The metabolic implications of long term cannabis use in patients with psychosis

FARRAH MUSHTAQ, VALERIA MONDELLI, CARMINE M. PARIANTE

Institute of Psychiatry, King's College London, Division of Psychological Medicine, London (United Kingdom)

SUMMARY. **Aims** – The aim of this paper is to summarise the effects of cannabis use on appetite and energy balance, and to subsequently investigate the possible implications this may have in patients with psychosis, in whom a high prevalence of cannabis use has been reported. **Methods** – A narrative review based on the recent literature regarding cannabis use in the general population and patients with psychosis. **Results** – The short-term abilities of cannabis to increase appetite and body weight, through actions on the endogenous endocannabinoid system, have been well characterised throughout the literature. The long term effects of cannabis use are however unclear and only a minority of studies have been conducted in the general population with overall conflicting results. In terms of the effects of cannabis in patients with psychosis, there has only been one study to date that has investigated this and interestingly found cannabis use to be associated with increased body weight and blood glucose levels, thus providing evidence that cannabis use may be an important contributing factor to the reduced life expectancy, as is currently observed in this vulnerable patient group. **Conclusions** – It is clear from the literature that patients with psychosis are at a high risk of metabolic and cardiovascular disease in comparison to the general population. However the contribution of cannabis use to this risk is as of yet undetermined and further long term studies are need to confirm current findings and evaluate hypothesised mechanisms.

Declaration of Interest: None.

KEY WORDS: cannabis, psychosis, weight, metabolic syndrome.

Received 23.04.2008 – Final version received 28.04.2008 – Accepted on 28.04.2008.

INTRODUCTION

Psychosis currently affects over 3 million people worldwide, and has detrimental consequences on all aspects of life including social functioning and psychological wellbeing. The disease is however further complicated by physical ailments (Samele, 2004), including a predisposition for metabolic syndrome and cardiovascular disease. For this reason, the identification and management of contributing risk factors is of great importance, as it allows psychiatrists and general practitioners to focus treatment on risk reduction, thereby improving the physical health of these patients.

Address for correspondence: Dr. V. Mondelli, Section and Laboratory of Stress, Psychiatry and Immunology (SPI-Lab), Centre for the Cellular Basis of Behaviour, The James Black Centre, Institute of Psychiatry, Kings College London, 125 Coldharbour Lane, London SE5 9NU (United Kingdom).

E-mail: valeria.mondelli@iop.kcl.ac.uk

The exact cause of the physical health consequences of psychosis have been attributed to several possibilities, namely the use of antipsychotics, which have been demonstrated to induce weight gain, insulin resistance (Tylee & Haddad, 2007), and increase the risk of vascular disease (Percudani *et al.*, 2006). Furthermore the psychosis itself is believed to influence cardiovascular risk, through mechanisms such as the influence of the disease on lifestyle & diet, and over activity of the hypothalamic-pituitary-adrenal (HPA) axis.

However, in addition to these factors, it has also been suggested that the high prevalence of cannabis use, as reported in patients with psychosis, could be a further contributing factor towards the increased physical health problems faced by these patients. In this paper, we will discuss the well characterised effects of cannabis on appetite, including an evaluation of the actions of cannabis on the endocannabinoid system, and the consequent implications this has on various health outcomes. Furthermore we will also review the current literature regarding the long term implications of cannabis use and evaluate the possible importance of this in patients with psychosis.

THE EFFECTS OF CANNABIS ON APPETITE

Cannabis Sativa, the plant from which cannabis and other related psychoactive substances are obtained, has been cultivated by humans for millennia. Its uses in history have ranged from utilising its fibres to manufacture textiles, to more spiritual and religious purposes, such as an ingredient in holy anointing oil (Guy *et al.*, 2004; Russo, 2007). Its medicinal properties have also been seen throughout history, going as far back as the 2nd century, where there has been documentation of its use by a Chinese emperor as an anaesthetic during surgery (Guy *et al.*, 2004). However it wasn't until 1842 when an Irish surgeon O' Shaughessy, who has been working in India, introduced the substance to the west. Since then its use as a medicinal and recreational drug has increased vastly, and is now one of the most widely used illicit drug in the western world (Kirkham, 2005). Although illegal in the UK, the latest Home Office report estimated that approximately 8.2% of the UK population, aged 16-59, used cannabis in 2006-07 (Home Office, 2007).

The more pharmacological actions of cannabis are due to substances, known as cannabinoids, which are present in various parts of the plant, including the leaves, the female flower head and glandular trichomes, the latter being the source of the more potent drug, known as resin or hashish (Russo, 2007).

Cannabis itself contains over 60 different types of cannabinoids, which are a group of terpenophenolic compounds (Ashton, 2001), including delta-9-tetrahydrocannabinol (THC), the major psycho-active ingredient of cannabis, discovered in 1964 by Gaoni and Mechoulam (Gaoni & Mechoulam, 1964).

The drug is known to have effects on virtually all systems of the body ranging from analgesia and euphoria to emphysema and immunosuppresion (Ashton, 2001). In addition one of its notorious effects is to cause "the munchies", as known by its drug taking counterparts, which refers to its ability to induce a remarkable increase in appetite with a preferential effect on sweet, palatable food intake.

Over the years, there have been numerous studies providing evidence for the appetite stimulating effects of cannabis. The earliest documented study was conducted in 1933 by Siler *et al.* in which a group of soldiers under the influence of cannabis reported feeling hungry and exhibited an increase in food intake in comparison to controls (Siler *et al.*, 1933). These results were later confirmed by a range of subsequent studies undertaken in the 1970s which all reflect the abilities of cannabis to increase body weight and food intake, with a preference for sweet palatable foods (Tart, 1970; Abel, 1971; Hollister, 1971; Greenberg *et al.*, 1976).

The problem with the majority of data obtained from these studies is that firstly the methods used lack scientific thoroughness (Cota *et al.*, 2003a) and thus, as a result, there is no consistency in terms of what dose was used and how subjects were randomised (Kirkham & William, 2001). Secondly, the average joint in the 1970s contained about 10mg of THC, however due to advances in cultivation and breeding techniques the potency of cannabis has increased 15 fold, with an average joint now containing approximately 150mg of THC (Ashton, 2001). Thus the average cannabis smoker of today is subjected to a much larger dose of cannabis than his counterparts back in the 1970s. Since the effects of cannabis are dose related, (Ashton, 2001) this makes most of what we once knew about the drug obsolete, as most of our knowledge has come from experiments done in the 1970s.

Unfortunately due to changes in legislation, and the negative public image associated with the drug, there has been very little research done on cannabis since. However, more recent data regarding its impact on metabolism has been obtained from studies looking at the therapeutic use of cannabis in patients with medical conditions associated with anorexia and weight loss, such as cancer and human immunodeficiency virus (HIV) (Gorter, 1999; Haney *et al.*, 2007). In a recent study, Haney *et al.* (2007) were able to demonstrate, using a double-blinded cross over trial, the effects of smoking cannabis in comparison to placebo in a group of HIV positive patients. The results showed a clear association between cannabis use and an increased daily caloric intake and body weight, in comparison to the placebo group.

THE ROLE OF THE ENDOCANNABINOID SYSTEM IN ENERGY BALANCE

Despite the lack of controlled trials in regards to the effects of cannabis on appetite, there is a clear body of evidence in support of cannabis having an effect on energy intake and body weight. The exact mechanism in which cannabis is able to exert its effects has been a subject of much interest over the past few decades.

Our initial understanding of the effects of cannabis arose from the discovery of the cannabinoid receptor type 1 (CB1), by Matsuda *et al.* (1990), to which endogenous cannabinoids, such as anandamide, bind and lead to the activation of downstream intracellular signalling pathways. Currently it is believed that exogenous cannabis

mimics the actions of endogenous ligands, by binding to the CB1 receptor and exerting a similar effect.

CB1, which is a G-protein coupled receptor, is widely distributed in the central nervous system (CNS), especially in the hypothalamus, an important area of the brain in the control of energy balance and body weight (Bellocchio *et al.*, 2006). CB1 is also widely distributed throughout the neurones of the mesolimbic system, which is an essential part of the "reward pathway" and has an important role in mediating the incentive value of food (Di Marzo & Matias, 2005). CB1 is expressed presynaptically, and activation of CB1, by either endogenous ligands or exogenous cannabis leads to modulation of the release of neurotransmitters that can affect appetite. For example, activation of CB1 receptors in the hypothalamus leads to the release of orexigenic mediators, such as neuropeptide Y (NPY) (Gamber *et al.*, 2005), thus stimulating appetite.

Cannabinoid receptors are also able to cross talk with, and thus influence the activity of other neurotransmitter receptor systems (Matias & Di Marzo, 2007). By doing so, they are able to recruit other intracellular signal transduction pathways, for example, enhancing the release of dopamine in the nucleus accumbens, thus increasing the incentive value of food stimuli (Di Marzo & Matias, 2005).

It has been suggested that as well as its effect on the CNS, cannabis is also able to exert an effect in the peripheries. A study by Greenberg *et al.* (1976) found that the well-characterised increased caloric intake associated with cannabis use disappeared after a few days but that the subjects still continued to gain weight over the following weeks, suggesting the presence of a peripheral mechanism of action on metabolism, independent of the effects of cannabis on the CNS. It has since been discovered that the CB1 receptor is also expressed in the peripheries, hence can interact with key organs in the regulation of energy metabolism (Matias & Di Marzo, 2007; Pagotto *et al.*, 2005). One such example is the stimulation of lipoprotein lipase by the activation of CB1 receptors in the adipose tissue (Cota *et al.*, 2003b), leading to enhanced lipogenesis. This is further supported by evidence from trials with the anti-obesity drug Rimonabant, a CB1 receptor antagonist, which has been shown to improve lipid profiles in obese individuals (Pi-Sunyer *et al.*, 2006). There is also evidence to suggest that CB1 is able to crosstalk with signals of peripheral origin e.g. leptin, adiponectin and ghrelin, (Pagotto *et al.*, 2005) all of which are involved in the regulation of metabolism.

Previous literature has also suggested a role for the endocannabinoid system in glycaemic control. A study in 1978 in dogs, found that cannabis administration caused increased blood glucose and decreased insulin levels (De Pasquale *et al.*, 1978). This is also supported by the recent trials with Rimonabant, which has been shown to improve insulin resistance and reduce HbA1c levels in obese patients (Pi-Sunyer *et al.*, 2006; Scheen *et al.*, 2006). These findings coupled with the recent discovery of functional CB1 receptors expressed in human pancreatic islets cells, provides plausible evidence that stimulation of the endogenous endocannabinoid system by exogenous cannabis could influence glucose homeostasis though as of yet unclear mechanisms.

THE LONG TERM METABOLIC IMPLICATIONS OF CANNABIS USE

The mechanisms of action of cannabis, as described, supports the findings from all of the studies discussed thus far, reflecting the short term abilities of cannabis to stimulate appetite and increase daily caloric intake. Unfortunately, due to limitations of human studies with cannabis, as discussed, there have only been a minority of studies that have evaluated the long term effects of cannabis use on metabolic health risks and furthermore, the results of these have been inconsistent and highly variable throughout the literature.

In a case-control study, Mittlemann *et al.* (2001) interviewed 3882 patients after an acute myocardial infarction and found that compared to non-users, cannabis users were more likely to be obese (43% vs 32%, p=0.008). However in contrast to this, results from the National Health and Nutrition Examination Survey (NHANES III) (Smit *et al.*, 2001), a cross-sectional study of over 10,000 20-59 year olds, conducted in the USA, found that, as predicted, heavy cannabis users had higher total caloric intake, but interestingly had lower mean body mass index (BMI) compared to non-current users ($p<0.0001$). The higher caloric intake was expected as from previous studies but the lower BMI, as seen among cannabis users, was much unexpected, and contradicts most of our current knowledge. The authors suggested that the lower BMI could be attributable to an increased metabolic rate in these subjects. This theory is supported by a previous study by Zwillich *et al.* (1978) who found that metabolic rate was significantly increased, as measured by dioxide consumption, by 28% in subjects after the administration of cannabis. However this study only observed the short-term, immediate effects of cannabis in a very small sample size of 8 participants, and there has been no further attempt to determine the long term effects of cannabis on metabolic rate since.

The most recent long term study in regards to the effects of cannabis on BMI is the Coronary Artery Risk Development in Young Adults (CARDIA) study (Rodondi *et al.*, 2006). This multicentre, longitudinal study, involving a cohort of 3617 individuals, followed over a period of 15 years, confirmed once again that cannabis use was associated with higher caloric intake. However, unlike previous studies, after correcting for alcohol use, they found no significant associations between cannabis use and either BMI or waist girth.

Overall, long term studies have confirmed that cannabis use is associated with a higher caloric intake, but there are still discrepancies as to whether it affects BMI and other cardiovascular risk factors in the long term. Thus, there is a clear need for further research in this area to elucidate whether chronic cannabis use has metabolic implications.

THE IMPORTANCE OF CANNABIS IN PATIENTS WITH PSYCHOSIS

Thus far, all research mentioned has focused on cannabis use in healthy individuals, however there is a particular interest in the effects of cannabis in patients with psychosis due to the fact that these patients are twice as likely to consume cannabis than the general population, with an estimated lifetime prevalence of use of 40% (Green *et al.*, 2005).

Numerous studies in patients with psychosis have revealed over activity of the dopaminergic system, which is believed to facilitate the onset of psychosis by increasing the significance and salience of everyday stimuli, thus leading towards delusions and other symptoms of psychosis (Murray *et al.*, 2007). Since cannabis is able to increase dopaminergic neuronal firing, via actions through the endogenous endocannabinoid system as explained earlier, it is believed that cannabis use might be an independent risk factor for developing psychotic symptoms (Verdoux & Tournier, 2004; Di Forti *et al.*, 2007). It is for this reason that most current research has been focused on the role of cannabis in causing psychosis while less time is being spent on studying the effects of cannabis on metabolism in patients with psychosis.

The reason why the metabolic implications of cannabis is of particular importance in these patients is that patients with psychosis are also known to have a reduced life expectancy, by approximately 20% (Newman & Bland, 1991), in comparison to the general population. This is partly due to an increased risk of suicide and accidents (Holt *et al.*, 2003); however it was also found that the risk of obesity, metabolic syndrome and cardiovascular illness is also significantly increased in these patients (Jacob & Chowdhury, 2008; Samele, 2004; Casey, 2005). In a meta-analysis of 18 international studies, 60% of excess mortality in patients with schizophrenia was attributable to physical illness, with cardiovascular disease being the major contributor (Brown, 1997). Therefore investigating the effects of cannabis on metabolism in these patients is of great interest, as it may be an important factor contributing to the increased risk of metabolic disease, as has been reported in these patients with psychosis.

So far, only one study to date has studied the metabolic implications of cannabis in patients with psychosis. Isaac *et al.* (2005) conducted a prospective, naturalistic study over a period of 3 years, concentrating on the effects of cannabis in a group of 115 patients with chronic psychosis in an intensive care unit (ICU) setting. It was found that the 60% of patients who were positive for cannabis on admission, were associated with higher blood glucose levels (5.3 ± 1.08mmol/l vs. 4.8 ± 0.8 $p=0.035$) and that the 25% of patients who took cannabis during admission, were associated with greater weight increase over 6 weeks, in comparison to patients who weren't using cannabis and on the same hospital diet (10.2kg vs. 2.2kg, $p<0.05$).

Overall Issac *et al.* (2005) have clearly demonstrated that cannabis may have a role in increasing the risk of metabolic disease in patients with psychosis, however the study was limited in the sense that it only concentrated on patients in an ICU setting and, being a naturalistic study, it failed to control for individual differences between patients such as age, ethnicity and use of antipsychotics, hence the results need to be taken with caution. Overall the study does however emphasise the need for further investigation into the long term metabolic effects of cannabis in patients with psychosis.

Furthermore there have been no studies in healthy controls or patients with psychosis regarding the effects of cannabis on leptin or C-reactive protein (CRP). Leptin is a satiety hormone released from adipose tissue that provides feedback to the hypothalamus in regards to the energy status of the body. Experiments have shown leptin to have inhibitory actions on endocannabinoid release (Di Marzo *et al.*, 2001), thus in subjects using exogenous cannabis, one may expect elevated leptin levels as a counter-regulatory response.

Moreover in studies evaluating the effects of the Rimonabant, significant reductions in CRP have been noted with inhibition of the endocannabinoid system (Despres *et al.*, 2005; Scheen *et al.*, 2006). As a result it

has been suggested that perhaps the reverse is true, and that enhanced activation of the endocannabinoid system, via exogenous cannabis, may increase CRP levels. Therefore investigations into the levels of both leptin and CRP, in chronic cannabis users, may provide further insight into the dynamics of cannabis and its interaction with metabolic and cardiovascular disease.

CONCLUSION

It is clear from the literature that patients with psychosis are at a high risk of metabolic and cardiovascular disease in comparison to the general population. Though the high prevalence of metabolic syndrome in these patients can be explained by the use of antipsychotic medication and possibly the effects of the psychosis itself, there are still a variety of other possible factors that could contribute to these adverse physical outcomes, the identification of which could enhance the management of these patients and thus prevent the excess mortality currently observed.

In this paper, we have reviewed the possible mechanisms by which cannabis use may lead to a higher prevalence of metabolic abnormalities. Most of the studies conducted thus far in the general population have only focused on the short term effects of cannabis, hence further studies are still needed to investigate some of the hypothesized mechanisms as well as to confirm current findings. However, the study by Isaac *et al.* (2005) provides plausible evidence for the proposition that the high prevalence of cannabis use, in patients with psychosis, is a contributing factor to the reduced life expectancy, as is currently reported in this at-risk patient group.

Essentially a further understanding of the mechanisms involved in the development of metabolic abnormalities in these patients could influence the way in which we currently manage patients with psychosis. Furthermore, it will allow us to predict individuals at high risk of developing cardiovascular disease, thus ultimately ameliorating the current burden of disease in this vulnerable patient group.

Acknowledgements. Valeria Mondelli is funded by the King's College Development Trust (UK) and the NARSAD Mental Health Research Association. Carmine M. Pariante is funded by the UK Medical Research Council (MRC), the American Psychiatric Institute for Research and Education (APIRE), the British Academy, the Guy's and St. Thomas' Charitable Trust, the NARSAD Mental Health Research Association, and the NIHR Biomedical Research Centre for Mental Health, the South London and Maudsley NHS Foundation Trust & the Institute of Psychiatry, King's College London.

REFERENCES

Abel E.L. (1971). Effects of marihuana on the solution of anagrams, memory and appetite. *Nature* 231, 260-261.

Ashton C.H. (2001). Pharmacology and effects of cannabis: a brief review. *British Journal of Psychiatry* 178, 101-106.

Bellocchio L., Mancini G., Vicennati V., Pasquali R. & Pagotto U. (2006). Cannabinoid receptors as therapeutic targets for obesity and metabolic diseases. *Current Opinion in Pharmacology* 6, 586-591.

Brown S. (1997). Excess Mortality of schizophrenia: A metaanalysis. *British Journal of Psychiatry* 171,502-508.

Casey D.E. (2005). Metabolic issues and cardiovascular disease in patients with psychiatric disorders. *American Journal of Medicine* 118, 15-22.

Cota D., Marsicano G., Lutz B., Vicennati V., Stalla G.K., Pasquali R. & Pagotto U. (2003a). Endogenous cannabinoid system as a modulator of food intake. *International Journal of Obesity* 27, 289-301.

Cota D., Marsicano G., Tschop M., Grubler Y., Flachskamm C., Schubert M., Auer D., Yassouridis A., Thone-Reineke C., Ortmann S., Tomassoni F., Cervino., Nisoli E., Linthorst A.C., Pasquali R., Lutz B., Stalla G.K. & Pagotto U. (2003b). The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. *Journal of Clinical Investigation* 112, 423-431.

De Pasquale A., Costa G. & Trovato A. (1978). The influence of cannabis on glucoregulation. *Bulletin on Narcotics* 30, 33-41.

Di Forti M., Morrison P.D., Butt A. & Murray R.M. (2007). Cannabis use and psychiatric and cognitive disorders: the chicken or the egg. *Current Opinion in Psychiatry* 20, 228-234.

Di Marzo V. & Matias I. (2005). Endocannabinoid control of food intake and energy balance. *Nature Neuroscience* 8, 585-589.

Di Marzo V., Goparaju S.K., Wang L., Liu J., Batkai S., Jarai Z., Fezza F., Miura G.I., Palmiter R.D., Sugiura T. & Kunos G. (2001). Leptin-regulated endocannabinoids are involved in maintain food intake. *Nature* 410, 822-825.

Despres J.P., Golay A. & Sjostrom L. (2005). Effects of Rimonabant on metabolic risk-factors in overweight patients with dyslipidemia. *New England Journal of Medicine* 353, 2121-2134.

Gamber K.M., Macarthur H. & Westfall T.C. (2005). Cannabinoid augment the release of neuropeptide Y in the rat hypothalamus. *Neuropharmacology* 49, 646-652.

Gaoni Y., Mechoulam R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society* 86, 1646-1647.

Gorter R.W. (1999). Cancer cachexia and cannabinoids. *Forschende Komplementarmedizin* 6, 21-22.

Green B., Young R. & Kavanagh D. (2005). Cannabis use and misuse prevalence amongst people with psychosis. *British Journal of Psychiatry* 187, 306-313.

Greenberg I., Kuehnle J., Mendelson J.H. & Bernstein J.G. (1976). Effects of marihuana use on body weight and colric intake in humans. *Psychopharmacology* 49, 79-84.

Guy G.W., Whittle B.A. & Robson P.J. (ed.) (2004). *The Medicinal Uses of Cannabis and Cannabinoids*. Pharmaceutical press: London.

Haney M., Gunderson E.W., Rabkin J., Hart C.L., Vosburg S.K., Comer S.D. & Foltin R.W. (2007). Dronabinol and marijuana in HIV-positive marijuana smokers. *Journal of Acquired Immune Deficiency Syndromes* 45, 545-554.

Hollister L.E. (1971). Hunger and appetite after single doses of marijuana, alcohol and dextroamphetamine. *Clinical Pharmacy* 12, 44-49.

Holt R.I.G., Pevelert R.C. & Byrne C.D. (2003). Schizophrenia, the metabolic syndrome and diabetes. *Diabetic Medicine* 21, 515-523.

Home Office. (2007). *Drug Misuse Declared: Findings from the 2006/07 British Crime Survey*. HMSO: London.

Isaac M., Isaac M. & Holloway F. (2005). Is cannabis an anti-antipsychotic? The experience in psychiatric intensive care. *Human Psychopharmacology* 20, 207-210.

Jacob R. & Chowdhury A.N. (2008). Metabolic comorbidity in schizophrenia. *Indian Journal of Medical Sciences* 62, 23-31.
Kirkham T.C. (2005). Endocannabinoids in the regulation of appetite and body weight. *Behavioural Pharmacology* 16, 297-313.
Kirkham T.C. & William C.M. (2001). Endogenous cannabinoids and appetite. *Nutrition Research Reviews* 14, 65-86.
Matias I. & Di Marzo V. (2007). Endocannabinoids and the control of energy balance. *Trends in Endocrinology and Metabolism* 18, 27-37.
Matsuda L.A., Lolait S.J., Brownstein M.J., Young A.C. & Bonner T.I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 346, 561-564.
Mittleman M.A., Lewis R.A., Maclure M., Sherwood J.B. & Muller J.E. (2001). Triggering myocardial infarction by marijuana. *Circulation* 103, 2805-2809.
Murray R.M., Morrison P.D., Henquet C. Di Forti M. (2007). Cannabis, the mind and society: the hash realities. *Nature Reviews Neuroscience* 8, 885-895.
Newman S.C. & Bland R.C. (1991). Mortality in a cohort of patients with schizophrenia: A record linkage study. *Canadian Journal of Psychiatry* 171, 502-508.
Pagotto U., Vicennati V. & Pasquali R. (2005). The endocannabinoid system and the treatment of obesity. *Annals of Medicine* 2005, 270-275.
Percudani M., Barbui C., Fortino I., Tansella M. & Petrovich L. (2006). Antidepressant and antipsychotic drug prescribing in Lombardy. *Epidemiologia e Psichiatria Sociale* 15, 59-70.
Pi-Sunyer F.X., Aronne L.J., Heshmati H.M. Decin J. & Rosenstock J. (2006). Effect of Rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients. *Journal of the American Medical Association* 295, 761-775.
Rodondi N., Pletcher M.J., Liu K., Hulley S.B. & Sidney S. (2006). Marijuana use, diet, body mass index and cardiovascular risk factors (from the CARDIA study). *American Journal of Cardiology* 98, 478-484.
Russo E.B. (2007). History of cannabis and its preparations in saga, science and sobriquet. *Chemistry & Biodiversity* 4, 1614-1648.
Samele C. (2004). Factors leading to poor physical health in people with psychosis. *Epidemiologia e Psichiatria Sociale* 13, 141-145.
Scheen A.J., Finer N., Priscilla H., Jensen M.D. & Van Gaal L.F. (2006). Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *The Lancet* 368, 1660-1672.
Siler J.F., Sheep W.L., Bates L.B., Clark G.F., Cook G.W. & Smith W.H. (1933). Marihuana smoking in Panama. *Military Surgeon* 73, 269-280.
Smit E. & Crespo C.J. (2001). Dietary intake and nutritional status of US adult marijuana users: results from the third national health and nutrition examination survey. *Public Health Nutrition* 4, 781-786.
Tart C.T. (1970). Marijuana intoxication experiences. *Nature* 226, 701-704.
Tylee A. & Haddad M. (2007). Managing complex problems: treatment for common mental disorders in the UK. *Epidemiologia e Psichiatria Sociale* 16, 302-308.
Verdoux H. & Tournier M. (2004). Cannabis use and risk of psychosis: an etiological link. *Epidemiologia e Psichiatria Sociale* 13, 113-119.
Zwillich C.W., Doekel, Hammil S., Weil J.V. (1978). The effects of smoked marijuana on metabolism and respiratory control. T*he American Review of Respiratory Disease* 118, 885-891.