhelmed. People are arriving with cannabis psychosis. They don't get good treatment, nor do these with problems unrelated to cannabis. Mental Health Services in big cities cannot cope. He had recently talked to 100 psychiatrists and asked whether any of them would invite relatives or friends in to see their units. Only *one* would be prepared to do this. "We are awash with mental health problems" he said, " and cannabis is a big contributor".

In a letter to The Guardian 19th January 2006, Professor Murray said, "The mistake was that in its 2002 report, The Advisory Council on the Misuse of Drugs denied that cannabis was a contributory cause of schizophrenia, continued to deny this for the next two years and thus mislead ministers into repeatedly stating that there was no causal link between cannabis and psychosis". On 8th October 2006, he said, "Five years ago, 95% of psychiatrists would have said that cannabis doesn't cause psychosis. Now, I would estimate that 95% say it does. It's a quiet epidemic".

On November 4th 2006 The Manchester Evening News carried a report that "Cannabis raids help patients".
Mark Holland, a senior health worker of 26 experience in the NHS as a consultant nurse and senior member of the Manchester Mental health and Social Care Trust, said, " I have definitely noticed a change in many of my clients. …I tell them their symptoms seem a bit milder because they haven't had a joint" Across Manchester there has been a drop in the number of people needing hospital treatment for acute psychotic episodes – one of the first falls in several years. Greater Manchester Police have been taking part in Operation keymer, set up to target hundreds of cannabis factories across the country, focusing particularly on the powerful "skunk" variety.

BBCNews carried a story on May 7th 2007 that admissions to mental health hospitals in England due to cannabis use had risen by 85% between 1996 and 2006. I 1996/7 there were 510 admissions, this rose to 946 in 2005/6. This was given in an answer to a parliamentary question from Andrew Lansley, Shadow Health Secretary. In the last 5 years alone, the rise was 65%. "This is the tip of the iceberg" said Professor Murray. He added that cannabis use was a contributory cause of up to 10% of cases of schizophrenia yet this was unrecognized.

I have therefore attempted to make a list of scientific studies on cannabis and psychosis and to make it available to anyone with an interest in this important subject.

The following list is not in any way meant to be comprehensive. As I researched this subject more and more thoroughly I uncovered literally dozens of other publications. I think I have mentioned all of the

most important ones, apologies to the authors of those I have not included but the literature and messages are there for anyone to access.

In the last few years increasing concern has been expressed about the association of cannabis with mental illness. The number of cannabis users is going up. In the USA in some age groups, almost as many people are smoking cannabis as cigarettes. Children are starting to use the drug at an increasingly early age, more and more studies are emerging which link cannabis use with psychological and social problems, demand for treatment for cannabis users is rising and there is a change in the THC content of some cannabis varieties. Selectively bred strains such as skunk and nederwied (netherweed) have much greater percentages of THC than did the marijuana of the sixties and seventies.

Jan Ramstrom, the Swedish psychiatrist and expert on substance abuse who wrote Adverse Health Consequences of Cannabis Use (2003) said, "At present we find ourselves in a curious situation where researchers and clinicians are becoming even more concerned, while the general public, not least in Europe, seems to grow less concerned".
He also said, "It is worth mentioning that the opiates (heroin etc), apart only from the development of dependence, produce far fewer toxic psychiatric complications than do cannabis preparations"

Two fundamentally different psychotic manifestations are involved.

Toxic psychosis: Cannabis-induced psychotic disorder, recognized as a diagnostic unit in the DSM 1V (Diagnostic and Statistical Manual of Mental Disorders) is caused by the toxic effects of the drug and involves a group of brain damage syndromes. The symptoms are caused by cannabis consumption and subside when drug use ceases. The use of anti-psychotic medicines to eliminate any residual symptoms means most patients make a full recovery unless he or she resumes the taking of cannabis or indeed other drugs. Symptoms of delirium often dominate, i.e. bewilderment and memory disturbance. Paranoia, hallucinations and aggression alternating with euphoria also occur. There is usually an absence of any heredity factor.

Functional psychosis: "Functional" in this sense applies to the absence of organic damage. Cullberg 2000, said that there probably is some organic damage, possibly taking the form of some subtle vulnerability as yet unknown. This category covers schizophrenia and schizophrenia-like psychosis which usually runs a chronic course. Symptoms of delirium are absent and there is often a feeling of outside interference with thought. Often the person has a "premorbid personality" with extreme reserve, loss of interest and bizarre suspicious ideas.

To quote Jan Ramstrom again, "…what we are dealing with here are the most profound disturbances known to psychiatry; even when they are short-lived, such disturbances can leave marks on those affected and on their families which may remain for many years or even be of life-long duration.…..there is both an abuse condition and a serious mental disorder. These "dual disorders" are among the most difficult to assess in the whole of psychiatry. Moreover, conditions of this type not rarely make demands on the most costly resources available in the field of psychiatric care".

French psychiatrist, Moreau de Tours 1845, first reported acute psychotic reactions in himself, students and patients after taking cannabis. Some of these were short-lived, lasting a few hours but some up to a week.

## Early Studies.

Papers as early as the 1970s saw researchers connecting cannabis consumption with psychosis.

1972. Tennant and Groesbeck studied American soldiers in Europe and found large numbers abusing drugs mostly hashish. Between 1968 and 1971, the number of acute psychotic reactions, not necessarily leading to schizophrenia increased from 16 in 1968 to 77 in 1971, an almost 5-fold increase in 4 years. They concluded that hashish smoking was the major contributor.

1974. Chopra and Smith described 200 patients admitted to a Calcutta psychiatric hospital between 1963 and 1968 with psychotic symptoms following cannabis use. Most cases were preceded by the ingestion of large quantities. One third had no previous psychiatric history and the symptoms were the same regardless of their history. The most potent cannabis preparations resulted in psychotic reactions

in the shortest period of time.

1974. DA Treffert allowed 4 schizophrenic patients, all on anti-psychotic medicine to act as their own controls. Having been warned not to, all of them smoked cannabis occasionally. All of them experienced deterioration in their condition, sometimes with very serious consequences. This clearly demonstrated that there was a direct association between relapses into pot smoking and serious deterioration in the schizophrenia condition.

1974. Breakey and others pointed to some sort of association between drug use, including cannabis, and the onset of schizophrenic illness. He considered that cannabis and other drugs could precipitate latent schizophrenia, but also thought that cannabis could do this in cases where the illness would not occur otherwise. They based this conclusion on the fact that the drug induces schizophrenia on average 4 years earlier than the onset in other types of schizophrenia. The onset was also more sudden, and the premorbid personality always better than a comparative group of non-drug using schizophrenics.

1976. Thacore and Shukla made a clear attempt to demonstrate the occurrence of a specific cannabis-provoked functional psychosis.

Other papers around this time, giving support to the findings include, Talbott and Teague 1969, Weil 1970, Bernardson and Gunne 1972 and Harding and Knight 1973.

So even as long ago as the early seventies some researchers were trying to ring alarm bells about the possible psychological problems of cannabis use.

**The eighties** brought another crop of papers on the subject.

1981. MB Holmberg found that 10% of 16 year-old consumers of large quantities of drugs, almost exclusively cannabis, by the age of 27, would have a record of psychosis. This was much higher than the 3% in the normal population.

1985. Bier and Haastrup looked at psychological admissions over one year in a Copenhagen hospital. Thirty patients had cannabis-provoked psychosis. They then estimated that 15 in a population of 100,000 would be admitted each year with psychosis either precipitated or caused by cannabis.

1986. Negrette and others concluded that interaction between cannabis smoking and schizophrenia had the following characteristics. Cannabis smokers have more relapses, more hospital visits, the positive symptoms of schizophrenia are more dramatic and the patients are less susceptible to neuroleptic medication.

1986. Ghodse said there was clear evidence from countries where heavy cannabis use is common, that cannabis causes a short-term toxic psychosis. This was supported by laboratory experiments.

Among the large body of reports from researchers and clinicians at this time are the following: Palsson, Thulin and Tunving 1982, Rottamburg et al 1982, Tsuang et al 1982, Carney 1984, Brook 1984, Tunving 1985 and Hollister 1986.

However the most important publication at this time was the large study of Swedish conscripts by Andreasson, Allebeck et al in 1987.

Forty-five thousand conscripts had their drug-taking details taken at entry, aged 18 or 19. The levels of schizophrenia were then recorded over the next 15 years. Those on admission who claim to have taken cannabis on more than 50 occasions were found to be 6 times more likely to be diagnosed with schizophrenia in the following 15 years than those who had never consumed the drug. When confounding factors were taken into account, the risk became smaller but remained statistically significant.

Although the study attracted some criticisms, Negrette, the doyen in this field judged the connection to be reasonable taking other previous studies into account, while accepting there were some weaknesses. Andreasson in 1989 and Allebeck in 1993 strengthened their position by further research. They examined the medical records of 112 cannabis-dependent and schizophrenic patients. The findings in

all significant respects confirmed the original study.

Further support came from the analysis of records of 100 schizophrenic patients between 1973 and 1977 randomly chosen by Dalman et al in 2002. A large measure of consistency was established with respect to regions, hospitals and timescale as well as the diagnostic criteria for schizophrenia, DSM-1V.

Over twenty years later in 2002, Zammit and others re-analysed the results. In the light of new research into the development of schizophrenia, they were able to discount more of the original objections.

## Research continued in the nineties.

1990. Tien and Anthony conducted an epidemiological analysis of drug and alcohol use and concluded that there was an association between cannabis use and psychosis. Daily use over a year suggested a 2.4 times greater risk than non-users, any use related to a risk of 1.3 times. The daily risk figure remained significant after adjustment for other substance abuse and baseline psychiatric diagnosis.

1991. Chaudry et al studied cannabis psychosis following bhang ingestion. Bhang drinkers in Pakistan were found to have mania and paranoid features. Treated with anti-psychotic medicines, the majority recovered completely in 5 days. None had residual symptoms.

1991. Johnson, from his own long experience and a review of the current literature, estimated that 10% of all of those who had used cannabis more than once, experienced either delirium or psychosis. Later estimates confirmed this figure, notably Thomas in 1996 who sent questionnaires to young New Zealanders. Johns as recently as 2001 supported this claim.

1995. Wylie observed a group of British consumers of Dutch cannabis with a high THC content. He recorded a “wave of psychosis and confusional states”. The risk therefore becomes greater the more often cannabis is used and the greater its strength.

1998. Hall concluded that cannabis can cause psychotic like symptoms during intoxication, can lead to a “cannabis psychosis” to increase the relative risk of schizophrenia, and affect the clinical course of established schizophrenia.

Other studies which deserve mention are: Thornicroft 1990, Eikmeir et al 1991, Mathers et al 1991, Rolfe et al 1993, Kristensen 1994, McBride and Thomas 1995, Castle and Ames 1996, Hambrecht and Hafner 1996 and Fowler 1998.

A paper by J Giedd et al in 1999 on development of the adolescent brain must be mentioned here. They conclude that the brain does not finish its development till the mid twenties or beyond. So the warning is that drug abuse could alter the normal course of the maturing of the brain in the teenage years. Research by Giedd on this subject is on-going.

## Since the year 2000 there has been a flood of publications.

2000 Wilson et al looked at brain morphology and early marijuana use. *Results*. There are three primary findings related to age of first use of marijuana. Subjects who started using marijuana before age 17, compared to those who started later, had smaller whole brain and percent cortical gray matter and larger percent white matter volumes. Functionally, males who started using marijuana before 17 had significantly higher CBF than other males. Both males and females who started younger were physically smaller in height and weight, with the effects being greater in males. *Conclusions*. These findings suggest that the age at which exposure to marijuana begins is important. Early adolescence may be a critical period for effects that are not present when exposure begins later. These results are discussed in light of reported effects of marijuana on gonadal and pituitary hormones.

2002. Louise Arsenault et al assessed 1100 New Zealand children at 11, 15, 18 and 26. Young adults smoking cannabis at the age of 15 were at a greater risk of developing schizophrenia or a schizophrenia-like illness by the age of 26. The risk was 10% times compared to 3% for non-users. Use at 15 was a stronger risk factor for schizophreniform disorder than use by the age of 18.

2002. The Nemesis Study by Van Os et al studied 4045 psychosis-free Dutch people and 59 who had a psychotic disorder, taken at random from 60 localities. They concluded that it must be considered proven that smoking cannabis can provoke a functional (non-toxic) schizophrenia-like psychosis. They replicated the Swedish study of Andreasson. It was of shorter duration and had fewer participants, but not the weaknesses. There was a baseline assessment and 2 follow up sessions, after 1 and 3 years, by questionnaire and clinical interviews. The study showed that individuals using cannabis at baseline were almost 3 times more likely to manifest psychotic symptoms at follow up. After confounding factors were taken into account the risk remained significant. A dose-response relationship was also found. The risk factor for the heaviest users rose to 6.8.
They concluded: "cannabis use is an independent risk factor for the emergence of psychosis in psychosis-free persons and that those with an established vulnerability to psychotic disorders are particularly sensitive to its effects, resulting in poor outcome".

2002. Nunez and Gurpegui compared 26 patients with cannabis-induced psychosis to 35 with acute schizophrenia. All used cannabis, they were repeatedly urine tested. They concluded that cannabis when continuously and heavily used can induce a psychotic disorder distinct from acute schizophrenia.

2002. Hiroshi Ujike found genetic abnormalities in the genes for the cannabinoid receptors on the brain cells of schizophrenics compared to non-schizophrenics. This implies a potential malfunction of their marijuana-linked circuitry, perhaps making them more vulnerable to schizophrenia.

Many people have argued and it seems logical that if the use of cannabis has increased then so must the incidence of schizophrenia.

2003. Boydell et al found that there was indeed a continuous and statistically significant rise in the incidence of schizophrenia between 1965 and 1997. It had doubled over the last 3 decades. The increase was greatest in people under 35.

2002. In a survey of 3142 prisoners, it was found that, first use of amphetamines or cocaine before the age of 16 and severe cannabis or cocaine dependence were related to an increased risk of psychosis. Severe dependence on heroin was associated with a reduced risk of this classification (Farrell et al 2002).

2002 Zammit et al followed up the Swedish Conscript study of 1969/70.

**Abstract:** *Objective*. 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.

2003. The Christchurch Health and Development Study. Fergusson et al looked at 1200 children from birth to the age of 21. The cannabis-dependent youngsters developed psychotic symptoms more often than those who were non-dependent. Individuals with cannabis-dependence disorder at 18 had a 3.7-fold increased risk of psychosis than those with no dependence disorder. At 21 the risk fell to 2.3 times.

They conclude that: “the findings are clearly consistent with the view that heavy cannabis use may make a causal contribution to the development of psychotic symptoms since they show that, independently of pre-existing psychotic symptoms and a wide range of social and contextual factors, young people who develop cannabis dependence show an elevated rate of psychotic symptoms”.

Another paper on the development of the brain appeared at this time.

2003. Chambers et al reviewed literature regarding the neurocircuitry underlying motivation, impulsivity and addiction. They focused on studies investigating adolescent neurodevelopment. They found that adolescent neurodevelopment occurs in brain regions associated with motivation, impulsivity and addiction. These developmental processes may advantageously promote learning drives for adaptation to adult roles but may also confer greater vulnerability to the addictive actions of drugs. This has significant implications for understanding adolescent behaviour, addiction vulnerability and the prevention of addiction in adolescence and adulthood.

2004. Veen et al. One hundred and thirty-three Dutch patients with schizophrenia were interviewed. There was a strong association between the use of cannabis and an earlier age of first psychotic episode in male schizophrenics. On average they were 6.9 years younger than non-using patients.

2004. D’Souza et al. Various doses of THC were administered to 22 healthy subjects, screened for any vulnerability to schizophrenia. Some of them developed symptoms resembling schizophrenia for 30 minutes to 1 hour. There were no side effects after 1, 3 and 6 months. The study findings go along with several other lines of evidence that suggest a contribution of cannabis and/or abnormalities in the brain cannabinoid receptor system to the pathophysiology of schizophrenia.

2004. Arendt et al. Findings: 1439 heavy cannabis users seeking treatment for abuse problems in Denmark were compared to 9122 abusers of other substances.
Conclusion: Co-morbid psychiatric disorders are common among heavy cannabis users seeking treatment. Some psychiatric disorders occur more frequently in this group compared to users of other substances.

2005. Isaac and Holloway did their research in PICUs (Psychiatric Intensive Care Units). There was a high rate of cannabis abuse (71.3%) among the PICU population. Patients with cannabis abuse spent longer as their psychosis was more severe. They were also younger at first hospital admission.
The conclusion was that cannabis abusers have more severe psychotic illness especially in schizophrenia. There are additional problems of weight gain.

2004. Frischer et al from Keele University monitored 3% of the population of England and Wales. The number of people using drugs and having mental illness rose by 62% between 1993 and 1998. (230 GP practices were looked at). Men accounted for 79% and women 44%.
The average age affected fell from 38 to 34. The number of cases of 25 to 34 year olds more than doubled. Drug abuse and psychosis were up by 147%, paranoia by 144% and schizophrenia by 128%. They said, “A long-term, well funded, innovative campaign aimed at publicising the real mental health risks associated with drugs including cannabis needs to be in place as soon as possible”.

2004. Stephanis et al looked at 3500 19-year olds in Greece.
Conclusions: These results add credence to the hypothesis that cannabis contributes to the population level of expression of psychosis. In particular, exposure early in adolescence may increase the risk for the sub-clinical positive and negative dimensions of psychosis, but not for depression.

2005 D’Souza and others, in a 3-day double blind randomized placebo-controlled study, injecting 2.5 mg and 5mg intravenous THC, studied the cognitive, motor, behavioural and endocrine effects in 13 stable, antipsychotic-treated schizophrenia patients and compared them with healthy subjects. They found that Delta-9-THC is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. No short or long-term adverse effects were found.

2005. Favrat et al. Clinical trials of THC on psychomotor function and driving performance were conducted on 8 occasional cannabis users with no history of psychosis. Low doses were used. Two young men reacted badly. One 22 year-old showed severe anxiety and psychotic symptoms 90 minutes later, and was unable to do the tests. The other, also 22, was unable to do the tests for several hours,

and experienced very unpleasant symptoms.
The doses were administered under clinical conditions and were much lower than would normally be found in a modern joint. The importance of this research is that oral administration of the THC caused significant psychotic reactions. Oral medicines are becoming increasingly available and doctors should be aware of these findings.

2005. Ferdinand. The "Zuid Holland" Study, a 14 year follow up study of 1580, initially 4 to16 year olds, drawn randomly from the Dutch population. (Because cannabis use is generally condoned in Holland, false negative reports of cannabis use may occur less frequently. This adds to the value of this study). Findings: Cannabis use in individuals who did not have psychotic symptoms before they began using cannabis, predicted future psychotic symptoms, the risk was almost 3 times greater. Also psychotic symptoms in those who had never used cannabis before the onset of psychotic symptoms also predicted future cannabis use.
Conclusion: The results either imply a common vulnerability with varying order of onset or a bi-directional causal relationship between cannabis use and psychosis.

2005. Van Os et al. Nearly 2500 young people between the ages of 14 and 24, with or without predisposition to psychosis were studied. Adjustment was done for confounding factors such as alcohol, cigarettes and other drugs.
There was a dose-response relationship with increasingly frequent use of cannabis.
Conclusions: Cannabis use in young people moderately increased the risk of developing psychotic symptoms. The risk for 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. This rejects the self-medication hypothesis i.e. that psychotic patients take drugs to relieve the symptoms of the illness.

2005. To investigate the overall effect size and consistency of the association between cannabis and psychosis, a meta-analysis from prospective studies was carried out. The pooled odds ration was 2.1 and could not be explained by confounding or reverse causality. Evidence suggests that cannabis is a component cause in the development and prognosis of psychosis, in which mechanisms of gene-environment interaction are most likely to explain this association (Henquet et al).

2005 Henquet investigsted the relation between cannabis use and psychotic symptoms in individuals with above average predisposition for psychosis who first used cannabis during adolescence. 2437 (14-24 years) with/without this predisposition were studied. They concluded that ' Cannabis use moderately increased the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis'.

An Australian study in 2006 tracked 81 young people mostly male in their early 20s, single, unemployed and who were addicted to cannabis. All of them had developed a psychotic mental illness in the previous 6 months. Dr Leanne Hides said, " We found that cannabis use contributes to a relapse in psychotic episodes and then as a result of that they are more likely to use cannabis. Basically they're going around in circles and they can't really win".

2005. Fergusson et al. This was a 25 year longitudinal study of 1055 New Zealand children from birth.
Conclusions: "Even when all factors were taken into account, there was a clear increase in rates of psychotic symptoms after the start of regular use, with daily users of cannabis having rates that were over 150% those of non-users. These findings add to a growing body of evidence from different sources, all of which suggest that heavy use of cannabis may lead to increased risks of psychotic symptoms and illness in susceptible individuals".

2005. Caspi et al. have found variants in a gene (COMT) which is involved in dopamine transmission. It was found to moderate the influence of adolescent cannabis use on the development of adult psychosis. One in four people carries this gene.
The research was carried out on 803 men and women born in Dunedin, New Zealand in 1972 and 1973. They were enrolled at birth. The gene comes in 2 variants, methionine and valine, and everyone has two copies of the gene.
If a person inherits 2 methionine types, the rate of psychotic illness is 3%, the normal rate for non-users. However if a person has 2 valine variants, the rate rises to 15% for those who have used cannabis in their teens. Dr Caspi said, "Research has shown that the valine gene variant and cannabis affect the

brain's dopamine system in similar fashion, suggesting that they deliver a "double dose" that can be damaging".
A report in The Independent on 13th May 2007 said that experts from The Institute of Psychiatry in London had isolated the gene and hoped that a mouth-swab test as an early warning system for identifying vulnerable youngsters. Dr Marta Di Forti said screening could help parents worried about their children.

Several review articles have also appeared in the last few years.

2001. Johns. Conclusion: "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 abuse".

2003. Degenhardt and Hall. Conclusion: "Cannabis use does not appear to be causally related to the incidence of schizophrenia but its use may precipitate disorders in persons who are vulnerable to develop psychosis and worsen the course of the disorder among those who have already developed it".

2004. Arsenault et al. A review of 5 papers was undertaken:
The Swedish Conscript cohort, Andreasson 1987 and Zammit et al 2002.
The Dutch Nemesis Sample, Van Os 2002.
The Christchurch Study, Fergusson et al 2003.
The Dunedin Study, Arsenault 2002.
The overall conclusion: "A twofold increase in the relative risk for later schizophrenia. At the population level, elimination of cannabis smoking would reduce the incidence of schizophrenia by around 8% assuming a causal relationship. Cannabis is a component cause for psychosis, part of a complex constellation of factors".

2004. Rey et al. Conclusion: The weight of evidence points in the direction of early and regular use of cannabis having substantial negative effects on psychosocial functioning and psychopathology.

2004. Drewe et al. This article appeared in response to the potential legalization of cannabis in Switzerland. Conclusion: "An increase in consumption would be expected therefore there would probably be an increase in the prevalence of psychosis, not only acute toxic but also chronic psychosis. Schizophrenic psychoses would be expected to be triggered at an earlier age so there could be deleterious consequences not only for many currently healthy individuals but for disablement pensions".

2004. Raphael and Wooding. Conclusion: "Of primary importance is the fact that cannabis use does have a number of significant associated harms. It is not a soft or safe option and its notable co-morbidity with psychotic and non-psychotic illnesses make it a significant and growing public health issue – a fact increasingly reflected in both the national and international scientific literature".

Other reviews deserving mention include: Leweke et al 2004, Witton and Murray 2004, John Macleod et al 2004 and Smit et al 2004.

In 2004 Marijuana and Madness was published by Cambridge University Press. The editors were, Professor David Castle of The Mental Health Research Unit, Melbourne, and Professor Robin Murray of The Institute of Psychiatry in London.

Twenty-nine contributors to 13 chapters are listed. Many of them have been mentioned in this article. The review from the journal "Addiction" says:

"Each chapter is well written and well presented…There is little doubt that the chapters are expertly written…Marijuana and madness illustrates clearly the benefits of a multi-disciplinary perspective in providing the tools for answering a complex question".

Professor Robin Murray of the Institute of Psychiatry, London, drew attention to the fact in 2003 that recent evidence had demonstrated that THC increases the release of dopamine, thus increasing its level in the brain. Psychotic symptoms in conditions like schizophrenia are mediated by dopamine.

“The Adolescent Brain: A Work in Progress” was published in June 2005 by The National Campaign to Prevent Teenage Pregnancy (USA), Weinberger DR et al. “In sum, a large and compelling body of scientific research on the neurological development of teens confirms a long-held, common-sense view: teenagers are not the same as adults in a variety of key areas such as the ability to make sound judgements when confronted by complex situations, the capacity to control impulses, and the ability to plan effectively. Such limitations reflect, in part, the fact that key areas of the adolescent brain, especially the pre-frontal cortex that controls many higher order skills, are not fully mature until the third decade of life”.

In November 2005 a study by Dr Andrew Campbell of the NSW Mental Health Review Tribunal, and a lecturer in psychology at the University of Sidney, found that 4 out of every 5 incurable schizophrenics had used cannabis regularly between the ages of 12 and 21. He studied schizophrenics committed to institutions or ordered to undergo compulsory treatment in NSW over a 5 year period. He warned that it was an epidemic to which we are blind and quoted figures from Britain and the Netherlands showing a base rate of schizophrenia 11 per 100,000 In Wales compared with London and Amsterdam of 60-70 per 100,000. He attributed the difference to the higher rate of cannabis use in these cities by 12 to 21 year olds.

A Danish study just published in The British Journal of Psychiatry, November 2005, by a team from Aarhus Psychiatric Hospital led by Mikkel Arendt, found that almost half (44.5%) of 535 patients taken from the Danish Psychiatric Central Register and treated for cannabis-induced psychotic symptoms, went on to develop a schizophrenic illness, a third developing paranoid schizophrenia. The signs of schizophrenic illness appeared earlier in cannabis users than others with the condition. Only one in six needed no further treatment. They were compared with 2721 people treated for schizophrenia-spectrum disorders who had no history of cannabis-induced illness. Symptoms appeared in male cannabis users at average age 24.6 years compared with 30.7 in the comparison group, with females it was 28.9 compared with 33.1 years,

On November 30th 2005 researchers from Zucker Hillside Hospital, New York, led by Mazar Ashtari and Sanjiv Kumra presented evidence to The Radiological Society of North America (RSNA) at their annual meeting. They used Diffusion Tensor Imaging (DTI), a sophisticated technique measuring the motion of water molecules in the brain to reveal microscopic abnormalities. They found similar abnormalities in the brains of daily adolescent cannabis users to adolescents with schizophrenia. These defects were in a part of the brain still developing during adolescence and associated with the higher aspects of language and auditory functions.
Their findings also suggested that heavy use of marijuana may lead to earlier onset schizophrenia in adolescents genetically predisposed to the disorder.

2005 Semple et al found that: Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia.
In conclusion, the available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.

2006. Barnes et al studied 152 people recruited to the West London First-Episode Schizophrenia Study. Information on mental state, cognition (IQ, memory, executive functions), social function, age at onset of psychosis and self-reported data on drug and alcohol use were collected. Cannabis use and gender had independent effects on age at onset of psychosis, after adjusting for alcohol misuse and use of other drugs. They concluded that “The strong association between self-reported cannabis use and earlier onset of psychosis provides further evidence that schizophrenia may be precipitated by cannabis use and/or that the early onset of symptoms is a risk factor for cannabis use”.

In February 2007, more evidence was obtained for structural abnormalities in the brain due to cannabis use. Szeszko et al investigated prefrontal grey and white matter regions in patients experiencing a first schizophrenia episode who also used, or were dependent on cannabis. Twenty of these patients were compared with 31similar patients with no cannabis use, and 56 healthy volunteers. “ Patients who used cannabis had less anterior cingulated anterior matter compared with both patients who did not use cannabis and healthy volunteers”. They concluded, “ A deficit in the anterior cingulated is associated

with a history of cannabis use among patients experiencing a first episode of schizophrenia and could have a role in poor decision-making and in choosing more risky outcomes".

The 21st January 2006 edition of the BMJ carried a paper by Fergusson DM et al entitled "Cannabis and Psychosis". It reviewed and brought together the 2 lines of research on this subject, the epidemiological and neuroscientific studies. The summary points were as follows: -

Epidemiological evidence suggests a persistent association between cannabis use and psychosis that is robust to methodological challenges.
Neuroscientific studies show that cannabis may lead to psychosis through effects on the processing of dopamine in the brain.
Taken together this evidence suggests a causal relation in which frequent use of cannabis leads to a greater risk of psychotic symptoms.

The latest review of the evidence linking cannabis to psychosis was published in August 2006 by Degenhardt and Hall. From 6 longitudinal studies in 5 countries they found that regular use of cannabis predicts an increased risk of a schizophrenia diagnosis or report of symptoms of psychosis. These relations persist after control for confounding factors and don't seem to result from the use of cannabis to self-medicate the symptoms of psychosis. A contributory caused relation is biologically plausible because psychological disorders involve disturbances in the dopamine neurotransmitter system with which the cannabinoid system interacts.
They also asked the question, "What are the policy implications of the evidence on cannabis and psychosis?
They said, " The observational evidence and biological plausibility of the hypothesis that cannabis is a contributory cause of psychosis is at least as strong as evidence for causal relations between heavy alcohol and amphetamine use and psychosis. On public health grounds there is a good case for discouraging cannabis use among adolescents and young adults". In the conclusion they called for young adults to be informed of the mental health risks, especially early and frequent use. " We must exercise caution in liberalizing cannabis laws in ways that may increase young individuals' access to cannabis, decrease their age of first use, or increase their frequency of cannabis use. We should consider the feasibility of reducing the availability of high-potency cannabis products".

Skosnik and others in October 2006 researching neural synchronization in cannabis users concluded that, "These data provide evidence for neural synchronization and early-stage sensory processing deficits in cannabis use. This finding, along with the observed increased rates of schizotypy in cannabis users, adds support for a cannabinoid link to schizophrenia spectrum disorders".

A paper by Lehrmann and others in December 2006 found similar brain changes caused by different drugs of abuse. The brains of 42 deceased drug abusers were examined. The drugs involved were cocaine marijuana and PCP. The researchers then measured the level of expression of more than 9000 individual genes in small tissue samples taken from the aPFC (anterior PreFrontal Cortex), a region important in decision-making. Nearly 80% of the drug abuse cases displayed similar alterations in genetic output compared with the controls. For example, genes involved in calcium signaling were turned down while genes involved in lipid and cholesterol-related pathways were turned up. "Our results show that cocaine, marijuana and PCP can alter the function of this critical brain area in similar ways, which could threaten the drug abuser's ability to make sound decisions".

An editorial in the Medical Journal of Australia at the beginning of January 2007 (Jorm and Lubman), announced the expenditure of $21.6 million by The Australian Government for a campaign to get the message right to help the public reduce their risk of mental illness and warn of the link with illicit drugs.

Barkus in a review article in The Psychiatric Times, January 2007 concluded that, "There appears to be evidence of substance use (at least cannabis use) as a component cause for psychotic disorders. However it is still unclear whether substance use operates as a causal factor in the absence of underlying biologic vulnerability to psychosis and whether the expression of isolated psychotic symptoms is directly related to clinical psychotic disorders. The evidence for the causal relationship between substance use and psychotic disorders is primarily based on epidemiologic studies; further clinical studies are needed to determine how substance use operates as a risk factor for psychotic disorders. It is possible that this evidence will emerge from the growing numbers of early intervention

services worldwide".

In March 2007, a paper by Dr Matthew Hickman and others warned that by 2010, up to 25% new cases of schizophrenia in Britons may be due to cannabis. In three English cities, Nottingham, Bristol and Southwark in London, the incidence of exposure to cannabis rose fourfold from 1972 to 2002. In the under-18s it rose 18-fold. The increase would be seen earlier particularly among young men. If cannabis use *causes* schizophrenia, these increases would lead to overall prevalence of 29% and 12% respectively between 1990 and 2010. They point out that up till now there is no *proof* that cannabis is a cause of the condition. Some answers would be forthcoming if the projected increase took place.

2007 Kristensen et al found that cannabis abuse for 'at risk' groups increased the risk of psychosis. 48 subjects, identified as at risk of psychosis (subsyndromal psychotic symptoms and/or family history) were examined. At one year follow-up, 6 had made the transition, of the 32 who had no/minimal use of cannabis, only 1 had progressed to psychosis. Of the 16 who had cannabis dependence, five converted to psychosis. Conclusion: The results showed a significant association between cannabis use and conversion to psychosis.

The April 2007 edition of NIDA (National Institute of Drug Abuse USA) Notes highlighted 2 papers on the brain development of adolescents by Galvan et al. "Children and adolescents both have an immature prefrontal area, but only adolescents make risky decisions", said Dr Galvan, " We speculated that the adolescent brain must be unique in some way that promotes risk-taking". They hypothesized that the nucleus accumbens (NAc) in the brain might play a complementary role to the OFC's (Orbitofrontal Cortex) in adolescent risk taking. The NAc alerts and motivates people when there is an opportunity to get something desirable. The OFC moderates these impulses in the interests of safety and longer-term goals. Thus if NAc activity is highly sensitised when the OFC is weak, the drive to act would over-rule the cautious response and more risks would be taken. From their experiment with 13 children, 12 adolescents and 12 adults, they confirmed their hypothesis. The implications are, they concluded that "disproportionate contributions of subcortical systems relative to prefrontal regulatory systems may underlie poor decision-making that predisposes adolescents to drug use and ultimately addiction".

A Conference on Cannabis and Mental Health is taking place this week (2-3rd May 2007) at the Institute of Psychiatry in London. Dr Deepak D'Souza of Yale University School of Medicine, USA will say that just half a joint of cannabis can trigger symptoms similar to schizophrenia. Small amounts of THC was given to healthy men and women and half developed symptoms, paranoia, hallucinations, and delusions. When THC, the equivalent of 2 joints was given, 60% suffered the side-effects. Schizophrenics were more vulnerable even though they were on medication. Professor Robin Murray said, "If something has an active effect in inducing the symptoms of psychosis after one dose, then it would not be at all surprising if repeated use induced the chronic condition".

Another paper will show, using brain scans, that the drug stifles activity in the part of the brain responsible for inhibition, the inferior frontal cortex. Professor Philip McGuire of The London Institute said the more paranoia the volunteers experienced, the greater the dampening of the emotion.

A third presentation from Markus Leweke of the University of Cologne will compare the effect of CBD (Cannabidiol) and a commonly used anti-psychotic Amisulpride, on 42 patients with a history of schizophrenia. Both showed reduction of psychotic symptoms after 4 weeks but the group on CBD had less side effects like weight gain, sexual dysfunction, liver problems and muscle stiffness. THC and CBD compete with each other in biochemical terms so a rise in THC levels diminishes any positive impact of CBD, as THC levels rise in stronger varieties, CBD levels diminish. "Maybe the cannabidiol ameliorates some of the effects of THC and maybe it actually might be good for you if you are psychotic" said Professor Murray.

A research note from Australia published on June 7th 2007, "Does cannabis use lead to mental-health problems?: findings from the research", concluded that, "it is crucial that emerging evidence about the links between cannabis use and mental health problems is communicated clearly (particularly to those most at risk) and in a way that acknowledges the complexity of the issues involved without obscuring the level and gravity of the risks posed by cannabis use to vulnerable groups" (Buckmaster and Thomas).

An Australian study released in June 2007 indicates that continuous cannabis use increases psychotic symptom severity but not depression symptom severity in schizophrenic patients. 101 patients from 16 to 50 years of age with schizophrenia and related disorders were examined over a 10-month period. Degenhardt and others estimate that daily cannabis users will see an average 3.9 point increase in BPRS (Brief Psychiatric Rating scale) scores in the following month. This indicates a deterioration in their psychotic symptoms compared with patients not using cannabis. "There was no evidence that cannabis was used in response to increased psychotic or depressive symptoms".

An article in Psychiatric News on July 6th 2007 highlighted a lecture by Dr Nora Volkow, director of NIDA entitled "The Neurobiology of Free Will" at APA (American psychiatric Association)'s annual meeting in San Diego in May. "Addiction and the progressive loss of control over behaviour that seems to accompany the addictive process are the result of changes in multiple regions of the brain. Changes occur initially as a result of the abnormal increase in dopamine that results from use of all drugs of addiction and eventually affect memory and attention, the regulation of impulsivity, and executive functioning". She said, " We have come to see addiction as a disease that involves the destruction of multiple systems in the brain that more or less are able to compensate for each other. When pathology erodes the various systems, you disrupt the ability to compensate, and the addictive disease erodes and destroys the life of the individual".

In July 2007 a paper was published in The Lancet. It was a systematic review of 35 studies into possible links between cannabis and psychotic illness. It caused a great stir in the press coming the week after Gordon Brown had announced another review of the classification of cannabis. It found that cannabis users were 40% more likely to develop a psychotic illness than non-users, with heavy users being more than twice as likely to suffer from a mental illness. The authors, led by THM Moore and S Zammit predicted that 14% of psychotic outcomes in young British adults may be due to cannabis. Professor Robin Murray of The Institute of Psychiatry in London said this estimate may be too low as the cannabis available today is stronger than in the past. He said, "My own experience suggests to me that the risk with skunk is higher"
(The Times 27/08/07). They concluded, "…there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life".

A 2-year study by Yucel et al published in August 2007 found, using brain-imaging technology, that opiate-addicted individuals have to make enormous efforts to exercise control over their drug-taking behaviour in the face of adverse health consequences and are vulnerable to relapse. The frontal cortex was working inefficiently, brain cells in this region were less healthy.

September 2007 saw the publication of a paper, "Cannabinoids influence Lipid-Arachidonic Acid pathways in Schizophrenia" by Smesny et al. "Results demonstrate an impact of long-term cannabis use on lipid-arachidonic acid pathways. Considering pre-existing vulnerability of lipid metabolism in schizophrenia, observed effects of cannabis use support the notion of a gene x environment interaction".

A letter to the editor of The American Journal of Psychiatry in October 2007 from Bowers and Kantrowitz described elevated levels of plasma dopamine metabolites in cases of cannabis psychosis. Three groups were studied in a small sample. Five cases of first admission cannabis-related psychosis showed significantly higher levels of homovanillic acid (24.8ng/ml) than 15 admitted for non-related cannabis psychosis (15.1ng/ml) and 17 non psychotic subjects (9.6ng/ml).

2007 Zammit et al found that their results did not support the presence of different effects of cannabis use on schizophrenia according to variation in the COMT gene.

Professor Robin Murray gave a speech at a meeting, "Cannabis and children – complacency is not an option" organized by the group "Talking About Cannabis" (www.talkingaboutcannabis.com) in the Boothroyd Room, House of Commons on October 30th 2007. He said that if THC is injected intravenously into "normal volunteers" then after 10 minutes delusions and hallucinations would occur, returning to "normality" at about 200 minutes. Volunteers said, "…I thought I was God", "I thought you were all trying to trick me" and "I felt you could read my mind, that's why I didn't answer…my mind was nude". He said if enough THC were used, hallucinations and paranoia would result. Because the THC content in cannabis commonly used by children was much higher now (traditional was 3%, skunk is 14%THC), he said it was not acceptable that 13 year olds were using the equivalent

of "a bottle of vodka a day".

He also explained how the balance between two constituents of cannabis had changed in the development of skunk. THC causes hallucinations and paranoid ideas but CBD (cannabidiol) is not hallucinogenic, has anxiety-relieving properties and no adverse effect on cognition. In other words it acts as a balance to the THC. In the old herbal cannabis the two ingredients were more or less balanced. Now in the case of skunk, the THC content has been greatly increased and the CBD has not altered, so the relative amount of CBD compared to THC is much smaller. In a report by The Home Office in 2008 about cannabis potency, it was found that cannabis resin had a meanCBD content of 3.5% (Range 0.1 to 7.3%) but in nearly all cases the CBD content of herbal cannabis was less than 0.1%.

He made an important observation, "By accident the controversy over the reclassification of cannabis provided an opportunity for unofficial public education. This has resulted in a fall in use. What we need now is a proper education campaign aimed especially at children".

A paper in April 2008 by Morgan and Curran took up this theme. Hair analysis was used to determine levels of THC and CBD in 140 drug users. 54 were positive for cannabis. 26 had both THC and CBD present and THC alone in 20 others. Among the 3 groups, THC alone, THC + CBD and no cannabinoid, the THC only group had significantly higher scores for psychosis proneness than the others. The THC+CBD group had significantly lower scores with social withdrawal than the no cannabinoid group.
Delusional thinking also scored highly in the THC group and greater than no cannabinoid in the CBD+THC one. This research highlights the importance of distinguishing between different cannabinoids, and the debate over cannabis-psychosis links.

Cannabis use and adult ADHD symptoms were investigated in a paper by Fergusson and Boden in 2008. The conclusion was, 'The current study suggested that the association between cannabis use and adult ADHD symptoms was mediated by other substance use that was associated with cannabis use. The results suggest that cannabis use leads to other drug use, which in turn leads to increased ADHD symptoms. However it should be noted that the potential influence of such factors as genetic predispositions may still be unaccounted for'.

Cannabis use and brain structural alterations were found in first-episode schizophrenia by Bangalore et al in January 2008. There was a decrease in gray matter density in the right posterior cingulated cortex . Cannabis use may be associated with altered brain structure in particular regions rich in CB1 receptors. A call was made for larger prospective studies.

2008 Feb Ashtari found that adolesceants and young adults who are heavy users of cannabis are more likely to have disrupted brain development. These were found in the memory, attention, decision-making, language and executive functioning skills areas. Subjects had an average age of 19.DTI (Diffusin Tensor Imaging) found an arrest in the developing of the myelin sheath. This could slow signaling in the brain and affect cognitive functioning. Ashtari emphasized the preliminary nature and said it needed more research.

Rais 2008 Excessive loss of brain volume was found in cannabis using first episode schizophrenia patients by Rais et al in April 2008. Gray matter volume in the cerebrum reduces over time in schizophrenics. A study involving 51 patients with recent onset schizophrenia were compared with 31healthy subjects. 19 of the patients used cannabis, but no other illicit drug in the 5-year follow-up period, the other 32 used no drugs. By using MRI scans it was found that schizophrenia patients showed a larger gray matter decrease than the healthy controls, also larger increases in lateral and third ventricle volumes then healthy subjects and patients who did not use cannabis in the follow-up period. The decrement was considerably more pronounced in the patients who continued to use cannabis. They concluded, "First episode schizophrenia patients who use cannabis show a more pronounced brain volume reduction over a five-year follow up than patients with schizophrenia who do not use cannabis".

2008 Crebbin et al investigated drug and alcohol misuse in first-episode psychosis in the UK. Information on patients in Northumberland between 16 and 36 years of age was collected at first presentation and annual follow-up from 1998 till 2005. Hospitalisation was used as an outcome measure and violence rates were examined in retrospect. Drug misuse without alcohol was associated

with a highly significant increase in hospital days. Alcohol problems with/without co-existing drug misuse was not predictive of increased hospital days. Drug and alcohol misuse together was associated with violence. They concluded that drug misuse may have a bigger impact than alcohol use on the outcome of first episode psychosis. (Drugs were, skunk, amphetamines and cocaine).

June 2008, in a paper by Miettunen and others, adolescents in Finland were found to have an association between cannabis use and prodromal symptoms of psychosis. 6330 children between 15 and 16 were investigated, the largest ever study of its type. Those who had tried cannabis (5.6% of the sample) were more likely to present 3 or more prodromal symptoms after controlling for confounding factors like behaviour. A dose-response effect was seen. " We conclude that cannabis use is associated with prodromal symptoms of psychosis in adolescence".

2008 June, Yucel and others found brain abnormalities in long-term (>10years) and heavy users (>5 joints/day) of cannabis, average age 39.8 years and mean duration 19.7 years, with no history of polydrug use or mental problems. Cannabis users had bilaterally reduced hippocampal and amygdale volumes. Conclusion: "These findings indicate that heavy daily cannabis users across protracted periods exerts harmful effects on brain tissue and mental health".

2008 Zammit et al conducted a systematic review of the effects of cannabis use on the outcomes of psychotic disorders. Cannabis use was consistently associated with increased relapse and non-adherence, but some confounders particularly alcohol had not been accounted for in some studies. They concluded, "Confidence that most associations reported were specifically due to cannabis use is low. Despite clinical opinion, it remains important to establish whether cannabis is harmful, and what outcomes are particularly susceptible, and how such effects are mediated. Studies to examine this urther are eminently feasible".
[Two co-authors had been co-opted on to the ACMD in their review of cannabis (PB Jones and TRE Barnes) and several had received fees for lectures, talks or consultancy work for pharmaceutical companies].

2008 Atakan Z. asked if the use of cannabis by people with severe mental illness was important. She said that cannabis use is more common among people with severe mental illness than in the general population. "It has detrimental effects on the course of the illness, physical health and social life of others, as well as being a financial burden on health services". Her article seeks to find out why they continue to use it despite the effects on their condition.

2008 July Lewis et al found that alterations in a molecular pathway activated by marijuana may contribute to the cognitive symptoms of schizophrenia. Expression of the receptor CB1R (cannabinoid receptor in the brain) is significantly reduced in schizophrenics. This results in the transmission of GABA, a neurotransmitter involved with working memory being impaired. Activation of the receptor by THC will worsen this deficit.

August 2008 Spanish researchers have found a strong and independent link between cannabis use and earlier onset psychosis. Gonzalez-Pinto et al said it was not related to gender or the use of other drugs, but to the amount of cannabis used. They estimate that cannabis use accounts for 10% of psychosis cases. Compared with non-users age at onset was reduced by 7, 8.5, and 12 years among users, abusers, and dependents respectively.

2008 August Henquet et al researched gene-environment interplay between cannabis and psychosis. They said that cannabis use is considered a contributory cause of schizophrenia and psychotic illness, but only a small proportion of users develop psychosis. Amount of the drug, duration of using, strength of THC and age of first exposure are all factors. Genetic factors in particular are likely to play a part. "Evidence suggests that mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. In this respect, multiple variations within multiple genes – rather than single genetic polymorphisms – together with other environmental factors )eg stress) may interact with cannabis to increase the risk of psychosis".

2008 September 166 patients in Massachusetts, USA admitted to hospital with bipolar disorder 1 for average 4.7 years were investigated. Patients were more likely to experience a manic or hypomanic episode in the same or subsequent quarter (3 month period) as they had used cannabis than at other times. Baethge et al was the lead German researcher.

Leweke 2008 found 'recent replication studies indicate that frequent cannabis use doubles the risk for psychotic symptoms and schizophrenia'.

Two papers on brain function have been published by McGuire et al in 2008 and 2009. They involved the administration of THC and CBD. Functional MRI scanning and behavioural measures were used in healthy male volunteers. Each subject was scanned at monthly intervals on 3 occasions preceded by administration of either THC, CBD or a placebo. In the first paper in 2008 they found that THC reduced activation in the part of the pre-frontal cortex that is normally critical for inhibiting a response. In the second one in 2009, anxiety was tested using faces with fearful expressions. Normally these would provoke anxiety, activate the amygdala and increase skin conductance. CBD reduced the response of the amygdale to the faces and this was correlated with its effect on skin conductance.

2008 November Arendt et al " People who have long-lasting (48 hours) psychotic episodes after smoking marijuana may be exhibiting early signs of schizophrenia". In a previous study, Arendt found that nearly half the people who had an episode of cannabis-induced psychosis went on to develop schizophrenia within the next 6 years. In this study they looked at the genetic roots of both conditions by comparing the family histories of 609 treated for cannabis induced psychosis and 6476 treated for schizophrenia or a related psychiatric condition. Those treated for cannabis-induced psychosis were found to have the same likelihood of having a 'first degree' relative with schizophrenia as did those treated for schizophrenia. This suggested to the researchers that the 2 conditions are the same. Other researchers have shown that pot-smoking roughly doubles the risk of schizophrenia but it happens sooner if they use cannabis. It looks like it is a gradual process but people should not use cannabis if they want to avoid an increased risk of schizophrenia. Anyone with prolonged period of psychosis after marijuana should seek help early. The sooner it is diagnosed and treated, the better the prognosis. ( Based on a nationwide survey of all individuals born in Denmark between Jan 1st 1995 and July 1st 1990 – 2,276,309 people).

2009 Henquet et al studied 31 patients with a psychotic disorder and 25 healthy controls. They found that carriers of the COMT Met/Val allele, but not the Met/Met genotype showed an increase in hallucinations after cannabis exposure. The findings confirm that in people with psychometric evidence of liability, COMT Val/Met genotype moderates the association between cannabis and psychotic phenomena in the flow of daily life.

2009 Aldandashi and Blackman looked at 12 to 17 year olds of both sexes presenting with either mood disorder or psychosis. They found that substance misuse is more likely to cause psychosis than mood disorder and cannabis (42.85%) use more likely than amphetamine (28.57%) or cocaine (14.28%). Alcohol is more likely to produce mood disorders than cannabis.

2009 Morrison and Murray published the results of their experiments carried out at London's Institute of Psychiatry and mentioned previously in this report. 21 healthy male participants (21 to 50) were recruited from staff and students from King's College, London. They had all previously taken cannabis on at least one occasion. They concluded that: 'THC can induce a transient acute psychotic reaction in psychiatrically well individuals. The extent of the psychotic reaction was not related to the degree of anxiety or cognitive impairment'.

2009 Hickman asked how many cannabis users may need to be prevented in order to prevent one case of schizophrenia (Engand and Wales). The figures he came up with were very large BUT he used data from 1997-1999 – before the huge increase in THC and skunk. So they are not really relevant now. In men 20-24 heavy users it ranged from 2800 to 4700 for 35-39 years old. In women, 20-24, 5470 (25-29) to 10,870 in 35-39s. For heavy use and psychosis men 20-24 1360, to 2480 in women of 16-19. around 2.2 million are thought to use cannabis regularly. If 200,000 men of 20-24 were heavy users it would mean around 70 cases. Schizophrenia is a chronic very serious condition and expensive to treat. Psychosis would occur in 147 of them! This is no light matter!

2009 Frisher et al found that the incidence of schizophrenia or psychosis in the general population between 1996 and 2005 had shown no increase. The data was collected from 183 GP practices in England, Wales, Scotland and N Ireland. Almost 600,000 patients each year were investigated, roughly 2.3% of the UK Population aged between 16 and 44. However Professor Robin Murray (Institute of Psychiatry, London, an expert in schizophrenia) criticized the experiment. He said,

*"I have known about this study since its inception and advised the authors that they were unlikely to be able to come up with meaningful results. Firstly, a major problem concerns the diagnoses. In my experience GP diagnoses of psychiatric disorders are not very accurate. Secondly, we do not know how many cases of psychosis are dealt with exclusively by psychiatrists and GPs don't know.*

*The only place with good data on schizophrenia over the years is Camberwell. The incidence has doubled since 1964. Migration accounts for some of that but it has gone up even in the white population. (Boydell et al 2003)*

*Perhaps more importantly from a theoretical point of view, we estimated that cannabis might account for 10% of all cases of schizophrenia. We do not know what has been happening to the other 90% caused for other reasons.*

*So I don't think this study tells us much".*

The leading researcher Dr Martin Frischer said, "We concentrated on looking into the incidence of schizophrenia during those years and not specifically at cannabis use. "It was relatively low-key research so I don't believe it will re-ignite the debate on whether the drug should be legalised." The research was partly commissioned by the ACMD of which Prof Llana Crome is a member.

Degenhardt et al in 2009 said that "Pot is a risk for psychosis". They conducted a review of the evidence for the relationship. One study found an interaction between marijuana use and a polymorphism of the gene that codes for dopamine. About 25% of the cohort who were homozygous for the polymorphism were nearly 11 times more likely to have developed a shizophreniform disorder than those with the same polymorphism who did not use cannabis. Another study estimated that eliminating all marijuana use would reduce the incidence in the UK by about 8%, "assuming the relationship was causal".

2009 Di Forte et al looked at 280 first-episode psychosis patients who had used cannabis and 174 controls, screened for previous psychotic illness. and recruited in the local PCT area. There was no difference in the cases or controls in terms of cannabis use. However the cases were around 6 times more likely to use daily and nearly 7 times more likely to use sinsemilla or skunk.

2010 A paper from Ontario by Joyce et al on anxiety and mood disorders (AMD) looking at 14,531 adults from 2001 to 2006 provided epidemiological evidence that both light and heavy cannabis use is linked with AMD.

2010 Malone and others looked at adolescent cannabis use and psychosis in a review. They concluded: 'Epidemiological evidence suggests that cannabis use is a risk factor for schizophrenia, while cannabis use in individuals with a predisposition for schizophrenia results in an exacerbation of symptoms and worsening of the schizophrenic prognosis. The neuro-developmental characteristic of adolescence probably creates a more vulnerable circumstance for cannabis to produce psychotic-like symptoms and possibly cause schizophrenia.

2010 March 26th Michael Compton MD, MPH wrote a paper, 'Evidence Accumulates for Links Between Marijuana and Psychosis' for Medscape Psychiatry and Mental Health.
He summarized 2 avenues of research: 1) 'associations between cannabis use and clinical manifestations of psychosis' and 2) 'the biologic plausibility of the observed links'.

1) First: Cannabis is the most frequently abused illegal drug among people suffering from schizophrenia . And in those with psychotic disorders, the initiation of cannabis often precedes onset by several years.

   Secondly: Adolescent cannabis use is more and more being recognized as an independent risk factor for both psychosis and schizophrenia.

   Third: Genetic factors like variants of the COMT gene (normal form met/met) may predispose adolescent users to an increased risk of psychosic disorders. A val/met form of the gene increases the risk in adolescents about fivefold while the val/val increases it around tenfold. The release of dopamine is substantially increased.

Fourth: Cannabis use before the appearance of psychiatric symptoms may be associated with an earlier age of onset of psychotic and perhaps prodromal symptoms.

Fifth: A potential association in the general population between cannabis use and schizotypal symptoms or proneness to psychosis is emerging in research studies.

2) First The endogenous cannabinoid (neurotransmitter anandamide) and so the exogenous cannabinoid THC modulate the release of neurotransmitters including dopamine and glutamate by interacting with the CB1 cannabinoid receptor in regions implicated in schizophrenia.

Secondly: There is an increased CB1 receptor density in brain regions associated with schizophrenia.

Third: Patients with schizophrenia have raised levels of endogenous cannabinoids in the blood and cerebrospinal fluid.

Fourth: Administration of THC to patients cause both patients and controls to experience transient cognitive impairments and schizophrenia-like symptoms, both positive and negative.

To sum up, it has been suggested that " the endocannabinoid system is altered in schizophrenia and that dysregulation of the system , perhaps induced by exogenous cannabis, can interact with neurotransmitter systems in a way so that a 'cannabis hypothesis' can be integrated with other neurobiologic hypotheses (e.g. those involving dopamine and glutamate)".

He concluded that, " A growing body of clinical and epidemiological research suggests significant but complex links between cannabis use and psychosis. Concurrently, ongoing neurobiologic research is revealing findings in the endocannabinoid system that appear to support the biologic possibility of such links".

2010 May, Foti et al examined the relationship between cannabis use and the course of illness in schizophrenia over 10 years of follow-up after first psychiatric hospitalization. 229 patients were assessed 5 times, at first admission, after 6 months, 2, 4 and 10 years. They conclude: 'Cannabis use is associated with an adverse course of psychotic symptoms in schizophrenia, and vice versa, even after taking into account other clinical, substance use, and demographic variables'.

June 2010 Henquet and others discovered that pot smoking can worsen schizophrenia. Marijuana gives people with schizophrenia a quick rush but worsens their psychotic symptoms within a few hours. 47 healthy people and 48 psychiatric patients were recruited in Holland, they were all regular cannabis users the results showed that the schizophrenics were more sensitive than the healthy individuals to both the positive and negative effects of the drug. These findings help to explain previous findings that show that schizophrenics who smoke marijuana require more hospitalization, respond less well to medication and have more trouble with memory tests. Henquet says it's likely that marijuana triggers schizophrenic symptoms in people who have genetic mutations that sensitize them to the drug's psychotic effects.

2010 Henquet and others investigated the effects of cannabis on psychotic symptoms and mood in patients with psychosis (n=42) and healthy controls (n=38). Conclusions: 'Patients with psychosis are more sensitive to both the psychosis-inducing and mood-enhancing effects of cannabis. The temporal dissociation between acute rewarding effects and sub-acute toxic influences may be instrumental in explaining the vicious circle of deleterious ue in these patients'.

2010 Dekker et al concluded that 'The findings indicate that patients suffering from schizophrenia have associations towards cannabis similar to controls, but they have stronger negative explicit cannabis associations. The strong negative explicit associations towards cannabis could imply that users of cannabis engage in a behaviour they do not implicitly like. Explicit relaxing expectancies of cannabis might be an important mediator in the continuation of cannabis use in patients and controls'.

2010 Marise Machielsen and others concluded there was a specific association between cannabis use and psychotic symptomatology.

2010 August, De Haan, a psychiatrist from Amsterdam Medical Centre found 60% of youngsters who have a psychosis are smoking marijuana. The risks have increased over the years because the joints are stronger. He says the cases confirm the link that has been established by science.

2010 September Morgan et al investigating the role of cannabidiol found that people who smoke potent strains of cannabis (e.g. Skunk) low in cannabidiol (CBD) are at far greater risk of acute memory loss than people who smoke other types of the drug e.g. hash. 134 users between 16 and 23 were tested for memory. The researchers found that people smoking cannabis with a low percentage of CBD performed much worse on the memory tests when intoxicated than when they were sober. In contrast those smoking cannabis high in CBD performed just as well on the tests when they were intoxicated as when sober. The amount of THC was identical.

*Unbelievably the authors issued some HR advice! 'On the back of this study we believe users should be made aware of the risk of memory impairment from smoking low-dose CBD strains. They should be encouraged to use strains containing higher levels of cannabidiol instead'.*

2010 October 8th CBS in the Netherlands (Centraal Bureau voor de Statistiek, Gov institution gathering statistical info about the Netherlands) reported that cannabis use increases the risk for mental health issues. 18,500 people were studied. 4% of 15 to 65 year olds had smoked cannabis in the previous month (more than a quarter reported smoking on a daily or near daily basis). The study found that nearly 20% of male cannabis users had psychological problems compared with nearly 10% of non-users. More than 28% of females had psychological problems versus more than 14% of non-users.

2010 November Staci Ann Gruber, speaking at Neuroscience 2010, the annual meeting of The Society of Neuroscience reported that people who start using marijuana at a young age have greater cognitive shortfalls. Researchers also found that the more marijuana a person used corresponded to greater difficulties in focus and attention. (Teen's brains are only about 80% developed and are not completed till the 20s or 30s).

2010 Skinner et al found among university students in Ireland (Galway) that cannabis use increases the risk of developing psychiatric symptoms, worsened by earlier and heavier use.

2010 McGrath and others, using sibling pairs among over 3800 young adults, concluded that 'Early cannabis use is associated with psychosis-related outcomes in young adults. The use of sibling pairs reduces the likelihood that unmeasured confounding explains these findings. This study provides further support for the hypothesis that early cannabis use is a risk-modifying factor for psychosis-relayed outcomes in young adults'.

2010 Stilo and Murray in a review on schizophrenia research said, ' Acute ingestion of cannabis or its active ingredient THC was found to precipitate acute psychotic episodes in experimental studies, and continuing use of cannabis is known to exacerbate existing psychotic illnesses'.

2011 January. Estrada G and others found more confirmation for the COMT polymorphism interaction with cannabis use. 157young psychiatric patients, mean age 17.01 years, were examined to find out if, a) age at first cannabis use and age at emergence of psychiatric disorders are related and b) such a relationship is modulated by the Val158Met genotype. It was found that those who started using cannabis earlier had an earlier age onset of psychiatric disorders, the distribution of the Val158Met was not different either between diagnosis groups or between cannabis and non-cannabis users. An interaction between Val158Met genotypes and cannabis use was observed specifically on age at emergence of psychiatric disorders with Val/Val genotype carriers showing an earlier age at onset than Met carriers. They concluded that The COMT Val158Met genotype seems to modulate the association between cannabis and age at onset of psychiatric disorders. These results are consistent with previous studies.

2011 Jan Lagerberg et al looked at the onset of bipolar disorder. They looked at 151 patients in treatment with a special focus on excessive alcohol and cannabis use. Patients with excessive alcohol

use had a significantly later onset compared with patients with excessive cannabis use, whether it preceded or followed bipolar disorder onset. Lifetime use of cannabis predicted an earlier onset independent of the sequence of onsets. This indicates that an early onset may increase the risk of cannabis use and cannabis use may trigger bipolar disorder in vulnerable individuals.

2012 Feb Ersche et al looked at the brain'wiring' of 50 biological siblings, one addicted to cocaine or amphetamines, the other with no history of drug abuse. A child of drug-addicted parents is 8 times more likely to become an addict than one in a drug-free home. Self-control was tested. People with poor self-control, including most drug addicts, find it difficult to exercise this. All of the sibling pairs did worse than the 50 unrelated healthy volunteer controls. Brain scans showed that each of the sibling pairs had abnormal interconnections between parts of the brain that exercise control and those involved with drive and reward. Also some individual brain structures were larger – the putamen, responsible for habit-forming, and the medial temporal lobe – learning and memory. The interesting thing is that although the sibling brains were similarly wired (wrongly) one of the pair had not used drugs. So there may be a way of helping vulnerable youngsters.

2011 June. Large et al. published a very important meta-analysis on psychosis and age of onset. They identified 83 studies involving 8167 particpants who used cannabis or other substances and 14,352 who did not. Individuals who used cannabis developed psychosis about 2.7 years younger than those who did not. Those who used any type of substance developed it 2 years younger while in those using alcohol there was no correlation. These findings support the view that cannabis use precipitates schizophrenia and other psychotic disorders perhaps through an interaction between genetic and environmental disorders by disrupting brain development.

'The results of this study provide strong evidence that reducing cannabis use could delay or even prevent some cases of psychosis. Reducing the use of cannabis could be one of the few ways of altering the outcome of the illness because earlier onset of schizophrenia is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex cannot be changed. " The results of this study confirm the need for a renewed public health warning about the potential for cannabis use to bring on psychotic illness".

2011 Feb Ashtari et al investigated adolescent brain development particularly on the hippocampus. They looked at 14 (18-20) 'treatment seeking' adolescents with heavy prior cannabis use (5.8 joints/day) after an abstinence of 6.7 months and 14 normal controls. The users showed significantly smaller volumes of the right and left hippocampus compared to controls. So heavy cannabis use after an average 6.7 months abstinence lend support to the theory that cannabis users may impart long-term structural and functional damage. Or the volumetric abnormalities may present a risk factor for cannabis dependence. These data have potential significance for understanding the observed relationship between early cannabis exposure at adolescence and subsequent development of adult psychopathology reported in the literature for schizophrenia and related psychotic disorders.

2011 Feb 23rd Morrison investigated whether cannabis (synthetic THC) elicits schizophrenia – like negative symptoms distinct from sedation. 22 healthy subjects attended 2 sessions in which either THC or placebo was given., random order and double blind conditions. They concluded that 'At plasma concentrations resembling recreational use, THC elicited schizophrenia-like negative symptoms that were not merely attributable to sedation. In the community, negative effects may be an adverse effect of cannabis use'.

2011 Demirakca et al found that a lower volume in the right hippocampus in chronic cannabis users was corroborated. Higher THC and lower CBD was associated with this volume reduction indicating neurotoxic effects of THC and neuroprotective effects of CBD. This confirms existing pre-clinical and clinical results. As a possible mechanism the influence of cannabinoids on hippocampal neurogenesis is suggested.

2011 March Compton et al looked at pre-illness cannabis use and the onset of psychosis. 109 first-episode hospitalised patients were studied. 42% of those who had used cannabis daily had an acute mode of onset of psychosis, only 20% of those without prior daily cannabis use had an acute onset.

2011 April, Solowij and others concluded that 'Long-term cannabis use in healthy individuals is associated with smaller cerebellar white-matter volume similar to that observed in schizophrenia.

Reduced volumes were even more pronounced in patients with schizophrenia who use cannabis. Cannabis use may alter the course of brain maturational processes associated with schizophrenia'.

2011 April Kuepper et al conducted a study into whether an urban environment plays a role in moderating the effects of adolescent cannabis use on psychosis risk. Nearly 2000, 14 to 24 year olds, living in Munich or the rural surrounding were investigated. Cannabis and psychotic symptoms were assessed over a 10 year period. They concluded that exposure to environmental influences associated with urban upbringing may increase vulnerability to the psychotomimetic effects of cannabis use later in life.

2011 Dr Jussi Hirvonen and others in a presentation at the annual meeting of the Society of Nuclear Medicine in San Antonio Texas on 6th June said that imaging scans show that chronic daily use of marijuana can have a detrimental effect on the brain. They found a decrease in the number of receptors involved in a variety of important mental and bodily functions, including pleasure, pain tolerance, movement coordination, memory, appetite and concentration. The brains of 30 chronic daily marijuana smokers were studied over roughly 4 weeks. The CB1 receptors had decreased by around 20% compared to those of the healthy controls who had limited lifetime exposure to cannabis. After a month of abstinence, 14 were re-scanned and the number of receptors were found to have notably increased, suggesting the effects may be reversible. This research has not yet appeared in a peer-reviewed journal. The study was a collaboration between The US National Institute of Mental Health and the US National Institute on Drug Abuse (NIDA).

2011Kuepper R et al concluded that, 'Cannabis use (in adolescence) is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder by impacting on the persistence of symptoms'. 1923 individuals (German), age 14 to 24 at baseline were studied and assessed 3 times for cannabis use and psychotic symptoms, baseline, 3.5 years (T2) and 8.4 years (T3). The incidence rate of psychotic symptoms over the time, baseline to T2 was 31% in exposed individuals, 20% in non-exposed. From T2 to T3 these rates were 14% and 8% respectively.

2011 October 25th Jones et al found that 'cannabis can cause chaos in the brain'. The nerve activity becomes unco-ordinated and inaccurate. Rats were given a drug mimicking the psychoactive ingredient in cannabis. Co-ordinated brainwaves across the hippocampus (memory) and prefrontal cortex (planning, decision making, social behaviour) were completely disrupted. The scientists believe the results may help explain the links between cannabis and schizophrenia. Jones said, ' Marijuana use is common among schizophrenia sufferers and recent studies have shown that the psychoactive ingredient of marijuana can induce some symptoms of schizophrenia in healthy volunteers'.

2011 Van Winkel et al looked at the AKT1 gene. In Holland and Belgium, 740 non-affected siblings of people with schizophrenia and similar conditions, and 419 controls with no first-degree relatives suffering from such disorders, were studied. Already known was that a gene associated with schizophrenia is AKT1, that cannabis has been associated with these disorders and that siblings of those with psychotic disorders were more likely to develop a psychotic disorder than the rest of the population. They found that the non-psychotic siblings of people with schizophrenia or similar disorders, were twice as likely to be diagnosed with psychotic illness after cannabis use than the general population. The ATK1 gene variation appears to be implicated.

2011 Zammit concluded that 'Cannabis increases risk of psychosis irrespective of underlying COMT genotypes. These findings argue against the widely held belief that the risk of developing psychosis following use of cannabis is dependent on variation within COMT.

2011 September Welch and others found that cannabis use impacts on brain thalamic volumes in people at familial risk of schizophrenia. In the Edinburgh High Risk Study (EHRS), MRI scans were obtained at point of entry to the study and approximately 2 years later. 66 individuals were involved in the study, substance use data were available for 57 of them of whom 25 consumed cannabis between the two assessments. They concluded that there was a significant volume loss bilaterally in the thalamus, more highly significant on the right. These losses remained significant when individuals using other drugs were removed from the analysis.

2011 Lebel found that in the development of the white matter in the brain, structural changes are still ongoing into young adulthood. 103 healthy people between 5 and 32 were scanned at least twice using MRI. Young adult brains were continuing to develop wiring to the frontal lobe., tracts responsible for complex cognitive tasks such as inhibition, high-level functioning and attention. An important observation was that in some people several tracts showed reductions in white matter integrity over time, which is associated with brain degeneration. Further research is needed to determine whether different clinical disorders like psychiatric disease and neurological disease may be linked to brain structure as the brain ages.

2011 December Cheetham discovered that cannabis users are born with smaller front part of brain. The orbitofrontal cortex controlling memory, reward and decision-making is 6% smaller in children who go on to smoke cannabis compared with those who don't. This could make them more likely to experiment with cannabis as they may be more impulsive and less capable of calculated decision making. This could act as an early warning system! Scans of 121 12 year olds were taken before they started to experiment, then questioned at 16. 28 admitted smoking pot, 23% less than 10 times. Co-founding factors eliminated, the group had the smaller brains. Other studies on long term users found that the drug seems to affect the size of other areas of the brain. These are normal in children who had smoked the drug so it seems to be regular heavy smoking that is causing the damage.

2012 Blakemore S-J looked at imaging the adolescent brain. She said, ' The past 15 years has seen a rapid expansion in the number of studies using neuro-imaging techniques to investigate maturinational changes in the human brain. I review MRI studies on structural changes in the developing brain and fMRI studies on functional changes in the social brain during adolescence. These studies point to adolescence as a period of continued neural development. This is an exciting time for developmental cognitive neuroscience, a young field that is set to continue to expand over the next 2 decades'.

2012 Bhattachharyya examined the effects of THC and CBD on regional brain functioning during salience processing. 15 healthy men, occasional cannabis users were given THC, CBD or a placebo on 3 occasions. The aberrant processing of salience is thought to be a fundamental factor underlying psychosis. 'THC and CBD differentially modulate prefrontal, striatal and hippocampal function during attentional salience processing. These effects may contribute to the effects of cannabis on psychotic symptoms and on the risk of psychotic disorders'. There was no significant difference between the cannabidiol and placebo conditions.

2012 April 29th ( Italy – 3rd Biennial Schizophrenia International Research Conference in Florence) O'Donoghue found that obstetric complications had the strongest significant influence on age of onset of psychosis, followed by cannabis.use. A total of 608 patients with first episode psychosis were studied. Five factors were considered – Sex, social class of origin, family history of psychosis, cannabis use and obstetric complications. 19% of patients had a family history of psychosis, 44% had had an obstetric complication. Only 3 of the 5 factors were associated with an earlier onset of psychosis – Being male, a history of cannabis use and obstetric complications. Patients with a history of cannabis use had a median age of onset of 22.8 years, obstetric complications was 24.6 years and being male, 26 years.

Dr Mary Cannon, Dublin, said 'Without these risk factors your age of onset is about 30, but if you have 2 of them, this drops to about 20. That amounts to 10 years of very significant life…'

2012 Jan 12th Lynch et al looked at 'The Cannabis-Psychosis Link'. Several findings are interesting:

1. More than 16m Americans regularly use cannabis, typically beginning in adolescence. In the USA, 4% of cannabis users have a diagnosis of either cannabis abuse or dependence, but in schizophrenics the proportion of people with a co-morbid cannabis use disorder is 25%. Cannabis use disorders are especially common in younger and 1st episode patient samples and in samples of high proportions of males.
2. THC interacts with the dopamine (pleasure neurotransmitter) system. Dopamine, which provides a pivotal role in mediating the reinforcing effects of most drugs of abuse, is increased. This increased dopaminergic drive could underlie the abusive property of the drug and increase the positive psychotic symptoms induced by THC. (Murray and many others believe that the increase in dopamine is likely to be the cause of the psychosis, those with schizophrenia and psychosis have an excess of dopamine in the brain)

3. Moore et al in The Lancet 2007 in a systematic review surveyed the literature on this topic. The 'psychosis' outcomes required a diagnosis of a primary psychotic disorder or affective psychosis, or the occurrence of delusions, hallucinations or thought disorder during the study period. Results from 7 cohort studies showed a 40% increased risk of psychosis in cannabis users compared with non-users. The data also revealed a dose-response effect – the risk of psychotic symptoms was increased approximately 50% to 200% in those who used cannabis frequently compared with non-users.

4 Age at onset of psychosis and cannabis use: The Dunedin Multidisciplinary Health and Development Study conducted a prospective longitudinal study of adolescent cannabis use, taking into account psychotic symptoms that occurred before cannabis use. The data were compiled from a birth cohort that consisted of 1037 individuals born in Dunedin, New Zealand. Information about psychotic symptoms was obtained at age 11, and drug use was assessed by self-reports at ages 15 and 18 and by a standardized interview schedule at age 26. Two psychosis-related outcomes were measured—the presence of symptoms of schizophrenia and the diagnosis of schizo-phreniform disorder.

The results showed that those who had used cannabis by ages 15 and 18 had more schizophrenia symptoms than controls, a finding that remained significant after controlling for the presence of psychotic symptoms at age 11. However, the increased likelihood of schizophreniform disorder at age 26 was no longer significant after controlling for psychotic symptoms at age 11. Taken together, this suggests that early cannabis use confers higher risk of psychosis.

2012 April Whelan et al found in brain scans almost 2000 14 year olds, that some nerve networks don't work so well in some teenagers, making them more impulsive These were in the orbitofrontal cortex, which is involved in decision-making and linked with experimentation with alcohol, cigarettes and illegal drugs in early adolescence, and offer poor inhibitory control. Another separate neural network which is involved with the symptoms of ADHD was NOT connected with this decision-making area. The researchers were able to 'fish out' 7 networks involved where impulses were successfully inhibited, but another 6 when inhibition failed. A genetic variation in a norepinephrine transporter gene was also involved.

2012 Feb Ersche et al looked at the brain'wiring' of 50 biological siblings, one addicted to cocaine or amphetamines, the other with no history of drug abuse. A child of drug-addicted parents is 8 times more likely to become an addict than one in a drug-free home. Self-control was tested. People with poor self-control, including most drug addicts, find it difficult to exercise this. All of the sibling pairs did worse than the 50 unrelated healthy volunteer controls. Brain scans showed that each of the sibling pairs had abnormal interconnections between parts of the brain that exercise control and those involved with drive and reward. Also some individual brain structures were larger – the putamen, responsible for habit-forming, and the medial temporal lobe – learning and memory. The interesting thing is that although the sibling brains were similarly wired (wrongly) one of the pair had not used drugs. So there may be a way of helping vulnerable youngsters.

2012 Feb Anglin et al used prospective data from 804 participants was used to determine associations between early cannabis use and later schizotypal symptoms, accounting for important potential confounds (e.g., adolescent schizotypal symptoms. They found that Cannabis use with onset prior to age 14 strongly predicted SPD symptoms in adulthood, independent of early adolescent SPD symptoms, major depression, anxiety disorder, other drug use, and cigarette use. There was no interaction effect of early cannabis use and early adolescent SPD symptoms on SPD symptoms into adulthood.

2012 May Manrique-Garcia and others found that cannabis-related psychosis may not increase the risk for schizophrenia. They looked again at the 50,000 individuals, military conscripts in Sweden, who had reported their cannabis use since adolescence and over a 35 year period.
'The study revealed that the individuals who used cannabis regularly were almost four times more likely to develop schizophrenia than those who never used cannabis and more than twice as likely to experience a brief psychosis episode. The results also showed that the risk for future psychosis and schizophrenia weakened over the long-term. Manrique-Garcia said, "Of the cases related to cannabis use, 60% occurred during the first decade compared with 45% among non-users of cannabis." However, the findings also demonstrated a clear relationship between dose and risk. In particular, those who used the highest amounts of cannabis for the longest periods of time had the highest risk of

schizophrenia. This risk was increased by early episodes of psychosis, regardless of whether they were cannabis induced or not. The individuals who experienced episodes of cannabis-induced psychosis and those who had non-cannabis-related psychotic episodes were equally at risk for schizophrenia. But Manrique-Garcia points out that the individuals with cannabis-related psychosis may not have experienced any psychotic episodes if they had not used cannabis. Further research is needed to determine if this would ultimately decrease their risk for the later development of schizophrenia'.

2012 May. Behan et al looked at adolescent cannabis use and its effects on the COMT gene, first written about in 2005 (Caspi). They used mice whose COMT gene had been 'knocked out'.

Behan said, "This is the first study to show that the combined effects of the COMT gene with adolescent cannabis use cause physical changes in the brain regions associated with schizophrenia. It demonstrates how genetic, developmental, and environmental factors interact to modulate brain function in schizophrenia and supports previous behavioural research which has shown the COMT gene to influence the effects of adolescent cannabis use on schizophrenia-related behaviours' The 3 areas of the brain assessed in this study were found to show changes in cell size, density and protein levels.

2012 October Degenhardt et al investigated the persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. Nearly 2000 children were recruited in secondary school at 15 years of age and surveyed 9 times afterwards. Conclusions: Regular (particularly daily) adolescent cannabis use is associated consistently with anxiety, but not depressive disorder, in adolescence and late young adulthood, even among regular users who then cease using the drug. It is possible that early cannabis exposure causes enduring mental health risks in the general cannabis-using adolescent population.

2012 Nov, Loeberg et al looked at cannabis use to see if it could lead to schizophrenic breakdown. They found a different brain activity pattern in MRI scans among schizophrenics with cannabis use, than schizophrenics without cannabis use. The 26 patients in the study showed that cannabis use causes a temporary cognitive breakdown in non psychotic individuals leading to long-term psychosis. This implies that the cannabis itself leads otherwise non-psychotic people down the nightmarish path towards schizophrenia by imitating the cognitive weakness that is the main risk factor for developing the psychological condition.

2012 Di Forti et al confirmed that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. 489 first-episode psychosis patients and 278 control subjects were investigated. They concluded that 'Our findings provide strong support for the initial report that genetic variation at rs2404732 of AKT1 influences the risk of developing a psychotic disorder in cannabis users.

2012 October Moller et al looked at self-harm and substance abuse among 4126 people. They concluded that self-harm in young and middle-aged adults appeared to be associated with current smoking, marijuana and 'dependent' alcohol use. Other independent predictors include younger age, male gender, bisexual orientation, financial strain, education level, psychological distress, adverse life events and sexual abuse by a parent.

2013 Hermens et al found that frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental health care. 2122 young people, aged 12 to 30 provided information as part of a patient register. 3 age groups, 12-17, 18-19 and 20-30 were used. The rates for 'at least weekly use' of alcohol were 12%, 39% and 45%, for cannabis, 7%, 14% and 18%. Rates of daily use of nicotine 23%, 36% and 41%. Age of onset across the 3 substances was approximately 15. They concluded: ' Frequent use of alcohol, nicotine or cannabis in young people seeking mental healthcare is common. Given the restricted legal access, the patterns of use in those aged 12-17 are particularly notable. Reductions in substance use needs to be prioritized within services for at-risk young people.

2013 Jan. Stefanis et al looked at age of initiation of cannabis use and onset of psychosis in 997 participants from the 2010 Survey of High Impact Psychosis (SHIP) in Australia. We tested for group differences in age at onset of psychotic illness and in the duration of premorbid exposure to cannabis (DPEC). The association between age at initiation of cannabis use and age at onset of psychotic illness was linear and significant, even after adjusting for confounders. A temporal direct relationship between age at initiation of cannabis use and age at onset of psychotic illness was detected with a premorbid

exposure to cannabis trend of 7-8 years, modifiable by higher severity of premorbid cannabis use and a diagnosis of SSD. Cannabis may exert a cumulative toxic effect on individuals on the pathway to developing psychosis, the manifestation of which is delayed for approximately 7-8 years, regardless of age at which cannabis use was initiated.

2013 Jan. Lev-Ran and others looked at 43,070 respondents aged 18 and above to examine the prevalence of cannabis use and CUDs ( Cannabis Use Disorders) in a wide range of mental illnesses.

RESULTS:
Rates of weekly cannabis use, less than weekly cannabis use and CUDs among individuals with 12-month mental illness were 4.4%, 5.4% and 4.0%, respectively, compared to 0.6%, 1.1% and 0.4%, respectively, among individuals without any 12-month mental illness. The odds ratio for cannabis use among individuals with 12-month mental illness vs. respondents without any mental illness was 2.5, and the odds of having a CUD among individuals with 12-month mental illness were 3.2, after adjusting for confounding variables and additional substance use disorders. Cannabis use and CUDs were particularly associated with bipolar disorder, substance use disorders and specific (anti-social, dependant and histrionic) personality disorders. Persons with a mental illness in the past 12months represented 72% of all cannabis users and we estimated they consumed 83% of all cannabis consumed by this nationally representative sample.

CONCLUSIONS:
The current study provides further evidence of the strong association between cannabis use and a broad range of primary mental illness. This emphasizes the importance of proper screening for frequent cannabis use and CUDs among individuals with primary mental illness and focusing prevention and treatment efforts on this population.

2013 January Castle D, 'Cannabis and psychosis: what causes what? Castle looked at the evidence for this and concluded: Applying the cumulative causal factor model, very few "cases" of schizophrenia (estimated population attributable fraction - PAF- around 8%) would actually be "prevented" with the global abolition of cannabis. This low PAF is compatible with epidemiological findings that schizophrenia is a ubiquitous accompaniment of the human condition and rates do not vary very much between cultures and settings despite wide variations in cannabis use. At an individual level, though, it would seem important to educate people at heightened risk of schizophrenia (e.g. through having a family history of the disorder, or having experienced psychosis-like symptoms) of the potential additive causal risk cannabis exposure might bestow.

2013 January Gage SH et al looked at the role of cannabis in schizophrenia. Conclusions:
Despite consistent evidence that individuals who use cannabis have an increased risk of psychotic outcomes, it should not be surprising that the role of cannabis in the aetiology of schizophrenia remains uncertain given the limits of observational epidemiology. In particular, the extent to which the incidence of schizophrenia will be altered by reducing cannabis use or changing the type of cannabis used in the population, or in specific subgroups, remains unclear. Whilst the evidence is "good enough" to continue promoting the public health message that cannabis is harmful, and that it may increase risk of schizophrenia, it is important not to overstate the evidence: the majority of people who use cannabis will not develop schizophrenia, and it appears that a considerable number of heavy cannabis users would need to be prevented in order to prevent one case of schizophrenia. From a scientific perspective, however, the extent to which use of cannabis leads to an increased incidence of schizophrenia, independently of confounding characteristics and separate from effects of chronic intoxication, remains uncertain. Whether preventing cannabis use will have any substantial impact on preventing psychotic disorders in the population, or within specific subgroups at risk, is yet to be adequately determined.

Allebek 2013 April 7th, revisited the study of male Swedish conscripts around 1969/70. This showed that shizophrenia patients with a history of cannabis use had longer hospital says, higher rate of hospital readmission, and a type of schizo that may be more severe than schizo cases in general. Altho there is increasing evidence of a link etween cannabis use and schizo, unclear whether prognosis and outcomes in these patients differ from their non-using cannabis counterparts. Over 50,000 male Swedish conscripts between 18 and 19 in 1969/70 were examined and adjusted for confounding factors. Of the conscripts, 5391 used cannabis, 350developed schizo, 58 were cannabis users. The median duration of first hosp admiss was almost twice as long for users as non(59 v 30 days) Athird of

users needed more than 90days, only 20% non-users were hosp for that long. Cannabis users had a median of 10 readmissions v 4 for non-users. After controlling for confounding factors, there was a more than 3-fold increased risk of long hosp days in can users, and the no of readmissions was also about 3-fold. He concluded that schizo caused or contributed by cannabis use may be more severe than schizo cases in general Patients + cannabis history seem to have more severe and more persistent history of schizo as indicated by duration of first vist, total duration of hosp days, nos of readmissions

2013 April, Morgan et al found that: 'Anandamide is a ligand of the endocannabinoid system. Animals show a depletion following repeated $\Delta^9$-tetrahydrocannabinol (THC) administration but the effect of cannabis use on central nervous system levels of endocannabinoids has not been previously examined in humans. Cerebrospinal fluid (CSF) levels of the endocannabinoids anandamide, 2-arachidonoylglycerol (2-AG) and related lipids were tested in 33 volunteers (20 cannabis users). Lower levels of CSF anandamide and higher levels of 2-AG in serum were observed in frequent compared with infrequent cannabis users. Levels of CSF anandamide were negatively correlated with persisting psychotic symptoms when drug-free. Higher levels of anandamide are associated with a lower risk of psychotic symptoms following cannabis use.

Professor Sir Robin Murray contributed the following thoughts on this paper:

Recently it was reported by Dr Anissa Abi-Dharghum cannabis dependent people with psychosis symptoms also had low striatal dopamine but if they were given amphetamine they developed exacerbation of their psychosis even with a tiny increase in striatal dopamine (within normal limits). So it may be that the cannabis users who develop psychosis may have somehow developed a supersensitive dopamine system. This could be because of an abnormality further downstream. For example, you know that we have shown an effect of the gene AKT1. This has a role in post-receptor signalling i.e. after the dopamine receptor. So, it is possible that a person with the AKT1 risk variant might have so sensitive a dopamine system that psychotic symptoms might ensue even with a small change in striatal dopamine.

So the above remains a possibility. An alternative is that an effect on the CB1 receptor directly affects AKT without going through the Dopamine system.

Another alternative is something entirely different that we can't even speculate about. So the bottom line is that we don't have a definitive answer. But at least people are now seriously looking at these questions.

2013 Bosker et al assessed psychomotor function in chronic daily cannabis smokers during 3 weeks continuously monitored abstinence on a research unit. Performance on critical tracking and divided attention tasks was assessed on 19 male daily chronic cannabis users. Psychomotor performance moderately improved over the 3 weeks of sustained abstinence but did not recover to equivalent control group performance. However: The smokers and controls were not matched for education, social economic status, life style and race.

**http://www.drugaddictiontreatment.com/types-of-addiction/marijuana-addiction/marijuana-withdrawal-added-to-dsm-5/**

# Marijuana Withdrawal Added to DSM 5

Posted on July 27, 2013 in Marijuana Addiction, Research & News3

Cannabis-related disorders are a group of mental health conditions that stem from the use of THC-containing marijuana or hashish. The American Psychiatric Association (APA) classifies these conditions as specific examples of a more comprehensive category of problems called substance-related disorders. Cannabis withdrawal, one of the cannabis-related disorders listed in the 2013 edition of the APA's *Diagnostic and Statistical Manual of Mental Disorders,* is a newly defined condition. Another one of the listed disorders, called cannabis use disorder, combines the diagnoses of two

conditions—cannabis abuse and cannabis dependence—formerly included as separate mental health issues in previous edition of the *Diagnostic and Statistical Manual*.

# Cannabis-Related Disorder Basics

The new *Diagnostic and Statistical Manual* (designated by the American Psychiatric Association as DSM 5) contains definitions for four cannabis-related disorders: cannabis intoxication, cannabis use disorder, cannabis withdrawal and "other" cannabis-induced disorders. Cannabis intoxication is the only one of these disorders that appears in DSM 5 in essentially the same form as it appeared in DSM IV, the previous edition of the *Diagnostic and Statistical Manual*. Cannabis use disorder replaces both cannabis abuse and cannabis dependence. Cannabis withdrawal was created for DSM 5 in recognition of the possible effects of suddenly stopping or heavily reducing habitual marijuana or hashish intake. The "other" cannabis-induced disorders listing replaces several different DSM IV disorders, including cannabis-induced anxiety disorder, cannabis-induced psychotic disorder with hallucinations, and cannabis-induced psychotic disorder with delusions.

# Cannabis Intoxication

People affected by cannabis intoxication have typically smoked or ingested marijuana or hashish within roughly two hours of the onset of their symptoms. Specific symptoms that indicate the presence of intoxication include a significant spike in the normal heart rate, mouth dryness, appetite elevation and unusual fluid accumulation in the eyelids (a condition known as conjunctival injection). In addition to at least two of these cannabis-related alterations, all diagnosed individuals must experience substantial psychological or behavioral impairments as a result of marijuana or hashish use. They must also lack other conditions that provide a more reasonable basis for their mental/physical state.

# Cannabis Use Disorder

Under the criteria listed in DSM IV, people with significant problems related to their cannabis use who show no signs of physical/mental dependence could receive a diagnosis of cannabis abuse. Examples of problems that qualified as significant include a frequent inability to meet any essential duties or responsibilities, frequent participation in dangerous activities while under the influence of cannabis, and an insistence on continuing cannabis use despite its known harmful life impact. The DSM IV criteria also allowed for a separate diagnosis of cannabis dependence in people who do show signs of physical/mental dependence on marijuana or hashish.

However, modern scientific thinking indicates that the difference between substance abuse and substance dependence is rarely cut-and-dried. In reality, doctors and researchers can find no consistently sensible way to address abuse and dependence as separate issues. For this reason, DSM 5 includes combined listings for specific substance use disorders instead of listings for various forms of abuse and dependence. This means that cannabis abuse and cannabis dependence are now addressed together under the cannabis use disorder heading.

# Cannabis Withdrawal

According to the guidelines established by the American Psychiatric Association, substance withdrawal qualifies as a mental health concern when it produces symptoms that significantly degrade participation in a functional routine or trigger troublesome states of mind. Prior to the publication of DSM 5, there was not enough scientific evidence to ascribe these types of effects to withdrawal from the use of marijuana or hashish. However, times have changed, and the APA now officially recognizes the fact that at least some of the people who withdraw from these substances meet the mental health criteria for substance withdrawal. Doctors can now use the cannabis withdrawal diagnosis to identify these people.

# "Other" Cannabis-Induced Disorders

Cannabis is known for its ability to produce symptoms in some users that strongly resemble the symptoms of certain diagnosable mental conditions. DSM IV identified two such conditions: anxiety—which produces unreasonable worry, fear or dread—and psychosis, which classically involves the onset of either sensory hallucinations or fixed, irrational beliefs known as delusions. DSM 5 still allows doctors to diagnose these conditions in cannabis users; however, it also acknowledges the fact the cannabis users can potentially develop other mental health problems directly related to their marijuana or hashish use. The "other" cannabis-induced disorders category was created in order to provide doctors with the freedom to specify exactly which issues they uncover in their cannabis-using patients.

2013 Niemi-Pynttari eta al looked at substance-induced psychosis converting into schizophrenia. Abstract: Using the nationwide Finnish Hospital Discharge Register, we followed all patients (N = 18,478) since their first inpatient hospital admission with a diagnosis of SIP (codes 2921 and 2928 in DSM-III-R and codes F10-F19 in ICD-10 with a third digit of 4, 5, or 7) between January 1987 and December 2003 in Finland. Patients (mean age = 43.7 years, standard deviation = 13.5 years) were followed until first occurrence of schizophrenia spectrum disorder, death, or the end of December 2003, whichever took place first. Conversions of discharge diagnoses into schizophrenia spectrum disorders (codes 2951-2959 and 2971 in DSM-III-R and codes F20, F22, and F23 in ICD-10) were recorded at follow-up. Eight-year cumulative risk to receive a schizophrenia spectrum diagnosis was 46% (95% CI, 35%-57%) for persons with a diagnosis of cannabis-induced psychosis and 30% (95% CI, 14%-46%) for those with an amphetamine-induced psychosis. Although alcohol-induced psychosis was the most common type of SIP, 8-year cumulative risk for subsequent schizophrenia spectrum diagnosis was only 5.0% (95% CI, 4.6%-5.5%). No differences were detected with regard to gender, except for amphetamine-induced psychosis, which converted into a schizophrenia spectrum disorder significantly more often in men (P = .04). The majority of conversions to a schizophrenia spectrum diagnosis occurred during the first 3 years following the index treatment period, especially for cannabis-induced psychosis. Substance-induced psychotic disorders predict schizophrenia spectrum disorders to a greater extent than previously thought.

Raver et al 2013 investigated whether adolescent cannabinoid exposure alters cortical oscillations in adults. Cortical oscillations are integral for cognitive processes and are abnormal in people with schizophrenia. The endocannabinoid system on which marijuana acts is a neuromodulatory system which actively develops cortical oscillations. They demonstrated that chronic adolescent but not adult cannabinoid exposure suppresses pharmacologically evoked cortical oscillations and impairs working memory performance in adults.

2013 Van der Pol and others compared mental health differences between frequent cannabis users with or without dependence and the general population. They concluded that 'Cannabis use patterns, childhood adversity and the use of other substances are similar in dependent and non-dependent frequent cannabis uses. With the exception of more externalizing disorders, the mental health condition of non-dependent frequent cannabis users is similar to that of the general population, whereas it is worse in dependent frequent cannabis users.

2013 Blakemore, S-J is rethinking the adolescent brain. In an article in The Lancet she documents her research on the subject. She became intrigued by the fact that people with schizophrenia predominantly experience their first episode of psychosis early in adulthood. She found that 'adolescence is not too late in terms of learning, training and intervention. The idea that if something goes wrong in the first 5 years of your life, it's too late to do anything about, is really contradicted by this new research, which suggests that developmental plasticity very much continues'.

2013 Di Forti et al found that daily use, especially of High-Potency Cannabis, Drives the Earlier Onset of psychosis in Cannabis Users. 410 first-episode psychosis patients were studied to investigate the association between gender, patterns of cannabis use and and AOP ( Age of Onset of Psychosis). Patients with a history of cannabis use presented with their first episode at a younger age than those who had never used cannabis. This association remained significant after adjusting for gender. Those who started at 15 or younger had an earlier onset than those over 15. Subjects who had been using the high potency cannabis (skunk) every day, had the earliest onset, on average 6 years earlier than non-users.

2013. Poulton, looking at the results of the Dunedin Study (running now 40 years and involving over 1,000 subjects) said that chronic cannabis use in early adolescence makes some people up to 11 times more likely to develop schizophrenia. For people who used cannabis heavily before the age of 18, the risk of schizophrenia went up 10.3%. Heavy usage after 18 increased the risk by 4.7%. He also said that for certain people with a specific gene combination the risk increased about 11 fold, and that a quarter of the population carries this combination.

2013 Van Haren et al looked at brain volume loss in schizophrenia and confounding factors. There is convincing evidence that schizophrenia is characterised by progressive brain volume changes during the course of the illness. It has now been discovered that medication intake and cannabis use are important confounding factors when interpreting brain volume anomalies. Continued use of cannabis but not smoking is associated with a more pronounced loss in grey matter in the anterior cingulated and prefrontal cortex.

Davis et al, 2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC Wave 2). Nearly 35,000 adults in the USA surveyed for cannabis use and psychotic-like symptoms in the first population-based study. The Association between lifetime cannabis use, psychosis and schizotypal personality features was examined. The prevalence of psychosis and schizotypal personality disorder significantly increased with greater cannabis use in a dose-dependent manner. Association for cannabis use and psychosis was 1.27, lifetime abuse 1.79 and lifetime dependence 3.69. There was a similar dose–response relationship for cannabis and shizotypal personality disorder, 2.02 for lifetime use, 2.83 for cannabis abuse and 7.32 for lifetime dependence.

2013 Rocchetti and others questioned whether cannabis is neurotoxic for the healthy brain. 14 studies (362 users and 365 non-users) were looked at for alteration in grey and white matters in non-psychotic subjects. The meta-analysis showed a consistent smaller hippocampus in users compared to non-users. Conclusion: ‘Chronic and long-term cannabis exposure may exert significant effects in brain areas enriched with cannabinoid receptors such as the hippocampus which could be related to a neurotoxic action’.

2013 Issa et al examined the effects of Dronabinol (synthetic THC) on patients to compare them with the effects of whole cannabis. 30 chronic non-cancer pain patients taking opioids but not cannabis were used. 10mg and 20mg doses of Dronabinol were used. These were found to have similar psychoactive effects to smoking marijuana. This risk must be considered when prescribing cannabinoid medications for pain relief.

2013 Hurd et al said that perception of marijuana as a ‘safe drug’ is scientifically inaccurate after looking at 120 teen brain studies. The current evidence suggests that cannabis exposure has a far-reaching influence on adult addictive behaviours particularly for certain subsets of vulnerable individuals. They looked at genetics, environment, brain biology, chemical reactions, gateway and psychosis. Data from epidemiological studies have repeatedly shown that association between cannabis use and subsequent addiction to heavy drugs and psychosis (schizophrenia). The risks are not the same for all of them. Genetic factors, age of initiation and intensity of use are all involve. When comparing older and younger adolescents the younger ones are worse in mental health, educational attainment, delinquency and ability to conform to adult roles. A quarter of adolescents will develop an abusive or dependent relationship with the drug.

2014 Smith and others found that regular teenage smokers of marijuana may be at increased risk of schizophrenia. Smoking daily for 3 years resulted in poor performance in tests of working memory and had abnormal changes in brain structure akin to those seen in patients with schizophrenia. These changes appeared to last at least a few years after stopping. The marijuana smokers started daily smoking between 16 and 17 and continued for 3 years. At study time they had been free of marijuana for 2 years. They did not abuse any other drugs.

2014 Proal et al, looked at familial morbid risk for schizophrenia is the crucial factor that underlies the association of adolescent cannabis use with the development of schizophrenia. All cannabis-using subjects had used no other drug except alcohol. They concluded: ‘Having an increased familial morbid risk for schizophrenia may be the underlying basis foe schizophrenia in cannabis users, not cannabis use by itself.

2014 Hartz et al investigated the co-morbidity of severe psychotic disorders with measures of substance abuse. The Genomic Psychiatry Cohort consists of 9142 clinically assessed multi-ethnic sample with various severe mental illnesses. Thee were 10,195 controls. The results were: Relative to the general population, Individuals with severe psychotic disorders have increased risks for smoking, odds ration 4.6, heavy alcohol use 4, heavy marijuana use 3.5,and recreational drug use 4.6. All races (African-American, Asian, European American and Hispanic) and both sexes had greatly elevated risks for smoking, alcohol, marijuana and drug use.

2014 Alemany and others investigated whether the psychotic-inducing effects of cannabis are related to both childhood abuse and the COMT genotypes. 533 individuals were assessed for psychotic experiences, childhood abuse, cannabis use and COMT Val/Met genotypes. Conclusion: Cannabis use after exposure to childhood abuse may have opposite effects on the risk of psychotic experiences depending on the COMT genotypes providing evidence for a qualitative interaction. Val carriers exposed to childhood abuse are vulnerable to the psychosis-inducing effects of cannabis.

2014 Clausen et al did a 5-year follow-up of patients with first-episode psychosis. They found that continuous cannabis use was associated with higher levels of psychotic symptoms after 5 years and this association was only partially explained by insufficient anti-psychotic medicine.

2014 Donoghue et al investigated cannabis use and age of onset of schizophrenia. Cannabis users had an earlier age of first symptom than non-users. The gender difference in age of onset was diminished in cannabis smokers compared with non-smokers.

2014 Lagerberg et al investigated a dose-response relationship between cannabis use and age at onset in bipolar disorder. They found a significant association indicating a dose-response relationship between cannabis use and age at onset in bipolar disorder, which remained statistically significant after controlling for possible confounders.

2014 April 15th Gilman et al found brain changes associated with casual marijuana use in young adults. MRI imaging was used to compare brains of 18 to 25 year olds who reported smoking cannabis at least once a week. None were dependent on the drug. The more they used, the greater the damage in 2 regions: the nucleus accumbens ( reward processing) was larger and altered in shape and structure compared with that of non-users and the amygdala ( emotions) had the same results.

2014 Freeman and others found out how cannabis causes paranoia. 121 people with paranoid ideation were randomised to receive placebo, THC or THC preceded by a cognitive awareness condition. THC significantly increased paranoia, negative effect (anxiety, worry, depression, negative thoughts about the self) and a range of anomalous experiences, and reduced working memory capacity. The increase in negative effect and anomalous experiences fully accounted for the increase in paranoia. It was definitely demonstrated that the drug triggers paranoid thoughts in vulnerable individuals.

2014 Ortiz-Gomez and others looked at factors associated with depression and suicide attempts in patients undergoing rehabilitation for substance abuse. 57 patients attending a centre for drug abuse treatment were involved in the study - alcohol and marijuana were the drugs studied. 68.4% had current major depression. They concluded that 'Patients with depression who attempted suicide prior to the use of drugs also experienced these conditions during the rehabilitation process. Substance use in the family was a risk factor for both.

2014 Lisdahl K, director of the brain imaging and neuropsychology lab at University of Wiskonsin-Milwaukee, in a presentation to American Psychological Association's 122nd Annual Convention said that: 'Frequent marijuana use (around once/week) can have a significant negative effect on the brains of teenagers and young adults, including cognitive decline, poor attention and memory, and decreased IQ. Abnormalities in the brain's gray matter (assoc with intelligence) have been found in 16 – 19 year olds who increased use over the past year.

2014 Battistella et al looked at the Long-term Effects of Cannabis on Brain Structure. Regular smokers were compared with occasional smokers matched by years of cannabis smoking. Regular cannabis use is associated with reduction of gray matter volume in the medial temporal cortex, temporal pole, para hippocampal gyrus, insula and orbitofrontal cortex. These are areas rich in cannabinoid CB1 receptors and functionally associated with motivational, emotional and affective processing. These changes

correlate with the frequency of cannabis use before inclusion in the study. Age of onset also influences the magnitude of these changes. Significant gray matter volume reduction could result either from heavy consumption unrelated to the age of onset or instead from recreational cannabis use initiated at an adolescent age. In contrast, the larger gray matter volume detected in the cerebellum of regular smokers without any correlation with the monthly consumption of cannabis may be related to developmental processes occurring in adolescence (lack of pruning).

2014 Van Gastel and others looked at changes in cannabis use in the general population and psychotic experiences. 705 (18-27 year olds) gave information on their cannabis use and again six months later, then after 5 years. A decrease in cannabis use was associated with a decrease in total psychotic experiences. An increase in use was associated with increased positive symptoms, but not significantly linked with negative and depression symptom scores nor total number of psychotic experiences.

2014 Filbey et al using MRI techniques found that chronic marijuana users have smaller brain volume in the OFC (Orbitofrontal Cortex, a part of the brain commonly associated with addiction), but also increased brain connectivity. 48 adult marijuana users (average 3 times/day) and 62 gender and age matched non-users were studied. The study provides evidence (according to the authors) that chronic marijuana use initiates a complex process that allows neurons to adapt and compensate for smaller gray matter volume. Eventually the structural conductivity (wiring) of the brain starts degrading with prolonged use, but marijuana users continue to display more intense conductivity than healthy non-users. This may help to explain why chronic long-term users seem to be doing 'just fine' despite smaller OFC volumes. Age of first use and duration of use are of vital importance.

2014 Gibbs et al looked at cannabis use and the incidence of manic symptoms and their occurrence in those already diagnosed with pre-existing bipolar disorder mania. A systematic review of the scientific literature were searched, 6 met the inclusion criteria. 2391 individuals had experienced manic symptoms, mean length of follow-up was 3.9 years. An association was found between cannabis use and the exacerbation of manic symptoms in those previously diagnosed with bipolar disorder. Also, a meta-analysis of 2 studies showed that cannabis use is associated with an approximately 3-fold increased risk for the new onset of manic symptoms. Although only a small number of studies was available, they concluded that cannabis use may worsen the occurrence of manic symptoms in those with bipolar disorder, it may also be a causal factor in the incidence of manic symptoms.

2014 Nov Renard et al investigated the log-term consequences of adolescent cannabinoid exposure in adult psychopathology. They concluded that early onset marijuana use has long-lasting consequences on cognition in humans and is associated with a two-fold increase in the risk of developing a psychotic disorder.

2014 Nov Zorrilla and others investigated bipolar disorder and quitting cannabis during manic/mixed episodes. They found that bipolar patients who stop using cannabis during manic/mixed episode have similar clinical and functional outcomes to never users, while continued use is associated with higher risk of recurrence and poorer functioning.

2014 Lorenzetti et al looked at brain changes with chronic heavy cannabis use. Fifteen very heavy smokers of cannabis with minimal psychiatric comorbidity or significant exposure to other substances were compared with 15 age and IQ matched non-cannabis using controls. The heavy users demonstrated smaller hippocampus and amygdala volumes but no alterations in the orbito-frontal and anterior- and paracingulate cortices or the pituitary gland.

2014 Di Forti et al looked at the age of onset of psychosis and the potency of skunk. Patients with a history of cannabis use (daily) presented with their first episode of psychosis at an earlier age than those who had never used. Those who started under 15 had an earlier onset than those who started after 15 years. Those who used high potency cannabis (skunk) every day had the earliest onset compared to never users among all the groups – average of 6 years earlier than that of non-users.

2014 Wilkinson et al found that marijuana may actually worsen PTSD symptoms and increase violent behaviour. 2,276 participants, admitted to specialised Veterans Administration treatment programmes for PTSD between 1991 and 2011 were split into 4 groups - 831 who started taking marijuana (starters), 850 who never used marijuana (never used) 296 who used marijuana at admission and after discharge (continuing use) and 299who stropped using marijuana after treatment. (stoppers).

Those who never used marijuana had significantly lower symptom severity 4 months later than those who continued or started use after treatment. On the other hand, the highest levels of violent behavior were found in the so-called "starters," those who were not using the substance at admission but who started use after discharge.

2014 Fleur et al predicted intimate partner violence by type of substance use disorder. All patients (N = 1799) were screened for IPV perpetration and victimization; almost one third of the sample committed or experienced any IPV in the past year. For males, an alcohol use disorder in combination with
a cannabis and/or cocaine use disorder significantly predicted any IPV (perpetration and/or victimization) as well as severe IPV perpetration. For females, alcohol and cocaine abuse/dependence predicted both any IPV (perpetration and/or victimization) and severe IPV perpetration. Results from the present study emphasize the importance of routinely assessing IPV in patients in substance abuse treatment and demonstrate that clinicians should be particularly alert for IPV in patients with specific substance use disorder combinations.

2014 Day et al looked at PME (Prenatal Marijuana Exposure), age of marijuana initiation, and the development of psychotic symptoms in young adults. 763 pregnant women who completed the birth assessment in their fourth prenatal month, were selected for follow-up. Women and their offspring were followed till the offspring were 22 years of age (596 offspring were evaluated). PME and EAOM (Early Age Onset Marijuana) significantly predicted increased rates of PS (Psychotic Symptoms) at 22 years of age, controlling for other significant co-variants. They concluded that PME in addition to EAOM, may also play a role in the association between marijuana use and the development of PS.

2014 Chabrol et al looked at the association between personality disorders traits and problematic cannabis use in adolescents. Participants were 111 high school students. They found that personality disorder traits explained a high part of the variance in problematic cannabis use symptoms. Schizotypal and borderline personality traits were positively associated to problematic cannabis use symptoms after adjustment for anxious and depressive symptoms.

2014 Large et al conducted a meta-analysis of outcomes associated with psychosis and co-morbid substance abuse. Current substance-using patients were significantly younger than non-substance-using patients and more likely to be male. They did not differ in age at onset of psychosis or in level of education. Current substance users had higher rates of positive symptoms and were more likely to have a history of violence. Older studies reported a stronger association between current substance abuse and positive symptoms than those more recently published. Current substance abusers did not differ from non-users on measurements of negative symptoms, depressive symptoms, social function, self-harm or number of hospital admissions. They concluded: Current substance users with psychosis may have more severe positive symptoms than patients never used substances, but this result should be interpreted with caution because of demographic differences between substance users and non substance users.

2014 Valmaggia et al looked at cannabis use and transition to psychosis in people at ultra-high risk. Among current cannabis users, frequent use, early onset use and continued use after clinical presentation were associated with transition to psychosis.

2014 Stone et al looked at cannabis and first episode psychosis: relationship with manic and psychotic symptoms and with age at presentation. They found that the level of cannabis use was associated with a younger age at presentation, manic symptoms and conceptual disorganisation, but not with delusions, hallucinations, negative symptoms or daily functioning. Cannabis users who reduced or stopped their use following contact with services had the greatest improvement in symptoms at one year compared with continued users and non-users. Continued users remained more symptomatic than non-users at follow-up. Conclusion: Effective interventions for reducing cannabis use may yield significant health benefits for patients with first-episode psychosis.

2014 Radhakrishnan et al reviewed the association of cannabis with psychosis. Abstract: 'Cannabis is the most commonly used illicit drug worldwide, with ~5 million daily users worldwide.

Emerging evidence supports a number of associations between cannabis and psychosis/psychotic disorders, including schizophrenia. These associations-based on case-studies, surveys, epidemiological studies, and experimental studies indicate that cannabinoids can produce acute, transient effects; acute, persistent effects; and delayed, persistent effects that recapitulate the psychopathology and psychophysiology seen in schizophrenia. Acute exposure to both cannabis and synthetic cannabinoids (Spice/K2) can produce a full range of transient psychotomimetic symptoms, cognitive deficits, and psychophysiological abnormalities that bear a striking resemblance to symptoms of schizophrenia. In individuals with an established psychotic disorder, cannabinoids can exacerbate symptoms, trigger relapse, and have negative consequences on the course of the illness. Several factors appear to moderate these associations, including family history, genetic factors, history of childhood abuse, and the age at onset of cannabis use. Exposure to cannabinoids in adolescence confers a higher risk for psychosis outcomes in later life and the risk is dose-related. Individuals with polymorphisms of COMT and AKT1 genes may be at increased risk for psychotic disorders in association with cannabinoids, as are individuals with a family history of psychotic disorders or a history of childhood trauma. The relationship between cannabis and schizophrenia fulfills many but not all of the standard criteria for causality, including temporality, biological gradient, biological plausibility, experimental evidence, consistency, and coherence. At the present time, the evidence indicates that cannabis may be a component cause in the emergence of psychosis, and this warrants serious consideration from the point of view of public health policy'.

2015 Di Forti et al looked at first-epsode psychosis attributable to high-potency cannabis in South London. 410 patients (2005-2011) with first episode psychosis were compared with 370 controls. The risk of individuals having a psychotic disorder showed a roughly 3 times increase in users of skunk-like cannabis compared with those who had never used. Use of skunk-like cannabis every day conferred the highest risk of psychotic disorders compared with the never-users - around 5 times. The population attributable fraction of first episode psychosis for skunk use for our geographical area was 24% probably because of the high prevalence of high potency cannabis by 218 of 410 patients (53%) in the study.

2015 Murray conducted a review of the links between cannabis and psychosis and schizophrenia, 'Appraising the Risks of Reefer Madness'.

2015 May, Estevez et al looked at ADHD and its association with substance use and substance use disorder in young men. 5677 Swiss young men (mean age 20 plus or minus 1.23 years) were studied.
Men with ADHD were more likely to report having used nicotine, cannabis and other illicit drugs at some time in their life, but not alcohol. ADHD was positively associated with early initiation of alcohol, nicotine and cannabis use, the risky use of these substances, and the presence of alcohol use disorders, and nicotine and cannabis dependence. Additionally, our analyses revealed that these patterns are also highly associated with ASPD ( Anti Social Personality Disorder). After adjusting for this disorder, the association between ADHD and licit and illicit substance use and the presence of SUD ( Substance Use Disorders) was reduced, but remained significant.

2015 May, Delforterie et al Looked at the relationship between cannabis involvement and suicidal thoughts and behaviours. All levels of cannabis involvement were related to SI (Suicidal ideation). Cannabis use and endorsing 3 or more cannabis use disorder symptoms were associated with unplanned, but not planned suicide attempts. Associations persisted even after controlling for other psychiatric disorders and substance involvement. Overlapping genetic and environmental factors were responsible for the covariance between cannabis involvement and SI. They concluded that cannabis involvement is associated, albeit modestly, with SI and unplanned suicide attempts. Such attempts are difficult to prevent and their association with cannabis use and cannabis use disorder symptoms requires further study, including in different samples and with additional attention to confounders.

2015 June 6th, Mizrahi et al found that pot can pose a psychosis risk for teens with developing brains. In those that are vulnerable, it doubles the risk. 'They present with hallucinations, seeing things, hearing things, sometimes they will try to self-harm or go after other people'. Genetics, social issues, marijuana strength and frequency of use are among the complex variables with how use starts. Brain development continues till the twenties and cannabis affects the brain's regulator system, the endo-cannabinoid system which controls things like mood and memory. Psychotic episodes can be short-

lived or trigger a long-term illness. Past-year use of cannabis in Ontario is estimated at 23% of grades 7-12, and 40% for those aged 18-29.

2015 Zaman et al studied the co-occurrence of substance-related and other mental health disorders among adolescent cannabis users. We analyzed intake data from 483 adolescents referred for evaluation at an adolescent substance abuse clinic, with information gleaned from the adolescents and their parents or caregivers. Forty-seven percent of our sample met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) criteria for cannabis dependence and another 32% for cannabis abuse. Among adolescents with cannabis use disorders, the co-occurrence of alcohol and opioid abuse or dependence was high. These individuals also suffered from significant psychiatric comorbidities otherwise. Our results show that cannabis use carries the risk of dependence and also carries with it significant risk of comorbidities, both with respect to other substance use disorders and other psychiatric illness. Given the growing body of research linking cannabis use with addiction and other psychiatric illness, public health efforts ought to center on the potential dangers of cannabis use.

2015 Wetherill and others investigated cannabis, cigarettes, their co-occurring use and differences in gray matter volume. 4 groups were used – cannabis dependents only (Cs), cannabis dependents smoking tobacco (CTs), tobacco dependents only (Ts) and healthy controls (HCs). Compared to HCs, the Cs, Ts and CTS exhibited larger gray matter volume in the left putamen. Cs had larger gray matter volume in the right pre-central gyrus than the HCs. Cs and CTs had smaller gray matter volume in the HCs in the thalamus, and CTs and Ts had smaller cerebellar gray matter volumes than the HCs. This provides evidence that cannabis and tobacco exposure are associated with alterations in brain regions associated with addiction.

2015 Hjorthoj et al assessed the association between mortality and lifetime substance use disorder in patients with schizophrenia, bipolar disorder or unipolar depression. 4,1470 people with schizophrenia, 11,739 with bipolar disorder and 88,270 with depression were studied. They concluded that Mortality in people with mental illness is far higher in people with substance-use disorders than in those without, particularly in people who misuse alcohol and hard drugs.

2015 French et al investigated whether the use of cannabis during early adolescence (by 16) was associated with variations in brain maturation as a function of genetic risk for schizophrenia as assessed with a polygenic risk score. 1,577 participants were studied. They reported a negative association between cannabis use in early adolescence and cortical thickness in male participants with a high polygenic risk score.

2015 Hamilton et al looked at cannabis psychosis and gender. Large data sets over 11 years were used. Data suggests that twice as many males as females use cannabis. This gender ratio is mirrored in rates of psychosis with males outnumbering females by 2:1. But the research team found that there is a significant widening of this ration for cannabis psychosis where males outnumber females by 4:1.

2015Mashhoon et al looked at cortical thinness and volume differences associated with marijuana abuse in emerging adults. Whole brain CT analysis revealed marijuana users had significantly less cortical thickess in their right fusiform gyrus compared to non-users. Thalamic volume was significantly smaller in users compared to non-users and associated with non-planning and overall impulsivity. So cortical thinness and smaller thalamic volume is associated with marijuana abuse. This may interfere with their known roles in regulating visuo-perceptual and object information processing.

2015 Tunbridge et al looked at the effect of the COMT gene on working memory and psychosis. The study investigated the moderation of the impact of experimentally administered THC by COMT. 78 participants, vulnerable to paranoia were used in a double-blind experiment. With respect to cognitive effects, the THC impaired performance in COMT Val/Val but not Met carriers. Psychosis was unaffected by the COMT genotype.

2015 Renard et al looked at long-term structural and functional changes in the prefrontal cortex (PFC) in chronic use by adolescent rats. They found that there were changes in synaptic structure and function in the PFC and that these changes provide key insight to structural functioning and molecular underpinnings of long-term cognitive deficits induced by adolescent cannabinoid exposure. ‘They

suggest that cannabinoids may impede the structural maturation on neuronal circuits in the PFC, thus leading to impaired cognitive functioning in adulthood'.

2015 Helle et al investigated cannabis use, schizophrenia and early onset. 1119 Norwegian patients with schizophrenia spectrum disorders were recruited and studied. Patients with substance abuse (627) had about 3 years earlier age at onset than the abstinent group. Only cannabis use was statistically significantly related to earlier age at onset. Gender or family history of psychosis did not influence the results.

2015 Cortes-Briones et al found that cannabis increases the noise in the brain. THC increases random neural activity in the brain (neural noise) of healthy individuals. Half to a single joint produced psychosis-like effects and increased neural noise. There is a dose-dependent and strong positive relationship between these findings, disrupting the brain's normal information processing. The electrical brain activity in 24 people was studied over 3 days.

2015 Rigucci et al investigated the effect of high-potency cannabis on the microstructure of the corpus callosum (crucial part of brain responsible for communication between the two brain hemispheres, composed of white matter fibres, called axons). They found 'the more cannabis you smoke and the higher the potency the worse the damage will be'. They examined the white matter in the brains of 56 people who reported a first episode psychosis at the South London and Maudsley NHS Foundation Trust, and 43 healthy participants from the local area. They also discovered that 'frequent use of high potency cannabis significantly affects the structure of white matter fibres in the brain whether you have psychosis or not'. The worst damage (lesions) was seen in the most posterior part of the corpus callosum.

2016 Laviolette et al looked at the risks of schizophrenia in adolescent rodents. Substantial and persistent behavioural, neuronal and molecular changes that arte identical to neuro-psychiatric conditions such as schizophrenia were observed. They were socially withdrawn, had increased anxiety, cognitive disorganisation and abnormal levels of dopamine – all factors present in clinical populations of schizophrenia. These changes continued into early adulthood, well past the initial exposure. Adults exposed in the same way did not show the same changes.

2016 Morgan et al looked at the AKT1 gene on 442 healthy young cannabis users while intoxicated with their own cannabis and 7 days after when drug free. Around half the population carries this gene. Variation at one locus of the AKT1 gene predicted acute psychotic response to cannabis along with dependence on the drug and baseline schizotypal symptoms. Working memory following cannabis acutely was worse in females. These are the first findings to demonstrate that AKT1 mediates the acute response to cannabis in otherwise healthy individuals and implicate the AKT1 pathway as a possible target for prevention and treatment of cannabis psychosis.

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 Patel et al looked at the association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis. Anonymised electronic mental health record data from The South London and Maudsley NHS Foundation Trust was used. They found **c**annabis use present in 46.3% of the sample at first presentation and was particularly common in patients who were 16–25, male and single. It was associated with increased frequency of hospital admission, increased likelihood of compulsory admission, and greater number of days spent in hospital. The number of unique antipsychotics prescribed, mediated increased frequency of hospital admission, increased likelihood of compulsory admission, and greater number of days spent in hospital. **Conclusions** Cannabis use in patients with FEP was associated with an increased likelihood of hospital admission. This was linked to the prescription of several different antipsychotic drugs, indicating clinical judgement of antipsychotic treatment failure. Together, this suggests that cannabis use might be associated with worse clinical outcomes in psychosis by contributing towards failure of antipsychotic treatment.

2016 Schoeler et al looked at continuing use and discontinuingof cannabis in patients with psychosis. Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

2016 Kelley et al looked at marijuana use in the immediate 5-year pre-mormid period and its association with increased onset of schizophrenia and related psychotic disorders. They concluded 'These data provide evidence of a clear temporal relationship between escalations in use in the five years pre-onset and an increased rate of onset, demonstrate that the strength of the association is similar pre- and post-onset of prodromal symptoms, and determine that early adult use may be just as important as adolescent use in these associations'.

2016 Bechtold et al looked at marijuana use in adolescence and the risk of psychotic symptoms. 1009 males from first grade through 18 years. Study participants were recruited in first and seventh grades. Marijuana use, subclinical psychotic symptoms and time-varying co-variants e.g. other substance use, internalizing/externalising problems were determined from ages 13 to 18 via self-reports. For each adolescent year boys engaged in regular marijuana use, their projected level of subsequent sumclinical psychotic symptoms increased by 21% and projected risk for subclinical paranoia or hallucinations increased by 133% and 92% respectively. This effect persisted through 1 year of abstinence.

2016 Filbey et al looked at long-term marijuana use and alteration in the brain's reward circuit. 59 adult marijuana users (average 12 years of use) and 79 non-users were involved. Researchers found that long-term marijuana users had more brain activity in the meso-corticolimbic reward system when presented with cannabis cues than with natural reward cues. 'This study shows that marijuana disturbs the natural reward circuitry of the brain , making marijuana highly salient to those who already use it heavily. In essence, these brain alterations could be a marker of transition from recreational marijuana use to problematic use', sad Dr Filbey. Cannabis cues included bongs, pipes, joints or blunts as compared with self-selected preferred fruit, banana, apple, orange or grapes.

2016 Martz et al found that marijuana use dampens brain response to reward over time. Measurable changes were found in the brain reward system with marijuana use even when other factors like alcohol and tobacco use were taken into account. 108 people in their early 20s, taking part in a larger study on substance abuse had brain scans at 3 points over 4 years (75% men, almost all white). In the moment of anticipating a reward (e.g. may win money) the nucleus accumbens (part of the reward system) pumps out dopamine (pleasure neurotransmitter), the greater the anticipation the more dopamine is produced. However the more marijuana used, the smaller the response over time. This suggests that long-term marijuana use dampens the emotional response of a person – anhedonia. These brain changes may increase the risk of continued drug use and addiction.

2016 Xie et al looked at associations between co-morbid cigarette, alcohol and marijuana use and psychopathology. A random community based sample of 973individuals, primarily white from upstate New York, with a mean age of 36.6 were studied. They found that in this large community based sample, long-term simultaneous use of alcohol, cigarettes and marijuana was associated with psychiatric disorders in adulthood, such as ASPD (Anti-social Personality Disorder, MDE (Major Depressive Episode), and GAD. Generalised Anxiety Disorder. Social and environmental factors were not examined and it may be possible that precursors to adult psychopathology such as childhood conduct disorder may precede long-term substance abuse.

2016 Mandelbaum et al looked at the adverse effects of marijuana on the brain. The legalisation push for medical and recreational use of marijuana is spreading. It is critical that societal passions not obscure objective assessments of its short and long-term adverse effects especially in relation to its onset of use and chronicity of exposure. 'This critical review focuses on evidence-based research designed to assess both therapeutic benefits and harmful effects of cannabis exposure, and is combined with an illustration of the neuropathological findings in a fatal case of cannabis-induced psychosis. The literature and reported case provide strong evidence that chronic cannabis abuse causes cognitive impairment and damages the brain, particularly white matter, where cannabinoid 1 receptors abound. Contrary to popular perception, there is little objective data supporting preferential use of cannabis over conventional therapy for restoration of central nervous system structure and function in disease states

such as multiple sclerosis, epilepsy, or schizophrenia. Additional research is needed to determine if sub-sets of individuals with various neurological and psychiatric diseases derive therapeutic benefits from cannabis'.

2016 Carey et al Looked at genetics and links with mental illness. "Our research shows that if someone is genetically predisposed towards having mental illness, they are also prone to use licit and illicit substances and develop problematic usage patterns," says Caitlin E. Carey, "This is important because if a mental illness, like depression, runs in your family, you are presumed at risk of that disorder. But we find that having a genetic predisposition to mental illness also places that person at risk for substance use and addiction." "Previous research on the genetic overlap of mental illness and drug use has been limited to family studies. This has made it difficult to examine some of the less common disorders," says Carey. "For example, it's hard to find families where some members have schizophrenia and others abuse cocaine. With this method we were able to compare people with various levels of substance involvement to determine whether they were also at relatively higher genetic risk for psychiatric disorders."
As well as finding an overall genetic relationship between mental health and substance involvement, the study revealed links between specific mental illnesses and drugs. "For example, we found that genetic risk for both schizophrenia and depression are associated with cannabis and cocaine involvement."

2016 Nielsen et al looked at abuse of alcohol and other illicit drugs and schizophrenia risk. Danish records of 3.1 million people's medical records were investigated. The y found the increased risk of schizophrenia from cannabis (skunk) use was 5.2 times, alcohol 3.4, hallucinogenic drugs 1.9, sedatives 1.7, amphetamines 1.24. and other substances 2.8 times. In a second study (Hjorthoj et al), they found that pregnant cannabis-using women had children 6 times more likely to be schizophrenic. For paternal cannabis use there was a 5.5 times increase risk of schizophrenia in the child before/after birth.

2016 Mok et al looked at parental psychiatric disease and risks of attempted suicide and violent criminal offending in offspring. All persons born in Denmark 1967 – 1997 were followed from their 15th birthday till occurrence of adverse outcome or December 31st 2012 whichever came first.
'1 743 525 cohort members (48.7% female) Risks for offspring suicide attempt and violent offending were elevated across virtually the full spectrum of parental psychiatric disease. Incidence rate ratios were the most elevated for parental diagnoses of antisocial personality disorder (suicide attempt, risk 3.96 times; violent offending, 3.62 times; and cannabis misuse (suicide attempt, 3.57 times risk; violent offending, 4.05; and for parental suicide attempt (suicide attempt, 3.42;; violent offending, 3.31 times. Parental mood disorders (and bipolar disorder in particular) conferred more modest risk increases. A history of mental illness or suicide attempt in both parents was associated with double the risks compared with having just 1 affected parent. Associations between parental psychiatric disease and offspring violent offending were stronger for female than for male offspring, whereas little sex difference in risk was found for offspring suicide attempt'. Early interventions to tackle parental mental disorders may be beneficial to both parents and children.

2016 Nesvag et al investigated cannabis use as a possible cause of psychosis. The risk of developing psychosis is more than tripled for those who abuse cannabis according to results from a new twin study at the NIPH (Norwegian Institute of Public Health). The researchers tested both the hypotheses that cannabis use causes psychotic symptoms and that psychotic symptoms lead to cannabis abuse. They found that the twin with symptoms of cannabis abuse had a 3.5 times higher risk of developing symptoms of psychosis compared with the twin with no cannabis abuse. This is also the case in the general population. The other hypothesis was less suited to the data.

2016 Amen et al found abnormally low blood flow in the brain of marijuana users. Abnormally low blood pressure occurred in almost every area of the brain in nearly 1,000 marijuana users compared to healthy controls. The hippocampus, the brain's key learning and memory centre, had the lowest blood flow in marijuana users suggesting higher vulnerability for altzheimer's disease. 28,268 patients were monitored.

2016 Marconi et al conducted a meta-analysis of the aassociation between the level of cannabis use and risk of schizophrenia. Abstract:Cannabis use has been reported to induce long-lasting psychotic disorders and a dose-response relationship has been observed. We performed a systematic review of

studies that investigate the association between the degree of cannabis consumption and psychosis and a meta-analysis to quantify the magnitude of effect. Published studies were identified through search of electronic databases, supplemented by manual searches of bibliographies. Studies were considered if they provided data on cannabis consumption prior to the onset of psychosis using a dose criterion (frequency/amount used) and reported psychosis-related outcomes. We performed random effects meta-analysis of individual data points generated with a simulation method from the summary data of the original studies. From 571 references, 18 studies fulfilled inclusion criteria for the systematic review and 10 were inserted in the meta-analysis, enrolling a total of 66 816 individuals. Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies. A logistic regression model gave an OR of 3.90 (95% CI 2.84 to 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers. Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis. Although a causal link cannot be unequivocally established, there is sufficient evidence to justify harm reduction prevention programs.

2017 Vaucher et al looked at cannabis use and the risk of schizophrenia. Using a genetic approach, we took 10 independent genetic variants previously identified to associate with cannabis use in 32 330 individuals to determine the nature of the association between cannabis use and risk of schizophrenia. Genetic variants were employed as instruments to recapitulate a randomized controlled trial involving two groups (cannabis users vs nonusers) to estimate the causal effect of cannabis use on risk of schizophrenia in 34 241 cases and 45 604 controls from predominantly European descent. Genetically-derived estimates were compared with a meta-analysis of observational studies reporting ever use of cannabis and risk of schizophrenia or related disorders. Based on the genetic approach, use of cannabis was associated with increased risk of schizophrenia (odds ratio (OR) of schizophrenia for users vs nonusers of cannabis: 1.37. The corresponding estimate from observational analysis was 1.43. The genetic markers did not show evidence of pleiotropic effects and accounting for tobacco exposure did not alter the association (OR of schizophrenia for users vs nonusers of cannabis, adjusted for ever vs never smoker: 1.41. This adds to the substantial evidence base that has previously identified cannabis use to associate with increased risk of schizophrenia, by suggesting that the relationship is causal. Such robust evidence may inform public health messages about cannabis use, especially regarding its potential mental health consequences.

2017 Bianco et al looked at cannabis use and the risk for substance use disorders and mood or anxiety disorders using longitudinal data. A nationally representative sample of US adults, 34,653, aged 18 or older, was interviewed in waves 3 years apart (2001-2002 to 2004-2005). Cannabis use was reported from1279 respondents and was significantly associated with substance disorders in wave2. |Any substance disorder Odds Ratio 6.2, alcohol use disorder 2.7, any cannabis use disorder 9.2, any other drug use disorder 2.6 and nicotine dependence 1.7, but not any mood or anxiety disorder.

2017 Dorard et al investigated a possible link between alexithymia (inability to express emotions or understand emotions in others) and cannabis use disorder (CUD).
’120 young patients (95 males - mean age 17.9years with a cannabis dependence or abuse, seeking treatment in an addiction unit, and 110 healthy control subjects (77 males - mean age 18.2years, participated in the study. They completed a battery of self-reports measuring alexithymia , depression and state and trait anxiety. They found that 35.3% of cannabis users were alexithymic, and logistic regression analysis showed that the alexithymic components of difficulties identifying and describing feelings combined with trait anxiety predicted group membership’.

2017 Libuy et al investigated the relative prevalence of schizophrenia among cannabis and cocaine users attending addiction services. ’A sample of 22,615 people treated for illicit drug use disorders was obtained from a national registry of addiction service users in Chile. Clinical diagnoses were established at admission to substance use treatment programs or at any point during the period of treatment. Prevalence rates of schizophrenia and related disorders, and affective disorders were calculated for the groups of people with cocaine use disorders, and cannabis use disorders. Odds ratios (OR) for schizophrenia and for affective disorders were calculated for cannabis users using the group of people treated for cocaine use disorders as reference category. They found that the prevalence of schizophrenia and related disorders was 1.1% in those with cocaine use disorders, but 5.2% in those with cannabis use disorders. The prevalence of affective disorders was 9.3% in cocaine use disorders, and 13.2% in cannabis use disorders. So the prevalence of schizophrenia and to a lesser extent affective

disorders is higher among people with cannabis use disorder than cocaine use disorder among those attending addiction services'.

2017 Chye et al examined cannabis-related hippocampal volumetric abnormalities specific to subregions in dependent users. 'The objective of the study is to investigate gray matter alteration in each of the hippocampal subregions (presubiculum, subiculum, cornu ammonis (CA) subfields CA1-4, and dentate gyrus (DG)) as associated with cannabis use and dependence. A total of 35 healthy controls (HC), 22 non-dependent (CB-nondep), and 39 dependent (CB-dep) cannabis users were recruited. We investigated group differences in hippocampal subregion volumes between HC, CB-nondep, and CB-dep users. We further explored the association between CB use variables (age of onset of regular use, monthly use, lifetime use) and hippocampal subregions in CB-nondep and CB-dep users separately. The CA1, CA2/3, CA4/DG, as well as total hippocampal gray matter were reduced in volume in CB-dep but not in CB-nondep users, relative to HC. The right CA2/3 and CA4/DG volumes were also negatively associated with lifetime cannabis use in CB-dep users. Our results suggest a regionally and dependence-specific influence of cannabis use on the hippocampus. Hippocampal alteration in cannabis users was specific to the CA and DG regions and confined to dependent users'.

2017 Chye et al looked at orbitofrontal and caudate volumes in cannabis users. 'The objective of this study was to investigate the association between CB use and dependence, and the volumes of brain regions critically involved in goal-directed learning and behaviour-the orbitofrontal cortex (OFC) and caudate. In the largest multi-site structural imaging study of CB users vs healthy controls (HC), 140 CB users and 121 HC were recruited from four research sites. Group differences in OFC and caudate volumes were investigated between HC and CB users and between 70 dependent (CB-dep) and 50 non-dependent (CB-nondep) users. The relationship between quantity of CB use and age of onset of use and caudate and OFC volumes was explored. CB users (consisting of CB-dep and CB-nondep) did not significantly differ from HC in OFC or caudate volume. CB-dep compared to CB-nondep users exhibited significantly smaller volume in the medial and the lateral OFC. Lateral OFC volume was particularly smaller in CB-dep females, and reduced volume in the CB-dep group was associated with higher monthly cannabis dosage. They concluded that smaller medial OFC volume may be driven by CB dependence-related mechanisms, while smaller lateral OFC volume may be due to ongoing exposure to cannabinoid compounds. The results highlight a distinction between cannabis use and dependence and warrant examination of gender-specific effects in studies of CB dependence'.

2017 Schoeler et al looked at poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis. In a prospective analysis of data acquired from four different adult inpatient and outpatient units of the South London and Maudsley Mental Health National Health Service Foundation Trust in London, UK, 245 patients were followed up for 2 years from the onset of first-episode psychosis. Continued cannabis use predicted poor outcome, including risk of relapse, number of relapses, length of relapse, and care intensity at follow-up. Between 20% and 36% of the adverse effects of continued cannabis use on outcome in psychosis might be mediated through the effects of cannabis use on medication adherence. Interventions directed at medication adherence could partly help mitigate the harm from cannabis use in psychosis.

2017 Bourque et al investigated marijuana and the vulnerability to psychosis. Progressing from occasional use to weekly or daily use of marijuana can increase the risk to an adolescent of having recurrent psychotic experiences by 159%. They discovered that an increase in symptoms of depression such as low mood and negative thoughts could explain this relationship. Approximately 4000 adolescents of 13 years of age from 31 Montreal schools. Every year from grades 7 to 11 they filled in computerized questionnaires.

2017 Ecker et al Looked at cannabis-related problems and social anxiety. 'Cannabis is the most commonly used illicit drug in the US, and is associated with a range of psychological, social, and physical health-related problems. Individuals who endorse elevated levels of social anxiety are especially at risk for experiencing cannabis-related problems, including cannabis use disorder, despite not using cannabis more often than those with more normative social anxiety. Identification of mechanisms that underlie the relationship between social anxiety and cannabis-related problems may inform treatment and prevention efforts. Post-event processing (PEP, i.e., cognitively reviewing past social interactions/performances) is a social anxiety-related phenomenon that may be one such mechanism. The current study sought to test PEP as a mediator of the relationship between social anxiety and cannabis-related problems, adjusting for cannabis use frequency.Cannabis-using (past 3-month) undergraduate students recruited in 2015 (N = 244; 76.2% female; 74.2% Non-Hispanic

Caucasian) completed an online survey of cannabis use, cannabis-related problems, social anxiety, and PEP. Bootstrap estimate of the indirect effect of social anxiety through PEP was significant, suggesting PEP is a mediator of the social anxiety-cannabis-related problems relationship. Conclusions/Importance: Treatment and prevention efforts may benefit from targeting PEP among individuals with elevated social anxiety and cannabis-related problems'.

2017 Malyshevskaya et al Found that natural THC and Spice could induce seizures. 'Natural cannabinoids and their synthetic substitutes are the most widely used recreational drugs. Numerous clinical cases describe acute toxic symptoms and neurological consequences following inhalation of the mixture of synthetic cannabinoids known as "Spice." Here we report that an intraperitoneal administration of the natural cannabinoid Δ9-tetrahydrocannabinol (10 mg/kg), one of the main constituent of marijuana, or the synthetic cannabinoid JWH-018 (2.5 mg/kg) triggered electrographic seizures in mice, recorded by electroencephalography and videography. Administration of JWH-018 (1.5, 2.5 and 5 mg/kg) increased seizure spikes dose-dependently. Pretreatment of mice with AM-251 (5 mg/kg), a cannabinoid receptor 1-selective antagonist, completely prevented cannabinoid-induced seizures. These data imply that abuse of cannabinoids can be dangerous and represents an emerging public health threat. Additionally, our data strongly suggest that AM-251 could be used as a crucial prophylactic therapy for cannabinoid-induced seizures or similar life-threatening conditions'.

2017 Guttmannova et al assessed the association between regular marijuana use and adult mental health outcomes. The present study is a prospective examination of the relationship between regular marijuana use from adolescence through young adulthood and mental health outcomes at age 33.Data came from a gender-balanced, ethnically diverse longitudinal panel of 808 participants from Seattle, Washington. Outcomes included symptom counts for six mental health disorders. Regular marijuana use was tracked during adolescence and young adulthood. Regression analyses controlled for demographics and early environment, behaviors, and individual risk factors.Nonusers of marijuana reported fewer symptoms of alcohol use disorder, nicotine dependence, and generalized anxiety disorder than any category of marijuana users. More persistent regular marijuana use in young adulthood was positively related to more symptoms of cannabis use disorder, alcohol use disorder, and nicotine dependence at age 33.Findings highlight the importance of avoiding regular marijuana use, especially chronic use in young adulthood. Comprehensive prevention and intervention efforts focusing on marijuana and other substance use might be particularly important in the context of recent legalization of recreational marijuana use in Washington and other U.S. states.

2017 Frissen et al examined Abstract: 'whether cannabis use, childhood trauma and urban upbringing are associated with total gray matter volume (GMV) in individuals with (risk for) psychotic disorder and whether this is sex-specific. T1-weighted MRI scans were acquired from 89 patients with a psychotic disorder, 95 healthy siblings of patients with psychotic disorder and 87 controls. Multilevel random regression analyses were used to examine main effects and interactions between group, sex and environmental factors in models of GMV. The three-way interaction between group, sex and cannabis ($\chi 2$ =12.43, $p<0.01$), as well as developmental urbanicity ($\chi 2$ = 6.29, p = 0.01) were significant, indicating that cannabis use and developmental urbanicity were associated with lower GMV in the male patient group (cannabis: B= -32.54, $p < 0.01$; developmental urbanicity: B= -10.23, p=0.03). For childhood trauma, the two-way interaction with group was significant ($\chi 2$ = 5.74, p = 0.02), indicating that childhood trauma was associated with reduced GMV in the patient group (B=-9.79, p=0.01). The findings suggest that reduction of GMV in psychotic disorder may be the outcome of differential sensitivity to environmental risks, particularly in male patients'.

2017 Foster et al looked at psychosocial functioning among regular cannabis users with and without cannabis use disorder. 'In the United States, cannabis accessibility has continued to rise as the perception of its harmfulness has decreased. Only about 30% of regular cannabis users develop cannabis use disorder (CUD), but it is unclear if individuals who use cannabis regularly without ever developing CUD experience notable psychosocial impairment across the lifespan. Therefore, psychosocial functioning was compared across regular cannabis users with or without CUD and a non-user control group during adolescence (age 17; early risk) and young adulthood (ages 18-25; peak CUD prevalence). Weekly cannabis users with CUD (n = 311), weekly users without CUD (n = 111), and non-users (n = 996) were identified in the Minnesota Twin Family Study. Groups were compared on alcohol and illicit drug use, psychiatric problems, personality, and social functioning at age 17 and from ages 18 to 25. Self-reported cannabis use and problem use were independently verified using co-twin informant report. In both adolescence and young adulthood, non-CUD users reported significantly higher levels of substance use problems and externalizing behaviors than non-users, but lower levels than CUD users. High agreement between self- and co-twin informant reports confirmed the validity of

self-reported cannabis use problems. Even in the absence of CUD, regular cannabis use was associated with psychosocial impairment in adolescence and young adulthood. However, regular users with CUD endorsed especially high psychiatric co-morbidity and psychosocial impairment.

2017 Kejser-Starzer et al looked at the rates of conversion to schizophrenia and bipolar disorder following substance-induced psychosis. All patient information was extracted from the Danish Civil Registration System and the Psychiatric Central Research Register. The study population included all persons who received a diagnosis of substance-induced psychosis between 1994 and 2014 (N=6,788); patients were followed until first occurrence of schizophrenia or bipolar disorder or until death, emigration, or August 2014. Overall, 32.2% of patients with a substance-induced psychosis converted to either bipolar or schizophrenia-spectrum disorders. The highest conversion rate was found for cannabis-induced psychosis, with 47.4% converting to either schizophrenia or bipolar disorder. Young age was associated with a higher risk of converting to schizophrenia. Self-harm after a substance-induced psychosis was significantly linked to a higher risk of converting to both schizophrenia and bipolar disorder. Half the cases of conversion to schizophrenia occurred within 3.1 years after a substance-induced psychosis, and half the cases of conversion to bipolar disorder occurred within 4.4 years.

2017 Marwaha et al looked at cannabis use and hypomania in young people. Abstract: Cannabis use in young people is common and associated with psychiatric disorders. However, the prospective link between cannabis use and bipolar disorder symptoms has rarely been investigated. The study hypothesis was that adolescent cannabis use is associated with hypomania in early adulthood via several potential etiological pathways. Data were used from the Avon Longitudinal Study of Parents and Children, a UK birth cohort study. The prospective link between cannabis use at age 17 and hypomania at age 22‐23 years was tested using regression analysis, adjusted for gender, early environmental risk factors, alcohol and drug use, and depression and psychotic symptoms at age 18 years. Path analysis examined direct and indirect effects of the link and whether gender, childhood family adversity, or childhood abuse are associated with hypomania via an increased risk of cannabis use. Data were available on 3370 participants. Cannabis use at least 2‐3 times weekly was associated with later hypomania (OR = 2.21) after adjustment. There was a dose‐response relationship (any use vs weekly). Cannabis use mediated the association of both childhood sexual abuse and hypomania, and male gender and hypomania. The cannabis use-hypomania link was not mediated by depression or psychotic symptoms. Adolescent cannabis use may be an independent risk factor for future hypomania, and the nature of the association suggests a potential causal link. Cannabis use mediates the link between childhood abuse and future hypomania.

2018 Manza et al looked at heavy cannabis use and altertion of the activity of brain regions linked to negative emotions. Abstract: Cannabis abuse has been associated with psychopathology, including negative emotionality and a higher risk of psychosis, particularly with early age of initiation. However, the mechanisms underlying this association are poorly understood. Because aberrant dopamine (DA) signaling is implicated in cannabis-associated psychopathology, we hypothesized that regular cannabis abuse (CA) would be associated with altered resting functional connectivity in dopamine midbrain-striatal circuits. We examined resting brain activity of subcortical regions in 441 young adults from the Human Connectome Project, including 30 CA meeting DSM criteria for dependence, and 30 controls matched on age, sex, education, BMI, anxiety, depression, and alcohol/tobacco usage. Across all subjects, local functional connectivity density (lFCD) hubs in subcortical regions were most prominent in ventral striatum, hippocampus, amygdala, dorsal midbrain, and the posterior-ventral brainstem. As hypothesized, CA showed markedly increased lFCD relative to controls in ventral striatum (where nucleus accumbens is located) and midbrain (where substantia nigra/ventral tegmental nuclei are located) but also in brainstem and lateral thalamus. These effects were observed in the absence of significant differences in subcortical volumes, and were most pronounced in the individuals who began cannabis use earliest in life and who reported high levels of negative emotionality.Together, these findings suggest that chronic cannabis abuse is associated with changes in resting brain function, particularly in dopaminergic nuclei implicated in psychosis but that are also critical for habit formation and reward processing. These results shed light on neurobiological differences that may be relevant to psychopathology associated with cannabis use.

2018 Mustonen et al looked at adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. The sample ($n$ = 6534) was composed of the prospective general population-based Northern

Finland Birth Cohort of 1986. Information on prodromal symptoms of psychosis and cannabis use was collected using questionnaires at age 15–16 years. Participants were followed up for ICD-10 psychotic disorders until age 30 years using nationwide registers. The risk of psychosis was elevated in individuals who had tried cannabis five times or more (hazard ratio, (HR) = 6.5, 95% CI 3.0–13.9). The association remained statistically significant even when adjusted for prodromal symptoms, other substance use and parental psychosis (HR = 3.0, 95% CI 1.1–8.0). Conclusion:Adolescent cannabis use is associated with increased risk of psychosis even after adjustment for baseline prodromal symptoms, parental psychosis and other substance use.

2018 Renard et al studied the effects of adolescent THC exposure on the prefrontal GABAergic system: Implications for schizophrenia-related psychopathy. Abstract: Marijuana is the most commonly used drug of abuse among adolescents. Considerable clinical evidence supports the hypothesis that adolescent neurodevelopmental exposure to high levels of the principal psychoactive component in marijuana, -delta-9-tetrahydrocanabinol (THC), is associated with a high risk of developing psychiatric diseases, such as schizophrenia later in life. This marijuana-associated risk is believed to be related to increasing levels of THC found within commonly used marijuana strains. Adolescence is a highly vulnerable period for the development of the brain, where the inhibitory GABAergic system plays a pivotal role in the maturation of regulatory control mechanisms in the central nervous system (CNS). Specifically, adolescent neurodevelopment represents a critical period wherein regulatory connectivity between higher-order cortical regions and sub-cortical emotional processing circuits such as the mesolimbic dopamine (DA) system is established. Emerging preclinical evidence demonstrates that adolescent exposure to THC selectively targets schizophrenia-related molecular and neuropharmacological signaling pathways in both cortical and sub-cortical regions, including the prefrontal cortex (PFC) and mesolimbic DA pathway, comprising the ventral tegmental area (VTA) and nucleus accumbens (NAc). Prefrontal cortical GABAergic hypofunction is a key feature of schizophrenia-like neuropsychopathology. This GABAergic hypofunction may lead to the loss of control of the PFC to regulate proper sub-cortical DA neurotransmission, thereby leading to schizophrenia-like symptoms. This review summarizes preclinical evidence demonstrating that reduced prefrontal cortical GABAergic neurotransmission has a critical role in the sub-cortical DAergic dysregulation and schizophrenia-like behaviors observed following adolescent THC exposure.

2018 Chye et al looked at alteration to the hippocampal volume and shape confined to cannabis dependence. Cannabis use is highly prevalent and often considered to be relatively harmless. Nonetheless, a subset of regular cannabis users may develop dependence, experiencing poorer quality of life and greater mental health problems relative to non-dependent users. The neuroanatomy characterizing cannabis use versus dependence is poorly understood. We aimed to delineate the contributing role of cannabis use and dependence on morphology of the hippocampus, one of the most consistently altered brain regions in cannabis users, in a large multi-site dataset aggregated across four research sites. We compared hippocampal volume and vertex-level hippocampal shape differences (1) between 121 non-using controls and 140 cannabis users; (2) between 106 controls, 50 non-dependent users and 70 dependent users; and (3) between a subset of 41 controls, 41 non-dependent users and 41 dependent users, matched on sample characteristics and cannabis use pattern (onset age and dosage). Cannabis users did not differ from controls in hippocampal volume or shape. However, cannabis-dependent users had significantly smaller right and left hippocampi relative to controls and non-dependent users, irrespective of cannabis dosage. Shape analysis indicated localized deflations in the superior-medial body of the hippocampus. Our findings support neuroscientific theories postulating dependence-specific neuroadaptations in cannabis users. Future efforts should uncover the neurobiological risk and liabilities separating dependent and non-dependent use of cannabis.

2018 Leadbeater et al looked at the age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults. Abstract: Adolescent data(V-HYS; N=662) were collected from a randomly recruited sample of adolescents in Victoria, British Columbia, Canada over a 10-year period(2003-2013). Adult cross-sectional data (NESARC-III; N=36,309) were collected from a representative sample from the US(2012-2013). MEASUREMENTS: Mental health symptoms were assessed using self-report measures of diagnostic symptoms. CU was based on frequency of past-year use. Past-year CUD was based on DSM-5 criteria. For youth in the V-HYS, CU was associated with psychotic symptoms following age 22(b=.13, 95%CI =[.002, .25]), with depressive symptoms from ages 16-19 and following age 25(b=.17, 95%CI =[.003, .34]), but not with anxiety symptoms. CUD was associated with psychotic symptoms following age 23(b=.51, 95%CI=[.01, 1.01]), depressive symptoms at ages 19-20 and following age 25(b=.71, 95%CI=[.001, 1.42]), and anxiety symptoms ages 26-27 only. For adults in the NESARC-III, CU was associated with

mental health symptoms at most ages(e.g., psychotic symptoms; age 18: b=.22, 95%CI=[.10, .33] to age 65: b=.36, 95%CI=[.16, .56]). CUD was associated with all mental health symptoms across most ages(e.g., depressive symptoms; age 18: b=.96, 95%CI=[.19, 1.73] to age 61: b=1.11, 95%CI=[.01, 2.21]). Interactions with sex show stronger associations for females than males in young adulthood(e.g. , V-HYS: CUD by sex interaction on psychotic symptoms significant after age 26; b=1.12, 95%CI=[.02, 2.21]). Findings were not moderated by early onset CU. Significant associations between CU and CUD and psychotic and depressive symptoms in late adolescence and young adulthood extend across adulthood and include anxiety.

2018 Windle et al looked at  Age sensitive associations of adolescent substance use with amygdalar, ventral striatum, and frontal volumes in young adulthood. This study evaluated an age sensitive model of substance use across adolescence to determine if substance use was associated with smaller volumes for an earlier developing brain region, the amygdala, a later developing region, the inferior frontal gyrus, and the ventral striatum. Participants (N = 110) were African American young adults who were members of a longitudinal cohort across childhood and adolescence. Measures of substance use were collected across early (ages 12-15 yrs.), middle (ages 16-18 yrs.), and later (ages 19-21 yrs.) adolescence; then, at age 25, a representative subset of the sample completed magnetic resonance imaging (MRI) that assessed regional brain volumes. Higher levels of substance use during early adolescence, but not middle or later adolescence, were significantly associated with smaller amygdalar volume in young adulthood. Higher levels of substance use during middle adolescence, but not early or later adolescence, were significantly associated with smaller pars opercularis volume. Substance use was not associated with the pars triangularis or ventral striatum. These findings support age sensitive associations between substance use and smaller gray matter volumes at age 25 and are consistent with literature supporting the differential nature of substance use and brain maturation across adolescence and into young adulthood.

2019 Saravia et al investigated concomitant THC and stress adolescent exposure induces fear extinction and related neurobiological changes in adulthood. Abstract: Δ9-tetrahydrocannabinol (THC) consumption during adolescence is reported to be a risk factor for the appearance of psychiatric disorders later in life. The interaction between genetic or environmental events and cannabinoid exposure in the adolescent period can also contribute to exacerbate behavioural deficits in adulthood. Here we investigate the effects of THC treatment as well as the consequences of concomitant THC and stress exposure during adolescence in the extinction of fear memory in adult mice. Adolescent mice treated with THC and exposed to stress exhibit impaired cued fear extinction in adulthood. However, no effect was observed in animals exposed to these two factors separately. Notably, resistance to fear extinction was associated with decreased neuronal activity in the basolateral amygdala (BLA) and the infralimbic prefrontal cortex, suggesting a long-term dysregulation of the fear circuit. These changes in neuronal activation were paralleled with structural plasticity alterations. Indeed, an increase of immature dendritic spines in pyramidal neurons of the BLA was revealed in mice simultaneously exposed to THC and stress. Corticosterone levels were also enhanced after the cued fear conditioning session in the same experimental group. These results show that an interaction between cannabis exposure and stress during adolescence may lead to long-term anxiety disorders characterized by the presence of pathological fear.

2019 Orr et al Abstract: Rates of cannabis use among adolescents are high, and are increasing concurrent with changes in the legal status of marijuana and societal attitudes regarding its use. Recreational cannabis use is understudied, especially in the adolescent period when neural maturation may make users particularly vulnerable to the effects of Δ-9-tetrahydrocannabinol (THC) on brain structure. In the current study, we used voxel-based morphometry to compare grey matter volume (GMV) in 46 fourteen year old human adolescents (males and females) with just one or two instances of cannabis use and carefully matched THC-naïve controls. We identified extensive regions in the bilateral medial temporal lobes as well as the bilateral posterior cingulate, lingual gyri, and cerebellum that showed greater GMV in the cannabis users. Analysis of longitudinal data confirmed that GMV differences were unlikely to precede cannabis use. GMV in the temporal regions was associated with contemporaneous performance on the Perceptual Reasoning Index and with future generalized anxiety symptoms in the cannabis users. The distribution of GMV effects mapped onto biomarkers of the endogenous cannabinoid system providing insight into possible mechanisms for these effects.Significance StatementAlmost 35% of American 10th graders have reported using cannabis and existing research suggests that initiation of cannabis use in adolescence is associated with long-term neurocognitive effects. We understand very little about the earliest effects of cannabis use, however, as most research is conducted in adults with a heavy pattern of lifetime use. This study presents evidence

suggesting structural brain and cognitive effects of just one or two instances of cannabis use in adolescence. Converging evidence suggests a role for the endocannabinoid system in these effects. This research is particularly timely as the legal status of cannabis is changing in many jurisdictions and the perceived risk by youth associated with smoking cannabis has declined in recent years.

2019 Di Forti et al looked at the contribution of cannabis use to variation in the incidence of psychotic disorder across Europe.

**Summary**:**Background** Cannabis use is associated with increased risk of later psychotic disorder but whether it affects incidence of the disorder remains unclear. We aimed to identify patterns of cannabis use with the strongest effect on odds of psychotic disorder across Europe and explore whether differences in such patterns contribute to variations in the incidence rates of psychotic disorder. **Methods** We included patients aged 18–64 years who presented to psychiatric services in 11 sites across Europe and Brazil with first-episode psychosis and recruited controls representative of the local populations. We applied adjusted logistic regression models to the data to estimate which patterns of cannabis use carried the highest odds for psychotic disorder. Using Europe-wide and national data on the expected concentration of Δ⁹-tetrahydrocannabinol (THC) in the different types of cannabis available across the sites, we divided the types of cannabis used by participants into two categories: low potency (THC low potency (THC <10%) and high potency (THC =/> 10%). Assuming causality, we calculated the population attributable fractions (PAFs) for the patterns of cannabis use associated with the highest odds of psychosis and the correlation between such patterns and the incidence rates for psychotic disorder across the study sites. **Findings** Between May 1, 2010, and April 1, 2015, we obtained data from 901 patients with first-episode psychosis across 11 sites and 1237 population controls from those same sites. Daily cannabis use was associated with increased odds of psychotic disorder compared with never users (adjusted odds ratio [OR] 3·2, 95% CI 2·2–4·1), increasing to nearly five-times increased odds for daily use of high-potency types of cannabis (4·8, 2·5–6·3). The PAFs calculated indicated that if high-potency cannabis were no longer available, 12·2% (95% CI 3·0–16·1) of cases of first-episode psychosis could be prevented across the 11 sites, rising to 30·3% (15·2–40·0) in London and 50·3% (27·4–66·0) in Amsterdam. The adjusted incident rates for psychotic disorder were positively correlated with the prevalence in controls across the 11 sites of use of high-potency cannabis (r=0·7; p=0·0286) and daily use (r=0·8; p=0·0109). **Interpretation** Differences in frequency of daily cannabis use and in use of high-potency cannabis contributed to the striking variation in the incidence of psychotic disorder across the 11 studied sites. Given the increasing availability of high-potency cannabis, this has important implications for public health.

2019 Weinberger et al looked at serious psychological distress and daily cannabis use.

ABSTRACT: Daily cannabis use is increasing in the United States (US). Yet, it is not known whether daily cannabis use is disproportionately common, or whether it has increased differentially over time, by mental health status. This study estimated the prevalence of daily cannabis use among adults in the US with and without past-month serious psychological distress (SPD; measured by the Kessler Psychological Distress Scale (K6)) in 2016 and estimated trends in daily cannabis use by past-30-day SPD status from 2008 to 2016. Data were drawn from adults age 18 and older in the 2008-2016 National Survey on Drug Use and Health (combined total analytic sample n = 356,413). Linear time trends of daily cannabis use, stratified by SPD status, were assessed using logistic regression models with continuous year as the predictor.In 2016, past-month daily cannabis use was significantly more common among those with past-month SPD (8.07%), compared to those without past-month SPD (2.66%). Daily cannabis use increased significantly from 2008 to 2016 among those both with and without SPD although use among those with SPD was persistently higher than use among those without SPD over the time period studied. Daily cannabis use is significantly more common among persons with serious psychological distress and is increasing in this group, as well as among those without. Given this increase and the high prevalence of cannabis use among those with SPD, it may be important to consider potential consequences of this increased use for those with mental health vulnerabilities.

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