ORIGINAL RESEARCH

Cannabis Use: Signal of Increasing Risk of Serious Cardiovascular Disorders

Emilie Jouanjus, PharmD, PhD; Maryse Lapeyre-Mestre, MD, PhD; Joelle Micallef, MD, PhD; The French Association of the Regional Abuse and Dependence Monitoring Centres (CEIP-A) Working Group on Cannabis Complications*

***Background*—**Cannabis is known to be associated with neuropsychiatric problems, but less is known about complications affecting other specified body systems. We report and analyze 35 recent remarkable cardiovascular complications following cannabis use.

***Methods and Results*—**In France, serious cases of abuse and dependence in response to the use of psychoactive substances must be reported to the national system of the French Addictovigilance Network. We identified all spontaneous reports of cardiovascular complications related to cannabis use collected by the French Addictovigilance Network from 2006 to 2010. We described the clinical characteristics of these cases and their evolution: 1.8% of all cannabis-related reports (35/1979) were cardiovascular complications, with patients being mostly men (85.7%) and of an average age of 34.3 years. There were 22 cardiac complications (20 acute coronary syndromes), 10 peripheral complications (lower limb or juvenile arteriopathies and Buerger-like diseases), and 3 cerebral complications (acute cerebral angiopathy, transient cortical blindness, and spasm of cerebral artery). In 9 cases, the event led to patient death.

***Conclusions*—**Increased reporting of cardiovascular complications related to cannabis and their extreme seriousness (with a death rate of 25.6%) indicate cannabis as a possible risk factor for cardiovascular disease in young adults, in line with previous findings. Given that cannabis is perceived to be harmless by the general public and that legalization of its use is debated, data concerning its danger must be widely disseminated. Practitioners should be aware that cannabis may be a potential triggering factor for cardiovascular complications in young people. **(*J Am Heart Assoc*. 2014;3:e000638 doi: 10.1161/JAHA.113.000638)**

Key Words: acute coronary syndrome • pharmacodependence • drug abuse • stroke • vascular complications • young

Cardiovascular diseases remain the most frequent cause of global death worldwide, and the most common is coronary artery disease, with a mortality rate of 12.8% in 2011.[1] Acute coronary syndromes significantly contribute to the burden of cardiovascular disease.[2] Reduction of cardiovascular diseases is therefore a key concern in Western countries. In the United States, the American Heart Association aims to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20% by 2020.[3] In Europe, the Systematic COronary Risk Evaluation (SCORE) system was developed to provide a risk-scoring system for the management of cardiovascular risk in clinical practice.[4] The frequency of cardiovascular diseases varies among countries related to geographic differences[1,5] and according to the generally acknowledged risk factors for cardiovascular diseases, the knowledge of which cannot be disassociated from efficient understanding, prevention, and management of cardiovascular diseases. Among these risk factors are obesity (and also, weight changes and sedentary lifestyle), age, metabolic factors such as elevated cholesterol levels, and tobacco

From the Centres d'Evaluation et d'Information sur la Pharmacodependance-Addictovigilance, Service de Pharmacologie Médicale et Clinique, Centre Hospitalier Universitaire, Faculté de Médecine, Toulouse, France (E.J., M.L.-M.); Inserm, UMR1027, Toulouse, France (E.J., M.L.-M., J.M.); Université de Toulouse III, UMR1027, Toulouse, France (E.J., M.L.-M., J.M.); Centres d'Evaluation et d'Information sur la Pharmacodependance–Addictovigilance, Centre Hospitalier Universitaire, Service de Pharmacologie Clinique, Institut de Neurosciences Timone, Aix Marseille Université, Marseille Cedex 5, France (J.M.).

An accompanying Table S1 is available at http://jaha.ahajournals.org/content/3/2/e000638/suppl/DC1

A list of the members of the French Addictovigilance Network Working Group on Cannabis Disorders is given in the Acknowledgments.

Correspondence to: Emilie Jouanjus, PharmD, PhD, Equipe "Pharmacoépidémiologie: Evaluation de l'utilisation et du risque médicamenteux," INSERM UMR1027: Epidémiologie et analyses en santé publique - Risques, maladies chroniques et handicaps, Faculté de Médecine, 37 allées Jules Guesde, Toulouse 31073, France. E-mail: emilie.jouanjus@univ-tlse3.fr

Received November 18, 2013; accepted February 2, 2014.

smoking.[2,6,7] Another possible risk factor is cannabis smoking, which has recently been added to the list of the potential triggers for myocardial infarction.[8] In addition, it was the substance, after tobacco and cocaine, most often identified as being involved in ischemic stroke associated with drugs with abuse potential.[9]

Yet, cannabis is the world's most widely used illicit substance.[10] It benefits from an image of safety for health, and its use has become trivialized. Communication about the potential therapeutic properties of cannabinoids and the marketing of cannabis derivatives in the treatment of pain, nausea, or anorexia in several countries must have contributed to reinforcing the belief that cannabis use could be safe or even healthy.[11] However, it is now acknowledged that cannabis use is harmful to health.[12–16] Although factors such as variety of plant, administration route, concomitant tobacco use, or possible adulterated products may complicate the identification of potential cannabis-related disorders,[17,18] it was suggested that cannabis and tobacco together precipitated the occurrence of coronary syndromes in patients with coronary history compared with tobacco taken alone.[19] Another study conducted in a population of nearly 4000 patients hospitalized for acute myocardial infarction suggested that cannabis use acutely increased the risk of myocardial infarction.[20] More recently, similar serious cardiovascular complications were identified as the reason for hospitalization of young cannabis users.[21] They emerged among all other subgroups of complications because the seriousness of cases and the particular profile of patients, principally of young and apparently healthy (apparently because they had no history) males. Among the events collected, myocardial infarctions, thromboses, and cerebral strokes were observed.

The French Addictovigilance Network involves 13 regional Addictovigilance centers, the Centres d'Évaluation et d'Information sur la Pharmacodépendance–Addictovigilance. The centers were created in the early 1990s with the aim of achieving reliable surveillance of abuse and pharmacodependence cases related to drugs of abuse—plants and medical or illicit drugs with psychoactive properties.[22] The network evaluates the impact of abuse and dependence of drugs on public health and thus contributes to prevention and harm reduction policies and to regulation and control in the area of abuse or dependence. Some remarkable cases of cannabis-related cardiovascular disorders have been reported to French Addictovigilance Network in the recent years. To confirm whether there is a signal of increasing risk of cardiovascular complications related to cannabis use in France, we investigated all cases reported to the French national system of addictovigilance from 2006 to 2010. The aim of this work was to describe all cases of cannabis-related cardiovascular complications and to estimate at the national level if there is a signal of increasing risk of these events.

Methods

In France, the addictovigilance system relies on the spontaneous reporting of serious abuse and dependence cases related to psychoactive drug use.[22] Health professionals have the legal obligation to report to their regional addictovigilance center all serious cases defined as one of the following criteria of seriousness: leading to temporary or permanent functional incapacity or disability, to inpatient hospitalization or prolongation of existing hospitalization, to congenital anomalies, or to an immediate vital risk or death.[23,24] These spontaneous reports related to drugs of abuse are recorded in a common database. Thus, the study was performed on anonymous routinely collected data and therefore, according to French regulation, did not require approval by a regulatory structure or an ethics committee.

The French Addictovigilance Network was requested to search cases of cannabis-related cardiovascular complications during the past 5 years (2006 to 2010), to cover the time when several outstanding cases of cannabis-related cardiovascular disorders had been reported to the network as well as the few preceding years. There was no restriction in the types of complications to include, because the study aimed to exhaustively assess and identify all potential cardiovascular outcomes in relation with cannabis use, including those with no obvious relation. To be included, cases had to be sufficiently documented with outcome chronology and diagnosis clearly stated. Cases could be included even if data such as management of patients or toxicologic analysis information were lacking.

Cases were described according to the type of complication, patient sex and age, cardiovascular history, and magnitude of cannabis exposure. Quantitative variable (age) was described by mean and interquartiles, and categorical variables were described using effective and percentages. All complications occurred in the context of cannabis use: last cannabis intake must not be confused with cannabis exposure. The latter was categorized into "actual," "recent," and "regular and daily" uses, respectively defined as (1) 1 or more uses in the past 12 months, (2) between 1 and 9 uses in the past 30 days, and (3) 10 or more uses in the past 30 days.[25] Cases for which exposure was not stated were considered as actual; that is, last use was considered the only use in the previous 12 months.

Concomitant use of other psychoactive substances was also taken into account if available and reported in the medical records or when investigated in toxicologic analyses.

Table 1. Number of Spontaneous Reports to the French Addictovigilance Network: Cannabis-Related Reports and Cardiovascular Cannabis-Related Reports From 2006 to 2010

	Total Number of Reports (for All Drugs)		Total Number of Cannabis-Related Reports		Number of Cardiovascular Cannabis-Related Reports
Year	N	%	n	%	n
2006	1858	0.3%	468	1.1%	5
2007	2005	0.2%	452	1.1%	5
2008	2188	0.3%	415	1.4%	6
2009	1926	0.4%	335	2.4%	8
2010	1959	0.6%	309	3.6%	11
Total	**9936**	**0.4%**	**1979**	**1.8%**	**35**

Results

During the 2006 to 2010 period, 1979 spontaneous reports related to cannabis were reported to the addictovigilance network, of which 35 corresponded to cardiovascular complications (Table 1). The percentage of cannabis-related cardiovascular complications increased from 1.1% in 2006 to 3.6% in 2010 of all cannabis-related reports.

Characteristics of Subjects With Cardiovascular Complications

Patients were mostly men (30/35) (Table 2), and the mean age was 34.3 years old (SD 8.8 years). Details of each case are presented in Table S1.

Details on cardiovascular history and risk factors could be found for 46% of cases (16/35): 9 subjects had personal and 7 had familial cardiovascular history. They are all presented in Table S1.

Personal cardiovascular history consisted of high blood pressure (n=2), acute coronary syndrome (n=2), and atherogenic hypercholesterolemia (n=1) in patients with cardiac complications and of Raynaud disease (n=3), intermittent claudication (n=2), high blood pressure (n=1), deep vein thrombosis (n=1), and acute coronary syndrome (n=1) in patients with extracardiac complications. Familial history of coronary (n=4) or vascular (n=2) diseases or cerebral stroke (n=1) was documented. Twenty-one patients (60%) were identified as concomitant tobacco smokers, of whom 6 had personal cardiovascular history. Details about these preexisting cardiovascular risk factors are presented in Table S1. Body mass index could be assessed in only 31% (11/35) of the patients. Among these patients, all of whom belonged to the "acute coronary syndrome" group, 6 (54%, 6/11) were in the normal healthy weight category, 4 (36%) were overweight, and 1 was in the first obese class (body mass index=32.1 kg/m^2).

Cannabis exposure was actual, recent, and regular or daily in 8, 6, and 16 patients, respectively. Duration of use, available in 5 cases only, varied from 2 to more than 25 years.

Toxicologic analyses were performed in 13 cases (Table S1). Δ9-*tetra*-Hydrocannabinol (THC) was detected in each. In 10 cases, THC was the only substance found for which the patient was positive. In 2 cases, THC and alcohol were found together but autopsy report dismissed alcohol in 1 of these cases, explaining this was most probably the result of post-mortem gastric fermentation. In 1 case, THC was associated with alcohol, opiates, morphine, salicylates, and phenothiazine. Among the 22 patients with no available toxicology data, cannabis was the only product mentioned in the medical file (n=3) or the following substances were quoted: tobacco and alcohol (alone: n=12 and 1, respectively; together: n=3); polydrug use (ie, Lysergic acid diethylamide (LSD), ecstasy, alcohol, and cocaine), and benzodiazepines, opiates, and cocaine (n=1, respectively).

Characteristics of Complications

Cases were discriminated based on cardiac[22] and extracardiac[13] complications (Table 2). Cardiac complications composed 20 cases of acute coronary syndromes and 2 heart rate disorders (Table S1). Extracardiac complications affected cerebral arteries with cases of "acute cerebral angiopathy," "transient cortical blindness," and "spasm of cerebral artery" (n=1, respectively), or consisted in lower limb or juvenile arteriopathies (n=4) and in Buerger-like diseases (n=6).

Patient management were heterogeneously described (Table 2). There were 18 hospitalizations, half of which were related to acute coronary syndrome (10/18), with a mean duration of 15 days (versus 7 days for hospitalizations in patients with peripheral or cerebral complications). As presented in Table S1, biology screening (12), electrocardiogrphy (7), or medical imaging (arteriography 12 cases [cardiac echography 7, radiography 5], magnetic resonance

Table 2. Characteristics of Spontaneous Reports of Cannabis-Related Cardiovascular Complications (2006–2010)

Characteristics	Total	Cardiac		Cerebral	Peripheral
		ACS	HRD		
N	35	20	2	3	10
Age (mean±SD)	34.3±8.8	35.5±9.0	32.5±13.4	25.3±3.1	35.2±8.0
Male	30	20	1	2	7
Exposure (A/R/D)	13/6/16	10/2/8	2/0/0	0/0/3	1/4/5
Cardiovascular history	9	4	0	0	5
Associated substances (as quoted in medical file)	24	12	1	2	9
Tobacco/alcohol	21/6	11/2	0/0	2/2	8/2
None declared	11	9	1	0	1
Cocaine	1	1	0	0	0
Benzodiazepine	1	0	1	0	0
Ecstasy	1	0	0	0	1
Lysergic acid diethylamide (LSD)	1	0	0	0	1
Management	26	13	1	3	9
Hospitalization, n (mean duration in days)	18 (15)	10 (20)	0 (0)	3 (2)	5 (9)
Invasive techniques	12	8	0	0	4
Noninvasive techniques	20	11	0	3	6
Evolution	18	9	0	2	7
Improvement	3	1	0	1	1
Worsening	9	4	0	0	5
Death	9	8	1	0	0

ACS indicates acute coronary syndrome; HRD, heart rate disorder; A, actual (≥1 use during the past 12 months); D, regular and daily (≥10 uses during the past 30 days); R, recent (≥1 use during the past 30 days).

imaging [MRI] 3 [CT scan 2, Doppler echography 2]) was performed. Cardiac resuscitation attempts were mentioned in 6 patients with acute coronary syndrome, of which 2 underwent thrombolysis. Invasive techniques were used in 12 cases (8 angioplasties, 6 cardiac stent placements, 3 coronary bypasses and 1 transmetatarsal amputation). None of the 9 deaths occurred in hospitalized patients, but all had cardiac complications.

Discussion

During the 2006–2010 period, the proportion of cardiovascular complications rose from 1.1% to 3.6% of all cannabis-related disorders reported to the French Addictovigilance Network. They were all serious and included cardiac and extracardiac complications, mainly acute coronary syndromes and peripheral arteriopathies. In comparison to the most recently assessed number of regular cannabis users in France (1.2 million), only a small proportion of complications was reported to the French addictovigilance system.

Our results may reasonably be considered a biased (underestimated) representation because the main limitation of this system is the underreporting, although the reporting of all serious cases related to drug abuse and dependence is compulsory and regulated in the French Public Health Code.[23] Indeed, currently, the reporting rate of adverse drug reactions is estimated to be 5% in the field of pharmacovigilance.[26] In other words, 95% of cases are usually not captured. Consequently, the number of cardiovascular complications in cannabis users should be much higher than we describe, especially that this rate should even be lowered in the field of addictovigilance because adverse reactions related to drugs of abuse (of which cannabis) are less frequently reported than those related to other medicines and was recently estimated to be 0.4%.[27] We considered that these cases were too few to be extrapolated by applying the reporting rate, although it would have definitely provided a more accurate estimation.

However, despite poor exhaustiveness, it has already been shown that the spontaneous reporting (as, for example, in the field of pharmacovigilance) is the cornerstone to identify signals. In the context of our study, the increasing reporting of

cardiovascular complications related to cannabis, and their extreme seriousness (with a death rate of 25.6%) could indicate cannabis as a possible risk factor for cardiovascular disease in young adults, in line with previous findings.[8]

Another possible explanation for the small number of cases is that cardiovascular disorders may hardly be connected to cannabis considering the lack of evidence-based data in this area and especially because cannabis-related disorders are frequently restricted to neuropsychiatric impairments. For instance, in a recent clinical review oriented to general practice in primary care that gives advice in the management of cannabis-related disorders, the cardiovascular system is not even mentioned.[28]

On the other hand, our work is somehow limited by the poor information available. Indeed, some cases were not exhaustively informed, and events were too few assess whether the cardiovascular events were actually due to the cannabis use rather than some other risk factors using statistical modeling. Toxicologic analyses were provided or available in only 37% of cases (13/35). More information about toxicology should have revealed odd associations of products among cases. In most of the available toxicologic analyses, which were mainly in forensic reports for unexplained deaths, cannabis was the only positive substance among all substances. History of cardiac or vascular disease and risk factors were not systematically available but were found in 46% (16/35) of patients. In particular, body mass index was assessed in only 31%. According to previous findings, cannabis use might be harmless to most young healthy users, whereas patients with preexisting cardiovascular weaknesses appear to be prone to the harmful effects of cannabis.[29] In our study, patients presented with these events with varied histories and ages (25% were younger than 28.3 years, median age 34.5 years, interquartile range 28.3 to 39 years).

A report of adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation was published recently.[30] The serious adverse events are very similar to those of the present study and include myocardial infarction, sudden cardiac death, cardiomyopathy, stroke, transient ischemic attack, and cannabis arteritis. A population-based study conducted in the area of preventive cardiology emphasized a strong association with unhealthy behaviors such as high caloric intake, tobacco smoking, and use of other illicit drugs, although it did not reveal any independent association between cannabis use and the occurrence of cardiovascular risk factors in young adults.[31] Case reports of acute coronary syndromes have long been noted and remain numerous,[31–35] and there are reports in the literature of myocardial infarction in adolescents who had used the synthetic cannabinoid K2, the effects of which being reported as cannabis-like after smoking.[32] Cases of cannabis-related limb ischemia possibly resulting in necrosis of the fingers or toes have also been reported.[14,33] In 2010, 70 case reports of cannabis arteritis were reported in the litterature.[34] In this 201- review, the patients were younger than our group of patients with peripheral arteriopathy, with a mean age of 28.5 years. However, patients with Buerger disease might be older, with an estimated mean age at onset of 35.0 years.[35]

In addition, a recent study on hospitalizations linked to cannabis in a university hospital has shown a non-negligible pproportion of cardiovascular complications, with 6.3% of all cannabis-related hospitalizations.[21] Among these cases, only a few were reported to the regional addictovigilance center. Therefore, a large underestimation of the cases described in the present study can be expected, especially because the reporting is low, estimated to be 0.4%.[27] Moreover, we are not certain that all areas were extensively and exhaustively covered in this study. Also, clinicians do not easily attribute these complications to cannabis, unless cannabis is the only product involved.

The 35 cases described must be compared with the 1.2 million regular users in France,[36] and to the incidence rates of cardiovascular complications in a comparable group. Yet, relevant comparable group is difficult to define because in the general population, patients with cardiovascular complications are much older than the patients in our study. Even in the event that rates of cardiovascular complications were available in the young, cannabis users would remain indistinguishable from nonusers. However, sudden unexpected cardiac death in persons younger than 35 years was assessed in Denmark from 2000 to 2006.[37] Many unexpected deaths remained unexplained (29%), which could result from a non-negligible part of death in relation with drug uses, including cannabis, the most prevalent illicit drug worldwide,[10] although only 9% of death with available toxicologic results had positive test for cannabinoids. In France, existing registries on coronary heart disease target only the 35- to 74-year-old population and exclude potential associated risk factors such as drug use history.[38] Between 2004 and 2007, average incidence rates of myocardial infarction and coronary deaths in patients aged 35 to 44 years were estimated to be 57 of 100 000 among men and 13 of 100 000 among woman: however, these data are hardly transferable to that of our study. Besides, the national Décès en Relation Avec l'abus de Medicaments et de Substances (DRAMES) study, which identifies and surveys deaths in relation to abuse, misuse, dependence, or accidental intake of psychoactive drugs, emphasized in 2011 a fair number (n=7) of cannabis-positive analyses in deaths by unexplained cardiac arrest.[39] This constitutes another signal in favor of the growing set of evidence on the possible involvement of cannabis in cardiovascular outcomes. In addition, the prevalence of cannabis use is high in Europe with 14.9% of young European (15 to 24 years old) using cannabis in the actual year, and

particularly in France, the third European country after the Czech Republic and Spain.[40]

Under pathologic conditions (eg, imbalance of the endocannabinoid system), cannabinoids have been associated with cardiovascular dysfunctions.[41] Thus, long-term use of cannabis should be responsible for long-lasting decreased blood pressure, heart rate and cardiac contractility; increased blood volume; and diminished circulatory responses to exercise: more generally, it is associated with decreased myocardial function. Moreover, because of these long- and short-term complications, heart function is carefully controlled in subjects who take part in experimental studies with cannabis administration.[42] These are consistent with centrally mediated, reduced sympathetic and enhanced parasympathetic activity.[43] The opposite can be observed in pathologic cardiovascular conditions: in animals, THC was shown to be responsible for vasoconstriction. Now, vasospasm could be a possible common origin for many of the cases we describe in the present study. Also, the direct impact of cannabinoids on factors such as nitric oxide or endothelial factors could explain the disparity of complications observed between cannabis and tobacco.[44] The latter is associated with deregulations observed after continuous exposition, which contrasts with the apparent immediacy of cannabis-related cardiovascular disorders.

Such complications can be seen among young adults who use stimulant drugs (ie, cocaine, methamphetamine) that are known to be responsible for cardiovascular complications.[9,45] These stimulant drug users are likely to also be regular cannabis users.[46,47] Stimulant drug use may be less likely acknowledged than cannabis use for societal reasons, but that is not sufficient to exclude cannabis from being possibly linked to such outcomes. Our findings indicate that cannabis intoxication should be more systematically investigated in the medical management of cardiovascular complications observed in young adults. They lead us to recommend systematic investigation for cannabis use, through oral interviewing and urinary analysis, as also advocated by Wolff and colleagues.[48]

Conclusion

Several striking cardiovascular complications following cannabis use raised the issue of the possible implication of cannabis in cardiovascular outcomes and the necessary national review. Despite the known underreporting, the rate of cannabis-related cardiovascular complications reported steadily rose during the past 5 years. Cardiovascular disorders represented 2% of the reports related to cannabis, classified into cardiac, cerebral, and peripheral complications. The majority consisted of acute coronary syndromes and peripheral arteriopathies. This result is consistent with previous findings and strengthens the idea that cannabis may be responsible for serious complications, in particular on the cardiovascular system. Among the difficulties in identifying these cases are the causality assessment when differential diagnoses coexist, and the raising but still poor awareness of health professionals toward this particular type of effects. Cannabis may trigger cardiovascular complications and therefore should be regarded as so by health practitioners and by users, who often admit the danger of drugs like cocaine or amphetamines but minimize that of cannabis. A prospective study with collection of all cardiovascular cases at hospital admission should complete the present findings, which add to the existing knowledge in the field of cannabis complications and must be considered as the starting point for further research.

Acknowledgments

The authors thank the members of the French Addictovigilance Network Working Group on Cannabis Disorders for their meaningful contribution to this collaborative work: Amelie Daveluy (Bordeaux), Reynald Le Boisselier (Caen), Nicolas Authier (Clermont-Ferrand), Claude-Elisabeth Barjhoux (Grenoble), Sylvie Deheul (Lille), Alexandra Boucher (Lyon), Michel Spadari (Marseille), Celine Eiden (Montpellier), Valerie Gibaja (Nancy), Marie Gerardin (Nantes), Samira Djezzar (Paris), and François Chavant (Poitiers).

Sources of Funding

Financial support was provided by the French InterMinisterial Mission for the Fight Against Drugs and Addiction (MILDT, Mission interministérielle de lutte contre les drogues et toxicomanies), and by the French drug agency (ANSM, Agence Nationale de Sécurité des Médicaments).

Disclosures

None of the authors has a conflict of interest to declare. This work was part of Emilie Jouanjus' study toward a PhD degree at Toulouse University.

References

1. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33:2569–2619.
2. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333:1091.
3. Rumsfeld JS, Alexander KP, Goff DC Jr, Graham MM, Ho PM, Masoudi FA, Moser DK, Roger VL, Slaughter MS, Smolderen KG, Spertus JA, Sullivan MD,

Treat-Jacobson D, Zerwic JJ; American Heart Association Council on Quality of Care and Outcomes Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Stroke Council. Cardiovascular health: the importance of measuring patient-reported health status: a scientific statement from the American Heart Association. *Circulation*. 2013;127:2233–2249.

4. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
5. De Backer GG, Maes L, Van de Mieroop E. Issues for cardiovascular disease risk factor development in Europe. *Prev Med*. 1999;29:S96–S101.
6. Stevens J, Erber E, Truesdale KP, Wang C-H, Cai J. Long- and short-term weight change and incident coronary heart disease and ischemic stroke: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2013;178:239–248.
7. Mallaina P, Lionis C, Rol H, Imperiali R, Burgess A, Nixon M, Malvestiti FM. Smoking cessation and the risk of cardiovascular disease outcomes predicted from established risk scores: results of the Cardiovascular Risk Assessment among Smokers in Primary Care in Europe (CV-ASPIRE) Study. *BMC Public Health*. 2013;13:362.
8. Nawrot TS, Perez L, Künzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet*. 2011;377:732–740.
9. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Arch Gen Psychiatry*. 2007;64:495–502.
10. UNODC. *World Drug Report 2012*. New York, NY: United Nations Office on Drugs and Crime (UNODC), United Nations publication; 2012:112. Disponible sur: http://www.unodc.org/documents/data-and-analysis/WDR2012/WDR_2012_web_small.pdf. Accessed March 3, 2014.
11. Sweetman S. *Cannabidiol, Dronabinol, Nabilone, Nabiximols*. 35th ed. Pharmaceutical press; 2007. Disponible sur: http://www.medicinescomplete.com/mc/martindale/current/18906-r.htm?q=cannabinoid&t=search&ss=text&p=3#_hit. Accessed March 3, 2014.
12. Kuepper R, Morrison PD, van Os J, Murray RM, Kenis G, Henquet C. Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. *Schizophr Res*. 2010;121:107–117.
13. Wagner D, Becker B, Gouzoulis-Mayfrank E, Daumann J. Interactions between specific parameters of cannabis use and verbal memory. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:871–876.
14. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ*. 2012;344:e536.
15. Sidney S. Cardiovascular consequences of marijuana use. *J Clin Pharmacol*. 2002;42:64S–70S.
16. Adverse effects of cannabis. *Prescrire Int*. 2011;20:18–23.
17. Graham JD. Cannabis and the cardiovascular system. *Br Med J*. 1978;1:857.
18. Wells DL, Ott CA. The "new" marijuana. *Ann Pharmacother*. 2011;45:414–417.
19. Aronow WS, Cassidy J. Effect of smoking marihuana and of a high-nicotine cigarette on angina pectoris. *Clin Pharmacol Ther*. 1975;17:549–554.
20. Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. *Circulation*. 2001;103:2805–2809.
21. Jouanjus E, Leymarie F, Tubery M, Lapeyre-Mestre M. Cannabis-related hospitalizations: unexpected serious events identified through hospital databases. *Br J Clin Pharmacol*. 2011;71:758–765.
22. Baumevieille M, Daveluy A, Maurain C, Bégaud B, Haramburu F. Medicines submitted to narcotics regulations in France, 1992–2007. *Fundam Clin Pharmacol*. 2009;23:345–349.
23. French Health CodeCSP. Article R.5132-114. August 8, 2004. Available from: http://www.legifrance.gouv.fr/affichCodeArticle.do;jsessionid=619DB47C93353C5E7CC664DB9F25526F.tpdjo02v_1?idArticle=LEGIARTI000006915744&cidTexte=LEGITEXT000006072665&dateTexte=20120514. Accessed March 3, 2014.
24. French Health Code. Article R.5132-99. April 27, 2012. Available from: http://www.legifrance.gouv.fr/affichCode.do?idSectionTA=LEGISCTA000006196620&cidTexte=LEGITEXT000006072665&dateTexte=20120514. Accessed March 3, 2014.
25. Beck F, Legleye S, Spilka S. *Cannabis, Cocaïne, Ecstasy: Entre Expérimentation Et Usage Régulier*. Baromètre santé 2005 [Internet]. Saint-Denis: Institut national de prévention et d'éducation pour la santé (INPES); 2007:169–221. Disponible sur: http://www.inpes.sante.fr/CFESBases/catalogue/pdf/1109.pdf. Accessed March 3, 2014.
26. Begaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. *JAMA*. 2002;288:1588.
27. Jouanjus E, Pourcel L, Saivin S, Molinier L, Lapeyre-Mestre M. Use of multiple sources and capture–recapture method to estimate the frequency of hospitalizations related to drug abuse. *Pharmacoepidemiol Drug Saf*. 2012;21:733–741.
28. Winstock AR, Ford C, Witton J. Assessment and management of cannabis use disorders in primary care. *BMJ*. 2010;340:c1571.
29. Reece AS. Chronic toxicology of cannabis. *Clin Toxicol Phila Pa*. 2009;47:517–524.
30. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardiol*. 2014;113:187–190.
31. Rodondi N, Pletcher MJ, Liu K, Hulley SB, Sidney S. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). *Am J Cardiol*. 2006;98:478–484.
32. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. *Pediatrics*. 2011;128:e1622–e1627.
33. Disdier P, Granel B, Serratrice J, Constans J, Michon-Pasturel U, Hachulla E, Conri C, Devulder B, Swiader L, Piquet P, Branchereau A, Jouglard J, Moulin G, Weiller PJ. Cannabis arteritis revisited–ten new case reports. *Angiology*. 2001;52:1–5.
34. Cottencin O, Karila L, Lambert M, Arveiller C, Benyamina A, Boissonas A, Goudemand M, Reynaud M. Cannabis arteritis: review of the literature. *J Addict Med*. 2010;4:191–196.
35. Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of buerger disease. *J Vasc Surg*. 2004;39:176–180.
36. Beck F, Guignard R, Tovar M, Spilka S. Les niveaux d'usage des drogues en France en 2010—exploitation des données du Baromètre santé. Tendances. *OFDT*. 2011;76:6.
37. Winkel BG, Holst AG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, Bundgaard H, Svendsen JH, Haunsø S, Tfelt-Hansen J. Nationwide study of sudden cardiac death in persons aged 1–35 years. *Eur Heart J*. 2011;32:983–990.
38. Wagner A, Arveiler D, Ruidavets JB, Bingham A, Montaye M, Ferrières J, Dallongeville J, Haas B, Ducimetière P. Gender- and age-specific trends in coronary heart disease mortality in France from 2000 to 2007: results from the MONICA registers. *Eur J Prev Cardiol*. 2014;21:117–122.
39. Richard N, Arditti J, Pépin G, Mallaret M, Castot A. Box 2—DRAMES (deaths related to drug and illegal substance abuse): an identification tool of drug-related deaths in France. *Bull Epidémiol Hebd*. 2010;40–41:416.
40. European Monitoring Centre for Drugs and Drug Addiction. *European Drug Report 2013: Trends and Developments*. Luxembourg: Publications Office of the European Union; 2013:72.
41. Bátkai S, Pacher P. Endocannabinoids and cardiac contractile function: pathophysiological implications. *Pharmacol Res*. 2009;60:99–106.
42. Gorelick DA, Heishman SJ. Methods for clinical research involving cannabis administration. *Methods Mol Med*. 2006;123:235–253.
43. Jones RT. Cardiovascular system effects of marijuana. *J Clin Pharmacol*. 2002;42:58S–63S.
44. O'Sullivan SE, Tarling EJ, Bennett AJ, Kendall DA, Randall MD. Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. *Biochem Biophys Res Commun*. 2005;337:824–831.
45. Milroy CM, Parai JL. The histopathology of drugs of abuse. *Histopathology*. 2011;59:579–593.
46. Wu L-T, Parrott AC, Ringwalt CL, Yang C, Blazer DG. The variety of ecstasy/MDMA users: results from the National Epidemiologic Survey on alcohol and related conditions. *Am J Addict*. 2009;18:452–461.
47. Smith DE. The process addictions and the new ASAM definition of addiction. *J Psychoactive Drugs*. 2012;44:1–4.
48. Wolff V, Armspach J-P, Lauer V, Rouyer O, Bataillard M, Marescaux C, Geny B. Cannabis-related stroke: myth or reality? *Stroke*. 2013;44:558–563.