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TRABALHO FINAL DO 6º ANO MÉDICO COM VISTA À ATRIBUIÇÃO DO GRAU DE MESTRE NO ÂMBITO DO CICLO DE ESTUDOS DE MESTRADO INTEGRADO EM MEDICINA

GONÇALO REINALDO CASTELO BRANCO DOMINGUES

MORTES RELACIONADAS COM O CONSUMO DE CANABINÓIDES ENTRE 2002 E 2009

DEATHS RELATED TO CANNABINOIDS CONSUMPTION FROM 2002 AND 2009

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RESUMO

Os canabinóides fazem parte do grupo de substâncias ilícitas mais usado em todo o mundo (Hall W. *et al*, 2007). Apesar do seu consumo ter estabilizado ou até mesmo diminuído ligeiramente nos últimos anos, este continua a ser, ainda, muito elevado (King L.A. *et al*, 2010*)*.

Os indivíduos toxicodependentes apresentam taxas de mortalidade bem mais elevadas do que os que não apresentam dependências, sendo que, nestes indivíduos, independentemente da substância em questão, a taxa de mortalidade por causas não naturais ultrapassa, em larga escala, as taxas de mortalidade por causa natural (Harris E.C. *et al*, 1997). Na grande maioria das mortes relacionadas com consumo de drogas é realizada uma autópsia médico-legal. No entanto, a simples detecção de uma droga no organismo do indivíduo não indica que essa substância tenha sido, efectivamente, a responsável por uma determinada morte. Isto é particularmente verdade e importante no que diz respeito aos canabinóides, onde raramente lhes é atribuída unicamente a causa directa da morte, sendo mesmo raros os casos onde tal é admitido (King L.A. *et al*, 2010).

O objectivo deste trabalho consistiu em determinar a prevalência do consumo de canabinóides em indivíduos autopsiados no Serviço de Patologia Forense (SPF) da Delegação do Centro do Instituto Nacional de Medicina Legal, I.P., e a sua possível relação com a etiologia da morte.

O material usado neste estudo incluiu todos os relatórios de autópsias realizados entre Janeiro de 2002 e Dezembro de 2009, pelo SPF da Delegação do Centro do Instituto Nacional de Medicina Legal, I.P. Os dados foram recolhidos pela informação contida nos processos de autópsia. O grupo caracterizou-se de acordo com o sexo, idade, data da morte, causa e etiologia da morte, pedidos de análise químico-toxicológica para determinação de canabinóides e outras substâncias.

Das 2885 autópsias realizadas pelo SPF da Delegação do Centro do INML, I.P., entre 2002 e 2009, 540 incluíram pedidos de exames complementares toxicológicos para a determinação de canabinóides. Assim, deste número, 17 (3.1%) casos foram positivos e todos eles em homens.

Três causas de morte tiveram a mesma taxa de pedidos positivos para canabinóides (indeterminada/desconhecida, acidente de viação e suicídios), com 4 casos cada. As mortes acidentais e as mortes naturais foram responsáveis, cada uma delas, por 2 casos, e a etiologia com menor número de casos positivos foi a correspondente aos homicídios, com apenas 1 caso.

Sabe-se que os canabinóides são, e tudo indicia que continuarão a ser, das substâncias ilícitas com maior prevalência de consumo em Portugal.

Apesar de algumas limitações, este estudo permite-nos concluir que, ainda há poucos pedidos de análises de canabinóides e que se deviam fazer os esforços necessários para que se tornasse uma análise *de rotina* dado a sua prevalência na sociedade actual.

Palavras-chave: canabinóides; acidentes de viação; suicídios; homicídios; acidentes de trabalho.

ABSTRACT

Cannabis is the most commonly used illicit drug worldwide (Hall W. *et al*, 2009). Despite stabilizing or even decreasing trend in cannabis use, its use still remains high (King L. *et al*, 2010).

Drug addict individuals have substantially high rates of mortality than matched peers. It is important to note that, across all substances, excess mortality rates due to unnatural causes far exceed those from natural causes (Harris E.C. *et al*, 1997). In most drug-related deaths an medico-legal autopsy is performed. The presence of a drug on the toxicological report does not necessarily indicate that this substance was responsible for the death (direct cause). This is particularly evident for cannabis, where only in a few reports it is indicated as the direct cause of death (King L.A. *et al*, 2010).

The main aim of this study was to determine the prevalence of cannabinoids and its possible relationship with the cause of death, among different medico-legal etiologies, from autopsies performed between 2002 and 2009 in the forensic pathology department of the Centre Branch of the National Institute of Legal Medicine of Portugal (INML, I.P.).

As data material of the present study, 2885 autopsies (performed between 2002 and 2009) were checked out for cannabis requests (involving all the present medico-legal etiologies). The target population consisted on people whose samples were tested for cannabis and its metabolites, with the main objective of determining the prevalence and, the possible, relationship to death cause with cannabinoids use.

The group was characterized according to age, gender, month and year of death, cause of death, aetiology of death, cannabis and other substances requests.

From the 2885 autopsies performed by the Centre Branch of the National Institute of Legal Medicine (INML, I.P.), 540 (18.7%) were subject of cannabinoids analysis. Only 17 (3.1%) were positive for cannabinoids, all men, mainly in their fifth life decade, with 6

cases. Three death etiologies had the same cannabis positive requests (undetermined/unknown, road crashes and suicides), with 4 cases. Natural and accidental deaths were responsible, both, for 2 positive cases. Homicides presented the lowest number of positive results (just one case).

Cannabis is and still will be the illicit drug with higher prevalence in Portugal.

Despite having some limitations, this study concluded that there are few requests for cannabinoids analysis and efforts should be made to make cannabinoids requests as *routine* as an ethanol analysis, once the high prevalence of cannabinoids on our society.

Keywords: cannabinoids; road crashes; suicides; homicides; labour fatalities.

1. INTRODUCTION

Cannabis is the most commonly used illicit drug worldwide (Hall W. *et al,* 2009). In Europe, cannabis use increased during the 1990s and early 2000s. Nowadays, data from general population and school surveys point to a stabilizing or even decreasing trend in cannabis use. However, their levels uses remain high *(*EMCDDA, 2010*).*

In 2001, Portugal made the first general population survey with a sample of 15000 individuals. In this study, 7.8% of the individuals aged between 15 and 64 had used illicit drugs, at least once in their lifetime. The most reported illegal substance was cannabis – 7.6% – with males using cannabis in a rate of 11.5% Vs 3.9% for women. In 2007, results from a sample of 12202 individuals showed that 12% of the individuals aged between 15 and 64 had used illicit drugs, at least once in their lifetime and cannabis was once again, the most used drug – 11.7% – with males keeping higher rates than women – 18.4% and 5.2%, respectively *(*EMCDDA, 2010*).* Also in 2007, the European School Survey Project on Alcohol and Other Drugs (ESPAD) results showed that the lifetime prevalence for cannabis was 13%, when compared to 18% in 2003 and 12% in 1999 (Hibell B. *et al,* 2007).

Cannabinoids are the active components of *Cannabis sativa,* and are responsible for several central and peripheral effects. The most known potent, psychoactive agent is Δ^9-tetrahydrocannabinol – Δ^9-THC or THC. Other important cannabinoids such as Δ^8-THC, cannabinol and cannabidiol have additive, synergic or antagonistic effects with THC (Ashton *et al,* 2001).

The main use for cannabis is its recreational purpose and its effects are dose related. Thus, in low doses (as low as 2.5 mg) it produces an euphoria state – *high*. This feeling (*high*) is accompanied with low anxiety, alertness and increased sociability. However, in higher doses, it can also produce dysphoric reactions, such as severe anxiety and panic, paranoia and psychosis. Cannabis is also known for the perceptual changes it causes.

Accordingly, cannabis has similar effects to those of alcohol and benzodiazepines in the impairment of psychomotor and cognitive performance (Ashton *et al*, 2001).

Addicted individuals have higher rates of mortality than matched peers. Of particular note, across all substances excess mortality rates due to unnatural causes far exceed those from natural causes (Harris E.C. *et al*, 2001).

Drug abuse may cause death directly, by overdose or by disease, or indirectly contribute to death by deteriorating motor, sensory or cognitive functions (Flanagan *et al*, 2002). However, significant substance user deaths are related to violence, whether homicide or suicide (Boles S.M. *et al*, 2003).

In most drug-related deaths an autopsy is performed, conducted by a forensic pathologist and toxicological analyses are often required as complementary exams. So, toxicology tests are conducted routinely in cases of unnatural or unexpected death in most communities throughout the developed world. These tests will help the pathologist to determine if any drugs were in the body at the time of death, and what role, if any, they played in the dead. Furthermore, the presence of a toxic substance in blood proves that the person had been under the influence of the drug before and at the time of death – the extent to which depends on the drug's characteristics and concentration and on the user's tolerance (Flanagan *et al,* 2002).

The detection of a drug in the report does not necessarily indicate that substance as the direct cause of death. In fact, it might happen to be an entirely inconsequential factor, or it may have been the combination of different substances that lead to death. This is particularly true for cannabis, which has only a few reports as the responsible of the death (King L.A. *et al,* 2010).

On the other hand, it is known that cannabinoids strongly interact with both cognitive and psychomotor abilities of men. So, it is important to establish a possible relationship

between its use and the increased risk of fatalities such as traffic accidents, labour accidents, murderers and suicides. The aim of the present study is to determine cannabinoids prevalence and if possible, its relationship with the cause of death among victims autopsied in the forensic pathology department of the Centre Branch of the National Institute of Legal Medicine of Portugal (INML, I.P.), between 2002 and 2009.

2. MATERIAL STUDIED

This study has been carried out by the National Institute of Legal Medicine of Portugal (INML, I.P), being all the samples collected by forensic pathologists from the Forensic Pathology Department (FPD) of the Centre Branch of the INML, I.P. (from January 2002 to December 2009).

As data material of the present study, 2885 autopsies (all the autopsies performed between the periods mentioned above) were checked out for cannabinoids analysis requests from the FPD to the Forensic Toxicology Laboratory. The target population consisted on people whose samples were tested for cannabinoids, in order to determine its prevalence and evaluate the possible relationship between cannabinoids and death.

Assessment of the examination protocols was conducted by means of a tabular database according to the following criteria: year, month, age, sex, marital status, cause of death, aetiology of death, cannabinoids requests and other substances presence requests and results. All these several variables were studied and all the pertinent data was registered, separated and statistically treated with the SPSS program (Statistical Package for Social Sciences).

3. RESULTS

3.1. Number of cases

At the Forensic Pathology Department of the Centre Branch of the INML, I.P., a total of 2885 autopsies were performed between January 2002 and December 2009, 540 with cannabinoids requests, representing 18.7% of all the analysed autopsies.

3.2. Year and month distribution

We could observe that 2008 had the highest request number for cannabinoids analyses, with 114 cases (34.6%) and the lowest percentage was achieved in 2002, with only 12 cases, corresponding to 2.2% of the total requests (Fig. 1).

When analysing the results by month, it can be observed that July had the highest number of cases, with 57 cases, corresponding to 10.6% of the cases, being March the month with fewer cannabinoids requests, only 35 (6.5%). [Data not shown]

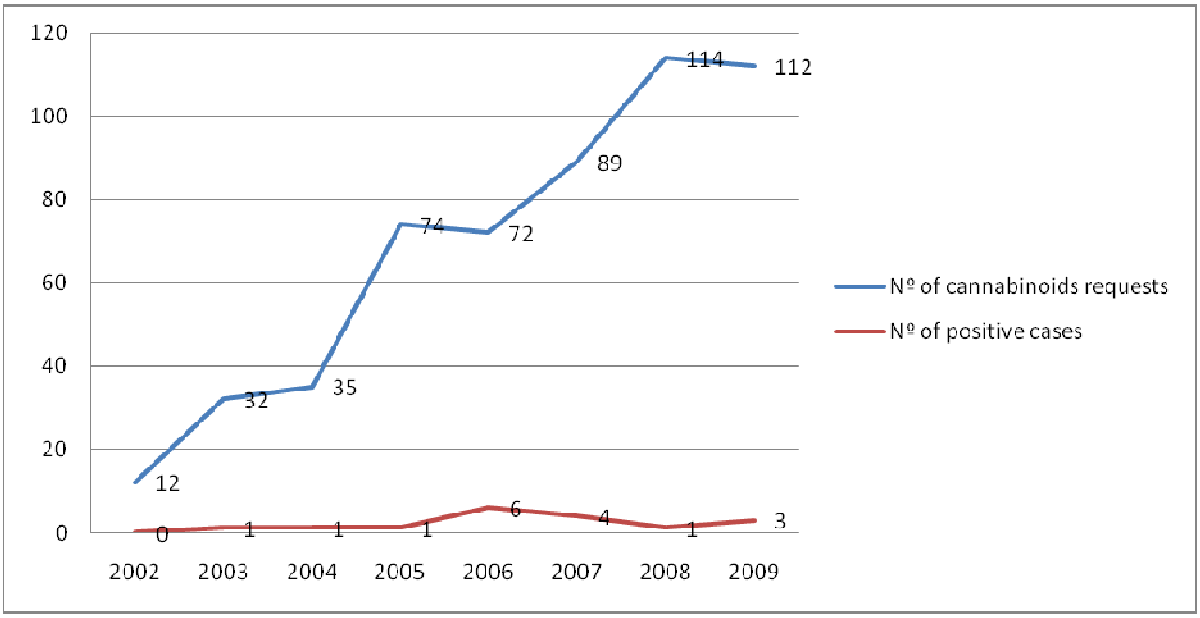

Fig. 1. Cannabinoids requests distribution through the years *versus* positive requests by year.

3.3. Sex and age distribution

The highest request number for cannabinoids occurred in males. In fact, from the 540 cannabinoids analysis, 80% occurred in males and 20% in females. [Data not shown]

Crossing these different variables, sex and age, we found that the most frequently analyzed age group was between 40 and 49 years-old, corresponding to 23.1% of the cases, and mainly in men, as previously mentioned (Fig. 2).

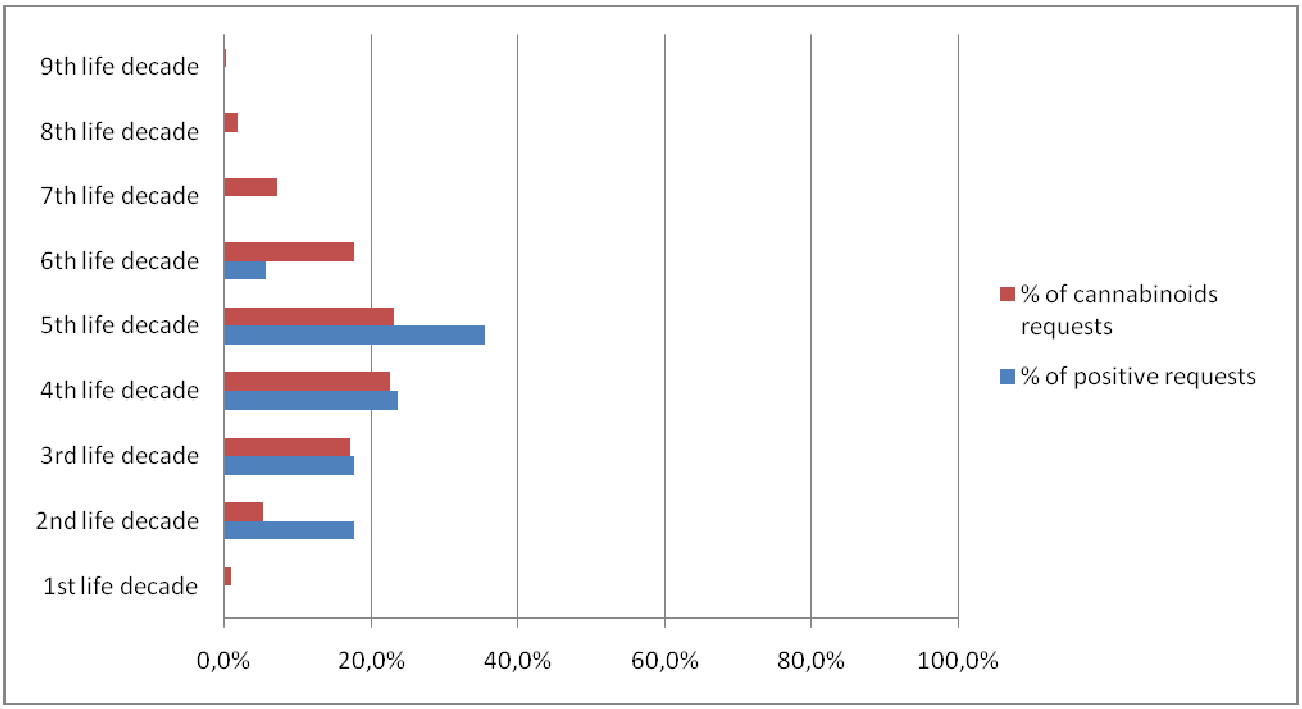

Fig. 2. Cannabinoids requests distribution and positive results by age (life decade).

3.4. Medico-Legal Etiology

When determining the death etiology we concluded that road traffic accident cases represent the major request number of cannabinoids, with 205 requests (38%). From these road traffic accident cases with cannabinoids analysis requests, 62 cases had no information concerning drivers/passengers/pedestrians distribution, 53 cases (25.9%) occurred in car drivers and 50 occurred due to two wheels vehicles crash. Deaths involving pedestrians had

only 27 cannabinoids requests, corresponding to 13.2%, and passengers were tested for cannabis just in 13 cases (6.3%).

Natural deaths were the second etiology with more cannabinoids analyses requests, 101 cases (18.7%). Accidental deaths, other than road traffic accidents, had also a high number of cannabinoids analysis requests, 67 cases (12.4%).

Suicides, with 59 cannabinoids requests (10.9%), were the fourth major cause of death that included this group determination. The great majority of these requests were connected to hanging suicides (37 cases, 6.9%), followed by firearm suicides (8 cases, 1.5%), drowning suicides (6 cases, 1.1%) and both slaughtered and falling suicides, both with 4 cases, corresponding to 0.7%.

Finally we observed that labour accidents and homicides, with 28 and 17 cases, corresponding to 5.2% and 3.1% each one, were a minor cause for cannabinoids requests. Homicides with firearms and stabs had both 6 requests for analysis (35.3%) (Fig. 3).

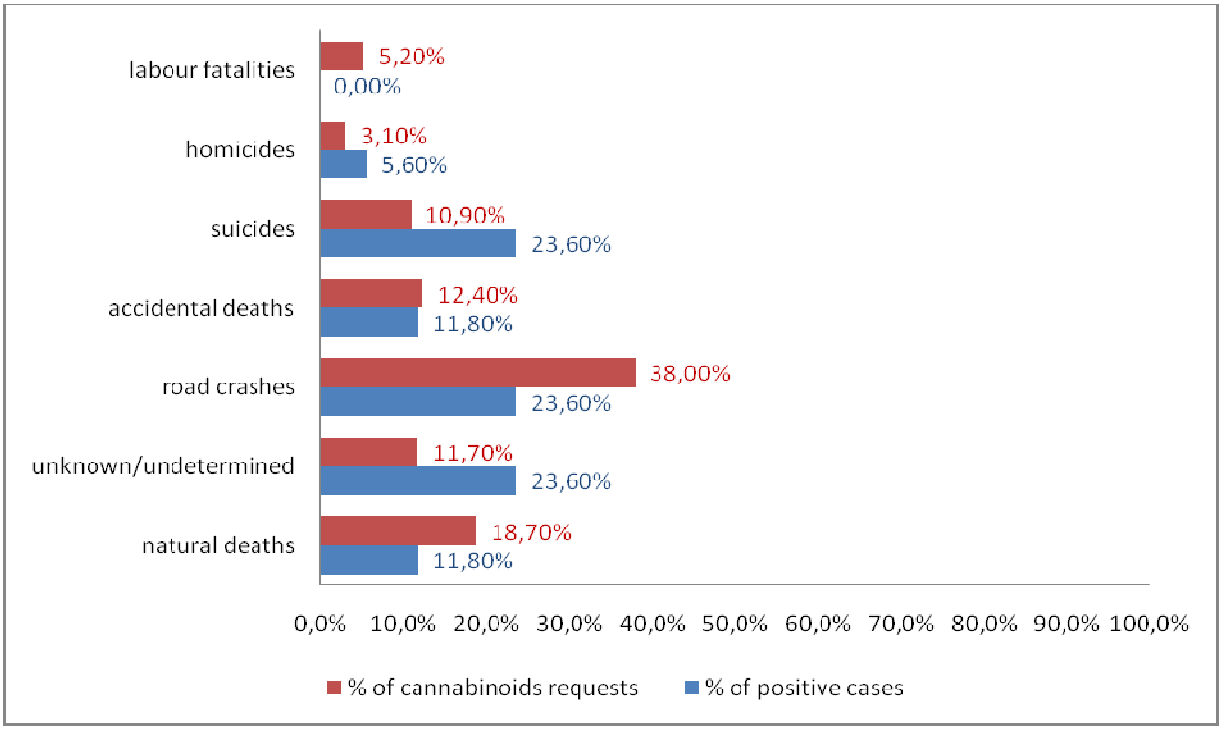

Figure 3- Distribution of cannabinoids requests and positive cases by death aetiology.

3.5. Cannabinoids and other substances requests/ results

As previously described, from the 2885 autopsies performed between 2002 and 2009, 540 had cannabinoids analyses, corresponding to 18.7% of the total, but only 17 presented positive results (3.1%) (Tables 1 and 2).

Table 1. Autopsies and cannabinoids analysis distribution per year.

Year	Total Autopsies (n)	Cannabinoids Requests (n)	Positive Results (n)
2002	427	12	-
2003	413	32	1
2004	362	35	1
2005	336	74	1
2006	333	72	6
2007	339	89	4
2008	329	114	1
2009	346	112	3

In all the cases where cannabinoids analyses were requested, there also was a request for other substance(s). In fact, all of them had ethanol analysis. However, in 283 cases (52.4%) no toxicological substances were detected in the analyzed biological samples.

Thus, 540 ethanol analysis requests were also performed and from these 162 were positive results, corresponding to 30% of the total requests. The great proportion of the positive cases corresponded to a Blood Alcohol Concentration (BAC) $\geq$ 1.2 g/L, with 49.4% (80 cases), followed by a BAC $\leq$ 0.5g /L, with 25.9% of the positive cases, and between 0.8 and 1.2 g/L, with 16% of the positive results. Finally, the lowest percentage corresponded to 0.5 <BAC <0.8 g/L (8.6%). We observed that ethanol was found, simultaneously, with cannabinoids in 3 cases (Table 2).

Table 2. Positive cases for Cannabinoids, during the studied period.

Year	Case	Gender	Age	Month	Medico-Legal Etiology	Detected substances
2002	–	–	–	–	–	–
2003	**1**	♂	60-70	04	Suicide – CO intoxication	Δ^9-THC-OH; CO (80%)
2004	**1**	♂	50-60	10	Natural death – pulmonary lesions	Cannabinol
2005	**1**	♂	50-60	03	Homicide – fire weapon	Δ^9-THC; Cannabinol; Cannabidiol
2006	**1**	♂	40-50	06	Suicide – hanging	Δ^9-THC; Δ^9-THC-OH; Δ^9-THC-COOH
	2	♂	20-30	07	Road Traffic Accident	Δ^9-THC-OH
	3	♂	40-50	09	Undetermined/unknown	Δ^9-THC-COOH
	4	♂	20-30	11	Suicide – hanging	Δ^9-THC-COOH; BAC = 0,9g/L
	5	♂	40-50	11	Suicide – pesticide intoxication	Δ^9-THC-COOH; paraquat
	6	♂	30-40	12	Accidental death - illicit drugs abuse	Δ^9-THC-OH; heroin; cocaine
2007	**1**	♂	20-30	04	Road Traffic Accident	Δ^9-THC-OH; BAC=1,1g/L
	2	♂	30-40	05	Accidental death - illicit drugs abuse	Δ^9-THC-OH; heroin; cocaine
	3	♂	50-60	06	Road Traffic Accident	Δ^9-THC-OH; BAC=1,4g/L
	4	♂	50-60	08	Undetermined/unknown	Δ^9-THC-OH; BAC=0,7g/L
2008	**1**	♂	30-40	10	Undetermined/unknown	Δ^9-THC-OH; cocaine
2009	**1**	♂	50-60	01	Natural death - cardiac lesions	Δ^9-THC-OH
	2	♂	50-60	05	Undetermined/unknown	Δ^9-THC-OH
	3	♂	40-50	10	Road Traffic Accident	Δ^9-THC; BAC=1g/L

Substances used in psychiatric diseases, like benzodiazepines, were found in 39 cases (7.2%) and anti-depressants in 47 cases, corresponding to 8.7%. In some cases there was an

association of these two medical substances classes. However, none of the positive cases for cannabinoids had medical substances.

Other illicit drugs such as opiates were found in 23 cases (4.2%) and cocaine was positive in 3.9% of the cases. In 12 cases, both drugs were detected. Moreover, in 3 cases, we observed that cannabinoids, opiates and cocaine were found simultaneously.

Pesticides were found in 8 requests (1.5%), and one was also positive for cannabinoids.

Table 2 also describes the positive cases found for cannabis.

4. DISCUSSION AND CONCLUSION

As previously mentioned, the main objective of our work was the analysis of all cannabinoids requests from autopsies performed at the Forensic Pathology Department of the Centre Branch of the INML, I.P., between 2002 and 2009.

Although a blood-positive finding of illicit drug(s) at the time of death inevitably suggests its influence, it does not prove any direct relationship between drug abuse and death. In fact, the half life time of cannabis inactive metabolites is around seven days and they can persist in the organism until thirty days over the use, being accepted that the metabolites may be detected in urine samples 72 days after cannabis use. However the estimated half time of THC elimination from serum is 4 days (Flanagan R.J. *et al*, 2002).

Frequently, the cannabinoid-related diagnosis is one of the factors that may contribute to death, both in natural and in violent deaths, but it is never the principal or only drug present in the intoxications and thus, responsible for death (King L.A. *et al*, 2010).

In this study it was not possible to have the sociodemographic or individual factors associated to increased suicide risk and increased cannabis use, or the possible previous

psychiatric diagnosis, factors that are intermediate pathways and that would help to prove the influence when analysing the final data (Wilcox H.C. *et al,* 2004; Dorard G. *et al,* 2008).

It is important to state that there are very few recent studies that evaluate the overall abuse of these substances in our country. In fact, the existent studies reflect the situation in the eighties and the nineties and are mainly focused on alcohol abuse (Antunes M.I. *et al,* 1992; Marques M.E.P. *et al,* 1994).

In Portugal, the legislation related to road traffic and safety is laid down in the Road Traffic Code and specific additional legislation. Since 1998, it states that all the drivers and pedestrians involved in road traffic accidents (fatal or not) must be tested to ethanol and illicit drugs, being forbidden to drive a vehicle under the influence of ethanol or illicit drugs, substances that affect driving proficiency. On the other hand, in fatal road traffic accidents, ethanol and illicit drugs must be analysed in drivers and pedestrians fatally injured. However, our law concerning labour monitoring significantly addresses the problem of psychotropic substances (including cannabis), because workers can, by law, be subject to a random check by the employer at any time of their activity, but its determination in postmortem cases is not fully informed or legislated, in relation to how to act specifically in labour accident autopsies. Once again, similar to labour accidents, we can find some differences between the illicit drugs requests among other medico-legal etiologies (for example, suicides and homicides) since the pathologists are not obliged to require illicit drugs analysis and this demand may depend on several factors such as the victim's circumstantial information (age, habits and antecedents), crime scene investigation, if possible, and the experience of the pathologist. Accordingly, the discrepancy of results concerns the practice carried out by experts who, more and more, are being aware and scientifically instructed to further research and evaluation of substance influence in different medico-legal situations and consequent forensic interpretation of the results.

As also surveyed by other authors, men are often more present in cannabis positive results than women, and in this particular study all the positive cases were, in fact, related to men (Laumon B. *et al,* 2005; King L.A. *et al,* 2010*).* Actually, male gender is often associated with risk behaviour and substance abuse *(*Hall W. *et al,* 2007*;* King L.A. *et al,* 2010*).*

We found that the average age with more positive cannabinoids requests involved the fifth life decade, with 35% of the cases. However this was not in agreement with other studies that concluded the average age with more positive cases were the second and third life decade (Laumon B. *et al,* 2005; Ramaekers J.G. *et al*, 2004; Kuhns J.B. *et al*, 2009; Carlini E.A., 2004). However, those studies were mainly conducted on in road traffic accidents, taking into account different variables, including age. Our study, as mentioned before, had as main purpose the analysis of all the requests (independently of the cause of death) and thus, different scenarios would be expected.

There are few studies describing the association of cannabis use and a natural death. An American study performed in 2008 stated that although marijuana use has not been associated to mortality in populations free of cardiac problems, it might pose a particular risk for those with coronary heart disease (Mukamal K.J. *et al*, 2008).

Our study showed that 5.2% of the cannabinoids requests corresponded to labour fatalities autopsies. However, none of these cases tested positive for cannabinoids. There are few studies in concern with labour fatalities as they are restricted by concerns for individual rights and fears of jeopardizing labour relations. In 1991, a study showed that in 459 deaths at work, the only illicit drug found was cannabis, present in 10 cases (Alleyne B.C. *et al*, 1991). Also an Australian study declared, in 2010, that from 355 work-related injury deaths, between 2001 and 2006, that toxicology screens showed 20 cases of cannabinoids, corresponding to 6% *(*McNeilly B. *et al,* 2010*).* However, a Japanese survey had data similar

to our study. In the Japanese study, performed in 2003, which showed that from the 847 autopsies made, 67 were labour related, corresponding to 7.7%. No case tested positive for cannabinoids *(*Maeda H. *et al,* 2003*).*

In this study we had 2 accidental deaths that were positive for cannabinoids, corresponding to 11.8% of the positive cases. Both occurred by an overdose of multiple illicit drugs – opiates, cocaine and cannabinoids. Like other authors have already stated cannabis is not the principal and responsible substance for this death aetiology *(*Pedersen C.L. *et al,* 2005*).*

In the studied period, cannabinoids analysis was requested in 59 suicides but, as stated above, only 4 were positive (6.8%) for this group. However several factors such as male gender, alcohol and other drug use may also be linked to a suicide aetiology, and may, therefore, confound even more, the relationship between cannabis and suicide *(*Andreasson S. *et al,* 1990*;* Dark S. *et al,* 2007*).* In fact, an association between cannabis use and suicide can be established. Other studies have found some association between cannabis and suicidal behaviour and completed suicides (Renault *et al*, 1974; Fergusson D.M. *et al*, 2002). Also, in a Swedish conscript cohort there was an increased risk of suicide in those who were heavy users of cannabis *(*Andreasson S. *et al,* 1990*).*

However, some other controversial studies have concluded that despite having a strong relationship between cannabis use and suicide, cannabis is unlikely to have a strong effect on risk of completed suicide *(*Price C. *et al*, 2009; Beautrais *et al*, 1999).

In our study, from the 17 cannabinoids requests made for homicides, only one was positive, corresponding to 5.6%. We found mainly active cannabinoids compounds - Δ^9-THC, cannabidiol and cannabinol – in the only homicide positive for cannabis. One meta-

analysis published in 2009, stated that, on average, 6% of homicide victims tested positive for cannabinoids *(*Kuhns J.B. *et al,* 2009*).*

Among violent deaths, road crashes had the same number of positive cases as suicides – 4 cases, corresponding to 23.6%. In other hand from the 205 deaths by road crashes, 4 were positive for cannabinoids corresponding to 1.9%. A French study in 2005 showed that driving under the influence of cannabis increased the risk of involvement in a crash. The same study stated that the fraction of fatal crashes attributed to cannabis was 2.5% *(*Laumon B. *et al, 2005).*

From the 4 road crashes cases, 2 were drivers, other was a pedestrian and the last one there was not mentioned on his death certificate the drivers/passenger/distribution. It is not surprising that drivers have a higher rate of positive cases, as they were the most analysed for cannabinoids with 53 requests, corresponding to 25.9% of all road crashes analysis. Also, because they are involved in much more accidents than other intervenients.

Given the long half life of THC, it is possible that some tested positive for cannabis without being impaired at the time of the crash *(*Laumon B. *et al,* 2005; Fergusson D.M. *et al,* 2001*).* Data from epidemiological and experimental studies together indicated that recent cannabis use may increase crash risk, whereas past use of cannabis as determined by the presence of inactive metabolites in drivers does not *(*Ramaekers J.G. *et al,* 2004; Kochanowski M *et al,* 2005*).* In this study all the 4 positive cases proved positive for an inactive cannabinoid – ac-nor-9-Δ-THC. Other problem of cannabinoids tests is the period elapsed between the death and testing time *(*Laumon B., *et al* 2005; Kochanowski M. *et al,* 2005*).*

Although all the work in this area, there isn't yet any dose threshold that establishes the limit to consider culpability. Thus there is an approach that needs to be carried out, in

order to resolve the possible association or no association at all between cannabis use and driving – determine the dose-response relationship between THC and driving performance (Ramaekers J.G. *et al,* 2005; Kelly E. *et al*, 2004).

It is well known that ethanol is the most common substance in multidrug fatalities (Gable R.S., 2004). Thus, in our study we found an association in 5 cases from the 17, corresponding to 29.6%. Similar to our results, a French study showed that 285 cases in a total of 681 were positive for both ethanol and cannabinoids (Laumon B. *et al*, 2005).

Epidemiological evidences show that the combination of alcohol and THC is often over-represented in dead drivers and it is important to be aware that consumption up to 300µg/kg of THC might be comparable to the impairing effects of an alcohol dose producing a BAC> 0.5g/L (Ramaekers J.G. *et al*, 2004; Bédard M. *et al,* 2007).

Thus, in conclusion, without the knowledge of total autopsies number for each death etiology we found in this study, it is impossible to make a valid and reasonable review of our study as we can not establish a direct relationship of cause-effect for cannabis use and possible association with death. In some autopsy reports when requested for illicit drugs toxicology analysis cannabinoids did not presented on the final statement.

As stated in some studies (EMCDDA, 2010; IDT, 2005; Hibell B. *et al*, 2007), cannabis is one of the illicit drugs with higher consumption prevalence we showed that there are few cannabinoids requests. Thus it is important to be aware of all crime scene information available, allowing pathologists to be more suspicious and thus request more often cannabinoids analysis.

In similar studies from various countries data showed that incidence of cannabis is variable, as it is the frequency of requests and thus the number of positive cases.

An increasing number of cases with illicit drugs will be expected in the following years and also with multiple drug intakes.

Thus, with all the new technologies provided and the knowledge needed, all elements are gathered for undertaking new prevention programs, with drugs of abuse testing either in drivers, or in workers.

We can, again, reassure the importance of requesting cannabinoids analysis in every road crashes, as law obliges, and also in labour fatalities and, at least in people under 55 years old or when information might suggest or rise any suspicion, independently of having already a death etiology, as cannabinoids can alter cognitive and psychological capacities. Apart the drug effects, there are other factors related to drug-taking patterns which influence the final effect the drug will have on driving ability – dosage, how the drug is administered, the taking of different substances simultaneously (even with alcohol), associated morbility, overdose and withdrawal symptoms, etc (Del Rio M.C. *et al*, 1995).

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