
o

**UNIVERSITY OF VALLADOLID**

**FACULTY OF**

**MEDICINE**

**DEPARTMENT OF**

**CELLULAR BIOLOGY, HISTOLOGY AND PHARMACOLOGY**

**PhD THESIS:**

# MEDICATION AND SUICIDAL BEHAVIOUR A CASE-CONTROL STUDY

Defended by **Ana Fructuoso Castellar** to obtain the title of Doctor of Philosophy (PhD) from the University



Directed by:

**Alfonso Carvajal García-Pando**

Universidad de Valladolid

**AUTHORIZATION OF THE PhD THESIS DIRECTOR**

(Art. 2.1c of the Regulations for the submission and defense of the doctoral dissertation of the UVa)

Alfonso Carvajal García-Pando, with ID number 6194373J, professor of the Department of Cellular Biology, Histology and Pharmacology, Centre: Faculty of Medicine of Valladolid, in his capacity of: Director of the PhD Thesis titled 'Medication and suicidal behavior. A case-control study', defended by Ana Fructuoso Castellar, student of the doctoral postgraduate programme in **RESEARCH IN HEALTH SCIENCES (COD. 5601197)**, delivered by the Department of Cellular Biology, Histology and Pharmacology, authorizes the submission of the same, considering that the work produced meets the applicable requirements of originality, rigor, scientific method and adequate formal presentation in order to be submitted and be eligible for the title of Doctor of Philosophy (PhD).

Valladolid, 28th September 2015

The Thesis Director

Fdo.: Alfonso Carvajal

PRESIDENT OF THE THESIS COMMITTEE

## *Table of contents*

# 1. Introduction

# 1.-Introduction

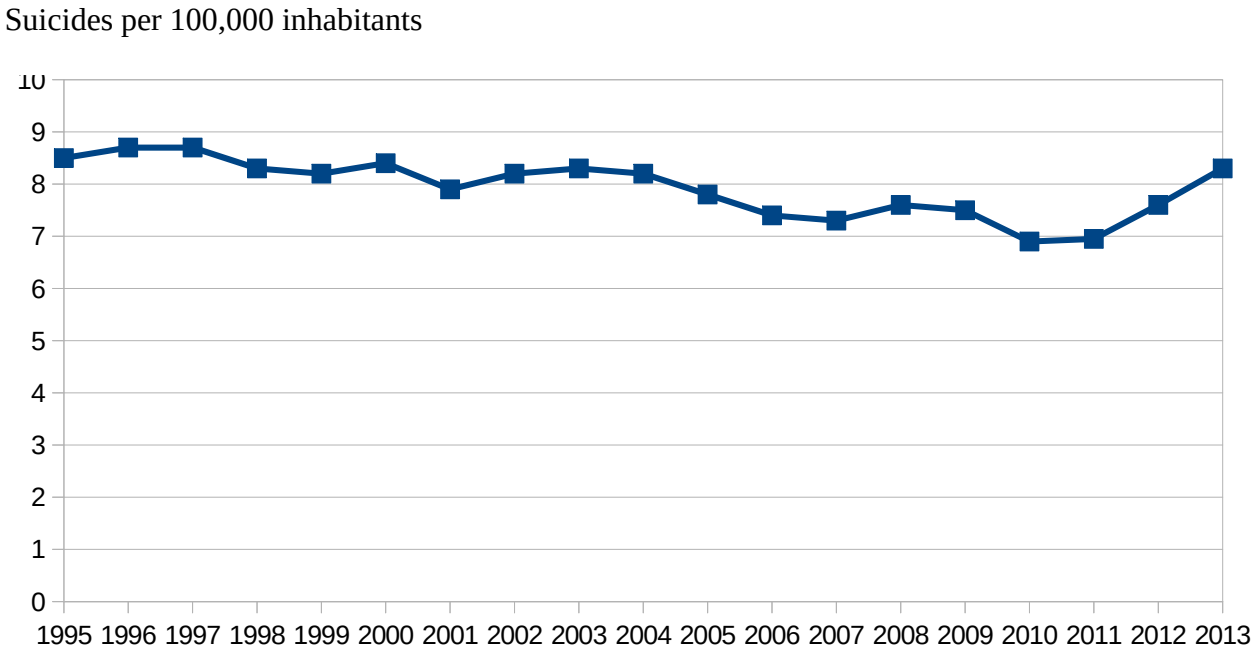
## *1.1. - Epidemiology of suicide*

According to the data provided by the World Health Organization (WHO), more than 800,000 people die each year by suicide (World Health Organization, 2014); this represents a suicide every 40 seconds. Other estimates suggest that 5% of adults will attempt suicide at any point in their lives (Nock MK et al., 2006). However, these figures only represent part of the problem, as, for every suicide committed, between 8 and 25 non consummated suicide attempts take place, although these figures vary depending on age. (Oquendo MA et al., 2009). Nevertheless, the lack of reliable national and international statistical data hinders a thorough understanding of the real extent of the problem.

According to the National Institute of Statistics (Instituto Nacional de Estadística - INE), suicide was by far the main external cause of mortality in Spain in the year 2012, followed by traffic accidents (INE, 2012). In 2013, the last year with available official figures, a total of 3,870 persons took their lives, which implies a 22% rise when compared with the year 2010 in which the number of cases was 3,158, the highest figure ever recorded in Spain in the last 24 years (Sanmartín OR, 2015). Even though suicides decreased in the first few

years of the economic crisis, from the year 2010 they started rising again. This rise was very slight in the first year but in 2012 that figure had gone up by 11.3%, whereas in the year 2013, it rose again by 9% (Sanmartín OR, 2015). In some autonomous communities such as Catalonia though, suicidality increased by 44.7% from the onset of the crisis (Mouzo J, 2015).

Figure 1.Evolution of suicides in Spain from 1995 until 2013

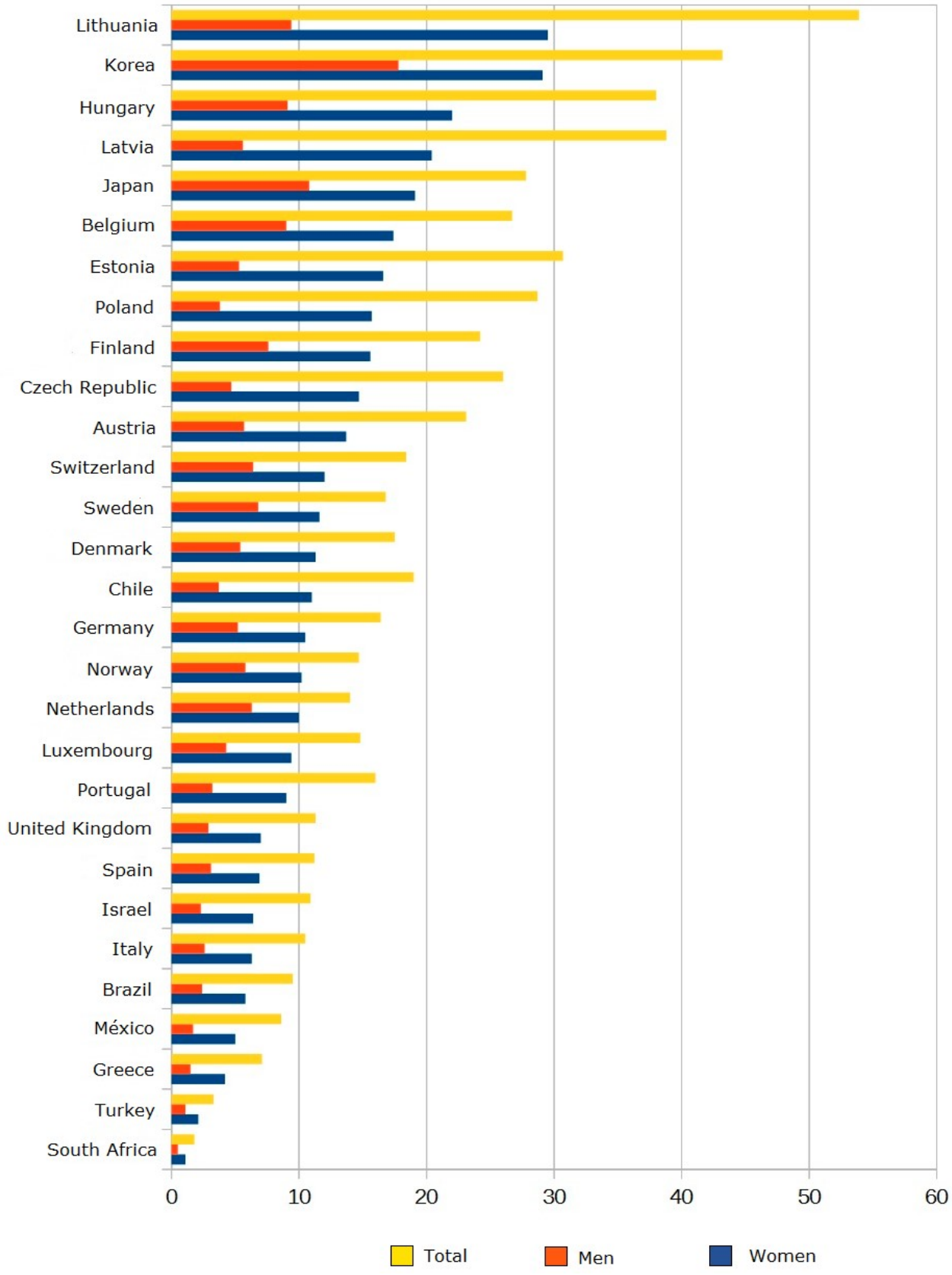



*Source: adapted from INE, 2014

In the last decades there has been an increase in suicidal behaviours in most eastern countries (García-Resa E et al., 2002). From the year 2007 until 2009, coinciding with the onset of the economic crisis, the

proportion of suicides in Europe experimented a remarkable increase, inverting the downward trend that was predominant until 2007. It is precisely in those countries where the crisis has had a more profound impact, such as Greece, Ireland or Spain that the number of suicides has increased (Stuckler D et al., 2011). In European Union countries nearly 60,000 people die each year by suicide (European Commission, 2008). In spite of the significance of those figures, it is thought that the real number has been underestimated (Hawton K et al., 2004). According to the data of the Organization for Economic Cooperation and Development (OECD, 2013), there are significant differences in the suicide figures for different countries. Figure 2 shows these differences.

Figure 2. Suicide in different countries




***Source: adapted from OECD, 2010**

The estimation of suicide attempts involves several methodological difficulties, as it is a very heterogeneous group of patients which encompasses aspects which are difficult to determine such as planning, choice of method and lethality, and the real suicidal intent (Mittendorfer E et al., 2009). On the other hand, using different definitions of what a suicide attempt is also contributes to the confusion as there are discrepancies about the definition of suicidal behaviour and its consequences. Perhaps that is why different terms have emerged such as consummated suicide, parasuicide, voluntary self-injury, etc, which respond to the different manifestations of that behaviour. Different denominations have been proposed, among others the one developed by O´Carroll (O'Carroll PW, 1996) in 1996 and later recommended by the American *National Institute of Mental Health* in its research programme about suicidal behaviour (García-Resa E et al., 2002). The consummated suicide would refer to self-inflicted death with evidence (explicit or implicit) that the person wanted to take their life; the suicide attempt would refer to deliberate and direct self-injury with at least some intention of taking their life and finally suicidal ideation would make reference to the thought of provoking their own death (Nock MK et al., 2009).

One of the most important studies promoted by the WHO to prevent suicidal behaviour was developed at the beginning of the 21st century.

An extensive collection of data was carried out in the six regions of the WHO (Africa, America, Southeast Asia, Europe, East of the Mediterranean and West Pacific) and several groups of researchers conducted a plethora of studies based on those data in the following years (Bertolote JM et al., 2005; Bertolote JM et al., 2010). Those data suggest that there is not always a chronological continuation between the appearance of the idea of death and the suicide attempt and that the aspects related to the suicidal conduct may vary according to the place where they are assessed.

### *1.2. Risk factors*

Usually, risk factors in suicidal behaviour have been classified into two groups, those which are modifiable and those which are not. Modifiable factors have social, psychological and psychopathological origin and may be altered in the clinic or through population interventions (García-Resa E et al., 2002). On the other hand, non-modifiable risk factors have nothing to do with the clinical situation of the patient nor with their life circumstances, on the contrary, they are associated with the patient themselves or with the social group to which the person belongs. They are usually long-lasting and even though some of them suffer variations, such as age, marital status or religious beliefs, they change independently from the clinical situation (González-Navarro MD et al., 2012). It is necessary, therefore, to know

well both types of risk factors in order to carry out a precise assessment of the suicide risk in each patient. Additionally, it is important to include the protective factors in the assessment and prevention of the risk of suicide (Ayuso-Mateos JL et al., 2012).

### *1.2.1. Non-modifiable risk factors*

#### *1.2.1.1. Heritability*

It was observed long ago that some families have a higher suicide risk than others. This family predisposition is not only attributed to the existence or not of a psychiatric illness, as those relatives with a mental condition do not always have a higher risk of suicide than those who are healthy (Brent DA et al., 2005). In a meta-analysis of 21 studies, it was observed that first degree relatives of people who had committed suicide had a three-fold higher suicide risk even without having a psychiatric pathology (Baldessarini RJ et al., 2004); When this pathology existed, the adjusted risk was 10 times higher for suicide and suicide attempts (Kim CD et al., 2005). In another study, it was considered as well that among first degree relatives who had attempted suicide (schizophrenia, 195; bipolar disorder, 315), the suicide risk was up to 8 times higher than in the comparison group (Tsuang MT, 1983). Endogamous populations like the Amish community in the United States, are perfect to conduct these studies;

this community has been the object of analysis of the transmission of affective disorders and suicides over 100 years, from 1880 until 1980 (Egeland JA et al., 1985). This analysis revealed that affective disorders were transmmitted and that 75% of the completed suicides within the Amish population, 26 in total, were limited to four families.

The study of twins and adopted siblings is another way of analyzing the famiy transmission of suicide and associated behaviour. With this approach, it has been appreciated that the frequency of suicide is greater among homozygous twins than between heterozygous twins (Roy A et al., 1995; Statham DJ y et al., 1998). The influence of genomic imprinting in suicide and suicide attempts is very high; different authors estimate that 43% of suicidal behaviour could be explained by this, while another 57% would respond to environmental factors (Roy A et al. 1995).

All in all, it seems that genetic inheritance is one of the main factors that predispose to suicidal behaviour. Thus, the transmission of this behaviour seems to be conditioned by, at least, two components: one of them would be the transmission of mental diseases itself, and the other, the genetic load related to impulsivity and other personality factors (Brent DA et al., 2005). According to many studies, the family association is apparently bigger depending on the seriousness of the

suicidal behaviour, being lower in the case of suicidal ideation, higher for suicide attempts and much higher in the case of consummated suicide (Baldessarini RJ, 2004).

#### *1.2.1.2. Gender*

There are variations in the etiology, risk level and the origin of the suicidal behaviour, as well as in its prevention and treatment, depending on the gender of that person (Hawton K, 2000). In most countries except for China and other Asian countries, the suicide risk is bigger in men than in women (Zhang J et al., 2005). However, the risk of suicide attempts is usually higher among women than men (Miret M et al., 2010). The prevalence of mental disease is high in attempted and completed suicides both among men and women. It has been observed when studying behaviour, personality and emotional state previous to the decease that depressive disorders stand out in the suicide of both genders. Coexistence with a personality disorder has also been detected in 40-50% of the cases (Foster T et al., 1997). The types of mental illness are different depending on the gender. Men show a higher incidence of personality disorders and disorders related to the consumption of toxic substances while women show a higher prevalence of affective disorders, above all depression (Arsenault-Lapierre G et al., 2004). In attempted suicide there are common

factors for both genders, such as suffering from a mental disease but others are gender-specific, like having low economic status, more linked to suicide risk for men or possessing low educational level, which increases the risk of attempting suicide for women (Zhang J y et al., 2005).

Concerning maternity, having a little child (Qin P et al., 2003) or being pregnant (Marzuk PM et al., 1997) have been identified as protective factors. Thus, it would be maternity or paternity rather than the fact of living together that would protect against suicide (Qin P et al., 2000). On the contrary, the death of a child is associated with a higher suicide risk on the part of the mother (Qin P et al., 2003). However, post-partum depression constitutes an exception to the above mentioned protective character of maternity as in this case, the suicide risk increases (Appleby L et al., 1998).

#### *1.2.1.3. Age*

The risk of suicide also increases with age (Shah A, 2011). The process of growing old goes hand in hand with worse health, whether physical or mental. In adult age and above all, during old age, interpersonal losses are common and added to this, old people are part of a less active and fruitful social group. Ageing brings along a change in behaviour. In advanced age, we can notice that the quotient

of suicide and attempted suicide increases progressively (Conwell Y et al., 2001).

#### *1.2.1.3.1. Adolescents and young adults*

Suicide is among the first causes of death among young people and adolescents (INE, 2012). Thus, the figures of potential lifetime years lost are very high (Doessel DP et al., 2009). Mental disease is again, also at this age, one of the key risk factors and major depression the most frequent disorder associated to completed and attempted suicides. Other factors present at this age are substance consumption and behaviour disorders (Beautrais AL, 2000). Among young people dead by suicide comorbidity seems the norm, with a prevalence of psychiatric disorder of 43%-70% (Beautrais AL, 2000). Also,the higher the number of diagnoses, the more serious the attempts (Beautrais AL y et al., 1996). Another remarkable factor is the influence of inheritance in the suicidal behaviour of young people. Thus, the suicide risk is bigger among young people with a family history of psychiatric pathology (Brent DA et al., 1994); it is estimated that approximately half of suicide attempts may be attributed to familial psychopathology (Mittendorfer-Rutz E et al., 2007). In keeping with this, a background of parental suicidal behaviour has been related to an increase in the risk of sucide and attempted suicide (Gould MS et al., 1996).

A higher risk of suicide has been detected among youths with low self-esteem, hopelessness, introversion, neuroticism, impulsivity, imprudence, aggressiveness and impulsive violence (McGirr A et al., 2008). Another studied variable in the suicidal behaviour of young people has been their sexual orientation. There are several studies which identify a higher risk of attempting suicide in young people with homosexual or bisexual orientation (Meyer IH et al., 2008). However, such connection has not been found in consummated suicide (Shaffer D et al., 1996). A personal background of attempting suicide is also related to a higher risk of consummating suicide. One third of the suicide cases among children below 14 years old had a background of suicide attempts (Dervic K et al., 2008) and the figures are quite similar between adolescents and young people (Gould MS et al., 1996). Several studies have also analysed the existing relationship between suicide attempts and social status. According to these studies suicide risk doubles in the case of young people with low socioeconomic status (Agerbo E et al., 2002), it is five-fold among those who have dropped out of school and almost eight-fold among those without higher education (Gould MS et al., 1996). Most of the suicides that were completed by adolescentes, between 70% and 98%, were associated with a previous stressful life event (Rich CL et al., 1991). Among these life events the most frequent ones are losses,

interpersonal conflicts, and discipline or legal problems, which are present not only in suicides (Brent DA et al., 1994) but also in suicide attempts (Donald M et al., 2001).

Family breakup, more specifically parents´separation, also seems to give rise to an increase in suicide risk (Agerbo E et al., 2002). The relation between suicide attempt in children and physical or sexual abuse has been observed by various authors (Maniglio R, 2011); the risk incresases in accordance with the seriousness and persistence of the abuse (Esposito CL et al., 2002). Parental problems of coexistence or the struggle for the children´s custody also increases the risk of attempting suicide among young people (Beautrais AL, 2000). Another present-day risk factor is conditioned by the new technologies, increasingly more accessible to everybody. Thus, the so-called *cyber-bullying* in vulnerable groups of the population, such as children or sexual minorities, causes the appearance of suicidal attempts, turning this phenomenon into a problem that should be tackled urgently (Aboujaoude E et al., 2015).

#### *1.2.1.3.2. Old age*

In advanced age there are differences between the sexes. Old men usually die more frequently on their first suicide attempt (Conwell Y et al., 2001). Widowhood or retirement are usually factors which have a

more profound effect on men. A second well-known risk factor is the presence of a psychiatric disorder, especially depressive episodes, which are considered to be a major risk factor in the elderly (Turvey CL et al., 2002); these are present in 87% of suicides in this population group (Conwell Yt al., 2001). The abuse of certain substances is also associated with suicide in the elderly, especially men. Thus, alcoholism would be related to approximately 50% of consummated suicides in this age group (Blow FC et al., 2004). Somatic disease, especially if it is disabling, chronic, painful or serious, seems to be essential in the suicide of persons of advanced age. Thus, the risk increaes more than five times in patients with pain (Juurlink DN et al., 2004), sight impairment (Waern M et al., 2002), cancer (Waern M et al., 2002) or neurological disease (Waern M et al., 2002). Dependence or the impossibility to fend for themselves in daily activities is also relatd to a higher risk of suicidal behaviour (Alexopoulos GS et al., 1999). Added to this, the greater the concurrence of several diseases, the higher the risk (Harris EC et al., 1997). As a result, due to the fact that old people usually suffer from several pathologies at the same time, it is logical that this group is characterized by a higher risk. Linked to this, we also find the phenomenon of polypharmacy, so frequent at this age. It should be pointed out that some of the most commonly prescribed medicines to old patients —enalapril, simvastatin, prednisone o

indomethacin—are associated with the apperance of depressive episodes (American Psychiatric Association, 2002). Additionally, a quarter of the patients with somatic disease suffer from depression (U.S. Department of Health and Human Services, 1999). Due to this, depression has been described as an intermediate step between somatic disease and the appearance of suicidal behaviour (Ratcliffe GE et al., 2008). Lastly, social isolation should be added to the risk factor of widowhood among men of advanced age. The relation between suicide and social isolation is clear; people who live alone have a higher risk of commiting a suicidal act (Heikkinen ME et al., 1995) as well as those with fewer friends or relatives to trust (Turvey CL et al., 2002). Depression is a confusion factor, on the one hand it favours isolation and on the other hand it increases the risk of suicide by itself.

#### *1.2.1.4. Marital status*

A great number of studies point out that marriage is a protective factor (Masocco M et al., 2010). The lack of a partner (Kposowa AJ, 2000; Wyder M et al., 2009) and the risk increase with the loss of a partner (Erlangsen A et al., 2004; Wyder M et al., 2009), seems to be more decisive among men than women. The suicide risk may be 15 times higher in the case of widowed persons (Erlangsen A et al., 2004). It seems that men need more time to overcome the grief, they

develop less close relationships outside marriage, which leads them to a sensation of disconnection with society without their partner, they express their feelings less frequently and in many cases, may find it more difficult to face domestic chores (Duberstein PR et al., 1998; Erlangsen A et al., 2004). The most delicate period is the first year after the loss or separation and remains high for some years (Duberstein PR et al., 1998). Apart from gender, the moment of the loss may also be a key factor. Two groups of widowed persons have been established: those who lose their partner the first part of their life, with a suicide risk which is 17 times higher in men, and those who suffer the loss in the second half, with a lower risk (Kreitman N, 1988). The risk in case of legal separation is four times as high as in the rest of civil statuses (Wyder M et al., 2009).

A recent prospective cohort study based on an adult Japanese population aged 40-64 years old, assessed different lifestyles related to health, including marital status (Fukuchi N et al., 2013). During the 18 years of follow-up, 106 and 40 deaths by suicide were registered in 20,671 men (344,813 persons-years) and 21,076 women (365,524 persons-years) respectively. Marital status was significantly associated with the risk of completing suicide only in the case of men, with a significant risk of death by suicide found among widowers and divorcees. Another study investigating the existing relation between

certain sociodemographic variables and the appearance of suicidal behaviours in the Iranian population observed that 75.5% of people committing a suicidal act were single as opposed to only 22.5 % of married people (Haghighi H et al., 2015). In a study conducted in Mexico with a sample of suicide attempters, it was found that the predominant marital status in men was single while it was married in the case of women (Fresán A et al., 2015). The results in a recent study with London population reveal that being single or living alone increases the risk of attempting suicide (Aschan L et al., 2013).

#### *1.2.1.5. Occupation and economic status*

Occupation is another factor that has been widely studied. In this section we can highlight health-related professions (Agerbo E et al., 2007). However, lack of employment is more relevant than the type of employment. Unemployment has been related to the number of suicides for a long time. (Durkheim E,1982; Platt S, 1984). This has been concluded by successive studies not only in consummated suicides (Heikkinen ME et al., 1997; Wong PW et al., 2008; Chang SS et al., 2010) but also in attempted suicides (Brown GK et al., 2000; Fu Q et al., 2002). Different types of studies show that an unemployment situation in people causes the risk to increase between two and five times and this is slightly higher in men (Wong PW et al., 2008). The inci-

dence of unemployment varies depending on age. Thus, it is more determining in some age groups like those between 35-45 (Biddle L et al., 2008), those who have lost their job recently (Kposowa AJ, 2001), those who abuse alcohol (Murphy GE et al., 1992), and those patients with personality disorders (Heikkinen ME et al., 1997). Other factors connected to being jobless can also be related to suicide, namely economic and relationship problems (Wong PW et al., 2008). Besides, psychological and psychopathological problems may make it difficult to find and maintain a job (Fu Q et al., 2002). It is also posible that the consumption of alcohol (Pirkola SP et al., 2000) or depressive episodes (Meltzer H et al., 2010) after losing a job might lead to suicidal behaviour.

#### *1.2.1.6. Religious beliefs*

Religious beliefs and their importance in people's lives have an influence on the inclination towards suicide (American Psychiatric Association, 2004). People with strong religious convictions who consider suicide as morally objectionable or whose religious beliefs give meaning to their lives seem to have more difficulty in taking the step from death thoughts to suicidal action (Hovey JD, 1999; Dervic K et al., 2006). Notwithstanding the above, suicide rate is higher among Protestants, followed by Jews, Catholics and Muslims in the last place

(Lester D, 2006). However, we must be cautious when dealing with data collected in countries where there might be a bias in the information due to cultural and religious influence or in which suicide is socially condemned or with a criminal conviction (Kelleher MJ et al., 1998). In a study in the United States aimed at investigating the influence of socioeconomic factors, the number of psychiatric disorders and religiousness over suicidal ideation, it was observed that Afro-American men with multiple psychiatric disorders and not particularly religious showed a high risk of suicidal ideation (Assari S, 2015).

#### *1.2.1.7. Social support*

Social integration has been the cornerstone in the social theory of suicide (Durkheim, E, 1982). It has been considered that the presence of an adequate social network represents a protective factor (Turvey CL et al., 2002) and social isolation, on the contrary, would entail a higher risk of suicidal behaviour at any age (Pompili M et al., 2008). However, it seems that isolation has more influence on suicide than on the suicide attempts, probably because the degree of isolation in the consummated suicide is higher (Saiz PA et al., 2011). Isolation can be related to diffiuculty in communicating with other people and establishing a love relationship, both being suicide attempt risk factors.

#### *1.2.1.8. Previous suicidal behaviour*

The most reliable indicator of suicide risk is having attempted suicide previously (Blumenthal SJ, 1988). 42% of men and 45% of women, who try to commit suicide, have already attempted it before. According to a study, 16% of men and 17% of women who have tried to commit suicide will have a suicide attempt again in the following year (Schmidtke A et al., 1996). Many studies point to the same idea, that previous suicide attempts are the best indicator of the probability of a future consummated suicide (Christiansen E et al., 2007; Haukka J et al., 2008; Ruengorn C et al., 2012). Thus, attempters are 40 times more likely to die by suicide (Harris EC et al., 1997). Other authors, however, warn about the limitation of that background. The reason is that an important amount of consummated suicides are completed in the first attempt, especially among men (62% against 38% for women) (Isometsä ET, 2001), while 82% of those who tried to commit suicide and did not succeed, completed it on a second attempt by shifting to a more lethal method (Isometsä ET, 2001).

In a systematic revision of 14 population groups totalling 21,385 individuals, it was estimated that those with suicidal background have almost 25 times more probabilities of dying from suicide than the general population (Neeleman J, 2001). Based on several prospective studies, it can be stated that between 1% and 6% of those who are

admitted in hospital for a suicide attempt will die from suicide in the following year. The risk is higher in old people or with several previous attempts (Suokas J et al., 2001; Silverman MM, 2006). Therefore, to avoid the repetition of those attempts, it is paramount to assess correctly the people who arrive at the health services after having attempted suicide. (Kapur N et al., 2008).

#### *1.2.1.9. Geographic distribution*

Suicide rate varies greatly across countries. On the whole, Latin American countries have a lower suicide rate than the USA, and countries in the South of Europe lower as well than those in the North and East (World Health Organization, 1998). Urban areas register a greater occurrence of suicide and suicide attempts. In fact, the number of attempted and completed suicides increases in accordance with the greater number of inhabitants in cities. It is in areas with an accumulation of ageing population or citizens on lower incomes where most cases are recorded. However, in residential areas with people with a higher standard of living, suicide rate diminishes (Lastra I et al., 1998).

#### *1.2.1.10. Season, day of the week and time of day.*

The majority of statistical studies available coincide in the fact that in the winter month's suicide occurrence decreases. The said

occurrence gradually increases as spring comes, with surges in the months of May and June (Buda M et al., 1990).

### *1.2.2. Modifiable risk factors*

#### *1.2.2.1. Mental disorder*

Suicide behaviour is, in most cases, a complication of a psychiatric disorder. More than 90% of suicide victims suffer a psychiatric disorder (Isometsä ET, 2001). Among psychiatric patients there is a greater occurrence, often more than 30% than among other types of patients (Muehlenkamp JJ et al., 2011; Glenn CR et al., 2013). In the meta-analysis published by Arsenault-Lapierre (Arsenault-Lapierre G et al., 2004), which included 27 studies with a total of 3,275 suicides, 87.3% of the patients had been diagnosed with a mental illness. In another epidemiological study based on a sample of 894 youths aged 10-30 years old who had committed suicide, 88.6% had at least one diagnosis of mental disorder, with affective disorders being the most frequent (42.1%), followed by substance abuse (40.8%) (Fleischmann A et al., 2005). It is worth noting that suicide risk is higher in the early stages of the illness (Harris EC et al., 1997); a higher risk has been identified in the first six months following discharge after hospital admission (King EA et al., 2001; Hawton K et al., 2009). Some of the most common previous psychiatric disorders are major depression

(Möller HJ, 2003), the most frequent, followed by alcohol and illegal drugs intake (Vijayakumar L y et al., 2011).

According to a different study, major depression increases 20 times the risk of suicide (Harris EC et al., 1997), bipolar disorder 15 times and dysthymia 12 times (Coryell W et al., 2005). The first three months after a major depression episode carry a higher suicide risk (Ruengorn C et al., 2012). The risk is especially high at the start or end of the episode. In the state phase, psychomotor retardation and inhibition hinder execution (Hawton K et al., 2005). It has been estimated that 15% of patients with a major depressive disorder will commit suicide (Guze SB et al., 1970). In a meta-analysis based on 41 studies and a total sample of 31,159 individuals, it was observed that the number of suicides in patients with a depressive disorder doubles that of suicides in hospitalizations for other reasons (8.6% against 4%) (Bostwick JM et al., 2000).

In a different study it was observed that the persons who were more likely to have resorted to health services for having death ideas or having attempted suicide turned out to be white women, white people, not hispanic, people with a poorer health condition in general, those with a more serious clinical condition and in particular those who had or had had a major depression diagnosis (Stanley IH et al., 2015).

#### *1.2.2.2. Schizophrenia*

A prevalence of consummated suicide of up to 10% has been reported in schizophrenic patients (Hawton K et al, 2005). In a systematic revision of 61 studies, with a total sample of 48,176 individuals, a prevalence of suicide of 4.9% among schizophrenic patients was estimated (Palmer BA et al., 2005); these patients have shown a suicide risk 8.5 times higher than the general population (Harris EC et al., 1997). Schizophrenic patients may also add other risk factors which should be taken into consideration, such as being male, of white race, having depression, being single, unemployed, living alone or being socially isolated. Factors with bad prognosis in schizophrenia like being young, having numerous relapses, an elevated number of psychiatric admissions, socio-labour or sexual deterioration and poor therapeutic adherence also increase the risk of suicide in those patients (Hawton K et al, 2005).

#### *1.2.2.3. Anxiety disorder*

Anxiety is often connected with death ideas and the appearance of suicide attempts (Allan NP et al., 2015). Almost 20% of patients with a disorder due to anguish or a social phobia attempts suicide at least once in their lives and if this disorder is compounded with depression, the likelihood of consummating suicide increases (Warshaw MG et al.,

2000; Khan A et al., 2002).

According to Harris and Barraclough (Harris EC et al., 1997), the risk of suicide increases between 6 and 10 times depending on the different anxiety disorders: generalized anxiety disorder, obsessive compulsive disorder or panic disorder. However, other studies have not identified a significant increase of suicide risk in the context of an anxiety disorder, without the presence of depressive symptoms (Beautrais AL, 2000). The relationship between suicide attempts and being prone to anxiety is coherent with theories which state that those attempts are the consequence of the inability to face unbearable anguish (Allan NP et al., 2015). Anxiety disorders and personality disorders are also associated with a rise in the risk of suicidal behaviour; especially the borderline personality disorder which is the most commonly associated one in the case of adolescents and young adults (Muehlenkamp JJ et al., 2011; Glenn CR et al., 2013).

#### *1.2.2.4. Substance abuse*

The consumption of toxic substances has been the focus of attention of authorities and researchers. It is known that disorders caused by the abuse of substances, especially alcohol, have been frequently related with suicide, both as a base risk factor and as a suicide trigger. (Allan NP et al.,2015). Up to 15% of alcoholic patients try to commit

suicide and alcohol abuse is present in 25-50% of all suicides (Conner KR et al., 2004). Alcohol consumption may also be associated with organic illnesses, mood disorders, personality disorders or impulse control disorders, which additionally implies a suicide risk rise (Gorwood P, 2001; Cherpitel CJ et al., 2004). Apart from alcohol, another toxic but legal substance is tobacco, whose influence on suicidal behaviour has been described in numerous studies. It has been observed that the risk of attempting suicide is greater among smokers (Yaworski D et al., 2011; Berlin I et al., 2015). It also appears that this risk would be greater in psychiatric patients who smoke and are hospitalized (Hooman S et al., 2013). Some studies have evaluated whether this risk is modified by patient gender, but the findings reveal that tobacco addiction is associated with the existence of an increased suicidal ideation (Scherrer JF et al., 2012). On the other hand, the majority of authors agree that the consumption of illegal drugs (opioids, cocaine, cannabis, etc.) may also increase the risk of suicide attempt, especially in the case of poly-consumption, where the risk may increase up to 20 times with respect to the base reference level (Harris EC et al., 1997). When analizing illegal substance intake in patients who had injured themselves, some authors found that drug consumption in young women was associated with higher scores in the suicide intent scale (Haw CM et al., 2011). In

a study carried out in Scotland, the use of illegal drugs, with or without the consumption of cannabis, was significantly associated with a greater likelihood of depression, suicide thoughts and suicide attempts (Rasic D et al., 2013). For other authors, the occasional use of cannabis over other illicit drugs would be indeed associated with an increased probability of attempting suicide (Artenie AA et al., 2015).

Other studies suggest that the use of other drugs such as inhalants or cocaine are particularly associated with suicidal behaviour and notably increase the risk, above all, when consumption takes place in persons with psychiatric disorders (Vijayakumar L et al., 2011). Therefore, most authors agree that the use and dependence on alcohol, tobacco and illegal drugs is related with suicidal behaviour (Miller M et al., 2011).

On the other hand, it is well-known that the combination of depressive disorders and addictions is especially deleterious (Wilcox HC et al., 2004). Depressive symptoms may be the consequence of a psychiatric disorder or the result of the toxic effects of alcohol, hepatic alteration and malnutrition, as well as organic brain syndromes secondary to head trauma. Another usual problem among addiction substance users is low adherence to treatments. If this is compounded with an elevated frequency of additional psychiatric disorders, mainly

of the depressive scope, the probability of a suicide attempt increases greatly (Conner KR et al., 2004).

#### *1.2.2.5 Personality disorders*

It is essential to consider personality traits as possible goals to prevent suicide (Menon V et al., 2015). These disorders play an important role as they can influence suicide behaviour in a number of ways. They predispose to more serious disorders such as depression and alcoholism, which, in turn, involve relationship and social adaptation problems (Pompili M et al., 2005). It has been stated that the majority of patients with personality disorders who take their lives also meet the criteria for other serious mental illnesses such as depression, substance abuse or both, and this association is still more frequent in cluster B personality disorders (Isometsä ET, 2001). Borderline personality disorder (BPD) is common among patients with non-oncological chronic pain, often more prone to the abuse of opioid analsegics and the prevalence of suicide is high in these patients (Campbell G et al., 2015). In the Harris and Barraclough revision mentioned above, personality disorders increase up to six times the risk of suicide (Harris EC et al., 1997). Despair, neuroticism and extroversion were the most clearly connected features (Brezo J et al., 2006); others, like aggressiveness, impulsivity, irritability, hostility or

anxiety have demonstrated less conclusive associations.

#### *1.2.2.6. Other mental disorders*

There are other mental disorders that also increase suicide risk. People with attention deficit disorder have a higher probability of consummating suicide, above all men suffering from depression and associated behaviour disorders (James A et al., 2004), also those with eating disorders (Pompili M et al., 2006), in particular those suffering from anorexia and bulimia nervosa with depressive symptoms and/or substance abuse.

An adjustment disorder can also increase the risk of committing a suicide attempt or consumating suicide. In those patients, a suicide risk increase of up to 14 times over the risk of the general population has been observed (Harris EC et al., 1997). Among previous life events the following can be highlighted: processes related to age (like the moment when the offspring marry or leave home, retirement, the need for home assistance, moving into an old people´s home, etc.) work, love relationship and health problems and disease or death of a relative (Conner KR et al., 2001).

Few studies have examined in a prospective way if depression symptoms and other risk factors are associated with a higher risk of death by suicide in those populations without a psychiatric or suicide

background. In a recent study, it was prospectively studied whether the depression symptoms assessed by the Beck Depression Inventory (BDI) are associated with a higher risk of death by suicide and whether depression symptoms and other risk factors are independent suicide predictors in the general population (Yi SW et al., 2015). The study concluded that depression symptoms in middle-aged men are a strong independent predictor for suicide attempt and the same happens with other factors like having a poor health state, a low educational level or a high consumption of alcohol.

#### *1.2.2.7. Physical Health*

Illnesses involving disability or pain, chronic and intense, are well-known suicide risk factors (Stenager EN et al., 2000). Chronic or disabling illnesses such as hypertension, diabetes, or migraine and some respiratory and neurological alterations also increase the risk of developing suicidal behaviour (Scott KM et al., 2010). Besides, a higher risk has been detected in patients diagnosed with cancer, HIV, Huntington disease, multiple sclerosis, renal insufficiency, spinal cord injury or lupus, among others (Pompili M et al., 2005). According to these studies, the appearance of depression symptoms may be a decisive factor in this type of patient (Tang NK Y et al., 2006). High intensity long-lasting chronic pain associated with insomnia is also an

important risk factor for suicide (Cheatle MD, 2011). A recent retrospective study investigated the influence of psychiatric comorbidity in the perception of pain (Ciaramella A et al., 2015); both agoraphobia and depression and other psychiatric disorders were associated with an overall increase of pain intensity.

#### *1.2.2.8. Psychological dimensions*

Impulsivity and aggressiveness are those dimensions most closely associated with suicidal behaviour in the majority of proposed models (Mann JJ et al., 1999; Conner KR et al., 2003). This relationship has been confirmed by several studies (Joiner TE et al., 2005; Zouk H et al., 2006). It seems clear that the most aggressive individuals are more likely to commit acts related to suicide, homicide and violence in general (Conner KR et al., 2001); those deceased by suicide therefore, display aggressive and violent conduct with more frequency than those deceased by other causes like traffic accidents. This relationship is more evident in young patients or adolescents, as well as those serving time in prison (Conner KR et al., 2003). The authors of the said studies highlight the importance of analysing personality traits in order to determine suicide risk accurately. Other psychological dimensions associated with suicidal behaviour are aggressiveness independently from impulsivity, hopelessness, dichotomous thinking,

cognitive rigidity and difficulty in problem solving. Aggressiveness, which is not always associated with impulsivity (Herpertz S et al., 1995), has been associated with violent suicide (Berglund M et al., 1998), with suicides in young men (Prigerson HG et al., 1999), with suicide attempts among the general population (Doihara C et al., 2008) and in psychiatric population (Mann JJ et al., 1999). Hopelessness, as an expression of the limitation of success expectations (Melges FT et al., 1969), has been connected with suicidal behaviour in psychiatric pathologies (Kamath P et al., 2007), especially in schizophrenia (Berlin I et al., 2015), and somatic pathologies (Pompili M et al., 2007). As a result, these psychological dimensions favour hopelessness and are associated, in an independent way, with the appearance of suicidal behaviour.

### *1.3. Protective factors*

The most common protective factors can be divided in two. Those particular to the individual and those coming from the environment (Center for Disease Control and Prevention, 2010). Among the first we can include individual attitudes, values and norms against suicide, like the value given to life itself. Besides, social skills, anger management and the ability for problem solving favour the decision not to commit suicide. Other characteristics connected with protection are the care

and search for mental and somatic health, religious beliefs which oppose suicide, fear of pain and risky actions, the presence of hope and optimism, self-control of impulsivity, self-esteem and adequate strategies for coping and high resilience. In a study it has been observed that mortality by suicide was inversely associated with the body mass index. In this sense, whereas an elevated body mass index is associated with a higher risk of depression and anxiety, the accumulated evidence indicates that it is a protective factor for suicide (Bjørngaard JH et al., 2015). The existence of an adequate social and family network with bonds towards their members, social participation, accessibility to healthcare services, a stable atmosphere and restrictions to the purchase of weapons or potentially lethal medication are some of the main environmental factors which have to be taken into consideration as protective factors (Wasserman D et al., 2012).

### *1.4. Summary*

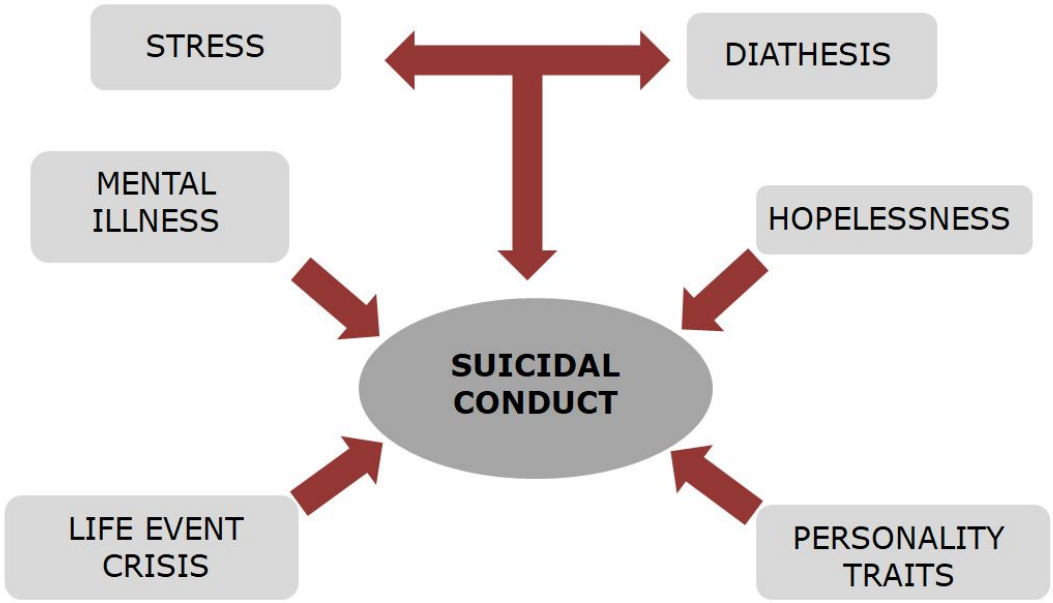
Suicidal behaviour is one of the greatest issues of public health these days, both in terms of economic costs and social, healthcare and personal ones (Martín YM et al., 2011). The extent of the problem is not only defined by the mortality caused by consummated suicide. The influence of the suicide thoughts, the suicide attempt and the consequences over the quality of life of the population is also

important. The WHO statistics pinpoint suicide as one of the main causes of lifetime years lost by illness. In spite of the differences among countries connected with availability or social acceptance, it seems obvious that men tend to opt for more violent methods and women for less aggressive ones (Sarró B et al., 1991). This is a key factor to understand why men consummate more suicides than women. In Spain, the most common methods are precipitation and hanging (Arranz Estévez FJ, 1997). Among suicide attempts the most common system is intoxication with 64% of men and 80% of women opting for this method in a Europe-wide study. (Schmidtke A et al.1996). It is necessary to take into account the associated risk factors in order to prevent suicidal behaviour. As we have seen, non-modifiable risk factors like a family or personal background of suicidal behaviour, the gender and age of the patient, are accompanied by social demographic variables which are hardly modifiable like marital status, work situation, religious beliefs and social support. We also know that almost every individual who consummates suicide and a high percentage of those who attempt it or think about it, suffer some type of associated mental disorder.

Although suicide risk is associated with the number of risk factors present, a wider model of diathesis-stress has been proposed, as a useful tool to understand the risk of suicidal behaviour (Mann JJ, 2003)

(Figure 3). The model includes two interrelated ingredients: those characteristics inherent to the person (genetics, substance abuse, personality and impulsivity) and the characteristics of the triggering or precipitating factors (acute psychiatric illness or adverse life events). The combination of both components would be more important in order to establish the risk of suicidal behaviour than a mere accumulation of risk factors. This highlights the importance of a correct assessment of patients with suicide risk which comprises both population risk factors and risk factors related to the mental illness itself.

Figure 3 Stress-diathesis model for suicidal behaviour (Adapted from Mann, 2003)




*Source: Own elaboration*

### *1.5. Medication and suicidal behaviour*

Nowadays, when the symptoms and signs of mental illness are sufficient to require the use of medication, it is considered that there is no reason to deprive patients of the potential benefits of pharmacological treatments (Hawton K et al, 2004). But however paradoxical it may seem, some of the drugs used in the treatment of psychiatric illness and more specifically in the treatment of suicidal behaviour have sometimes been associated with the appearance of that same conduct.

Thus it turns out that the possible inducement to suicide by certain drugs which seek precisely its prevention is a cause for concern, controversy and intense discussion.

It is admitted that serotonin and some of its receptors are altered in the case of the suicidal and depressed patient. For this reason, drugs that inhibit serotonin reuptake (SSRIs) are often used to treat patients with depression symptoms associated with suicidal behaviour. Every patient with depression or suicide ideas has to be hospitalized, receive adequate treatment and be under constant supervision. However, although the right medication reduces in the short and long term the morbidity and mortality of suicide, suicidal behaviour is a complex problem which goes beyond the effect of antidepressants and other medication (Sakinofsky I, 2007; Rihmer Z et al., 2015).

A review of psychodrugs and suicide has been carried out recently (Yerevanian BI et al., 2013) including all the articles published on this area from January 1960 to January 2013 and using relevant key words to identify the studies. The updated information of the FDA was also consulted. The available studies used different methods which hindered the interpretation of the findings. In general, the majority of studies suggest that antidepressants may increase the risk of suicide in bipolar disorder and other disorders of the depressive spectrum.

There is no evidence that antiepileptic drugs increase the risk of suicide. Little is known about the effect of antipsychotics as well as the effect of anxiolytic and hypnotic drugs over suicidal behaviour.

### *1.5.1. Antidepressants*

Antidepressants have been used profusely in the treatment of depression on the basis of the known results of clinical studies. Depression, as it has been commented before, is the psychiatric disorder which is associated with the highest risk of suicide. Also, the lethality of the suicide attempts is connected with the seriousness and duration of the depression. It is accepted that adequate treatment of depression reduces attempts and death by suicide. Among the patients with major depression disorder, the occurrence of suicide attempts varies remarkably depending on the seriousness of depression, with a higher incidence during acute episodes of major depression (Holma KM et al., 2010). Consequently, the serotonergic hypothesis of suicide together with the apparently low profile of toxicity that they possess provided SSRI antidepressants with a major role in the pharmacological treatment of suicidal behaviour in principle. This group of drugs includes fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine and citalopram, among others.

For years after these drugs were first marketed, these drugs were welcomed warmly. Some studies described a decrease of suicidal behaviour through the use of SSRIs, which would seem to support the effectiveness of these drugs. (Martínez JC et al., 2007). An example of this is the prospective study developed in the USA where the effects of fluoxetine in patients with depression were evaluated (Milane MS et al., 2006); according to the results of this study, the period 1988-2002 saw a decrease of suicide in patients taking this drug. Another study conducted in Sweden concluded that the enormous increase in the use of SSRIs in the 90s was accompanied by a significant decrease in the number of suicides with respect to previous years to their introduction in the market (Isacsson G et al., 1997). Nevertheless, the relationship between some antidepressants and suicide risk increase has been controversial. From the year 1990 the first warnings appeared about the relationship between suicidal behaviour and the use of SSRIs in children and adolescents (Bailly D, 2006); these behaviours included excitation, motor restlessness, social disinhibition and self-destructive behaviour. However, clinical tests provided little data that could help to confirm these initial observations. Thus, in March 2004, the FDA suggested restricting and monitoring the use of some types of SSRIs in the face of the possibility of depressive symptoms and suicide ideas worsening. Finally, in October 2004, after assessing 26 studies, the

FDA issued a warning (*black warning*) in the packets of these drugs aimed at the prevention of these risks in under-18s (Brent DA et al., 2004). Later, the original warning was modified and the FDA specified that the use of SSRIs may produce and increase of suicide ideas and suicidal behaviour but not consummated suicide. In June of that year, the body made the announcement that the risk of suicide attempts in adults treated with SSRIs would also be increased (Brent DA et al., 2004). Following that, the warning was extended to persons over 18 years old, with the labelling in the packets indicating that depression itself was associated with a higher risk of suicide at any age. Besides, the agency stated that patients being treated with antidepressants and especially those being treated for major depression should be under close surveillance given the probable worsening and appearance of suicidal thoughts or behaviour through the use of this medication (FDA, 2004). The mechanisms responsible for the risk increase in children and adolescents could be various. It might be connected with the intrinsic action of the drug itself, have something to do with accidental overdoses, inefficacy of the treatment and consequently with the persistence of the depressive symptoms and finally it might be associated with the initial activation that these drugs produce and would take the patient from the stage of suicide ideation to the suicide act (Healy D et al.,1999). As the warnings were originally targeted at

children and adolescents, there was a decrease of drug prescription for this group of patients (Olfson M et al., 2008). However, the clinical and real public health consequences of these steps are unknown (Kurian BT et al., 2007). As a result, even though SSRIs continued as a first line pharmacological treatment for this group of patients, they were reserved to those cases where no psychotherapy was available or this was insufficient (Sharp SC et al., 2006).

Nevertheless, and despite the warnings, some researchers did not find an increase of the suicide attempt risk in SSRI users (Helgason T et al., 2004; Zahl PH et al., 2010). Thus, controlled studies including ample samples of patients did not evidence a greater risk of suicidal behaviour comparing the placebo with some specific SSRIs (Sharp SC et al., 2006; Baldwin DS et al., 2007; Tauscher-Wisniewski S et al., 2007). It has been argued that SSRIs have a protective action in adults and that there is no evidence to support its connection with suicide (Gibbons RD et al., 2007). As regards children and adolescents, even though some epidemiological data suggested that SSRIs could increase this risk, other epidemiological data showed that mortality by suicide in children and adolescents might have decreased since their introduction (Bailly D, 2006). Although in the case of the most vulnerable patients the risk of attempting suicide might increase in the

first days of antidepressant treatment, no evidence was found that the risk was greater with SSRIs than with other antidepressants or non-pharmacological treatments (Hegerl U, 2007).

Other studies have found approximately twice as much relative suicide risk with antidepressants than with patients taking a placebo (Healy D et al., 2005); paradoxical suicide ideas have been observed associated with desimipramine (Damluji NF et al., 1988), even with maprotiline (Rouillon F et al., 1989) and amitriptiline (Soloff PH et al., 1987). In patients taking venlafaxine, a greater risk of attempting suicide was observed than with the use of other antidepressants (Tiihonen J et al., 2006). A different study compared the presence or absence of SSRIs in the plasma of patients who had attempted suicide, regardless of whether this had been consummated or not (Fazel S et al., 2007); among more than 14,000 cases studied, around 13% had detectable plasma levels of SSRIs, not finding differences by age or gender and with a smaller use of violent methods. In a similar study with very young patients, rests of imipramine or fluoxetine, but not other antidepressants, including paroxetine, were only found in around 6% of the patients (Leon AC et al., 2007). It is known that even though antidepressant drugs are the cornerstone of treating patients with depression, they may also carry serious risks (Teicher MH et al., 1993). In recent study 238,963 patients aged 20-64 were analysed for

a period of 12 years with an initial diagnosis of depression. During follow-up, 87.7% of patients (n = 209,476) were prescribed one or more antidepressants. The duration median of the treatment was 221 days (interquartile range 79-590 days). In the first five years of follow-up, 198 cases of consummated suicide and 5,243 cases of attempted suicide or self-injury took place. The authors did not find a significant difference between the users of tricyclic antidepressants and SSRIs as regards the risk to commit consummated suicide. (OR=0.84; CI 95%=0.47-1.5) but the risk of consummated suicide risk increased significantly in the periods of treatment with other antidepressants (OR=2.64; CI 95%=1.74-3.99). The risk ratio for consummated suicide increased significantly for mirtazapine in comparison with citalopram (OR=3.7; CI 95%=2-6.84). The absolute suicide risks in a year ranged from 0.02% for amitriptiline to 0.19% for mirtazapine. No greater risk of attempting suicide or self-injury was found with tricyclic antidepressants (RR= 0.96; CI 95%=0.87-1.08) in comparison with selective serotonin reuptake inhibitors (SSRIs). The adjusted risk of suicide attempt or self-injury increased significantly for three of the most prescribed drugs in comparison with citalopram: venlafaxine (OR=1.85; CI 95%=1.61-2.13), trazodone (OR=1.73; CI 95%=1.26-2.37) y mirtazapine (OR=1.70; CI 95%=1.44-2.02), and was reduced significantly in the case of amitriptiline (OR=0.71; CI 95%=0.59-

0.85). The risk was greater in the first 28 days after initiating treatment and remained the same after suspending it (Coupland C et al., 2015). Another recent study centred around describing the appearance of suicide ideas and suicide attempts in a group of adolescents who were hospitalized due to depression and treated with SSRIs for a period of three months after discharge (Ghaziuddin N et al., 2014); the risk of appearance of suicide ideas or suicide attempts was associated with the intake of an antipsychotic drug in combination with an SSRI. Another study compared the proportion of suicide attempts during treatment with antidepressants with the previous proportion to the commencement of the treatment (Termorshuizen F et al., 2015). In this study, an increased risk of suicide attempt was found among those over 25 years old in the month prior to the commencement of the pharmacological treatment as well as an increased risk in the first month of treatment and a tendency for risk to diminish in later months with antidepressants, although in none of the cases were the results statistically significant. Besides, it was observed that the appearnce of events connected with suicide was greater in persons over 40 years old and in the first month of treatment.

To this day, there is no clear explanation of why SSRIs might increase this risk. In any case, it seems that these effects are not only

unique to children and adolescents but they have also been observed in adults (Bailly D, 2006). Different mechanisms have been proposed to explain this adverse effect, namely, encouraging patients with depression to act in the context of a preexistent suicide idea to the start of the treatment, paradoxical worsening of depression, inducing akathisia, aggressiveness and autolysis impulses secondary to the discomfort that it provokes, inducing panic attacks, swerving from a depressive stage to a maniac or mixed stage, with the corresponding activation of impulses and scarce restraint of conduct, causing serious insomnia or interference in the sleep patterns with worsening of the depressive clinical state, heightened psychopathological alterations such as obsessive behaviour and lack of control of impulses, as well as other neurological alterations (Teicher MH et al., 1993).

Another vulnerable group is that of the elderly. This group requires careful anamnesis given the high frequency of depression and the elevated risk of suicide among them (Fischer LR et al., 2003). The exploration of death ideas during treatment with SSRIs in the elderly is compulsory. It must be noted that suicide thoughts might occur or increase in the first days of any antidepressant treatment (Healy D et al., 1999). Besides, we are aware that suicide ideas in the early stages of pharmacological treatment are frequently associated with the

worsening of the symptoms (Perlis RH et al., 2007). Likewise, in some patients the suicide risk might increase in the first days of any treatment, not only pharmacological, but also theurapeutic. This mechanism is common to any antidepressant and is greater in the first stage of treatment, when the mechanisms start to have effects, therefore, explicit warnings and monitoring the early stages of treatment might reduce to a great extent these risks (Healy D et al., 1999). It is therefore advisable to monitor the treatment closely (Kölch M et al., 2007) and consider an alternative treatment in the case that other symptoms appear, such as restlessness (Andrade C et al., 2006). Pharmacological treatment must be restricted to those cases where psychotherapy is not effective (Bhatia SK et al., 2007), with the combined use of SSRIs and psychotherapy being an alternative (Hughes CW et al., 2007). It is paramount to remember that suicide attempts are more frequent in the months before and after the start of the treatment, regardless of the type of drug used or the psychotherapy (Simon GE et al., 2007; Schneeweiss S et al., 2010). SSRIs must be used selectively and carefully with children and adolescents, avoiding their routine prescription; their use must be reserved to serious cases or when psychotherapy itself is not sufficient (Bailly D, 2006). Besides, when dealing with children and adolescents, only psychiatrists should prescribe and supervise the treatment with

SSRIs (Cohen D, 2007). Choice of antidepressant will depend on gender, age, abuse or dependence on drugs and the number of medicines prescribed and clinical response (Kim HM et al., 2015). Close monitoring of the treatment must be made in order to detect the appearance of adverse effects, as is the case with patients of advanced age. Suicide prevention population schemes tend to centre on early diagnosis and the treatment of major depression and the factors associated with risk, above all in the case of individuals being treated with SSRIs and the most vulnerable groups (Bernal M et al., 2007).

In any case, study results do not seem conclusive: it is not possible to put suicide risk only down to antidepressants since depression itself typically involves suicide ideas and suicide risk (Martínez JC et al., 2007). It is currently accepted that there is an increase in the appearance of suicidal behaviour in children treated with SSRIs connected with an increase in the appearance of impulsive conduct in the first few weeks of treatment. As a result, the use of this type of medication remains controversial (Sakinofsky I, 2007). Untreated depression is associated with suicide risk and additionally there are negative impacts on the normal life of patients. However, available studies do not make it clear whether SSRIs would modify this risk in a clinically significant way (Hetrick S et al., 2007). The majority of

studies carried out had numerous limitations; there are remarkable differences between patients seeing a professional and those participating in studies so it is difficult to draw definitive conclusions. The studies conducted up to this day only provide limited data; clinical tests, while providing useful data about the efficacy of the drug, present limitations in order to identify certain adverse effects (Bailly D, 2006). However, these studies have been useful to guide future research (Sharp SC et al., 2006; Jiménez-Arriero MA et al., 2007). For all of the above, the relationship between antidepressants and suicide tendencies still remains today a topic of uncertainty and controversy (Olmer A et al., 2012).

### *1.5.2. Antiepileptics*

Antiepileptic drugs are a heterogenous group of drugs, with different action mechanisms, that share a depressive action over the Central Nervous System. They take effect, among others, on the gabaergic receptors (Czapiński P et al., 2005). Although they constitute the main treatment for epilepsy, they are also used for mania, migraine and neuropathic pain; they also have anxiolytic action, both clinically and experimentally (Elliot EE et al., 2000; Ashton H et al., 2003; Stahl SM, 2004).

In different studies the efficacy of carbamazepine, la fenitoine and

valproic acid has been observed in the treatment of impulsivity, in the reduction of the frequency and intensity of behaviour alterations and in the treatment of anguish and hostility (Donovan SJ et al., 2000). Thus, apart from diminishing the risk of suicide associated with epilepsy, antiepileptics could be efficient in the reduction of impulsivity and associated suicidal conduct (Stein DJ et al., 1995). In this sense, the different antiepileptics have been analysed; lamotrigine proved effective — in a number of cases of personality disorder— in the reduction of impulsive symptoms and suicidal behaviour (Pinto OC et al., 1998). Other antiepileptics like gabapentine or topiramate have proved to be effective against impulsiveness in different psychiatric disorders as in the case of binge shopping or eating (Halmi KA, 2013; Ye L et al., 2014).

However, in spite of these properties, apparently beneficial, in the year 2008 the FDA issued a warning with respect to the probable risk of appearance of suicidal behaviour associated with the use of various antiepileptic drugs, among which lamotrigine was present (U.S. Food and Drug Administration, 2008). Later, in order to confirm the warning issued by the FDA, a cohort study was conducted in patients who had started anticonvulsant treatment (Patorno E et al., 2010); the study identified 26 consummated suicides, 801 suicide attempts and 41

violent deaths out of 297,620 new cases of treatment with anticonvulsant medication (global average tracking of 60 days). The incidence of the combined result of consummated suicides, suicide attempts and violent deaths for the antiepileptics used in at least 100 episodes of treatment ranged from 6.2 out of 1,000 persons per year for primidone to 34.3 out of 1,000 persons per year for oxcarbazepine. When compared with topiramate, the risk of suicide acts was greater for gabapentina (OR=1.42; CI 95%=1.1-1.8), lamotrigine (OR=1.8; CI 95%=1.4-2.4), oxcarbazepine (OR=2.1; CI 95%= 1.5-2.8), tiagabine (OR=2.4; CI 95%=1.6-3.5), and valproate (OR=1.6; CI 95%=1.2-2.2). Consequently, in this study it was observed that the use of gabapentine, lamotrigine, oxcarbazepine and tiagabine, in comparison with topiramate or carbamazepine, was associated with a greater risk of committing suicide acts or suffer violent deaths. In this same study, alterations in the mood and behaviour changes associated with the intake of antiepileptics were identified. Other observations on the contrary suggest that valproate and carbamacepine may be protectors or neutral whereas only topiramate and lamotrigine would have a profile related to the idea of death (Fountoulakis KN et al., 2012). The relationship between the consumption of antiepileptic drugs and the appearance of suicide behaviour has also been studied, using the data of a representative sample of the general population of

the United Kingdom (Arana A et al., 2010); in a cohort of 5,130,795 patients the estimated incidence of episodes related with suicide for every 100,000 persons/year was 15.0 among patients without epilepsy, depression, bipolar disorder or treatment with antiepileptic medication, 38.2 for every 100.000 persons/year among patients with epilepsy who were not treated with antiepileptic medication and 48.2 for every 100.000 persons/year among patients with epilepsy taking antiepileptic medication. In the adjusted analysis, a risk associated to this medication taken as a whole was identified, both in patients who did not suffer from epilepsy (OR=1.6; CI 95%= 1.2-2.2) and in patients with depression or bipolar disorder (OR=2.6; CI 95%=1.8-3.7), however, a greater risk of suicidal behaviour was not identified in patients with epilepsy (Arana A et al., 2010). The authors concluded that antiepileptic drugs were not associated with an increased risk of episodes related with suicide among patients with epilepsy but they were indeed in the case of patients with depression and those who did not suffer from epilepsy, depression or bipolar disorder. Other studies did not find an increased risk of suicide attempts or consummated suicides associated with the use of different antiepileptic drugs in patients diagnosed with bipolar disorder (Nilsson L et al., 2002; Leon AC et al., 2012). A recent prospective and observational study from 2015 has assessed the action of lamotrigine in a sample of 969

patients with bipolar disorder (Rihmer Z et al., 2015). At the start of the study, 17% of patients showed a clinically significant suicide risk that went down gradually to 2.1%. During the six-month study period, there was no suicide attempt or consummated suicide.

### *1.5.3. Antipsychotics*

Antipsychotics achieved the so-called deinstitutionalization, that is, psychiatric patients going out of the old asylums and mental institutions. However, even though patients under treatment with those drugs might live outside traditional enclosed institutions, there is, for the purpose that concerns us, a greater risk of suicide. It is estimated that up to 40% of patients with schizophrenia will try to commit suicide at least once in the course of their illness (Barak Y et al., 2004).

There is evidence to suggest that atypical antipsychotics, apart from having therapeutic effects over depression and hostility, can also reduce suicidal behaviour in schizophrenics due to their action over the 5-HT2A receptors since aggression and suicide ideas are directly related to the increase of the expression of these receptors in the prefrontal cortex (Mann JJ et al., 1986; Pandey GN et al., 1990; Keck PE Jr et al., 2000).

Soon after the first antipsychotics were introduced in medicine, an increase of the incidence of suicides in the population of hospitalized schizophrenics was observed in some studies (Beisser AR et al., 1961; Husar AF, 1962) but some older studies did not find these differences (Cohen S et al., 1964). Apparently a significant number of suicides took place after an abrupt interruption of the treatment with antipsychotics. Consistent with the observations above are the results of another study in which individuals from a sample of schizophrenic patients who were kept stable for 12 and 48 months through neuroleptic treatment were randomly distributed between two groups, one which maintained the neuroleptic treatment and another in which it was withdrawn (Johnson DA et al., 1983); the cases of suicidal behaviour increased significantly in the untreated group: for a tracking period of 18 months suicidal behaviours were observed in 27% of the untreated group as opposed to 11% of the group taking the neuroleptic medication. Likewise, a retrospective study of 88 schizophrenic patients who took their lives found that a considerable proportion of patients were not taking the antipsychotic treatment at the correct dose, did not follow the treatment or did not respond to an adequate antipsychotic treatment (Heilä H et al., 1999). It was also found that the majority of suicides, 78% of the total sample took place during an active stage of the illness and from that number, only 54%

were being treated with the correct dose of antipsychotics, which led the authors to conclude that it is necessary to improve the treatment of these patients, especially in the active stage, with the goal of reducing the risk of suicide. In more recent studies, the effects of the different antipsychotics, in this respect, have been analyses; it was observed for instance that olanzapine, an antipsychotic with low risk of inducing extrapyramidal reactions, decreases suicidal behaviour to a greater extent than haloperidol (Beasley CM et al., 1998). Besides, it has been noticed that clozapine, risperidone, olanzapine, quetiapine and ziprasidone might be useful in the treatment of psychotic disorders with frequent symptoms of hostility, depression and suicidal tendencies (Keck PE Jr et al., 2000). In other studies, quetiapine and other atypical antipsychotics like aripiprazol (Ulcickas Yood M et al., 2010; Nishiyama A et al., 2013) were neither associated with a greater risk of suicide. Clozapine has the most protective action of all antipsychotics; in 2003 its use was approved for this indication by the FDA (Beasley CM et al., 1998). Clozapine action has been studied in patients with schizophrenia resistant to treatment who had had one or more suicide attempts comparing it with another group of patients who were not taking it (Duggan A et al., 2003). It was observed that the use of clozapine not only improved the typical symptoms of the illness but also prevented the appearance of suicidal behaviour. Consequently,

in view of the results of the different studies, it seems to exist a certain protective effect, at least in the case of atypical antipsychotics as regards suicidal behaviour. There are several mechanisms that would explain the decrease of suicidal behaviour in the case of atypical antipsychotics. In the first place, the profile of more favourable side effects of atypical antipsychotics promotes adherence to the treatment and improves therapeutic efficacy (Marazziti D et al,.2005). On the other hand, it is worth noting a greater reduction of the psychotic symptoms and the effects over impulsivity as well as the alleviation of the affective symptoms with the corresponding enhancement of social interaction (Barak Y et al., 2004).

Recently, a population-based cohort study has been developed in Sweden with patients taking different types of antipsychotics as treatment for schizophrenia (n = 26,046) (Ringbäck Weitoft G et al., 2014). After being adjusted for age and gender, the patients treated with clozapine showed a smaller risk of death by suicide (OR=0.4; CI 95%=0.2-1.0) and suicide attempts (OR=0.4; CI 95%=0.3-0.7) than those treated with haloperidol; the study concluded that clozapine and olanzapine as well reduce the risk of suicide attempt, and the frequency of rehospitalization.

### *1.5.4. Benzodiazepines*

Depression, as has been said before, favours the appearance of

suicidal behaviour, especially when patients face a period of intense anxiety (Lecrubier Y, 1998). As a result, the probability of suicide attempts would be greater when the depression is associated with an anxiety disorder or social phobia (Weissman MM et al., 1989). In a study on this particular conducted in France including more than 4,000 patients it was concluded that: a) anxiety and depression coexist in 41.9% of the cases; b) benzodiazepines have no effect over depression and many anxiety disorders, in spite of the prolonged treatments; c) in coping with affective disorders, the first line of treatment should be SSRIs, but not benzodiacepines (Pélissolo A et al., 2007).

However, given that antidepressants take a few weeks to take effect, the expected benefits of benodiacepines would be mainly to obtain an immediate improvement of the anxiety associated with depression (Doraiswamy PM, 2001). Therefore, the anxiety reduction would prove beneficial in dealing with patients with suicidal ideation and the use of anxiolytics like benzodiacepines would be advisable for many of those patients (Sachs GS et al., 2001). Paradoxically, numerous studies have identified an association between the use of benzodiacepines and the appearance of suicidal behaviour. A decline has been observed of peripheral receptors of benzodiazepines in hospitalized adolescents with a record of suicide attempts (Marazziti D et al., 2005) and in

schizophrenic patients who had attempted suicide in a violent way (Ritsner M et al., 2003). With diazepam, an increase of self-aggressive conduct has been described in an experiment (Berman ME et al., 2005). In the said experiment, volunteers could choose a form of aggression (electric shocks) through a task based on time of reaction; it was found that those who had taken diazepam chose the maximum intensity in the applied shock, which was even more evident in individuals with a hostile personality (Ben-Porath DD et al., 2002) and the same results were repeated using alprazolam (Bond AJ et al., 1995). Flunitrazepam and nitrazepam were also found in the plasma of corpses of elderly suicide victims (Carlsten A et al., 2003). Some connection between suicide and the use of alprazolam has also been described (Kravitz HM y et al., 1993). The appearance of behaviour disinhibition, death thoughts, suicide attempts and self-mutilation have been described with the use of clonazepam (Kandemir H et al., 2008). It has been noted that the changes in the regimen of benzodiacepines could lead to autolysis phenomena (Neale G et al., 2007).

In conclusion, we know that depression is typically accompanied by anxiety and, in both cases, suicidal bevaviour may be present (Jiménez-López JL et al., 2015). Although benzodiacepines could be employed as adjuvant therapy to other drugs so as to improve anxiety,

it has to be noted that their benefits in the long run are questionable and should be watched closely (Gilbert DA et al., 1998; American Psychiatric Association, 2008). The use of benzodiacepines should be applied at moderately low doses and watch as well the possible behavioural disinhibition that might favour suicidal behaviour (Bousoño M et al., 1990).

### *1.5.5. Analgesics*

Analgesics are used, among other situations, in cases involving chronic pain. Numerous studies reveal that patients with pain are more prone to depression than patients without it. Besides, the presence of pain can obscure the detection and treatment of depression, increasing the risk of suicide (Cheatle MD, 2011; Moix J et al., 2011).

#### *1.5.5.1. Opioid analgesics*

Several explanations have been provided for the relationship between pain and suicidal behaviour. There are areas of the brain involved both in the control of pain and in the adjustment of emotions (Ochsner KN et al., 2005; Ribeiro SC et al., 2005). In some of these areas –for example, the anterior cingulate cortex- there is a great number of opioid receptors (Zubieta JK et al., 2001). It has been observed that there is an alteration in the opioid receptors of the

brains of suicide victims (Sher L et al., 2008).

Endogen opioids are involved in a wide range of processes in the nervous system, including modulation of reward, pain and emotions (Ribeiro SC et al., 2005; Roth-Deri I et al., 2008).

This way, the modification of pain perception present in people suffering from depression and that may condition suicide vulnerability is connected with the opioid system (Olié E et al., 2013). Given the juxtaposition of the systems involved in the regulation of affection and pain, it seems reasonable to suppose that the alteration of a type of sensation such as pain might lead to an alteration of mood. (Bresin K et al., 2013).

An increased analgesic consumption in patients with a history of suicidal behaviour suggests the existence of an increased sensitivity to pain in those patients (Olié E et al., 2013). On another note, some studies have proved that psychiatric illness is a risk factor for analgesic intoxication (Skegg K, 2005) and, at the same time, such intoxication could be a risk marker for the appearance of later psychiatric disorders (Jepsen P et al., 2005).

Persons with a record of suicide attempts are more prone to the consumption of analgesics than those without it (Olié E et al., 2013). The consumption of opioids is signficantly increased in individuals with

a history of depression and previous suicide attempts. It also appears that a history of intoxication by analgesics is a predictor of a later consummated suicide (Welcher B et al., 1993; Hawton K et al., 2003). Intensive and frequent monitoring of patients taking this medication for the first time and avoiding the prescription of long-acting opioids might help to prevent suicide attempts (Im JJ et al., 2015).

#### *1.5.5.2. Non-opioid analgesics*

It is understood that the neurological substrate of physical pain is activated as well by psychic discomfort ("mental pain"). This discomfort is associated as well with suicide risk and, consequently, this risk could dwindle with analgesic intake including opioids and ketamine (Gaillard R et al., 2010). A study has been carried out to assess the effect of paracetamol consumption over certain emotions (Durso GR et al., 2015). The participants taking this drug tolerated better being exposed to unpleasant emotional stimuli in comparison with the participants taking a placebo. The stimuli that they were exposed to (both negative and positive) entailed a smaller emotional load in comparison with the individuals taking a placebo.

However, the relationship presented between the existence of chronic pain and the appearance of death thoughts and suicidal behaviour is frequent. It is estimated that up to 50% of patients with

chronic pain have suicidal ideation (Hitchcock LS et al., 1994). Thus, some countries have considered the availability and use of analgesics as part of the strategies of suicide prevention (Simkin S et al., 2012; Madadi P et al., 2014). That said, the exact origin of an overdose is unclear since it might include an accidental overdose in the case of patients trying to alleviate the suffering of poorly controlled pain or induce sleep (Scott KM et al. 2010). Nevertheless, distinguishing what proportion of these cases is connected with intentional death by suicide and how many deaths are caused by accidental overdoses is complicated due to the existence of classification errors. Therefore, the relationship between analgesic consumption and suicide should be further investigated.

### *1.5.6. Justification or expected usefulness of the study*

The importance of this study lies in the possibility of preventing the onset of suicidal behaviour. A better understanding of suicidal behaviour allows the introduction of prevention schemes and the prevention of suicidal behaviour would diminish the costs of therapeutic interventions.

Another aspect to take into consideration is the improvement of the quality of life of the population and especially those patients with a greater suicide risk who might benefit from these prevention schemes.

## 2. Goals

# 2. Goals

## *2.1. General goals*

- The goal of this essay is to find out whether there is a connection between the consumption of certain drugs and the appearance of suicidal behaviour.

## *2.2. Specific goals:*

- Analyse the risk of attempting suicide of patients taking antidepressants.
- Analyse the suicide risk of patients taking anxiolytics (benzodiacepines).
- Analyse the suicide risk of patients taking antipsychotics.
- Analyse the suicide risk of patients taking antiepileptics.
- Analyse the suicide risk of patients taking analgesics (opioids and non-opioids).
- Know the variables that have an influence over the suicide risk associated with drugs.

# 3. Material and method

# 3. Material and method

## *3.1. Study design*

In order to learn about the association between suicide behaviour and the different risk factors considered, a study of retrospective cases and controls was conducted. Two groups of individuals were compared according to whether they had had a suicide attempt (cases) or not (controls). The groups formed in such a way were compared in accordanc with the exposure to the different drugs studied and other variables of interest. The aim was to obtain an estimator of the strength of the association between one or several risk factors and the outcome of interest.

This estimator is called *odds ratio* (OR) and is represented by the Greek letter psi (Ψ). When a small proportion of the population is affected by an illness, as is the case with rare diseases, the number of exposed cases (a) is very small compared to the number of exposed controls (b) and the number of unexposed cases (c) is very small compared to the number of unexposed controls (d). In this situation, the value of OR approximates (a x d) / (b x c). The OR indicates how many more times the cases are exposed with respect to the controls. Table 1 shows the organization of results in a 2x2 table and the corresponding estimation of risk.

Table 1. Positioning of data for the calculation of OR (2x2 table)

| | Presence illness | Absence illness | Total |
|---|---|---|---|
| Exposed | a | b | a+b |
| Unexposed | c | d | c+d |
| Total | a+c | b+d | a+b+c+d |

OR=axd/cxb

An *odds ratio* of 1, or not significantly different from 1, would indicate that there is no association between the considered risk factor and the illness studied. Conversely, an odds ratio value higher than 1 would indicate that this factor is associated with the illness as causal factor. The contrary would happen if the odds ratio value is lower than 1, in this case we would consider it a protective factor. The odds ratio value must be accompanied by a confidence interval, in general 95%. This confidence interval is an indicator of the precision of the estimation and the statistical significance of the association, and provides more information than the test value of $\chi 2$ and its associated

probability (p). The smaller the confidence interval, the more reliable the results of the association analysis. One of the disadvantages of this type of study is the possibility of introducing a bias which is difficult to detect.

### *3.2. Study development*

The period of identification of patients of interest and data collection went from January 2000 to January 2004. For each case, two controls were identified which were matched to the cases by age (with a difference of more/less 5 years), gender and period of hospitalization (more/less three months from the date of admission).

### *3.3. Selection of cases*

For the purposes of this study they were considered as cases those patients over 18 years old who were hospitalized in the Short-Term Psychiatric Unit after having attempted suicide during the period of study. However, different exclusion criteria were also considered as follows:

*Exclusion criteria:* patients under 18 years old were excluded and so were patients whose medical history did not include accurately the medication they were taking in the months previous to the hospital admission. Those cases in which the patient did not take the

personality test with the application of the MCMI-III questionnaire during admission (see appendices) were also excluded.

It was considered that patients were exposed to each of the drugs studied when there was a prescription of the said drugs in their medical history in the three months previous to the index day, day in which the suicide attempt which motivated hospital admission took place.

### *3.4. Selection of controls*

Patients who were considered adequate controls for the identified and selected cases were patients over 18 years old hospitalized in the Short-Term Psychiatric Unit in the same period (more/less 3 months from the date of admission) whose reason for admission might be any, other than having attempted suicide. The criteria for exclusion were the same as in the cases.

### *3.5. Data collection for the study*

The information about patients was obtained from the computer-based clinical records and in physical format from the general register of clinical records of the University Health Complex of Palencia (Complejo Asistencial Universitario de Palencia). The digital records with clinical information are available from the year 2005 to this day.

The study also included the paper documentation including the previous period from the year 2000 to 2004. Collection of information took place in the hospital environment (San Telmo and Rio Carrión hospitals, both in Palencia). Valid information was collected for a total sample of 1,680 patients from which 560 were controls and 1,120 the total of the cases.

### *3.6. Included variables*

The variables analysed in the study are specified below:

a) Sociodemographic variables:

- Age (continuous variable in years)
- Gender (male/female)
- Marital status (single/married/separated-divorced/widowed)

b) Variables related with suicidal behaviour or with clinical severity:

- Psychiatric background (according to DSM-IV criteria)
- Number of previous suicide attempts
- Family history (first degree) of suicide (yes/no)
- Number of visits to Emergency for all reasons

c) Variables related with the consumption of addictive substances (dichotomous variabes yes/no)

- Tobacco consumption
- Alcohol consumption
- Cannabis consumption
- Cocaine consumption
- Heroine consumption
- Amphetamine consumption

d) Variables related with the pathology

- Main somatic diagnosis (according to CIE-10 criteria)
- Main psychiatric diagnosis (according to DSM-IV criteria)
- Diagnosis of major depression in the first three months previous to the index day (according to DSM-IV criteria) (yes/no)
- Personality (according to MCMI-III items)

e) Variables related to the consumption of drugs in the first three months previous to hospital admission (dichotomous variables yes/no):

- Consumption of antipsychotics
- Consumption of antidepressants
- Consumption of SSRIs
- Consumption of antiepileptics
- Consumption of anxiolytics (benzodiacepines)
- Consumption of opioid analgesics
- Consumption of non-opioid analgesics

As regards the variables related with the pathology, the main somatic and psychiatric diagnoses were collected. The non-psychiatric diagnosis was the one present in the clinical history of the patient. This diagnosis had to be made in the three months prior to admission, both in the cases and controls. The main psychiatric diagnosis was the one present in the hospital discharge report after admission, both in the cases and controls.

Apart from the main psychiatric diagnosis, the major depression diagnosis was collected due to its special interest as an independent variable. This diagnosis had to have been made in the three months prior to hospital admission (index day), both in the cases and controls.

For this purpose, the clinical history of the sample patients was revised retrospectively. Information about the personality of the cases was also collected, taking into consideration the score on MCMI-III

items. In every case, the feature with the highest score was chosen and the rest were excluded.

All the information contained in this interview was collected in an Excel data base designed for that purpose and adjusted later. In order to maintain patient anonymity, a unique numerical code was assigned to the new records generated, so that during data processing, it was impossible to associate them with any specific patient.

### *3.7. Statistical analysis*

In the descriptive analysis of the sample, there are absolute frequencies (n) and relative (percentage) for the categorical variables and the mean with its standard deviation (SD) for the numerical variables. The differences between groups were analysed through Pearson´s Chi Square test. For the first variables and through Student´s T-Test for the second. Logistic regression was used to analyse the possible relationship between the consumption of some drugs and suicide attempts. The results feature the Odds Ratio (OR), raw and adjusted, with their confidence interval of 95% (CI 95%). Adjusted OR corresponds with a final model, obtained through the procedure of successive steps forward. This procedure was the one chosen, once possible interaction and confusion effects were analysed

and discarded between the different factors and covariables considered. Thus, successive models of regression executed with different procedures were posed. The suitability of the adjustment was assessed with the Hosmer-Lemeshow test.

To make sure that the possible colinearity between the variables did not produce a degradation in the estimations of the parameters, the variance inflation factors were taken into account (VIF). As a general rule VIFs lower than 10 are acceptable (Belsley DA et al., 1980).

As a measure of the capacity to discriminate (degree to which the model distinguishes individuals attempting suicide and those who do not), the area under the ROC curve (Received Operative Curve) is presented, built with the probability of the attempt predicted by the model for each of the records of the study (cases and controls).

The statistical analysis was carried out with the programme SPSS v.20.0. The level of statistical significance was established at $p \leq 0.05$ for all tests.

### *3.8. Ethical and legal aspects*

This study has taken every precaution to ensure the confidentiality of the personal data of the patients included in the sample. It has been approved by the Clinical Investigation Committee of the University of Palencia (Complejo Asistencial Universitario de Palencia)*.

*Appendices.

# 4. Results

## 4. Results

The final sample – with valid information- consisted of 1,680 patients, 560 cases and 1,120 controls. Table 2 displays the distribution, between the cases and controls, of the main dependent variables considered in the study.

Table 2. Sample variables. Distribution between the cases and controls.

| | n (%) | | |
|---|---|---|---|
| | Controls (n=1,120) | Cases (n=560) | |
| Age (years; SD) | 38.5; 15.3 | 38.0; 15.3 | P = 0.474 |
| Gender | | | |
| male | 406 (36.3) | 181 (32.3) | P = 0.111 |
| female | 714 (63.8) | 379 (67.7) | |
| Marital status | | | |
| single | 373 (33.3) | 277 (49.5) | P < 0.0001 |
| Married | 551 (49.2) | 197 (35.2) | |
| divorced | 117 (10.4) | 62 (11.1) | |
| widowed | 79 (7.1) | 24 (4.3) | |
| Suicide attempt | | | |
| yes | 95 (8.5) | 134 (23.9) | P < 0.0001 |
| no | 1025 (91.5) | 426 (76.1) | |
| Main diagnosis, depression | | | |
| yes | 200 (17.9) | 276 (49.3) | P < 0.0001 |
| no | 920 (82.1) | 284 (50.7) | |
| Consumption of abuse substances | | | |
| yes | 831 (74.2) | 331 (59.1) | |
| no | 289 (25.8) | 229 (40.9) | P < 0.0001 |

Table 3 shows the consumption of different drugs (antidepressants, antiepileptics, antipsychotics and analgesics) that the patients were taking in the three months prior to admission for a suicide attempt.

Tabla 3. Exposure to drugs. Distribution of exposure between cases and controls.

| | n (%) | | |
|---|---|---|---|
| | Controls (n=1,120) | Cases (n=560) | |
| Antidepressants | | | |
| yes | 730 (65.2) | 413 (73.8) | p < 0.0001 |
| no | 390 (34.8) | 147(26.3) | |
| Antipsychotics | | | |
| yes | 698 (62.3) | 146 (26.1) | p < 0.0001 |
| no | 422 (37.7) | 414 (73.9) | |
| Anticonvulsants | | | |
| yes | 342 (30.5) | 115 (20.5) | p < 0.0001 |
| no | 778 (69.5) | 445 (79.5) | |
| Benzodiacepines | | | |
| yes | 797 (71.2) | 399 (71.3) | p=0.970 |
| no | 323 (28.8) | 161 (28.8) | |
| Non-opioid analgesics | | | |
| yes | 268 (23.9) | 336 (60) | p < 0.0001 |
| no | 852 (76.1) | 224 (40) | |
| Opioid analgesics | | | |
| yes | 47 (4.2) | 28 (5.0) | p=0.452 |
| no | 1037 (95.8) | 532 (95.0) | |

The consumption of alcohol, tobacco and illegal toxic substances (cannabis, cocaine, heroine and amphetamines) of the patients is presented in table 4.

Table 4. Exposure to toxic substances. Distribution of exposure between cases and controls.

| | n (%) | | |
|---|---|---|---|
| | Controls (n=1,120) | Cases (n=560) | |
| Tobacco | | | |
| yes | 663 (59.2) | 249 (44.5) | p<0.0001 |
| no | 457 (40.8) | 311(55.5) | |
| Alcohol | | | |
| yes | 340 (30.4) | 203 (36.3) | P=0.015 |
| no | 780 (69.6) | 357 (63.8) | |
| Cannabis | | | |
| yes | 135 (12.1) | 72 (12.9) | p=0.637 |
| no | 985 (87.9) | 488 (87.1) | |
| Cocaine | | | |
| yes | 18 (1.6) | 27 (4.8) | P<0.0001 |
| no | 1102 (98.4) | 533 (95.2) | |
| Heroine | | | |
| yes | 6 (0.5) | 2 (0.4) | P=0.616 |
| no | 1114 (99.5) | 558 (99.6) | |
| Amphetamines | | | |
| yes | 6 (0.5) | 9 (1.6) | P=0.028 |
| no | 1114 (99.5) | 551 (98.4) | |

Tables 5 and 6 include the distribution between the cases and controls of the different psychiatric and somatic pathologies respectively.

Tabla 5. Psychiatric pathologies. Distribution between cases and controls.

| | n (%) | |
|---|---|---|
| | Controls (n=1,120) | Cases (n=560) |
| Affective disorders | 334 (29.9) | 340 (60.7) |
| Major depression | 200 (17.9) | 276 (49.3) |
| Bipolar disorder | 94 (8.4) | 11 (2.0) |
| Dysthymia | 40 (3.6) | 53 (9.5) |
| Anxiety disorders | 80 (7.1) | 29 (5.2) |
| Unspecified anxiety disorder | 27 (2.4) | 20 (3.6) |
| Generalized anxiety disorder | 36 (3.2) | 0 |
| Obsessive-compulsive disorder | 17 (1.5) | 9 (1.6) |
| Eating habits disorders | 64 (5.7) | 0 |
| Sleep disorders | 20 (1.8) | 0 |
| Adjustment disorders | 153 (13.7) | 34 (6.1) |
| Personality disorders | 150 (13.4) | 55 (9.8) |
| Substance abuse disorders | 42 (3.8) | 16 (2.9) |
| Cognitive deterioration | 0 (0) | 8 (1.4) |
| Psychotic disorders | 214 (19.1) | 62 (11.1) |
| Schizophrenia | 135 (7) | 60 (0.4) |
| Delusional disorder | 39 (3.5) | 2 (0.4) |
| Schizoaffective disorder | 24 (2.1) | 0 |
| Toxic psychosis | 16(1.4) | 0 |
| Impulse control disorders | 2 (0.2) | 0 |
| Undiagnosed | 61 (5.4) | 16 (2.9) |

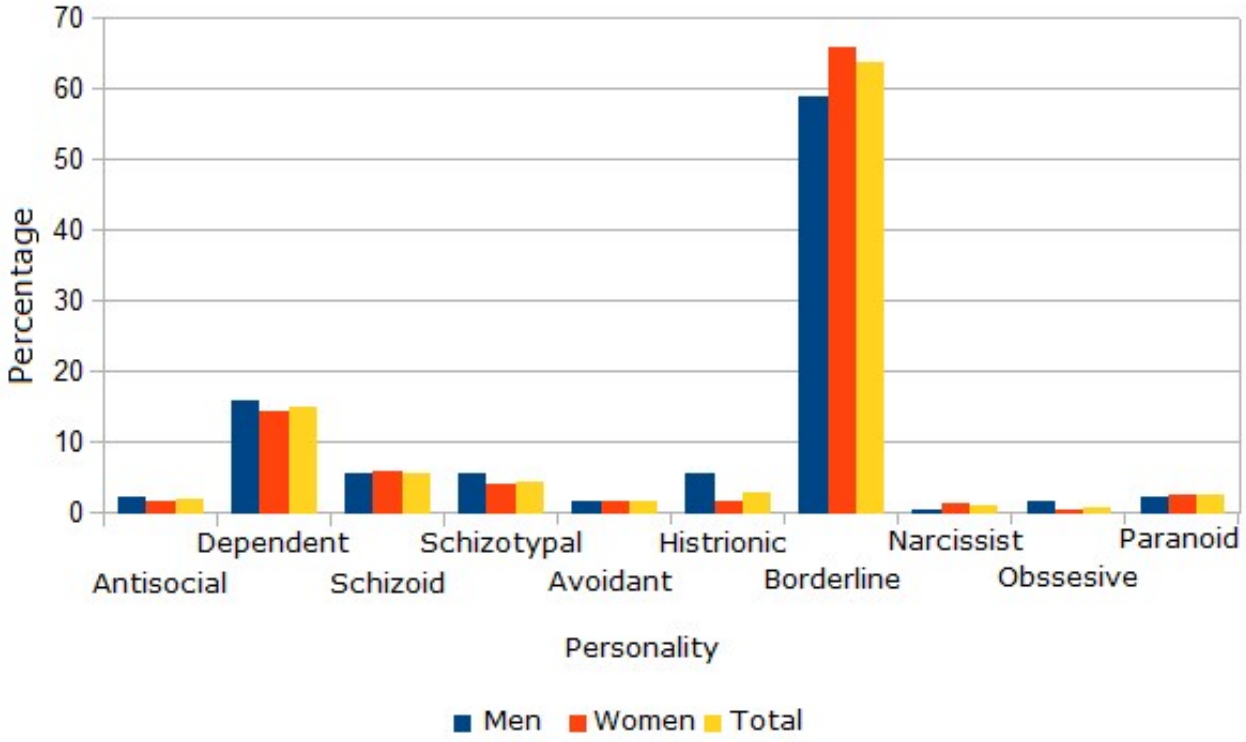
The most prevalent non-psychiatric pathologies among the cases were, in decreasing order, musculoskeletal, neurological and oncological (Table 6). A variable percentage, greater among the controls, did not have a consigned somatic diagnosis.

Table 6. Somatic pathologies. Distribution among cases and controls

| | n (%) | |
|---|---|---|
| | Controls (n=1,120) | Cases (n=560) |
| Cardiovascular | 86 (7.7) | 5 (0.9) |
| Pulmonary | 7 (0.6) | 0 |
| Neurological | 45 (4.0) | 134 (23.9) |
| Genitourinary | 8 (0.7) | 2 (0.4) |
| Gastrointestinal | 87 (7.8) | 48 (8.6) |
| Endocrine-metabolic | 37 (3.3) | 5 (0.9) |
| Musculoskeletal | 199 (17.8) | 249 (44.5) |
| Ocular | 8 (0.7) | 0 |
| Dermatological | 9 (0.8) | 0 |
| Infectious | 6 (0.5) | 2 (0.4) |
| Oncological | 58 (5.2) | 48 (8.6) |
| Hematological | 12 (1.1) | 1 (0.2) |
| Respiratory | 62 (5.5) | 0 (0) |
| Nephrological | 14 (1.3) | 1 (0.2) |
| Immunological | 10 (0.9) | 0 |
| Undiagnosed | 472 (42.1) | 65 (11.6) |

Figure 5 shows the personality traits which are most frequent among the cases and their distribution by gender. There were no significant differences in the personality types between men and women ($X^2_9$=9.836; p=0.364).

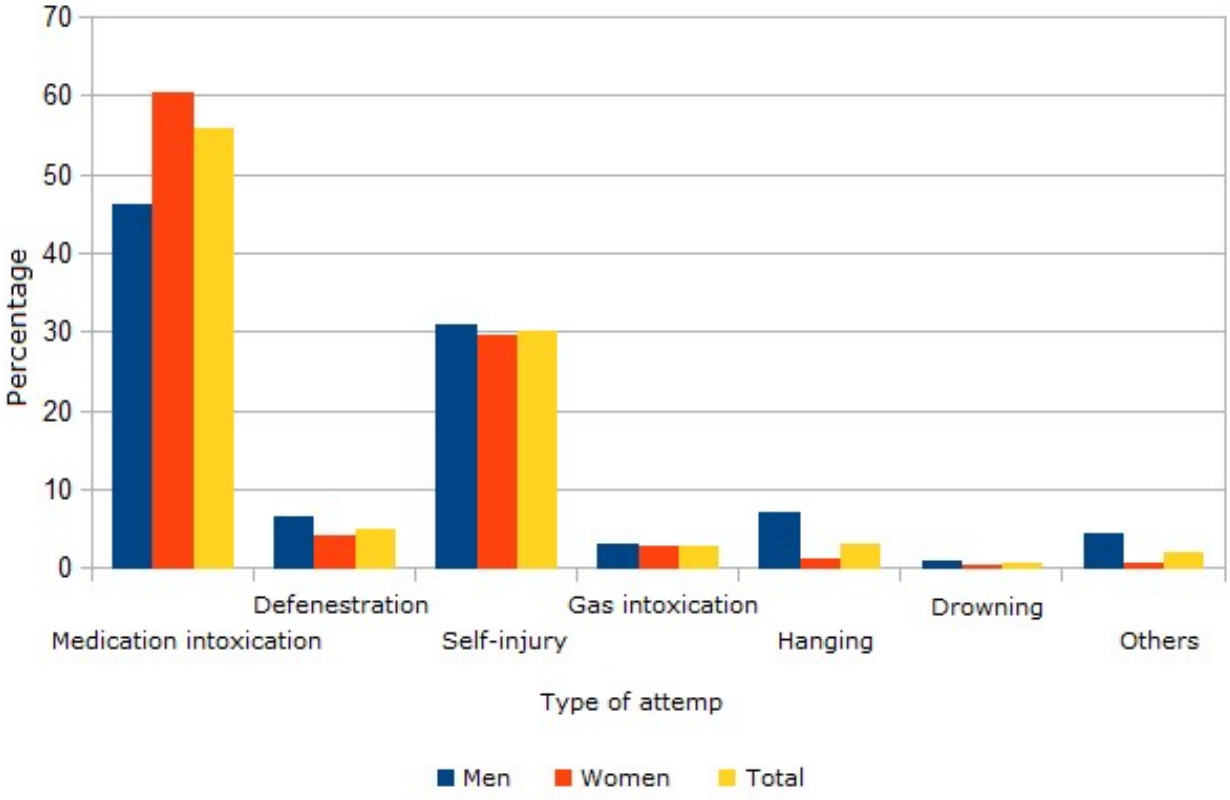
Figure 5. Personality of the cases (percentage for men and women).




As we can observe, 63.8% of the cases scored higher in the items corresponding to borderline personality. The patients with dependent personality were in second place and with a much smaller prevalence, making up 15% of the cases. Next were the schizoid and schizotypal features, with similar frequencies (5.7% and 4.5%, respectively). As for the rest of personality types, 3% of the cases had histrionic personality traits, 2.5% paranoid and 2% antisocial. The least

prevalent personality trais among the cases were the ones corresponding with the following personalities: avoidant (1.6%), narcissist (1.1%) and obsessive (0.9%) (see appendices). On the other hand, figure 6 shows in percentage the types of suicide attempt carried out by men and women. There are significant differences as regards the different methods employed by men and women ($X^2_6$=7.72; p<0.0001).

Figure 6. Suicide methods among the cases (percentages in men, women and total).

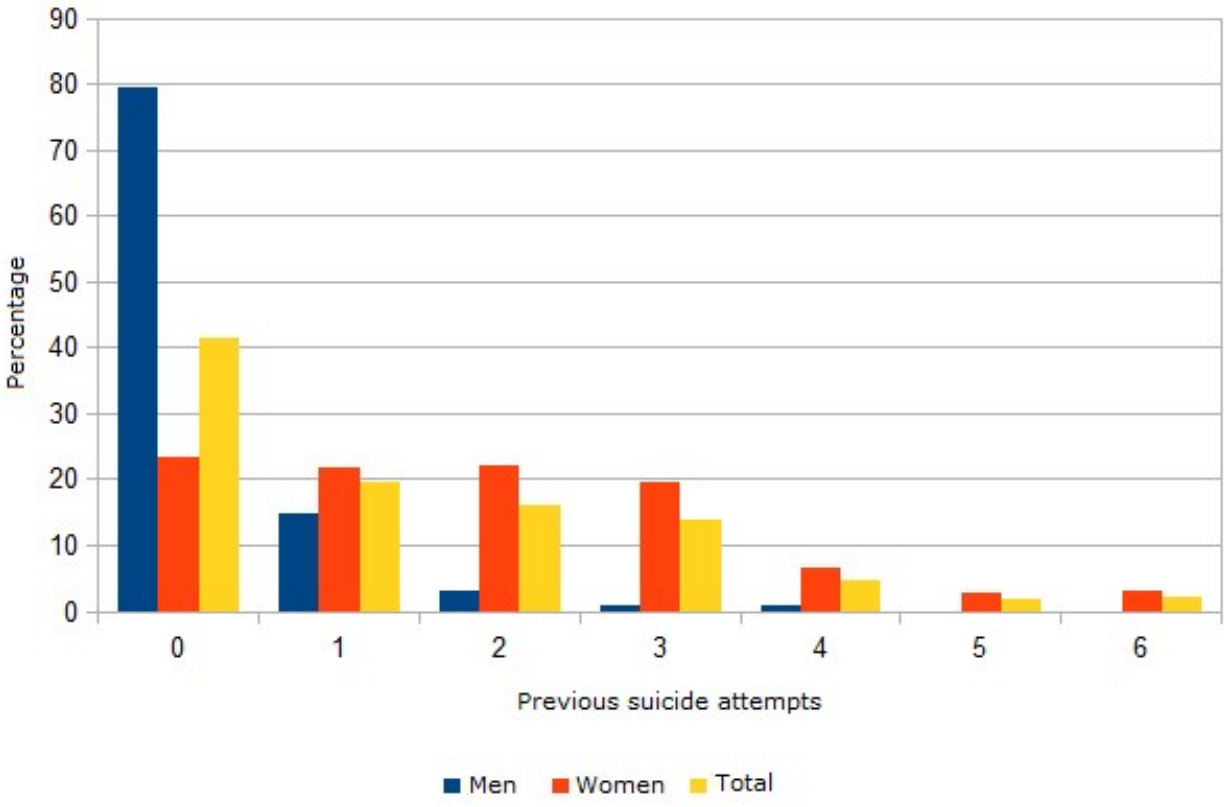



The most frequently employed method for the suicide attempts was intoxication with medication (56%); women resorted to this procedure

with more frequency. The second most common method, with a percentage of 30.1%, was self-injury, with no differences between men and women given the similar values (30.9% and 29.6%, respectively). With much less frequency the cases in the sample made use of other self-injury methods like defenestration (5.0%), hanging (3.2%), gas intoxication (3.0%) and drowning (0.7%). In all these methods the difference between men and women turned out to be significant. Men used more often methods of greater lethality, like defenestration (6.6% in men and 4.2% in women) and hanging (7.2% in the case of men and 1.3% in the case of women). As regards drowning, the percentage was greater in the case of men (1.1%) than women (0.5%) (see appendices).

Figure 7 shows previous suicide attempts; 58.4% of the cases had had autolythic attempts before (20.4% of men and 76.5% of women), with significant differences between the sexes ($X^2$= 158.5; p< 0.0001).

Figure 7. Previous suicide attempts by number of attempts (n=1,680)




In accordance with the model of this study, different factors have been identified associated with a bigger or smaller probability of attempting suicide.

As for the sociodemographic factors (Table 7), the risk of suicide attempt was greater for women than for men (adjusted OR [CI 95%]= 1.88 (1.41-2.52), and the same happened with single patients with respect to the rest of the sample (OR=2.04; CI 95% =1.56-2.69).

On the other hand, the likelihood of a suicide attempt among patients with a family history of suicidal behaviour would be much higher than those patients without such a history (OR= 4.10; CI 95%=2.79-6.03). Taking into account the main psychiatric diagnosis, the patients with a major depression diagnosis would be the ones with the highest risk (OR=3.77; CI 95%=2.82-5.06).

Besides, regardless of whether the main psychiatric diagnosis was depression or any other psychiatric illness, the probability of a suicide attemp would be higher among those who had had symptoms of major depression diagnosed in the three months previous to hospital admission (OR=1.92; CI 95%=1.45-2.53).

The presence of non-psychiatric comorbidity would also increase notably the risk of suicide in those patients (OR= 5.06; CI 95%=3.58-7.15).

Table 7. Suicide attempts and related factors. Estimation of the strength of the association.

| | n (%) | | Raw OR (CI 95%) | Adjusted OR (CI 95%) |
|---|---|---|---|---|
| | Controls | Cases | | |
| Gender, women | 714 (63.8%) | 379 (67.7%) | 1.19 (0.96-1.48) | 1.88 (1.41-2.52) |
| Single | 373 (33.3%) | 277 (49.5%) | 1.96 (1.59-2.41) | 2.04 (1.56-2.69) |
| Previous history [a] | 95 (8.5%) | 134 (23.9%) | 3.39 (2.55-4.52) | 4.10 (2.79-6.03) |
| Depression [b] | 331 (29.6%) | 263 (47.0%) | 2.11 (1.71-2.60) | 1.92 (1.45-2.53) |
| Depression, main diagnosis | 200 (17.9%) | 276 (49.3%) | 4,47 (3.57-5.60) | 3.77 (2.82-5.06) |
| Another pathology[c] | 647 (57.8%) | 495 (88.4%) | 5.57 (4.19-7.40) | 5.06 (3.58-7.15) |

[a] Previous family history of suicide
[b] Major depression diagnosed in the three months prior to the suicide attempt
[c] Another non-psychiatric pathology, one or several diagnoses

Table 8 describes the association between the consumption of the medication of interest and the risk of appearance of suicide attempts.

Table 8. Suicide attempts and medication. Estimation of the strength of the association

| | n (%) | | Raw OR (CI 95%) | Adjusted OR (CI 95%) |
|---|---|---|---|---|
| Medication | Controls | Cases | | |
| SSRIs | 416 (37.1%) | 301 (53.8%) | 1.97 (1.60-2.42) | 1.67 (1.27-2.19) |
| Antipsychotics | 698 (62.3%) | 146 (26.1%) | 0.21 (0.17-0.27) | 0.19 (0.15-0.26) |
| Opioid analgesics | 47 (4.2%) | 28 (5.0%) | 0.83 (0.52-1.34) | 0.42 (0.23-0.76) |
| Other analgesics | 268 (23.9%) | 336 (60.0%) | 4.77 (3.84-5.93) | 3.96 (3.01-5.22) |

There would be a greater risk of suicide among patients under treatment with SSRIs (OR=1.7; CI 95%=1.27-2.19), and even greater in those patients under treatment with non-opioid analgesics (OR=3.96; CI 95%=3.01-5.22). Nevertheless, the treatment with antipsychotics would diminish the probability of committing a suicide attempt (OR=0.2; CI 95%=0.15-0.26) and the same would apply in the case of opioid analgesic consumption (OR=0.4; CI 95%=0.23-0.76). Other independent factors associated with the risk of suicide

attempts are related with the intake of several substances such as alcohol, tobacco and certain illegal drugs (Table 9).

Table 9. Suicide attempts and consumption of toxic substances. Estimation of the strength of the association.

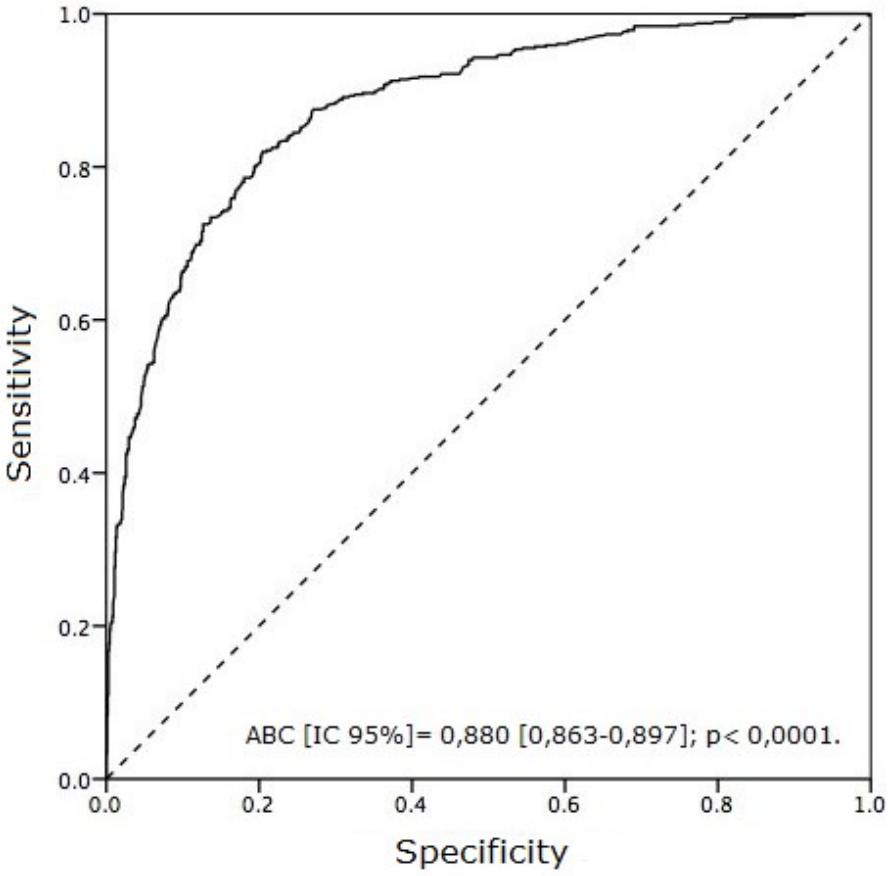
| | n(%) | | Raw OR (CI 95%) | Adjusted OR (CI 95%) |
|---|---|---|---|---|
| Toxic substances | Controls | Cases | | |
| Tobacco | 663 (52.9%) | 249 (44.5%) | 0.55 (0.45-0.68) | 0.58 (0.44-0.78) |
| Cannabis | 135 (12.1%) | 72 (12.9%) | 1.08 (0.79-1.46) | 2.07 (1.35-3.19) |
| Cocaine | 12 (1.6%) | 27 (4.8%) | 3.10 (1.69-5.68) | 3.67 (1.60-8.39) |

Consumption of cannabis would increase the risk of a suicide attempt (OR=2.1; CI 95%= 1.35-3.19); the risk of such an attempt would be even greater among consumers of cocaine (OR=3.7; CI 95%= 1.60-8.39). However, in connection with the consumption of toxic substances, being a smoker would be associated with a decrease of the risk of a suicide attempt (OR= 0.6; CI 95%=0.4-0.8).

In total, 13 independent risk factors were identified related to the suicide attempt. The model of logistic regression shows good

calibration (Hosmer-Lemeshow test=7.038; p=0.532) and good capacity to discriminate between cases and controls (Area below the curve and confidence interval at 95%= ABC [CI 95%]= 0.880 [0.863-0.897]; p< 0.0001). Figure 8 shows the ROC (*Receiver Operating Characteristic)* curve built with the probability of suicide attempt predicted by the model.

Figure 8. ROC curve (*Receiver Operating Characteristic)* for the probability of suicide attempt predicted by the model of logistic regression.



# 5. Discussion

# 5. Discussion

Suicide makes up one the first causes of death in developed countries and constitutes a severe problem of public health. It has been estimated that in the year 2013 842,000 deaths by suicide took place all over the world (World Health Organization, 2012; Pitman A et al., 2012). The problem, far from decreasing, is growing and it has been estimated that the death toll for this cause rose by 60% between the year 1960 and 2012 (World Health Organization, 2012). Nevertheless, it is a complex issue and it can stated that, apart from clear risk factors like psychiatric illness, there are other contributing factors whose identification will allow us to better understand the multicausal dimension of the phenomenon and tackle its prevention. The importance of biological factors, so relevant these days, might be pointed out.

Enzyme protein kinase A, an essential component of the signal transduction pathway of adenyl cyclase, has been identified as a possible predictive factor (Dwivedi Y et al., 2011). This enzyme is involved in genetic transcription and cellular plasticity and survival. As far as we are concerned, drugs have been associated with suicide or more specifically with suicidal behaviour. Recent studies have tested the relationship between some drugs, of common use in different

areas other than psychiatry, and suicidal behaviour, among these are corticosteroids (Fardet L et al., 2012), isotretionine (Sundström A et al., 2010), varenicline and bupropion used in the supression of the smoking habit (Thomas KH et al., 2013; Gibbons RD et al., 2013), antiasthmatic leukotriene modulators (Schumock GT et al., 2012) and efavirenz (Mollan KR et al., 2014).

Our study of an observational nature has analysed the existing relatonship between psychotropic substances and analgesics and suicidal behaviour. One of the most worrying problems of this type of studies is the comparability of the groups. In our case-control study, the comparability of the case group with the control group. In order to make the groups comparable, we have resorted to matching by important predictive variables and the adjustment of the statistical analysis.

The matching employed achieved a balance in the distribution of patients by sex and age in the two groups being compared (Table 2); other variables, as expected, had an unequal distribution. As regards marital status, for instance, single and divorced patients represented a bigger percentage in the cases than in the controls. If we adscribe some civil statuses like being single, divorced or widowed with the situation of living alone, of isolation, that situation in general would be

more frequent in the cases. Other risk factors like the major depression diagnosis or the previous suicide attempt were more frequent in the cases. The major depression diagnosis as main diagnosis at the time of admission and a previous history of suicide attempts were in effect distributed unevenly: among the cases, 49.3% had a major depression diagnosis as opposed to 17.9% among the controls. For the suicide attempts, these percentages were 23.9% and 8.5%, respectively.

The diagnosis of affective disorder which includes depression and mania and all the intermediate stages was more frequent among the cases than among the controls, but this was not the case for the diagnoses of anxiety, adjustment, personality or psychotic disorders. The connection of all these disorders with suicidal behaviour has been thoroughly studied (Isometsä ET, 2001; Muehlenkamp JJ et al., 2011; Glenn CR et al., 2013).

It is well known that one of the distinctive features of depression in particular is suicidal ideation and it is this symptom precisely what makes this disorder so serious. However, an excessive medicalisation of the psychiatric illness makes it difficult to understand the true relationship between the illness and the suicidal thoughts. It is also difficult to establish the connection between the somatic illness and

the suicidal behaviour. One striking aspect is the fact that the frequency of these diagnoses of somatic illnesses is greater in the cases: for the cases, the percentage of patients diagnosed was almost 90%, whereas for the controls this percentage did not reach 60%. It is worth noting the high value of risk, the most elevated of all found in the study, for the patients with these non-psychiatric pathologies (OR=5.1; CI 95%=3.6-7.1). If we consider the diagnosis and its number as indicators of seriousness, the situation that these somatic diagnoses represent in the study is that the cases, regardless of the suicide thoughts, were more serious for reasons other than the controls. This is corroborated if we take into account the percentage of specific diagnoses that would be *a priori* associated with a greater seriousness. Thus, neurological illnesses for instance had a relative frequency of 23.9% in the cases and 4% in the controls, musculoskeletal 44.5% and 17.8%, respectively and, similarly, oncological ones, with 8.6% and 5.2%. The notable exception was cardiovascular illnesses where these percentages were inverted, with 0.9% in the cases and 7.7% in the controls. It is possible that the degree and intensity of pain in the different illnesses mentioned, apart from other circumstances like degree of disability that they cause could explain this different distribution. This coincides with the increase of suicide risk and consummated risk observed in a cohort of

220,336 patients after suffering a cerebrovascular accident (Eriksson M et al., 2015). This might also be consistent with the findings in a cohort of over 2,198 adults who suffered serious trauma (March J et al., 2014); when this group was compared with a control group (n=10,990), it was observed that the risk of suicidal behaviour was very high, even after adjustment for different variables (OR=3.3).

Two sociodemographic factors were associated with a greater risk of suicide, namely being a woman and being single. It is a well-kown fact that women consummate suicide less than men, although the risk of a suicide attempt is greater among women (Miret M et al., 2010); as a result, with the same number of attempts women would have more failed attempts. It could be added that the more longevity of women would also partly explain the greater number of suicide attempts. Age, though, was a matching and adjustment factor. The fact that men resort to more lethal methods is difficult to explain without using commonplace clichés: a greater aggressiveness due to the predominance of male hormones. As for marital status, 49.5% of the cases were single as opposed to 33.3% of the controls, although being single does not necessarily imply living alone, if by that word we mean a certain isolation. On the one hand, this isolation could be understood as a risk factor for depression and suicidal behaviour. On the other

hand, it could be considered a risk marker: a person lives alone because they are ill and illness, in this case of a psychiatric nature, separates them from the others. Being single was associated with twice as much risk of suicide attempts in comparison with other marital statuses taken as a whole (OR=2.0; I CI 95%=1.6-2.7). The percentage of divorcees and widowed persons was 15.4% in the cases and 17.5% in the controls. It could be pointed out that marital status has little informative value; the situations in which people live today are very diverse and changing. As a predictive factor, and from a clinical point of view, it would be more useful to explore the real situation of cohabitation than the official marital status.

A family history of suicide was associated with one of the hightest risks found (OR=4.1; CI 95%=2.8-6.0), very similar to the risk value that depression as main diagnosis entails (OR=3.8; CI 95%=2.8-5.1). The hereditary character of certain psychiatric illnesses associated with suicide and emotional contagion might explain this high risk value.

The study has identified a significant risk of suicide attempt associated with SSRI antidepressants. This risk, in a wide sense of suicidal behaviour, has been identified in other studies and has given rise to different regulatory interventions. Even though there are well-founded doubts about this risk and its magnitude since depression,

which tends to be the main cause for the use of these drugs, would be a confusion factor in the usual estimations. The cases of our study were exposed more frequently to antidepressants of any type than the controls (73.8% against 65.2%); this difference was even more marked for SSRI antidepressants (53.8% against 37.1%). In our study, the model used tries to adjust the risk estimation for different factors, among others the depression diagnosis. It is evident that the adjustment in our study gives rise to a modification of the raw risk of SSRIs (OR=2.0; CI 95%=1.6-2.4), which decreases (OR=1.7; CI 95%=1.3-2.2), but continues in values close to 2 and, in any case, significant. In favour of our estimation it must be said that currently these drugs are used not only in the treatment of depression but also for other illnesses or conditions (both psychiatric - anxiety disorders or eating disorders - and somatic - migraine or irritable bowel - ) and as a result a great number of patients were taking this medication for conditions other than depression. It is difficult to know if these other conditions are also associated with suicidal ideation and behaviour. Our estimation partly coincides with the one observed in a recent study comprising 826 patients with bipolar disorder monitored for three and a half years (Toffol E et al., 2015). The said study identified a relative risk of suicide, mortality by suicide and mortality by other causes of 1.5 (CI 95%=1.2-1.8). It is noteworthy that the type of patients and

their clinical circumstances, together with the type of dependent variable studied, could greatly influence the estimations. Our dependent variable, suicide attempt, althouth part of it, does not coincide with the compound variable used in the cited study.

Antiepileptics were not associated with suicide attempts in our study. A percentage, smaller in the cases (20.5%) than in the controls (30.5%), was exposed to this medication. The drugs which make up this group are of a different chemical nature although they share a depressor effect over the CNS. However, their more specific mechanisms are quite different. Some of the oldest ones like valproic acid have been associated with an increase of overall risk of suicide attempts, death by suicide and by other causes (RR=1.5; CI 95%=1.3-1.8); this has been observed in the study mentioned before including patients with bipolar disorder (Toffol E et al., 2015). The association of antiepileptics as a group with suicidal behaviour dates from 2008 when the FDA, based on the results of a meta-analysis, issued a warning on this particular (U.S. Food and Drug Administration, 2008); it was found that patients taking this medication had double the risk in comparison with the placebo. The study of Arana et al. (2010) also identified a risk associated with this medication taken as a whole, both in patients not suffering from epilepsy (OR=1.6; CI 95%= 1.2-2.2) and patients with depression or

bipolar disorder (OR=2.6; CI 95%=1.8-3.7); surprisingly, this study did not identify risk of suicidal behaviour in patients with epilepsy (Arana A et al., 2010). In our study, a high percentage of patients, as already stated, were diagnosed with affective disorders. Years after the warning issued by the FDA, the relationship between antiepileptics and suicidal behaviour remains controversial (Mula M et al., 2015). It is probable that the use in our sample of newer antiepileptics, perhaps deprived of this risk, might explain the abscence of risk found. In the context of psychiatric care, these antiepileptics are being used profusely as supposed 'mood stabilizers', as in the case of lamotrigine; this drug in particular has been associated with a decrease of suicide risk in a study including 969 patients being tracked for 6 months (Rihmer Z et al., 2015). The results that we have obtained in our study in connection with antiepileptics, namely the abscence of risk of suicide attempt, coincides with the observations of Pugh et al. (2013) in a cohort of more than 90,000 individuals (Pugh MJ et al., 2013). In this quasi-experimental 'before and after' study the probability of episodes of suicidal behaviour the month prior to the intake of antiepileptics was greater than the probability observed the month after the intake, nevertheless it must be pointed out that there were 87 episodes the year before index day (74 individuals) and 106 the year after (92 individuals). Similarly, our results coincide with those of

Leon et al. (2012). In a retrospective study including 199 patients with bipolar disorder who provided 1,077 intervals of exposure or non-exposure to antieplileptics (carbamazepine, lamotrigine or valproato) an adjusted risk of 0.9 was estimated (CI 95%=0.4-1.9) (Leon AC et al., 2012).

Antipsychotics are, just like antiepileptics, depressors of the CNS. It is no coincidence that they have been called 'chemical straitjackets'. The action mechanism that has been related to their antipsychotic effect of blocking dopaminergic receptors. They all have this effect to a greater or lesser extent, but they interact with other receptors like the serotoninergic receptors. There is unanimity in the studies published about the effects of these drugs over suicidal ideas. Clozapine in particular has been chosen as the most efficient antipsychotic for this purpose (Raja M et al., 2014). In our study, 26.1% of the cases and 62.3% of the controls were taking antipsychotics.

The value of adjusted risk found (OR=0.2; CI 95%=0.1-0.3) gives an idea of a remarkable protective effect in those exposed to this medication when compared to those unexposed. This effect is of enormous interest if we consider that schizophrenia, the condition in which this drug is used most frequently, is associated with a greater suicide rate and that the suicides have been observed in periods in

which the medication has been abandoned or not properly continued (Reutfors J et al., 2013).

Numerous studies have identified pain as a cause of suicide, apart from the fact that pain can mask a depression (Cheatle MD, 2011; Moix J et al., 2011). It seems consistent that pain by itself or as an indicator of an illness in its terminal stage might be associated with suicide. As a matter of fact, it has been estimated that up to 50% of the patients with chronic pain have suicide thoughts (Hitchcock LS et al., 1994). In a recent study conducted in Spain, it was observed in patients with fibromyalgia (n=180) that there was a positive correlation between the degree of pain measured by means of a scale and the score obtained in the Plutchik scale that measures suicide risk (Pearson's quotient, 0.51) (Calandre EP et al., 2011).

Analgesics, insofar as they avoid or mitigate the pain, might have a protective effect. Opioid analgesics were used in similar percentages both in the cases (5%) and controls (4.2%); non-opioid analgesics on the contrary were used in a bigger proportion by the cases (60.0%) than by the controls (23.9%), so these drugs appear to be a true marker of risk. It has been stated that the rise in the consumption of analgesics in patients with a history of suicidal behaviour suggests the existence of an increase of sensitivity to pain in these patients. (Olié E

et al., 2013). In our study, opioid analgesics were associated with a protective effect over suicide attempts (OR=0.4; CI 95%=0.2-0.8), whereas non-opioid analgesics were associated with an elevated risk (OR=4.0; CI 95%=3.0-5.2), the highest risk identified in the analysed drugs. The protective effect of opioids that has been identified might be a similar real effect, although averaged through different paths, than that of ketamine (Autry AE et al., 2011). In any case, the protective effect of opioids present in this study is consistent with the well-known anxiolytic and sedative effects of these drugs. It is noteworthy that this effect has not been described in the literature. Less consistent and more difficult to explain is the association between non-opioid analgesics and the risk of suicide attempt. The risk should be interpreted not as much in the sense that these drugs produce suicidal thoughts but because of the prevalence of the use of these analgesics among depressive patients more prone to suicidal ideation but also in other somatic illnesses, and that the adjustment carried out in the analysis has not been capable of avoiding this spurious association. The adjustment made has produced a diminishment of the risk value but not its disappearance. It should be added that in a high proportion of suicide attempts self-intoxication by analgesics is employed, so this medication is more present in the cases than in the controls. Somatic illnesses associated with pain, as has been said

before, are connected with the risk of suicide attempt.

The proportion of smokers among the cases was smaller than among the controls (44.5% against 59.2%); tobacco appeared with statistical significance as a protective factor (OR=0.6; CI 95%=0.4-0.8). It is very common for psychiatric patients to be smokers and even more so in the case of patients treated with antipsychotics. If antipsychotics exert a protective action over suicidal behaviour and these are associated to a greater extent with tobacco use, the distribution of this medication found in the cases (26.1%) and controls (62.3%) would be consistent with this fact: that apparent protection of tobacco or at least part of it might be due to other associated factors like the intake of antipsychotics. However, when it is adjusted for possible confusion factors, tobacco remains protective as the values of the adjusted estimator (OR=0.6; CI 95%=0.4-0.8), although modified, do not differ from those of the raw estimator (OR=0.5; CI 95%=0.4-0.7). This beneficial effect of tobacco is difficult to explain. Its protective effect over the risk to suffer from Parkinson's is well-known, possibly through a stimulating action over the dopaminergic receptors. It does not seem possible that this path, at least not uniquely, is involved in suicidal behaviour. It must be pointed out that the studies conducted on the relationship between tobacco or nicotine and suicidal behaviour have

reached contradictory results; while some identified a positive association (Yaworski D et al., 2011), others did not (Kessler RC et al., 2007, Berglund PA et al., 2007; Kessler RC et al., 2009), which coincides with our results. These discrepancies might be put down to the type of samples studied, that is, the general population against population with a psychiatric disorder.

The other substances of abuse considered, especially cocaine and amphetamines, presented higher percentages of consumption in the cases. Cocaine in particular, with a consumption percentage of 4.8% in the cases and 1.6% in the controls, was associated with a very high risk of suicide attempt (OR=3.7; CI 95%=1.6-8.4). When explaining suicidal behaviour, the stimulus necessary to execute the action is important. This stimulus, undoubtedly, might be produced by cocaine. This explanation is in line with one which has been put forward to understand the possible action of SSRIs over suicidal behaviour ('initial activation') (Healy D et al., 1999). Let us not forget that SSRIs and cocaine share a similar mechanism in the post-ganglionic nerve endings, the inhibition of neurotransmittor reuptake. Finally, cannabis had a very similar prevalence of use in the cases and controls, 12.1% and 12.9%; in the estimation of adjusted risk there was a higher risk of suicide attempts of twice as much associated with this substance (OR=2.1; CI 95%=1.3-3.2). This risk coincides with the findings of

other recent studies (Delforterie MJ et al., 2015). The deterioration of personality and shift to depression produced by its chronic use together with its occasional hallucinogenic effect might explain this increased risk found.

Both the cases and controls were exposed to benzodiacepines to a high percentage, 71.3% and 71.2%, respectively; although it is not the aim of our study, the high proportion of use of these substances should be cause for critical reflection on the justification of their prescription. In our study these substances were not associated with a higher risk of suicide attempt. Our results somehow coincide with the findings of a meta-analysis about alprazolam and suicidal ideation including more than 3,000 patients (Jonas JM et al., 1996). In this study alprazolam was not associated with a higher risk of suicidal thoughts when compared with different drugs or the placebo. Benzodiacepines have been associated in the literature with depression and higher mortality (Weich S et al., 2014), however, there is great uncertainty in this respect. There is no doubt that, in a similar manner to other psychotropic substances mentioned, they are notable depressors of the NCS and that their action would depend on dosage. It could be said that these drugs, at low doses, behave like anxiolytics and, at progressively higher doses, they are hypnotic, sedative and

anaesthetic. Although these substances have a very wide therapeutic margin, high doses can be lethal and are in fact the cause of many accidental or suicidal intoxications with deadly consequences. Benzodiacepines have been associated with all kinds of psychiatric disorders, for instance triazolam was subjected to strict administrative regulation as it was associated with 'criminal behaviour' (Camiñas T, El País, 1989; Institut Català de Farmacologia, 1991; Dyer C, 1999); the disinhibition it causes could explain this conduct.

Some of the limitations of this study could be the relatively small size of the sample, the quality of the information recorded in the history and, in general, its retrospective character which has an effect on the quality, already mentioned, and the type of information included in the histories. In short, the information, although extremely useful and in general very comprehensive, was not collected for the purposes of this study. As is the case with all observational studies, this one is also subjected to the possible existence of biases or residual confusion factors due to variables that were not assessed. Nevertheless, it should be pointed out that it is difficult to have access to such a high number of cases like the ones in our study and that having them entails accepting the limitations of the data collection usual in healthcare centres. But all in all, the consistence of the estimations obtained and the value of the reflection generated by its

analysis provides interest to the study. The results are compatible with others already obtained and, in this sense, contributes to consolidating and qualifying information which is already known. It also provides useful data for later studies such as the protective effect over suicide attempts of tobacco and the same effect of opioids.

In essence, our work is fundamentally aimed at the study of the risk of suicide attempts associated with medication as well as the study of that same risk in the case of addiction substances like tobacco, cannabis or cocaine. No symptom, however small it may seem, is alien to drugs and, in their habitual use, these drugs have been associated with a host of reactions, both somatic and psychic. Besides, the study has estimated the risk of suicide attempt by gender, marital status and different clinical situations. The estimations obtained are consistent with what is already known in the literature and with the natural history of depressive illness.

A family history of suicide and a depression diagnosis are well-known risk factors which appear as outstanding factors in our study. It is worth pointing out as an interesting piece of information the already mentioned protective effects of tobacco and antipsychotics and opioids, as well as the effect, which should be further analysed, of an elevated risk associated with non-opioid analgesics.

As recommendations that could be drawn from the study in connection with the suicide risk, and with every caution possible, would be paying attention to certain situations like social isolation or the intake of abuse substances like cocaine and cannabis, the intake of SSRI antidepressants in certain circumstances and pathologies involving pain. The good calibration of the model with an area under the ROC curve of 0.880 offers the possibility of using the variables included in the logistic regression for the construction of a risk scale that might serve to detect patients presenting a high risk of suicide. This way, the pharmacological treatment could be adjusted or modified according to the influence of the different risk factors.

# 6. Conclusions

# 6. Conclusions

1. Suicidal behaviour is a cause for concern due to the rise of its prevalence and lethality. Suicide represents one the main causes of death in the world.

2. Numerous drugs and especially several psychotropic substances have been connected with suicidal behaviour.

3. Being a woman and social isolation have been associated with a greater risk of suicide attempts in our study.

4. A family history of suicide and a diagnosis of major depression were associated as well with a greater risk of suicide attempts.

5. Exposure to SSRI antidepressants, non-opioid analgesics, cannabis and cocaine were associated with a greater risk of suicide attempts in our study.

6. Exposure to antipsychotics, opioids and tobacco was associated with a protective effect over the risk of attempting suicide.

7. Computer-based clinical histories represent a useful resource in pharmacoepidemiological research. Promoting their use for research purposes can lead to better healthcare assistance.

8. Tracking certain situations such as social isolation, intake of abuse substances like cocaine and cannabis, SSRI antidepressants in certain situations and pathologies associated with pain may prevent suicidal behaviour.

# 7. Bibliography

## 7. Bibliography


- Aboujaoude E, Savage MW, Starcevic V, Salame WO. Cyberbullying: Review of an Old Problem Gone Viral. J Adolesc Health. 2015 Jul; 57(1):10-8.

- Ajdacic-Gross V, Weiss MG, Ring M, Hepp U, Bopp M, Gutzwiller F, Rössler W. Métodos de suicidio: comparación internacional a partir de la base de datos de mortalidad de la OMS [Internet]. 2007. Available from: http://www.who.int/bulletin/volumes/86/9/07-043489-ab/es/

- Agerbo E, Gunnell D, Bonde JP, Mortensen PB, Nordentoft M. Suicide and occupation: the impact of socio-economic, demographic and psychiatric differences. Psychol Med. 2007 Aug;37(8):1131-40.

- Agerbo E, Nordentoft M, Mortensen PB. Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. BMJ. 2002 Jul 13; 325(7355):74.

- Alexopoulos GS, Bruce ML, Hull J, Sirey JA, Kakuma T. Clinical determinants of suicidal ideation and behavior in geriatric depression. Arch Gen Psychiatry. 1999 Nov; 56(11):1048-53.

- Allan NP, Norr AM, Boffa JW, Durmaz D, Raines AM, Schmidt NB. Examining the unique relations between anxiety sensitivity factors and suicidal ideation and past suicide attempts. Psychiatry Res. 2015 Aug 30; 228(3):441-7.

- Altamura C, VanGastel A, Pioli R, Mannu P, Maes M. Seasonal and circadian rhythms in suicide in Cagliari, Italy. J Affect Disord. 1999 Apr; 53(1):77-85. Review.

- Andrade C, Bhakta SG, Singh NM. Controversy revisited: Selective serotonin reuptake inhibitors in paediatric depression. World J Biol Psychiatry. 2006; 7(4):251-60.

- Appleby L, Mortensen PB, Faragher EB. Suicide and other causes of mortality after post-partum psychiatric admission. Br J Psychiatry. 1998 Sep; 173:209-11.

- Arana A, Wentworth CE, Ayuso-Mateos JL, Arellano FM. Suicide-related events in patients treated with antiepileptic drugs. N Engl J Med 2010; 363:542-51.

- Arranz Estévez FJ. Epidemiología de la conducta suicida. En: Montalbán R, editor. La conducta suicida. Editorial libro del año; 1997.

- Arsenault-Lapierre G, Kim C, Turecki G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. BMC Psychiatry. 2004 Nov 4; 4:37.

- Artenie AA, Bruneau J, Roy É, Zang G, Lespérance F, Renaud J, Tremblay J, Jutras-Aswad D. Licit and illicit substance use among people who inject drugs and the association with subsequent suicidal attempt. Addiction. 2015 Oct; 110(10):1636-43.

- Aschan L, Goodwin L, Cross S, Moran P, Hotopf M, Hatch SL. Suicidal behaviours in South East London: prevalence, risk factors and the role of socio-economic status. J Affect Disord. 2013 Sep 5; 150(2):441-9.

- Ashton H, Young AH. GABA-ergic drugs: exit stage left, enter stage right. J Psychopharmacol. 2003 Jun; 17(2):174-8.

- Assari S. Ethnic and Gender Differences in Additive Effects of Socioeconomics, Psychiatric Disorders, and Subjective Religiosity on Suicidal Ideation among Blacks. Int J Prev Med. 2015 Jun 17; 6:53.

- Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, Kavalali ET, Monteggia LM. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 2011; 475(7354):91-5.

- Ayuso-Mateos JL, Baca-García E, Bobes J, Giner J, Giner L, Pérez V, Sáiz PA, Saiz Ruiz J. Grupo RECOMS. Recommendations for the prevention and management of suicidal behaviour. Revista de Psiquiatría y Salud Mental (English Edition). 2012 Jan-Mar; 5(1):8-23.

- Bailly D. Safety of selective serotonin reuptake inhibitor antidepressants in children and adolescents. Presse Med 2006; 35:1507-15.

- Baldessarini RJ, Hennen J. Genetics of suicide: an overview. Harv Rev Psychiatry. 2004 Jan-Feb; 12(1):1-13. Review.

- Baldwin DS, Reines EH, Guiton C, Weiller E. Escitalopram therapy for major depression and anxiety disorders. Ann Pharmacother. 2007 Oct; 41(10):1583-92. Epub 2007 Sep 11.

- Barak Y, Mirecki I, Knobler HY, Natan Z, Aizenberg D. Suicidality and second generation antipsychotics in schizophrenia patients: a case-controlled retrospective study during a 5-year period. Psychopharmacology (Berl). 2004 Sep; 175(2):215-9.

- Barak Y, Mirecki I, Knobler HY, Natan Z, Aizenberg D. Suicidality and second generation antipsychotics in schizophrenia patients: a case-controlled retrospective study during a 5-year period. Psychopharmacology (Berl). 2004 Sep; 175(2):215-9.

- Beasley CM, Sayler ME, Kiesler GM. The influence of pharmacotherapy on self-directed and extremally directed aggression in schizophrenia (abstract). 9th Biennal Winter Workshop on Schizophrenia, Davor, Switzerland, February 7-13, 1998.

- Beautrais AL, Joyce PR, Mulder RT, Fergusson DM, Deavoll BJ, Nightingale SK. Prevalence and comorbidity of mental disorders in persons making serious suicide attempts: a case-control study. Am J Psychiatry. 1996 Aug; 153(8):1009-14.

- Beautrais AL. Risk factors for suicide and attempted suicide among young people. Aust N Z J Psychiatry. 2000 Jun;34(3):420-36.

- Beisser AR, Blanchette JE. A study of suicides in a mental hospital. Dis nerv Syst. 1961 jul; 22:365-9.

- Belsley DA, Kuh E, Welsh RE. Regression Diagnostics: Identifying Influential Data and Sources of Collinearity. New York: John Wiley and Sons; 1980.

- Ben-Porath DD, Taylor SP. The effects of diazepam (valium) and aggressive disposition on human aggression: an experimental investigation. Addict Behav. 2002 Mar-Apr;27(2):167-77.

- Berglund M, Ojehagen A. The influence of alcohol drinking and alcohol use disorders on psychiatric disorders and suicidal behavior. Alcohol Clin Exp Res. 1998 Oct;22(7 Suppl):333S-345S. Review.

- Berglund PA, Borges G, Castilla-Puentes RC, Glantz MD, Jaeger SA, et al. Smoking and suicidal behaviors in the National Comorbidity Survey: Replication. J Nerv Ment Dis. 2007; 195: 369–377.

- Berlin I, Hakes JK, Hu MC, Covey LS. Tobacco use and suicide attempt: longitudinal analysis with retrospective reports. PLoS One. 2015 Apr 7; 10(4):e0122607.

- Berman ME, Jones GD, McCloskey MS. The effects of diazepam on human self-aggressive behavior. Psychopharmacology (Berl). 2005 Feb; 178(1):100-6. Epub 2004 Aug 17.

- Bernal M, Haro JM, Bernert S, Brugha T, de Graaf R, Bruffaerts R, Lépine JP, de Girolamo G, Vilagut G, Gasquet I, Torres JV, Kovess V, Heider D, Neeleman J, Kessler R, Alonso J. ESEMED/MHEDEA Investigators. Risk factors for suicidality in Europe: results from the ESEMED study. J Affect Disord. 2007 Aug; 101(1-3):27-34.

–
– Bertolote JM, Fleischmann A, De Leo D, Bolhari J, Botega N, De Silva D, Huong Tran Thi Thanh, Phillips M, Schlebusch L, Värnik A, Vijayakumar L, Wasserman D. Suicide attempts, plans, and ideation in culturally diverse sites: the WHO SUPRE-MISS community survey. Psychological Medicine. 2005. 35: 1457-1465.

– Bertolote JM, Fleischmann A, De Leo D, Phillips MR, Botega NJ, Vijayakumar L, De Silva D, Schlebusch L, Van Tuong N, Sisask M, Bolhari J, and Wasserman D. Repetition of suicide attempts: data from five culturally different low- and middle-income country emergency care settings participating in the WHO SUPRE-MISS study. Crisis. 2010. 31(4): 194-201.

– Bhatia SK, Bhatia SC. Childhood and adolescent depression. Am Fam Physician. 2007 Jan 1; 75(1):73-80.

– Biddle L, Brock A, Brookes ST, Gunnell D, Simon. Suicide rates in young men in England and Wales in the 21st century: time trend study. BMJ. 2008 Mar 8; 336(7643):539-42.

– Bjørngaard JH, Carslake D, Lund Nilsen TI, Linthorst AC, Davey Smith G, Gunnell D, Romundstad PR. Association of Body Mass Index with Depression, Anxiety and Suicide-An Instrumental Variable Analysis of the HUNT Study. PLoS One. 2015 Jul 13; 10(7):e0131708.

– Blow FC, Brockmann LM, Barry KL. Role of alcohol in late-life suicide. Alcohol Clin Exp Res. 2004 May;28(5 Suppl):48S-56S.

– Blumenthal SJ. Suicidio: guía sobre factores de riesgo, valoración y tratamiento de los pacientes suicidas. Clin Med Norteam 1988; 4: 99-1026.

– Bobes García J, Sáiz Martínez PA, González García-Portilla MP, Bousoño garcía M. Bases biológicas de las conductas suicidas y parasuicidas. Area de Psiquiatría, Facultad de Medicina, Universidad de Oviedo. 1996.

– Bond AJ, Curran HV, Bruce MS, O'Sullivan G, Shine P. Behavioural aggression in panic disorder after 8 weeks' treatment with alprazolam. J Affect Disord. 1995 Dec 13; 35(3):117-23.

– Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry. 2000 Dec; 157(12):1925-32.

– Bousoño García M, Bobes García J, González-Quirós Corujo P. Tratamiento psicofarmacológico. In: Bobes García J, González Seijo JC, Sáiz Martínez PA, editors. Prevención de las conductas suicidas y parasuicidas. Barcelona: Masson, S.A.; 1997.

- Bousoño M, Bobes J, González Quirós P. Tratamiento psicofarmacológico. Prevención de las conductas suicidas y parasuicidas. Barcelona: Masson; 1990.

- Brent DA, Birmaher B. British warnings on SSRIs questioned. J Am Acad Child Adolesc Psychiatry. 2004 Apr;43(4):379-80.

- Brent DA, Mann JJ. Family genetic studies, suicide, and suicidal behavior. Am J Med Genet C Semin Med Genet. 2005 Feb 15; 133C(1):13-24. Review.

- Brent DA, Perper JA, Moritz G, Baugher M, Roth C, Balach L, Schweers J. Stressful life events, psychopathology, and adolescent suicide: a case control study. Suicide Life Threat Behav. 1993 Fall; 23(3):179-87. Erratum in: Suicide Life Threat Behav 1994 Spring; 24(1):111.

- Brent DA, Perper JA, Moritz G, Liotus L, Schweers J, Balach L, Roth C. Familial risk factors for adolescent suicide: a case-control study. Acta Psychiatr Scand. 1994 Jan; 89(1):52-8.

- Bresin K, Gordon KH. Endogenous opioids and nonsuicidal self-injury: a mechanism of affect regulation. Neurosci Biobehav Rev. 2013 Mar;37(3):374-83.

- Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. Acta Psychiatr Scand. 2006 Mar;113(3):180-206. Review.

- Brown GK, Beck AT, Steer RA, Grisham JR. Risk factors for suicide in psychiatric outpatients: a 20-year prospective study. J Consult Clin Psychol. 2000 Jun;68(3):371-7.

- Brunner J, Parhofer KG, Schwandt P, Bronisch T. Cholesterol, essential fatty acids, and suicide. Pharmacopsychiatry. 2002 Jan;35(1):1-5. Review.

- Buda M, Tsuang MT. The epidemiology of suicide: implications for clinical practice. En: Blumenthal SJ, Kupfer DJ, editors. Suicide over life cycle. Risk factors, assessment, and treatment of suicidal patients. Washington DC: American Psychiatric Press; 1990. Capítulo 2; p.17-37.

- Calandre EP, Vilchez JS, Molina-Barea R, Tovar MI, Garcia-Leiva JM, Hidalgo J, Rodriguez-Lopez CM, Rico-Villademoros F. Suicide attempts and risk of suicide in patients with fibromyalgia: a survey in Spanish patients. Rheumatology (Oxford). 2011 Oct; 50(10):1889-93.

- Campbell G, Bruno R, Darke S, Degenhardt L. Associations of borderline personality with pain, problems with medications and suicidality in a

community sample of chronic non-cancer pain patients prescribed opioids for pain. Gen Hosp Psychiatry. 2015 Sep-Oct; 37(5):434-40.

- Carlsten A, Waern M, Holmgren P, Allebeck P. The role of benzodiazepines in elderly suicides. Scand J Public Health. 2003; 31(3):224-8.

- Center for Disease Control and Prevention. Risk and Protective Factors [Internet]. 2010. Available from: http://www.cdc.gov/ncipc/dvp/suicide/Suicide-risk-p-factors.htm

- Chang SS, Sterne JA, Huang WC, Chuang HL, Gunnell D. Association of secular trends in unemployment with suicide in Taiwan, 1959-2007: a time-series analysis. Public Health. 2010 Jan; 124(1):49-54.

- Cheatle MD. Depression, chronic pain, and suicide by overdose: on the edge. Pain Med. 2011 Jun; 12 Suppl 2:S43-8.

- Cherpitel CJ, Borges GL, Wilcox HC. Acute alcohol use and suicidal behavior: a review of the literature. Alcohol Clin Exp Res. 2004 May; 28(5 Suppl):18S-28S. Review.

- Choca JP, Grossman SD. Evolution of the Millon Clinical Multiaxial Inventory. J Pers Assess. 2015 Jul 7:1-9.

- Christiansen E, Jensen BF. Risk of repetition of suicide attempt, suicide or all deaths after an episode of attempted suicide: a register-based survival analysis. Aust N Z J Psychiatry. 2007 Mar;41(3):257-65.

- Ciaramella A, Poli P. Chronic Low Back Pain: Perception and Coping with Pain in the Presence of Psychiatric Comorbidity. J Nerv Ment Dis. 2015 Aug; 203(8):632-40.

- CIE 10. Décima revisión de la clasificación internacional de enfermedades. Trastornos mentales y del comportamiento. Pautas diagnósticas y actuación en Atención Primaria. OMS. Madrid: Meditor; 1996.

- Dyer C. European court upholds UK ban on Halcion. BMJ. 1999 Feb 13; 318(7181): 418.

- Clark DC, Fawcett J. Review of empirical risk factors for evaluation of the suicidal patient. En: Bongar B, editor. Suicide: guidelines for assessment, management, and treatment. New York: Oxford University Press; 1992; p.16-48.

- Cohen D. Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned? Psychother Psychosom. 2007; 76(1):5-14.

- Cohen S, Leonard CV, Farberow NL. Tranquilizers and suicide in the schizophrenic patients. Arch Gen Psychiatry 1964; 11:312-321.

- Conner KR, Conwell Y, Duberstein PR. The validity of proxy-based data in suicide research: a study of patients 50 years of age and older who attempted suicide. II. Life events, social support and suicidal behavior. Acta Psychiatr Scand. 2001 Dec; 104(6):452-7.

- Conner KR, Duberstein PR, Conwell Y, Caine ED. Reactive aggression and suicide: Theory and evidence. Aggres Violent Behav; 2003 Jul-Aug;8(4): 413-32.

- Conner KR, Duberstein PR. Predisposing and precipitating factors for suicide among alcoholics: empirical review and conceptual integration. Alcohol Clin Exp Res. 2004 May; 28(5 Suppl):6S-17S. Review.

- Conwell Y, Duberstein PR. Suicide in elders. Ann N Y Acad Sci. 2001 Apr; 932:132-47; discussion 147-50.

- Coryell W, Young EA. Clinical predictors of suicide in primary major epressive disorder. J Clin Psychiatry. 2005 Apr; 66(4):412-7.

- Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. BMJ. 2015 Feb 18; 350:h517.

- Czapiński P, Blaszczyk B, Czuczwar SJ. Mechanisms of action of antiepilepticdrugs. Curr Top Med Chem. 2005; 5(1):3-14.

- Damluji NF, Ferguson JM. Paradoxical worsening of depressive symptomatology caused by antidepressants. J Clin Psychopharmacol. 1988 Oct;8(5):347-9.

- Delforterie MJ, Lynskey MT, Huizink AC, Creemers HE, Grant JD, Few LR, Glowinski AL, Statham DJ, Trull TJ, Bucholz KK, Madden PA, Martin NG, Heath AC, Agrawal A. The relationship between cannabis involvement and suicidal thoughts and behaviors. Drug Alcohol Depend 2015; 150:98-104.

- Dervic K, Brent DA, Oquendo MA. Completed suicide in childhood. Psychiatr Clin North Am. 2008 Jun; 31(2):271-91.

- Dervic K, Oquendo MA, Currier D, Grunebaum MF, Burke AK, Mann JJ. Moral objections to suicide: Can they counteract suicidality in patients with cluster B psychopathology? J Clin Psychiatry. 2006 Apr;67(4):620-5.

– Doessel DP, Williams RF, and Whiteford H. Policy-appropriate measurement of suicide: headcount vs. potential years of life lost, Australia, 1907-2005. Arch Suicide Res. 2009;13(1):87-99.

– Doihara C, Kawanishi C, Yamada T, Sato R, Hasegawa H, Furuno T, Nakagawa M, Hirayasu Y. Trait aggression in suicide attempters: a pilot study. Psychiatry Clin Neurosci. 2008 Jun;62(3):352-4.

– Donald M, Dower J, Lucke J, Raphael B. Prevalence of adverse life events, depression and suicidal thoughts and behaviour among a community sample of young people aged 15-24 years. Aust N Z J Public Health. 2001 Oct;25(5):426-32.

– Donovan SJ, Stewart JW, Nunes EV, Quitkin FM, Parides M, Daniel W, Susser E, Klein DF. Divalproex treatment for youth with explosive temper and mood lability:a double-blind, placebo-controlled crossover design. Am J Psychiatry. 2000 May; 157(5):818-20.

– Doraiswamy PM. Contemporary management of comorbid anxiety and depression in geriatric patients. J Clin Psychiatry. 2001;62 Suppl 12:30-5.

– Duberstein PR, Conwell Y, Cox C. Suicide in widowed persons. A psychological autopsy comparison of recently and remotely bereaved older subjects. Am J Geriatr Psychiatry. 1998 Fall;6(4):328-34.

– Duggan A, Warner J, Knapp M, Kerwin R. Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. Br J Psychiatry. 2003 Jun; 182:505-8.

– Durkheim E. El suicidio. Madrid: Ediciones Akal; 1982.

– Durso GR, Luttrell A, Way BM. Over-the-Counter Relief From Pains and Pleasures Alike: Acetaminophen Blunts Evaluation Sensitivity to Both Negative and Positive Stimuli. Psychol Sci. 2015 Jun; 26(6):750-8.

– Dwivedi Y, Pandey GN. Elucidating biological risk factors in suicide: role of protein kinase A. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Jun 1; 35(4):831-41.

– Egeland JA, Sussex JN. Suicide and family loading for affective disorders. JAMA. 1985 Aug 16; 254(7):915-8.

– Elliot EE, White JM. Long-term abecarnil administration produces tolerance and withdrawal signs in the rat. Eur J Pharmacol. 2000 Apr 14; 394(2-3):237-45.

– Eriksson M, Glader EL, Norrving B, Asplund K. Poststroke suicide attempts

and completed suicides: a socioeconomic and nationwide perspective. Neurology. 2015 Apr 28; 84(17):1732-8.

- Erlangsen A, Jeune B, Bille-Brahe U, Vaupel JW. Loss of partner and suicide risks among oldest old: a population-based register study. Age Ageing. 2004 Jul;33(4):378-83.

- Esposito CL, Clum GA. Social support and problem-solving as moderators of the relationship between childhood abuse and suicidality: applications to a delinquent population. J Trauma Stress. 2002 Apr; 15(2):137-46.

- European Commission. European Pact for Mental Health and Well-being, EU High-Level Conference Together for Mental Health and Well-being. Bruselas. 2008 Jun 12-13.

- Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. Am J Psychiatry. 2012 May; 169(5):491-7.

- Fazel S, Grann M, Ahlner J, Goodwin G. Suicides by violent means in individuals taking SSRIs and other antidepressants: a postmortem study in Sweden, 1992-2004. J Clin Psychopharmacol. 2007 Oct;27(5):503-6.

- FDA. FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated With Antidepressant Medications. 2004 Oct 15.

- Fischer LR, Wei F, Solberg LI, Rush WA, Heinrich RL. Treatment of elderly and other adult patients for depression in primary care. J Am Geriatr Soc. 2003 Nov;51(11):1554-62.

- Fleischmann A, Bertolote JM, Belfer M, Beautrais A. Completed suicide and psychiatric diagnoses in young people: a critical examination of the evidence. Am J Orthopsychiatry. 2005 Oct; 75(4):676-83.

- Foster T, Gillespie K, McClelland R. Mental disorders and suicide in Northern Ireland. Br J Psychiatry. 1997 May; 170:447-52.

- Fountoulakis KN, Gonda X, Samara M, Siapera M, Karavelas V, Ristic DI, Iacovides A. Antiepileptic drugs and suicidality. J Psychopharmacol 2012; 26:1401-7.

- Fresán A, González-Castro TB, Peralta-Jiménez Y, Juárez-Rojop I, Pool-García S, Velázquez-Sánchez MP, López-Narváez L, Tovilla-Zárate CA. Gender differences in socio-demographic, clinical characteristics and psychiatric diagnosis in/of suicide attempters in a Mexican population. Acta Neuropsychiatr. 2015 Jun;27(3):182-8.

- Freud S. Traner und melancholie. Int Z Psychoanal 1917; 4(6): 288-301.

- Fu Q, Heath AC, Bucholz KK, Nelson EC, Glowinski AL, Goldberg J, Lyons MJ, Tsuang MT, Jacob T, True MR, Eisen SA. A twin study of genetic and environmental influences on suicidality in men. Psychol Med. 2002 Jan; 32(1):11-24.

- Fukuchi N, Kakizaki M, Sugawara Y, Tanji F, Watanabe I, Fukao A, Tsuji I. Association of marital status with the incidence of suicide: a population-based Cohort Study in Japan (Miyagi cohort study). J Affect Disord. 2013 Sep 25; 150(3):879-85.

- Gaillard R, Loo H, Olie JP. Mental pain: is it a symptom?. Bull Acad Natl Med. 2010 Mar; 194(3):567-78; discussion 578-81.

- García-Resa E, Braquehais D, Blasco H, Ramírez A, Jiménez L, Díaz-Sastre C, Baca-García E, Sáiz J. Aspectos sociodemográficos de los intentos de suicidio. Fundación Jiménez Díaz. Madrid. 2002; 30(2):112-119.

- Ghaziuddin N, Merchant C, Dopp R, King C. A naturalistic study of suicidal adolescents treated with an SSRI: suicidal ideation and behavior during 3-onth post-hospitalization period. Asian J Psychiatr. 2014 Oct; 11:13-9.

- Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. Am J Psychiatry. 2007 Jul; 164(7):1044-9.

- Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. Am J Psychiatry. 2013 Dec; 170(12):1460-7.

- Gilbert DA, Altshuler KZ, Rago WV, Shon SP, Crismon ML, Toprac MG, Rush AJ. Texas Medication Algorithm Project: definitions, rationale, and methods to develop medication algorithms. J Clin Psychiatry. 1998 Jul;59(7):345-51.

- Glenn CR, Bagge CL, Osman A. Unique associations between borderline personality disorder features and suicide ideation and attempts in adolescents. J Pers Disord. 2013 Oct;27(5):604-16.

- Golier JA, Marzuk PM, Leon AC, Weiner C, Tardiff K. Low serum cholesterol level and attempted suicide. Am J Psychiatry. 1995 Mar; 152(3):419-23.

- González E, Pérez F. La historia clínica electrónica. Revisión y análisis de la actualidad. Diraya: la historia de salud electrónica de Andalucía. Rev Esp Cardiol Supl. 2007;7(C):37-46. - Vol. 7 Núm.Supl.C.

- González-Navarro MD, Lorenzo MI, Luna A, Gómez M, Imbernón E, Ruiz J. Análisis de los intentos de autolisis en un área de salud. 2008-2010. Semergen. 2012; 38(7):439-444.

- Gorwood P. Biological markers for suicidal behavior in alcohol dependence. Eur Psychiatry. 2001 Nov;16(7):410-7. Review.

- Gould MS, Fisher P, Parides M, Flory M, Shaffer D. Psychosocial risk factors of child and adolescent completed suicide. Arch Gen Psychiatry. 1996 Dec;53(12):1155-62.

- Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry. 1970 Oct; 117(539):437-8.

- Haghighi H, Golmirzaee J, Mohammadi K, Moradabadi AS, Dadipoor S, Hesam AA. Investigating the relationship between the demographic variables associated with suicide in different seasons, among suicidal people in the Shahid Mohammadi Hospital, Bandar Abass, Iran. J Educ Health Promot. 2015 Feb 23; 4:3.

- Halmi KA. Perplexities of treatment resistance in eating disorders. BMC Psychiatry. 2013 Nov 7; 13:292. doi: 10.1186/1471-244X-13-292.

- Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. Br J Psychiatry. 1997 Mar; 170:205-28.

- Haukka J, Suominen K, Partonen T, Lönnqvist J. Determinants and outcomes of serious attempted suicide: a nationwide study in Finland, 1996-2003. Am J Epidemiol. 2008 May 15; 167(10):1155-63.

- Haw CM, Hawton K. Problem drug use, drug misuse and deliberate self-harm: trends and patient characteristics, with a focus on young people, Oxford, 1993-2006. Soc Psychiatry Psychiatr Epidemiol. 2011 Feb;46(2):85-93.

- Hawthon K, Cowen P, Owens D, Bond A, Elliott M. Low serum cholesterol and suicide. Br J Psychiatry. 1993 Jun; 162:818-25.

- Hawton K, Harriss L, Simkin S, Bale E, Bond A. Suicidal Behaviour in England and Wales. In: Schmidtke A, Bille-Brahe U, De Leo D, & Kerkhof A, editors. Suicidal Behaviour in Europe: Results from the WHO/EURO Multicentre Study of Suicidal Behaviour. Göttingen. Hogrefe & Huber Publishers; 2004. p. 123-9.

- Hawton K, Sutton L, Haw C, Sinclair J, Deeks JJ. Schizophrenia and suicide: systematic review of risk factors. Br J Psychiatry. 2005 Jul;187:9-20. Review.

- Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. J Clin Psychiatry. 2005 Jun;66(6):693-704. Review.

- Hawton K, van Heeringen K. Suicide. Lancet. 2009 Apr 18;373(9672):1372-81.

- Hawton K, Zahl D, Weatherall R. Suicide following deliberate self-harm: long-term follow-up of patients who presented to a general hospital. Br J Psychiatry. 2003 Jun; 182:537-42.

- Hawton K. Sex and suicide. Gender differences in suicidal behaviour. Br J Psychiatry. 2000 Dec; 177:484-5.

- Healy D, Aldred G. Antidepressant drug use & the risk of suicide. Int Rev Psychiatry. 2005 Jun;17(3):163-72.

- Healy D, Langmaak C, Savage M. Suicide in the course of the treatment of depression. J Psychopharmacol. 1999;13(1):94-9.

- Hegerl U. Antidepressants and suicidality. Risk-benefit analysis. Nervenarzt. 2007 Jan;78(1):7-14.

- Heikkinen ME, Henriksson MM, Isometsä ET, Marttunen MJ, Aro HM, Lönnqvist JK. Recent life events and suicide in personality disorders. J Nerv Ment Dis. 1997 Jun;185(6):373-81.

- Heikkinen ME, Isometsä ET, Marttunen MJ, Aro HM, Lönnqvist JK. Social factors in suicide. Br J Psychiatry. 1995 Dec; 167(6):747-53.

- Heilä H, Isometsä ET, Henriksson MM, Heikkinen ME, Marttunen MJ, Lönnqvist JK. Suicide victims with schizophrenia in different treatment phases and adequacy of antipsychotic medication. J Clin Psychiatry. 1999 Mar; 60(3):200-8.

- Helgason T, Tómasson H, Zoega T. Antidepressants and public health in Iceland. Time series analysis of national data. Br J Psychiatry. 2004 Feb; 184:157-62.
- Herpertz S, Steinmeyer SM, Marx D, Oidtmann A, Sass H. The significance of aggression and impulsivity for self-mutilative behavior. Pharmacopsychiatry. 1995 Oct; 28 Suppl 2:64-72.

- Hetrick S, Merry S, McKenzie J, Sindahl P, Proctor M. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004851.

- Hitchcock LS, Ferrell BR, McCaffery M. The experience of chronic nonmalignant pain. J Pain Symptom Manage. 1994 Jul;9(5):312-8.

- Holma KM, Melartin TK, Haukka J, Holma IA, Sokero TP, Isometsä ET. Incidence and predictors of suicide attempts in DSM-IV major depressive disorder: a five-year prospective study. Am J Psychiatry. 2010 Jul;167(7).

- Hooman S, Zahra H, Safa M, Hassan FM, Reza MM. Association between cigarette smoking and suicide in psychiatric inpatients. Tob Induc Dis. 2013 Feb 18;11(1):5.

- Hovey JD. Religion and suicidal ideation in a sample of Latin American immigrants. Psychol Rep. 1999 Aug;85(1):171-7.

- Hughes CW, Emslie GJ, Crismon ML, Posner K, Birmaher B, Ryan N, Jensen P, Curry J, Vitiello B, Lopez M, Shon SP, Pliszka SR, Trivedi MH. Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. Texas Children's Medication Algorithm Project: update from Texas Consensus Conference Panel on Medication Treatment of Childhood Major Depressive Disorder. J Am Acad Child Adolesc Psychiatry. 2007 Jun;46(6):667-86.

- Husar AF. Effect of tranquilizers on medical morbility and mortality in a mental hospital. JAMA 1962; 179:682-686.

- Im JJ, Shachter RD, Oliva EM, Henderson PT, Paik MC, Trafton JA. PROGRES Team. Association of Care Practices with Suicide Attempts in US Veterans Prescribed Opioid Medications for Chronic Pain Management. J Gen Intern Med. 2015 Jul;30(7):979-91.

- INE. Defunciones según la causa de muerte [Internet]. 2012 Available from: http://www.ine.es/prensa/np830.pdf

- INE. Defunciones según la causa de muerte [Internet]. 2014. Available from: http://www.ine.es/jaxi/menu.do?type=pcaxis&path=/t15/p417/&file=inebase

- Institut Català de Farmacologia. La dudosa seguridad del triazolam [Internet]. 1991. Butlletí Groc 1991; Vol. 4, nº 4. [Consultado el 13 de septiembre de 2015;] Available from: http://www.icf.uab.cat/es/pdf/informacio/bg/bg44.91e.pdf

- Isacsson G, Holmgren P, Druid H, Bergman U. The utilization of antidepressants a key issue in the prevention of suicide: an analysis of 5281 suicides in Sweden during the period 1992-1994. Acta Psychiatr Scand. 1997 Aug; 96(2):94-100.

–Isometsä ET. Psychological autopsy studies a review. Eur Psychiatry. 2001 Nov; 16(7):379-85. Review.

–Isometsä ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lönnqvist JK. Suicide in major depression. Am J Psychiatry. 1994 Apr; 151(4):530-6.

–James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. Acta Psychiatr Scand. 2004 Dec; 110(6):408-15. Review.

–Jepsen P, Qin P, Nørgård B, Agerbo E, Mortensen PB, Vilstrup H, Sørensen HT. The association between admission for poisoning with paracetamol or other weak analgesics and subsequent admission for psychiatric disorder: a Danish nationwide case-control study. Aliment Pharmacol Ther. 2005 Oct 1;22(7):645-51.

–Jiménez-Arriero MA, Fernández I, Vidal J, Herráez C, Parellada M, Cruz MA, Pérez-Cayuela P, Ausejo M. Selective serotonin reuptake inhibitors: use in children and adolescents with major depressive disorder. Actas Esp Psiquiatr. 2007 Sep-Oct;35(5):342-50.

–Jiménez-López JL, Arenas-Osuna J, Angeles-Garay U. [Depression, anxiety and suicide risk symptoms among medical residents over an academic year]. Rev Med Inst Mex Seguro Soc. 2015 Jan-Feb;53(1):20-8.

–Johnson DA, Pasterski G, Ludlow JM, Street K, Taylor RD. The discontinuance of maintenance neuroleptic therapy in chronic schizophrenic patients: drug and social consequences. Acta Psychiatr Scand. 1983 May; 67(5):339-52.

–Joiner TE, Bernert RA, Jack DC. The bidimensional structure of suicidal symptoms in Nepal. Arch Suicide Res. 2005;9(4):345-51.

–Jonas JM, Hearron AE Jr. Alprazolam and suicidal ideation: a meta-analysis of controlled trials in the treatment of depression. J Clin Psychopharmacol 1996; 16(3):208-11.

–Juurlink DN, Herrmann N, Szalai JP, Kopp A, Redelmeier DA. Medical illness and the risk of suicide in the elderly. Arch Intern Med. 2004 Jun 14; 164(11):1179-84.

–Kamath P, Reddy YC, Kandavel T. Suicidal behavior in obsessive-compulsive disorder. J Clin Psychiatry. 2007 Nov; 68(11):1741-50.

–Kandemir H, Yumru M, Kul M, Kandemir SB. Behavioral disinhibition, suicidal ideation, and self-mutilation related to clonazepam. J Child Adolesc

Psychopharmacol. 2008 Aug;18(4):409.

- Kaplan HI, Sadock BJ. Sinopsis de Psiquiatría. Ciencias de la conducta. Psiquiatría clínica. Madrid: Editorial Médica Panamericana; 1999.

- Kapur N, Murphy E, Cooper J, Bergen H, Hawton K, Simkin S, Casey D, Horrocks J, Lilley R, Noble R, Owens D. Psychosocial assessment following self-harm: results from the multi-centre monitoring of self-harm project. J Affect Disord. 2008 Mar;106(3):285-93.

- Keck PE Jr, Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry. 2000;61 Suppl 3:4-9.

- Kelleher MJ, Chambers D, Corcoran P, Williamson E, Keeley HS. Religious sanctions and rates of suicide worldwide. Crisis. 1998;19(2):78-86.

- Kessler RC, Berglund PA, Borges G, Castilla-Puentes RC, Glantz MD, Jaeger SA, Merikangas KR, Nock MK, Russo LJ, Stang PE. Smoking and suicidal behaviors in the National Comorbidity Survey: Replication. J Nerv Ment Dis. 2007 May; 195: 369–377.

- Kessler RC, Borges G, Sampson N, Miller M, Nock MK. The association between smoking and subsequent suicide-related outcomes in the National Comorbidity Survey panel sample. Mol Psychiatry. 2009 Dec; 14:1132–1142.

- Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord. 2002 Apr; 68(2-3):183-90.

- Kim CD, Seguin M, Therrien N, Riopel G, Chawky N, Lesage AD, Turecki G. Familial aggregation of suicidal behavior: a family study of male suicide completers from the general population. Am J Psychiatry. 2005 May; 162(5):1017-9.

- Kim HM, Zivin K, Choe HM, Stano CM, Ganoczy D, Walters H, Valenstein M. Predictors of start of different antidepressants in patient charts among patients with depression. J Manag Care Spec Pharm. 2015 May; 21(5):424-30.

- King EA, Baldwin DS, Sinclair JM, Baker NG, Campbell MJ, Thompson C. The Wessex Recent In-Patient Suicide Study, 1. Case-control study of 234 recently discharged psychiatric patient suicides. Br J Psychiatry. 2001 Jun; 178:531-6.

- Kölch M, Fegert JM. Medical treatment of depression in children and adolescents. Prax Kinderpsychol Kinderpsychiatr. 2007;56(3):224-33.

- Kposowa AJ. Marital status and suicide in the National Longitudinal Mortality Study. J Epidemiol Community Health. 2000 Apr;54(4):254-61.

- Kposowa AJ. Unemployment and suicide: a cohort analysis of social factors predicting suicide in the US National Longitudinal Mortality Study. Psychol Med. 2001 Jan;31(1):127-38.

- Kravitz HM, Fawcett J, Newman AJ. Alprazolam and depression: a review of risks and benefits. J Clin Psychiatry. 1993 Oct;54 Suppl:78-84; discussion 85.

- Kreitman N. Suicide, age and marital status. Psychol Med. 1988 Feb;18(1):121-8.

- Kurian BT, Ray WA, Arbogast PG, Fuchs DC, Dudley JA, Cooper WO. Effect of regulatory warnings on antidepressant prescribing for children and adolescents. Arch Pediatr Adolesc Med. 2007 Jul;161(7):690-6.

- Lastra I, Rodríguez Pulido F, González de Chaves González F, Vázquez-Barquero JL. Prevención de las conductas suicidas. En: Vázquez-Barquero JL, dir. Psiquiatría en Atención Primaria. Grupo Aula Médica, S.A.; 1998.

- Lecrubier Y. Comorbidity in social anxiety disorder: impact on disease burden and management. J Clin Psychiatry. 1998;59 Suppl 17:33-8.

- Leon AC, Marzuk PM, Tardiff K, Bucciarelli A, Stajic M, Piper TM, Galea S. Antidepressants in adult suicides in New York City: 2001-2004. J Clin Psychiatry. 2007 Sep;68(9):1399-403.

- Leon AC, Solomon DA, Li C, Fiedorowicz JG, Coryell WH, Endicott J, Keller MB. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study. Am J Psychiatry. 2012 Mar;169(3): 285-91.

- Lester D. Seasonal variation in suicidal deaths. Br J Psychiatry. 1971 Jun; 118(547):627-8.

- Lester D. Suicide and islam. Arch Suicide Res. 2006;10(1):77-97.

- Litman RE. Sigmund Freud on suicide. En: Shneidman ES, dir. Essays in self-destruction. Science House; 1967.

- Madadi P, Persaud N. Suicide by means of opioid overdose in patients with chronic pain. Curr Pain Headache Rep. 2014 Nov;18(11):460.

- Maes M, De Meyer F, Thompson P, Peeters D, Cosyns P. Synchronized annual rhythms in violent suicide rate, ambient temperature and the light-dark span. Acta Psychiatr Scand. 1994 Nov;90(5):391-6.

- Maniglio R. The role of child sexual abuse in the etiology of suicide and non-suicidal self-injury. Acta Psychiatr Scand. 2011 Jul;124(1):30-41.

- Mann JJ, Stanley M, McBride PA, McEwen BS. Increased serotonin2 and beta-adrenergic receptor binding in the frontal cortices of suicide victims. Arch Gen Psychiatry. 1986 Oct;43(10):954-9.

- Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry. 1999 Feb; 156(2):181-9.

- Mann JJ. Neurobiology of suicidal behaviour. Nat Rev Neurosci. 2003 Oct;4(10):819-28. Review.

- Marazziti D, Dell'Osso B, Baroni S, Masala I, Di Nasso E, Giannaccini G, Conti L. Decreased density of peripheral benzodiazepine receptors in psychiatric patients after a suicide attempt. Life Sci. 2005 Nov 12;77(26):3268-75. Epub 2005 Jul 12.

- March J, Sareen J, Gawaziuk JP, Doupe M, Chateau D, Hoppensack M, Nour S, Husarewycz W, Palitsky D, Khan S, Leslie WD, Enns MW, Stein MB, Asmundson GJ, Medved M, Logsetty S. Increased suicidal activity following major trauma: a population-based study. J Trauma Acute Care Surg. 2014 Jan; 76(1):180-4.

- Marcinko D, Pivac N, Martinac M, Jakovljević M, Mihaljević-Peles A, Muck-Seler D. Platelet serotonin and serum cholesterol concentrations in suicidal and non-suicidal male patients with a first episode of psychosis. Psychiatry Res. 2007 Feb 28; 150(1):105-8.

- Maris R, Berman A, Silverman M. Comprehensive textbook of suicidology. New York: The Guilford Press; 2000.

- Martín YM, Caro MP, Rio-Valle JS, Rufián AQ, Sánchez BG. Preliminary study of the characteristics of attempted suicide in the province of Granada. An Sist Sanit Navar. 2011 Sep-Dec;34(3):431-41.

- Martínez JC, González C. Antidepresivos y Suicidio: Una polémica actual. Rev Chil Pediatr 2007; 78 (5): 461-471.

- Marzuk PM, Tardiff K, Leon AC, Hirsch CS, Portera L, Hartwell N, Iqbal MI. Lower risk of suicide during pregnancy. Am J Psychiatry. 1997 Jan;154(1):122-3.

- Masocco M, Pompili M, Vanacore N, Innamorati M, Lester D, Girardi P, Tatarelli R, Vichi M. Completed suicide and marital status according to the Italian region of origin. Psychiatr Q. 2010 Mar;81(1):57-71.

- McGirr A, Renaud J, Bureau A, Seguin M, Lesage A, Turecki G. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. Psychol Med. 2008 Mar;38(3):407-17.

- Melges FT, Bowlby J. Types of hopelessness in psychopathological process. Arch Gen Psychiatry. 1969 Jun;20(6):690-9. Review.

- Meltzer H, Bebbington P, Brugha T, Jenkins R, McManus S, Stansfeld S. Job insecurity, socio-economic circumstances and depression. Psychol Med. 2010 Aug;40(8):1401-7.
- Menninger K: Man against himself. New York: Harcourt Brace and World; 1938.

- Menon V, Sarkar S, Kattimani S. Association between personality factors and suicide intent in attempted suicide: Gender as a possible mediator? Personal Ment Health. 2015 Aug;9(3):220-6.

- Meyer IH, Dietrich J, Schwartz S. Lifetime prevalence of mental disorders and suicide attempts in diverse lesbian, gay, and bisexual populations. Am J Public Health. 2008 Jun;98(6):1004-6.

- Milane MS, Suchard MA, Wong ML, Licinio J. Modeling of the temporal patterns of fluoxetine prescriptions and suicide rates in the United States. PloS Med. 2006 Jun;3(6):e190.

- Miller M, Borges G, Orozco R, Mukamal K, Rimm EB, Benjet C, Medina-Mora ME. Exposure to alcohol, drugs and tobacco and the risk of subsequent suicidality: findings from the Mexican Adolescent Mental Health Survey. Drug Alcohol Depend. 2011 Jan 15;113(2-3):110-7.

- Millon T, Davis RD. The MCMI-III: present and future directions. J Pers Assess. 1997 Feb;68(1):69-85.

- Miret M, Nuevo R, Morant C, Sainz-Cortón E, Jiménez-Arriero MA, López-Ibor JJ, Reneses B, Saiz-Ruiz J, Baca-García E, Ayuso-Mateos JL. Calidad de los informes médicos sobre personas que han intentado suicidarse. Rev Psiquiatr salud Ment. 2010;3: 13-8.

- Mittendorfer E, Schmidtke A. Suicide attempts in Europe. In: Wasserman D, Wasserman C, editors. Oxford Textbook of suicidology and suicide prevention. Oxford: Oxford University Press; 2009 Mar 26.

- Mittendorfer-Rutz E, Rasmussen F, Wasserman D. Familial clustering of suicidal behaviour and psychopathology in young suicide attempters. A register-based nested case control study. Soc Psychiatry Psychiatr Epidemiol. 2008 Jan;43(1):28-36. Epub 2007 Oct 12.

- Moix J, Kovacs FM, Martín A, Plana MN, Royuela A; Spanish Back Pain Research Network. Catastrophizing, state anxiety, anger, and depressive symptoms do not correlate with disability when variations of trait anxiety are taken into account. A study of chronic low back pain patients treated in Spanish pain units. Pain Med. 2011 Jul;12(7):1008-17.

- Mollan KR, Smurzynski M, Eron JJ, Daar ES, Campbell TB, Sax PE, Gulick RM, Na L, O'Keefe L, Robertson KR, Tierney C. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014; 161(1):1-10.

- Möller HJ. Suicide, suicidality and suicide prevention in affective disorders.Acta Psychiatr Scand Suppl. 2003 ;(418):73-80. Review.

- Morales ML, Jiménez IA. El suicidio desde la perspectiva forense. Revista colombiana de psiquiatría. 1996;25, 29-37.

- Mouzo J. Los suicidios aumentan un 45% desde el inicio de la crisis. El País [Internet]. 2015 May 28. Available from: http://ccaa.elpais.com/ccaa/2015/05/28/catalunya/1432813015190553.html

- Muehlenkamp JJ, Ertelt TW, Miller AL, Claes L. Borderline personality symptoms differentiate non-suicidal and suicidal self-injury in ethnically diverse adolescent outpatients. J Child Psychol Psychiatry. 2011 Feb;52(2):148-55.

- Mula M, Sander JW. Suicide and epilepsy: do antiepileptic drugs increase the risk? Expert Opin Drug Saf 2015; 14(4):553-8.

- Murphy GE, Wetzel RD, Robins E, McEvoy L. Multiple risk factors predict suicide in alcoholism. Arch Gen Psychiatry. 1992 Jun;49(6):459-63.

- Neale G, Smith AJ. Self-harm and suicide associated with benzodiazepine usage. Br J Gen Pract. 2007 May;57(538):407-8.

- Neeleman J. Suicidality. Ned Tijdschr Geneeskd. 2001 Mar 17;145(11):515-20. Review. Dutch.

- Nilsson L, Ahlbom A, Farahmand BY, Asberg M, Tomson T. Risk factors for suicide in epilepsy: a case control study. Epilepsia 2002; 43: 644-51.

- Nishiyama A, Matsumoto H. Quetiapine reduces irritability and risk of suicide in patients with agitated depression. Tokai J Exp Clin Med. 2013 Jul 20;38(2):93-6.

- Nock MK, Kessler RC. Prevalence of and risk factors for suicide attempts versus suicide gestures: analysis of the National Comorbidity Survey. J Abnorm Psychol. 2006 Aug;115(3):616-23.

- Nock MK, Prinstein MJ, Sterba SK. Revealing the form and function of self-injurious thoughts and behaviors: A real-time ecological assessment study among adolescents and young adults. J Abnorm Psychol. 2009 Nov;118(4):816-27.

- O'Carroll PW, Berman AL, Maris RW, Moscicki EK, Tanney BL, Silverman MM. Beyond the Tower of Babel: a nomenclature for suicidology. Suicide Life Threat Behav. 1996 Fall;26(3):237-52.

- OCDE. Health Status. Suicide rates [Internet]. 2013. Available from: https://data.oecd.org/healthstat/suicide-rates.htm

- OCDE. Health Status. Suicide rates [Internet]. 2013. Available from: http://www.oecdilibrary.org/docserver/download/3012021ec097.pdf?expires=1438978523&id=id&accname=guest&checksum=752FDF58EF52A3C09AFF3A2D2E60CFBB

- Ochsner KN, Gross JJ. The cognitive control of emotion. Trends Cogn Sci. 2005 May;9(5):242-9.

- Olfson M, Marcus SC, Druss BG. Effects of Food and Drug Administration warnings on antidepressant use in a national sample. Arch Gen Psychiatry. 2008. Jan;65(1):94-101.

- Olié E, Courtet P, Poulain V, Guillaume S, Ritchie K, Artero S. History of suicidal behaviour and analgesic use in community-dwelling elderly. Psychother Psychosom. 2013;82(5):341-3.

- Olié E, Picot MC, Guillaume S, Abbar M, Courtet P. Measurement of total serum cholesterol in the evaluation of suicidal risk. J Affect Disord. 2011 Sep;133(1-2):234-8 .

- Olmer A, Iancu I, Strous RD. Exposure to antidepressant medications and suicide attempts in adult depressed inpatients. J Nerv Ment Dis. 2012 Jun; 200(6):531-4.

- Oquendo MA, Currier D. Can novel nosological strategies aid in the identification of risk for suicidal behavior? Crisis. 2009;30(4):171-3.

- Palmer BA, Pankratz VS, Bostwick JM. The lifetime risk of suicide in schizophrenia: a reexamination. Arch Gen Psychiatry. 2005 Mar;62(3):247-53.

- Pandey GN, Pandey SC, Janicak PG, Marks RC, Davis JM. Platelet serotonin-2 receptor binding sites in depression and suicide. Biol Psychiatry. 1990 Aug 1;28(3):215-22.

- Patorno E, Bohn RL, Wahl PM, Avorn J, Patrick AR, Liu J, Schneeweiss S. Anticonvulsant medications and the risk of suicide, attempted suicide, or violent death. JAMA 2010; 303:1401-9.

- Pélissolo A, Maniere F, Boutges B, Allouche M, Richard-Berthe C, Corruble E. Anxiety and depressive disorders in 4,425 long term benzodiazepine users in general practice]. Encephale. 2007 Jan-Feb;33(1):32-8.

- Perlis RH, Beasley CM Jr, Wines JD Jr, Tamura RN, Cusin C, Shear D, Amsterdam J, Quitkin F, Strong RE, Rosenbaum JF, Fava M. Treatment-associated suicidal ideation and adverse effects in an open, multicenter trial of fluoxetine for major depressive episodes. Psychother Psychosom. 2007;76(1):40-6.

- Pinto OC, Akiskal HS. Lamotrigine as a promising approach to borderline personality: an open case series without concurrent DSM-IV major mood disorder. J Affect Disord. 1998 Dec; 51(3):333-43.

- Pirkola SP, Isometsä ET, Heikkinen ME, Lönnqvist JK. Suicides of alcohol misusers and non-misusers in a nationwide population. Alcohol Alcohol. 2000 Jan;35(1):70-5.

- Pitman A, Krysinska K, Osborn D, King M. Suicide in young men. Lancet. 2012; 379:2383–2392.

- Platt S. Unemployment and suicidal behaviour: a review of the literature. Soc Sci Med. 1984; 19(2):93-115.

- Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in borderline personality disorder: a meta-analysis. Nord J Psychiatry. 2005;59(5):319-24.

- Pompili M, Girardi P, Ruberto A, Tatarelli R. Suicide in the epilepsies: a meta-analytic investigation of 29 cohorts. Epilepsy Behav. 2005 Sep;7(2):305-10.

- Pompili M, Girardi P, Tatarelli G, Ruberto A, Tatarelli R. Suicide and attempted suicide in eating disorders, obesity and weight-image concern. Eat Behav. 2006 Nov;7(4):384-94. Epub 2006 Jan 23.

– Pompili M, Innamorati M, Masotti V, Personnè F, Lester D, Di Vittorio C, Tatarelli R, Girardi P, Amore M. Suicide in the elderly: a psychological autopsy study in a North Italy area (1994-2004). Am J Geriatr Psychiatry. 2008 Sep;16(9):727-35.

– Pompili M, Vanacore N, Macone S, Amore M, Petriconi G, Tonna M, Sasso E, Lester D, Innamorati M, Gazzella S, Di Bonaventura C, Giallonardo A, Girardi P, Tatarelli R, De Pisa E. Depression, hopelessness and suicide risk among patients suffering from epilepsy. Ann Ist Super Sanita. 2007;43(4):425-9.

– Practice guideline and resources for the assessment and treatment of patients with suicidal behaviors [Internet]. 2003. Arlington, VA: American Psychiatric Association. Retrieved July 2, 2008. Available from: http://www.psychiatryonline.com/pracGuide/pracGuideHome.aspx

– Practice guideline for the assessment and treatment of patients with suicidal behaviors. Am J Psychiatry. 2003 Nov;160(11 Suppl):1-60. Review. Erratum in: Am J Psychiatry. American Psychiatric Association. 2004 Apr; 161(4):776.

– Practice guidelines for the treatment of psychiatric disorders, Washington, D. C., and American Psychiatric Association 2002.

– Prigerson HG, Slimack MJ. Gender differences in clinical correlates of suicidality among young adults. J Nerv Ment Dis. 1999 Jan;187(1):23-31.

– Pugh MJ, Hesdorffer D, Wang CP, Amuan ME, Tabares JV, Finley EP, Cramer JA, Kanner AM, Bryan CJ. Temporal trends in new exposure to antiepileptic drug monotherapy and suicide-related behavior. Neurology. 2013 Nov 26; 81(22):1900-6.

– Qin P, Agerbo E, Westergård-Nielsen N, Eriksson T, Mortensen PB. Gender differences in risk factors for suicide in Denmark. Br J Psychiatry. 2000 Dec; 177:546-50.

– Qin P, Mortensen PB. The impact of parental status on the risk of completed suicide. Arch Gen Psychiatry. 2003 Aug;60(8):797-802.

– Raja M, Raja S. Clozapine safety, 40 years later. Curr Drug Saf. 2014;9(3):163-95. Review.

– Rasic D, Weerasinghe S, Asbridge M, Langille DB. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. Drug Alcohol Depend. 2013 Apr 1; 129(1-2):49-53.

–Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. Clin J Pain. 2008 Mar-Apr; 24(3):204-10.

–Reutfors J, Bahmanyar S, Jönsson EG, Brandt L, Bodén R, Ekbom A, Osby U.Medication and suicide risk in schizophrenia: a nested case-control study. Schizophr Res. 2013 Nov; 150(2-3):416-20.

–Ribeiro SC, Kennedy SE, Smith YR, Stohler CS, Zubieta JK. Interface of physical and emotional stress regulation through the endogenous opioid system and mu-opioid receptors. Prog Neuropsychopharmacol Biol Psychiatry. 2005 Dec;29(8):1264-80.

–Rich CL, Warstadt GM, Nemiroff RA, Fowler RC, Young D. Suicide, stressors, and the life cycle. Am J Psychiatry. 1991 Apr;148(4):524-7. Erratum in: Am J Psychiatry 1991 Jul;148(7):960.

–Rihmer Z, Gonda X, Kálmán J. Treatment of bipolar disorder with lamotrigine relapse rate and suicidal behaviour during 6 month follow-up. Neuropsychopharmacol Hung. 2015 Mar;17(1):7-13.

–Ringbäck Weitoft G, Berglund M, Lindström EA, Nilsson M, Salmi P, Rosén M. Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden-a register-based study. Pharmacoepidemiol Drug Saf. 2014 Mar;23(3):290-8.

–Ritsner M, Modai I, Gibel A, Leschiner S, Silver H, Tsinovoy G, Weizman A, Gavish M. Decreased platelet peripheral-type benzodiazepine receptors in persistently violent schizophrenia patients. J Psychiatr Res. 2003 Nov-Dec;37(6):549-56.

–Rives W. Emergency department assessment of suicidal patients. Psychiatr Clin North Am. 1999 Dec;22(4):779-87, viii. Review.

–Roth-Deri I, Green-Sadan T, Yadid G. Beta-endorphin and drug-induced reward and reinforcement. Prog Neurobiol. 2008 Sep;86(1):1-21.

–Rouillon F, Phillips R, Serrurier D, Ansart E, Gérard MJ. [Recurrence of unipolar depression and efficacy of maprotiline]. Encephale. 1989 Nov-Dec;15(6):527-34.

–Roy A, Segal NL, Sarchiapone M. Attempted suicide among living co-twins of twin suicide victims. Am J Psychiatry. 1995 Jul;152(7):1075-6.

–Roy A. Family history of suicide. Arch Gen Psychiatry. 1983 Sep; 40(9):971-4.

–Roy A. Genetic factors in suicide. Psychopharmacol Bull. 1986;22(3):666-8.

–Ruengorn C, Sanichwankul K, Niwatananun W, Mahatnirunkul S, Pumpaisalchai W, Patumanond J. Factors related to suicide attempts among individuals with major depressive disorder. Int J Gen Med. 2012;5:323-30.

–Sachs GS, Yan LJ, Swann AC, Allen MH. Integration of suicide prevention into outpatient management of bipolar disorder. J Clin Psychiatry. 2001; 62(suppl 25): 3-11.

–Saiz PA, García-Portilla P, Paredes B, Corcoran P, Arango C, Morales B, Sotomayor E, Alvarez V, Coto E, Flórez G, Bascaran MT, Bousoño M, Bobes J. Role of serotonergic-related systems in suicidal behavior: Data from a case-control association study. Prog Neuropsychopharmacol Biol Psychiatry. 2011 Aug 1;35(6):1518-24.

–Sakinofsky I. Treating suicidality in depressive illness. Part 2: does treatment cure or cause suicidality? Can J Psychiatry. 2007 Jun;52(6 Suppl 1):85S-101S.

–Sakinofsky I. Treating suicidality in depressive illness. Part I: current controversies. Can J Psychiatry. 2007 Jun;52(6 Suppl 1):71S-84S. Review.

–Sanmartín OR. La cifra de suicidios crece en España por tercer año consecutivo. El Mundo [Internet]. 2015 Feb 27. Available from: http://www.elmundo.es/espana/2015/02/27/54f0cff4e2704ef9158b4573.html

–Sarró B y de la Cruz C. Los suicidios. Martínez Roca, Barcelona, 1991.

–Scherrer JF, Grant JD, Agrawal A, Madden PA, Fu Q, Jacob T, Bucholz KK, Xian H. Suicidal behavior, smoking, and familial vulnerability. Nicotine Tob Res. 2012 Apr; 14(4):415-24.

–Schmidtke A, Bille-Brahe U, DeLeo D, Kerkhof A, Bjerke T, Crepet P, Haring C, Hawton K, Lönnqvist J, Michel K, Pommereau X, Querejeta I, Phillipe I, Salander-Renberg E, Temesváry B, Wasserman D, Fricke S, Weinacker B, Sampaio-Faria JG. Attempted suicide in Europe: rates, trends and sociodemographic characteristics of suicide attempters during the period 1989-1992. Results of the WHO/EURO Multicentre Study on Parasuicide. Acta Psychiatr Scand. 1996 May;93(5):327-38.

–Schneeweiss S, Patrick AR, Solomon DH, Mehta J, Dormuth C, Miller M, Lee JC, Wang PS. Variation in the risk of suicide attempts and completed suicides by antidepressant agent in adults: a propensity score-adjusted analysis of 9 years' data. Arch Gen Psychiatry. 2010 May;67(5):497-506.

–Schumock GT, Stayner LT, Valuck RJ, Joo MJ, Gibbons RD, Lee TA. Risk of suicide attempt in asthmatic children and young adults prescribed leuko-

triene-modifying agents: a nested case-control study. J Allergy Clin Immunol. 2012 Aug; 130(2):368-75.

–Scott KM, Hwang I, Chiu WT, Kessler RC, Sampson NA, Angermeyer M, Beautrais A, Borges G, Bruffaerts R, de Graaf R, Florescu S, Fukao A, Haro JM, Hu C, Kovess V, Levinson D, Posada-Villa J, Scocco P, Nock MK. Chronic physical conditions and their association with first onset of suicidal behavior in the world mental health surveys. Psychosom Med. 2010 Sep;72(7):712-9.

–Shaffer D, Fisher P, Hicks RH, Parides M, Gould M. Sexual orientation in adolescents who commit suicide. Suicide Life Threat Behav. 1995;25 Suppl:64-71. Erratum in: Suicide Life Threat Behav 1996 Summer;26(2):218.

–Shah A. Are elderly dependency ratios associated with general population suicide rates? Int J Soc Psychiatry. 2011 May; 57(3):277-83.

–Sharp SC, Hellings JA. Efficacy and safety of selective serotonin reuptake inhibitors in the treatment of depression in children and adolescents: practitioner review. Clin Drug Investig. 2006;26(5):247-55.

–Sher L, Stanley BH. The role of endogenous opioids in the pathophysiology of self-injurious and suicidal behavior. Arch Suicide Res. 2008;12(4):299-308 .

–Shneidman ES, Farberow NL, Litman RE. The Psychology of Suicide. New York: Science House; 1970.

–Shneidman ES. Perturbation and lethality as precursors of suicide in a gifted group. Suicide Life-Threatening Behavior 1971; 1: 23-35.

–Shneidman ES. Suicidio. In: Freedman AM, Kaplan HI, Sadock BJ, editors. Tratado de Psiquiatría, tomo 2. Barcelona: Salvat editores, S.A.; 1982.

–Silverman MM. The language of suicidology. Suicide Life Threat Behav. 2006 Oct;36(5):519-32. Review.

–Simkin S, Hawton K, Kapur N, Gunnell D. What can be done to reduce mortality from paracetamol overdoses? A patient interview study. QJM. 2012 Jan; 105(1):41-51.

–Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Psychiatry. 2007 Jul; 164(7):1029-34.

–Skegg K. Self-harm. Lancet. 2005 Oct 22-28;366(9495):1471-83.

–Soloff PH, George A, Nathan RS, Schulz PM, Perel JM. Behavioral dyscontrol in borderline patients treated with amitriptyline. Psychopharmacol Bull.1987;23(1):177-81.

–Stahl SM. Anticonvulsants as anxiolytics, part 1: tiagabine and other anticonvulsants with actions on GABA. J Clin Psychiatry. 2004 Mar;65(3):291-2.

–Stanley IH, Hom MA, Joiner TE. Mental Health Service Use Among Adults With Suicide Ideation, Plans, or Attempts: Results From a National Survey. Psychiatr Serv. 2015 Jul 15.

–Statham DJ, Heath AC, Madden PA, Bucholz KK, Bierut L, Dinwiddie SH, Slutske WS, Dunne MP, Martin NG. Suicidal behaviour: an epidemiological and genetic study. Psychol Med. 1998 Jul;28(4):839-55.

–Stein DJ, Simeon D, Frenkel M, Islam MN, Hollander E. An open trial of valproate in borderline personality disorder. J Clin Psychiatry. 1995 Nov;56(11):506-10.

–Stenager EN, Stenager E, Jensen K. Attempted suicide, depression and physical diseases: a 1-year follow-up study. Psychother Psychosom. 1994;61(1-2):65-73.

–Stenager EN, Stenager E. Physical illness and suicidal behaviour. Hawton K, Van Heeringen K. editors. The international Handbook of Suicide and Attempted Suicide. Chichester: John Wiley & Sons; 2000. pp. 405-20.

–Strack S, Millon T. Contributions to the dimensional assessment of personality disorders using Millon's model and the Millon Clinical Multiaxial Inventory (MCMI9-III). J Pers Assess. 2007 Aug;89(1):56-69.

–Stuckler D, Basu S, Suhrcke M, Coutts A, McKee M. Effects of the 2008 recession on health: a first look at European data. Lancet. 2011 Jul 9; 378(9786):124-5.

–Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. BMJ. 2010 Nov 11; 341:c5812.

–Suokas J, Suominen K, Isometsä E, Ostamo A, Lönnqvist J. Long-term risk factors for suicide mortality after attempted suicide--findings of a 14-year follow-up study. Acta Psychiatr Scand. 2001 Aug; 104(2):117-21.

–Tang NK, Crane C. Suicidality in chronic pain: a review of the prevalence, risk factors and psychological links. Psychol Med. 2006 May;36(5):575-86.

- Camiñas T. Una organización de consumidores pide la retirada de un somnífero del mercado [Internet]. El País. 1989 Jan 5.Available from: http://elpais.com/diario/1989/01/05/sociedad/599958004_850215.html Acceso, 13 de septiembre de 2015.
- Tauscher-Wisniewski S, Nilsson M, Caldwell C, Plewes J, Allen AJ. Meta-analysis of aggression and/or hostility-related events in children and adolescents treated with fluoxetine compared with placebo. J Child Adolesc Psychopharmacol. 2007 Oct;17(5):713-8.
- Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Saf. 1993 Mar;8(3):186-212.
- Termorshuizen F, Palmen SJ, Heerdink ER. Suicide behavior before and after the start with antidepressants: a high persistent risk in the first month of treatment among the young. Int J Neuropsychopharmacol. 2015 Jul 18.
- Thomas KH, Martin RM, Davies NM, Metcalfe C, Windmeijer F, Gunnell D. Smoking cessation treatment and risk of depression, suicide, and self-harm in the Clinical Practice Research Datalink: prospective cohort study. BMJ. 2013 Oct 11; 347:f5704.
- Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry. 2006 Dec;63(12):1358-67.
- Toffol E, Hätönen T, Tanskanen A, Lönnqvist J, Wahlbeck K, Joffe G, Tiihonen J, Haukka J, Partonen T. Lithium is associated with decrease in all-cause and suicide mortality in high-risk bipolar patients: A nationwide registry-based prospective cohort study. J Affect Disord 2015; 183:159-65.
- Tsuang MT. Risk of suicide in the relatives of schizophrenics, manics, depressives, and controls. J Clin Psychiatry. 1983 Nov;44(11):396-7, 398-400.
- Tubaishat A, Tawalbeh LI, AlAzzam M, AlBashtawy M, Batiha AM. Electronic versus paper records: documentation of pressure ulcer data. Br J Nurs. 2015 Mar 26-Apr 8;24(6):S30, S32, S34-7.
- Turvey CL, Conwell Y, Jones MP, Phillips C, Simonsick E, Pearson JL, Wallace R. Risk factors for late-life suicide: a prospective, community-based study. Am J Geriatr Psychiatry. 2002 Jul-Aug;10(4):398-406.
- U.S. Department of Health and Human Services. Mental Health: A Report of the Surgeon General-Executive Summary, Rockville, MD. 1999.
- U.S. Food and Drug Administration. Information for healthcare professionals: suicidal behavior and ideation and antiepileptic drugs. 2008.

- Ulcickas Yood M, Delorenze G, Quesenberry CP Jr, Tsai AL, Phillips S, Willey VJ, Niemcryk SJ, Wells K, Skovron ML, Cziraky MJ, Carson W, Oliveria SA. Epidemiologic study of aripiprazole use and the incidence of suicide events. Pharmacoepidemiol Drug Saf. 2010 Nov;19(11):1124-30.
- Vijayakumar L, Kumar MS, Vijayakumar V. Substance use and suicide. Curr Opin Psychiatry. 2011 May;24(3):197-202.
- Waern M, Rubenowitz E, Runeson B, Skoog I, Wilhelmson K, Allebeck P. Burden of illness and suicide in elderly people: case-control study. BMJ. 2002 Jun 8;324(7350):1355.
- Warshaw MG, Dolan RT, Keller MB. Suicidal behavior in patients with current or past panic disorder: five years of prospective data from the Harvard/Brown Anxiety Research Program. Am J Psychiatry. 2000 Nov;157(11):1876-8.
- Wasserman D, Rihmer Z, Rujescu D, Sarchiapone M, Sokolowski M, Titelman D, Zalsman G, Zemishlany Z, Carli V. The European Psychiatric Association (EPA) guidance on suicide treatment and prevention. Neuropsychopharmacol Hung. 2012 Jun;14(2):113-36.
- Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, Frisher M. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. BMJ. 2014 Mar 19; 348:g1996.
- Weissman MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks. N Engl J Med. 1989 Nov 2;321(18):1209-14.
- Welcher B, Rubin P, Nordentoft M. Admission of self-poisoned patients during one year at the Poisoning Treatment Centre, Copenhagen, Denmark. Acta PsychiatrScand Suppl. 1993;371:38-44.
- Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. Drug Alcohol Depend. 2004 Dec 7;76 Suppl:S11-9. Review.
- Wong PW, Chan WS, Chen EY, Chan SS, Law YW, Yip PS. Suicide among adults aged 30-49: a psychological autopsy study in Hong Kong. BMC Public Health. 2008 May 1;8:147.
- World Health Organization. International Classification of Diseases (ICD 9), WHO. 1998.
- World Health Organization. Preventing suicide: A global imperative [Internet]. 2014 Available from: http://apps.who.int/iris/bitstream/10665/131056/1/9789241564779_eng.pdf

- World Health Organization. Public health actions for the prevention of suicide: A framework [Internet]. 2012. Accessed November 12, 2014. Available from: http://apps.who.int/iris/bitstream/10665/75166/1/9789241503570_eng.pdf

- World Health Organization. Suicide data [Internet]. 2014. Available from: http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/

- Wyder M, Ward P, De Leo D. Separation as a suicide risk factor. J Affect Disord. 2009 Aug; 116(3):208-13.

- Yaworski D, Robinson J, Sareen J, Bolton JM. The relation between nicotine dependence and suicide attempts in the general population. Can J Psychiatry. 2011 Mar; 56(3):161-70.

- Ye L, Kadia S, Lippmann S. Topiramate and compulsive buying disorder. J Clin Psychopharmacol. 2014 Feb; 34(1):174-5.

- Yerevanian BI, Choi YM. Impact of psychotropic drugs on suicide and suicidal behaviors. Bipolar Disord. 2013 Aug; 15(5):594-621.

- Yi SW, Hong JS. Depressive symptoms and other risk factors predicting suicide in middle-aged men: a prospective cohort study among Korean Vietnam War veterans. PeerJ. 2015 Jul 2; 3:e1071.

- Zahl PH, De Leo D, Ekeberg Ø, Hjelmeland H, Dieserud G. The relationship between sales of SSRI, TCA and suicide rates in the Nordic countries. BMC Psychiatry. 2010 Aug 6; 10:62.

- Zhang J, McKeown RE, Hussey JR, Thompson SJ, Woods JR. Gender differences in risk factors for attempted suicide among young adults: findings from the Third National Health and Nutrition Examination Survey. Ann Epidemiol. 2005 Feb;15(2):167-74.

- Zouk H, Tousignant M, Seguin M, Lesage A, Turecki G. Characterization of impulsivity in suicide completers: clinical, behavioral and psychosocial dimensions. J Affect Disord. 2006 Jun;92(2-3):195-204.

- Zubieta JK, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, Meyer CR, Koeppe RA, Stohler CS. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science. 2001 Jul 13;293(5528):311-5.

# 8. Appendices

# 8. Appendices

## *8.1. Theories about suicide*

### 8.1.1. Biological models

#### *8.1.1.1. Genetic hypotheses*

Nearly half of the patients whose families have had a suicide case have also attempted suicide. (Roy A, 1983). As well as the psychological mechanisms that could justify this fact (e.g. identification with the suicidal patient), genetic factors have been put forward. The process by which suicidal conduct would be transmitted could be the transmission of the psychiatric base illness or the existence of a heritability of the suicidal behaviour (Egeland JA et al., 1985; Roy A, 1986). The studies conducted, especially with twins, in the Amish population in the USA or adopted ones have not cleared the doubts between heritability or imitation so as to explain the results.

#### *8.1.1.2. Neurochemical hypotheses*

Suicidal behaviour is often attributed to serotonin as a neurotransmittor connected with this type of conduct. Several proceedings have found a deficit of this substance (postmortem tests, measurement of 5-Hydroxyindolacetic acid (5-HIAA) in

the Cerebrospinal Fluid (CSF), platelet tests and neuroendocrine tests). A decreased amount of 5-HIAA in the CSF has been linked with the violence of the suicide act and some authors have also linked it with low impulse control, which is consistent with similar findings in other related diagnoses (Bobes García J et al., 1996). Another line with a great deal of biological research is connected with the hypothalamus-pituitary-suprarenal axis. 17-hydroxycorticosteroids and free cortisol in urine, or cortisol in blood or in the CSF have been measured. On the other hand, several studies have observed that the patients who have tried to take their lives had lower levels of cholesterol in plasma (Marcinko D et al., 2007; Brunner J et al., 2002; Golier JA et al., 1995; Hawthon K et al., 1993). Consequently, cholesterol level in serum might be a risk factor in patients with depressive symptoms (Olié E et al., 2011).

### *8.1.2. Psychological models*

#### *8.1.2.1. Psychoanalytic theories*

Freud placed the problem of suicide in the centre of the human soul. In *Mourning and Melancholia* (Freud S, 1917) he describes suicidal impulses as homicidal, aimed at the object loved previously introjected. Karl Menninger reproduced Freud's

concepts on suicide. (Menninger K, 1938). He highlighted three hostile pulsions present in suicide: the wish to kill, the wish to be killed and the wish to die. For Litman, there are other factors to take into account apart from hostility: guilt, anxiety, dependence (Litman RE, 1967).

#### *8.1.2.2. Psychosocial theories*

Although not unique, Emile Durkheim's theories are a decisive contribution from the field of sociology to the understanding of the suicide phenomenon. His studies in the 19th Century, among the modern investigations on the topic, are groundbreaking. He has had an influence on all modern studies, even from different standpoints. For Durkheim, already in 1897 (Durkheim E, 1982), suicide is ruled by the interaction between society and the individual. He distinguishes three main types of suicide, depending on the relationship between man and environment. In altruistic suicide, individuals decide to put an end to their lives for the benefit of society and certain rules and situations that so demand it: to carry on with life would be unacceptable (‘hara-kiri’ would be an example of this). Egotistical suicide, on the contrary, is an individual decision against society, whose norms they do not reach. This would

explain why suicide is more frequent among single people. Anomic suicide responds more to the abrupt breakdown of the mechanism that maintains the person integrated into society, the loss of habitual rules: suicides after economic catastrophes, for instance (Schmidtke A et al., 1996).

### *8.2. Evaluation of the suicidal patient*

Confronting a person with suicide ideas or who has attempted suicide provokes psychic discomfort in the professionals. They have to handle such discomfort because most of the times this will interfere with the treatment. As a result, it is important to hightlight several mistakes which are common in dealing with suicidal persons in order to avoid them (Table 9).

In spite of the fact that it is not easy to create an adequate atmosphere for dialogue in the context of an Emergency Unit or Primary Care Centre, the most important thing is to create an adequate setting, a peaceful atmosphere, without interruptions, where the patient can feel confident and safe.

Table 10; Mistakes about suicide

| |
|---|
| All suicides are mentally ill |
| Those who talk about killing themselves do not carry it out |
| It is good to have a patronizing or moralistic attitude |
| It is not bad to get infected by the sick person’s pessimism |
| One should not ask questions about suicidal ideation |
| Manipulative efforts should not be taken seriously |

### *8.2.1. Anamnesis and exploration*

When the patient is ready to take the interview, psychopathological exploration should take place. It is advisable to let the patient talk. In order to achieve this, open questions, not hurtful, must be asked but without avoiding diving into the suicidal ideation or act. The following paragraghs are dedicated to reasonable steps to take. Initially, the patient's conventional medical history must be obtained, with special interest in the data considered risk factors (e.g. chronic or disabling organic illnesses) (Kaplan HI et al., 1999). Besides, a detailed psychiatric history will be written, searching for the psychiatric diagnoses which are most closely associated with the suicide acts, especially depression. The suicidal behaviour or ideation

originates from some psychic, existential, familial or social crisis, if not psychiatric. It is fundamental to know the circumstances which trigger the attempt. It is also crucial to know the suicidal behaviour, if it takes place, in detail and particularly important to identify any psychosocial crisis, so often associated with suicide attempts, especially 'dyadic' crises (e.g. with a love partner o a parent) that might precipitate the act. Psychopathological exploration, in the case of persons with suicidal intent, pursues the exploration of the autolythic ideation. Much could be said about this but, in order to provide a clear scheme, we will follow Clark and Fawcett's work (Clark DC et al., 1992). These authors classify suicidal patients in accordance with the immediacy of the suicide act: the lowest risk is assigned to those who do not have suicide thoughts. A greater risk is assigned to those who have passive ideation (they wish to die), even more risk for those who have active ideation (they wish to kill themselves) and finally, the highest risk is assigned to those who think about a method to consummate suicide. It seems interesting to include here the recommendations of the World Health Organization in the CIE-10 for primary care, for the correct assessment of the suicide patient (WHO CIE 10, 1996):

**1. Evaluation of the suicide risk in an immediate future:**

a) Suicide ideation (sporadic against persistent)
b) Intent (the suicide is a possibility or the patient has already decided it?)
c) Suicide plan (the more elaborate the plan, the greater the risk and even more so if resources are available).
d) Loneliness (poor family or social support).
e) Alcohol (it limits self-control).
f) Social difficulties (marginalization, unemployment, Durkheim's anomy)

**2. Evaluation of a patient with a recent suicide attempt:**

a) ¿Was the chosen method dangerous?
b) ¿Did the patient believe that the method was going to work? ¿Were they surprised to have survived?
c) ¿Was it possible to be discovered?
d) ¿Were they relieved to be saved?
e) ¿Was the patient trying to get a message across or did they only want to die?
f) ¿Was it an impulsive or planned attempt?
g) ¿Have the life and psychological circumstances that determined the attempt changed?

A correct assessment of a suicidal patient must include an interview with the family or persons who are important to the patient. In that interview, data of the previous history of the patient, their psychopathology and the attempt details, if this has taken place, must be collected. Of course, it is necessary to try to obtain the family's cooperation, if an outpatient treatment is required.

### *8.2.2. Assessment of suicide risk*

From a dynamic point of view, we all have, inherently to our nature, suicide wishes to a greater or lesser extent. Thus, any person has contemplated the possibility of committing suicide or has carried out an act that has put their life at risk. However, it cannot be considered that all those persons will commit suicide one day. According to Shneidman, the main aim of evaluating a person with suicide ideas, whether they have attempted it or not, is to determine their lethality, that is, establish the mortality of the suicide ideas or acts (Shneidman ES, 1971). Although there is consensus about the fact that somebody who commits suicide or attempts it is not in a good condition, it is possible that suicide may occur with a minimum of psychic disturbance and, as a result, making it impossible to specify a psychiatric diagnosis. On the other hand, patients undergoing profound psychopathological crises might carry out autolythic attempts of very low lethality. So, when it comes to assessing the patient, it is important to bear in mind that the degree of lethality is not proportional to the type and intensity of psychic disturbance.

In order to assess lethality and suicide risk, one must have a sociodemographic and behavioural profile connected with a

higher risk in accordance with the associated risk factors. In spite of the fact that the professional must consider the data present in the patient which are statistically associated with a higher suicide risk, they must always consider that the intrapsychic factors are predominant when it comes to assessing the patient's vulnerability (Buda M et al., 1990). As Rives says, the evaluation of these patients is an art and cannot be reduced to a list (Rives W, 1999). Bearing this in mind, the person with more dangerous suicide ideation tends to have meditated the decision for long. He also shows signs that the doctor, often from Primary Care Centres or an Emergency Unit, must be able to recognize (Shneidman ES et al., 1970). Normally these persons are very agitated and frequently depressed. Many of them will mention their intentions, invalidating the general belief among many doctors that those who announce it do not execute it. Frequently, there will be changes in the eating, sexual or sleep habits of the patients. Especially alarming is the fact that the patient parts with objects which are very valuable to the person.

It is also interesting to assess the degree of suicide intent. As opposed to the unmistakable determination to commit suicide by some persons and which is of course associated with a high

risk, there are many suicide attempts where the main wish appears to be changing one's own life or that of significant persons more than ending one’s life. The most dangerous psychological characteristics present in suicide ideation are: the short duration of the ‘suicide crisis’ since a sick person might be agitated for a long period of time but will rarely have a high-risk suicide ideation for a long time before either they become exhausted or carry it out; the ambivalence towards the fact of death, often wishing to die and being saved at the same time and the presence of 'another person' and suicide as a dyadic act.

### *8.2.3. Suicide methods*

The suicide methods employed are quite diverse. The greater or lesser lethality of the method often depends on accessibility to the self-harm mechanism. Consequently, restricton of access to the most common suicide methods constitutes a necessary and useful prevention tool (Ajdacic-Gross et al., 2007). Some of the most commonly used methods are: precipitation, hanging, asphyxia, medication intoxication, gas intoxication (inhalation), poisoning with plants, mushrooms, metals, cleaning products and pesticides, starvation, suspending the prescribed

medication, provoked traffic accidents, throwing oneself in front of vehicles (car, train, lorry...), shot by firearm, bomb in explosive belt, self-immolation, swallowing sharp or cutting objects, self-stabbing or eventration (Maris, Berman and Silverman, 2000; Asociación de Investigación, prevención e Intervención del Suicidio, 2009). In the choice of method to carry out the suicide act, sociocultural and even geographic influence (sea, railway, farming area-pesticides) plays a role since the geographic area is connected with access to tools to facilitate suicide (Morales y Jiménez, 1996). A tendency has been recorded in some countries to replace traditional methods with death by pesticides or gunshot. Pesticides were commonly used in Asian countries and South America whereas medication intoxication was more common in Nordic countries and the United Kingdom. Hanging was the preferred method in Eastern Europe and firearms in the USA and jumping out of a window in cities and urban societies like the Special Administrative Region of Hong Kong, China. Lester (Lester, 1971) classified the methods as active like hanging, precipitation, firearms, knives and passive like gases, drugs or poisons. In the same line, Isometsa et al., (1994) consider suicide by hanging, gunshot, knife, precipitation and train run-over as violent and suicide by

drowning, gases, toxic substances, drugs or poisons as non-violent. Maes y et al. (1994) add as violent the suicides by explosives and sharp instruments while they consider drowning as non-violent. Altamira and other authors (1999) on the other hand include traffic accident within the group of violent suicides and the intake of solid or liquid substances as non-violent methods. The males tend to choose active methods (gunshot, precipitation or hanging) while the females opt for passive methods (poisoning). The method classification as violent or non-violent is in keeping with the impulsivity of the suicide act. A stressful life event might generate a crisis that leads to an impulsive suicide attempt. It is essential in order to create strategies and prevention programmes to have information about the habitual suicide methods.

### *8.2.4. Therapeutic attitude*

The first aim before patients who have hurt themselves is to treat the effect of the aggression. This aspect includes the treatment of the intoxication, whatever it may be, closing the wound in the forearm, etc. Once this is done, the following step is to ensure the patient's safety.

The attitude before a suicidal patient could be the traditional

one between a therapist and a sick person (Shneidman ES, 1982). The doctor may appear more empathic, active, showing their intention to understand the patient's situation. It is no time to appear cold, neutral or critical and it is worth getting involved more than usual. This does not exclude having a firm attitude inspiring confidence (Sarró B et al., 1991). A first diagnosis of the psychiatric illness, if applicable, must have been made. It is therefore compulsory to initiate, recover or correct the psychopharmacological treatment of the illness. The most common drugs are antidepressants (Bousoño García M et al., 1997) since they are effective in order to diminish impulsivity and aggressiveness as well as the depressive mood. It is convenient to choose antidepressants whose hazard level in case of intoxication is lower. The help of the family is a key factor in order to store and administer the medication correctly. In general, any person with suicidal ideation or any type of suicidal conduct should be assessed by a psychiatrist. The period of time in which the doctor should provide psychiatric evaluation, will depend on the clinical characteristics of the patient and the healthcare service possibilities. In a great deal of cases, the suicide act does not seek death and it is of very low lethality. It is the case of the so called “parasuicides” that

can even be a cathartic act which may improve the state of the patient or give rise to a more favourable family or relationship situation. On those occasions the doctor should understand that the urgency of the specialised evaluation does not exist. In cases or greater lethality, the patient should be seen by a psychiatrist urgently. Here, the most important decision is whether or not to hospitalise the patient. On the whole, hospitalisation of the suicidal patient will cause associated problems and besides, the doctor cannot ignore the fact that there will never be enough beds so as to admit any person with suicide ideas. Apart from the evaluation of the suicide risk of the patient and according to all of the above, the main factor to bear in mind in an outpatient treatment is the capacity of the own individual to acquire the commitment to seek assistance if they reach a critical point. It is also important to count on the family's support and important persons for the sick person (Arranz Estévez FJ, 1997).

### *8.2.5. Summary*

As it has been recognized by the World Health Organization, suicide is a major problem of public health. In Spain, where the proportion of suicides has traditionally been low, it is increasing

with the passage of time. There are sociodemographic data statistically related with a higher suicide risk. Men have a higher suicide risk while women have a greater number of attempts. Suicide is more usual in old people and attempt in young people. Single, separated, divorced and widowed people have more suicide risk statistically as well as unemployed people and those with lower education. Suicide is more frequent in the north of Europe and among city dwellers. The most reliable aspect to predict suicide is the presence of previous autolythic attempts. In a high percentage of cases, suicidal people also suffer from organic illnesses with chronic or disabling diseases involving a higher risk. People who try to commit suicide are in a difficult psychic and/or social situation. Although many of them do not suffer from any mental disorder, the majority of those who complete suicide do. The psychiatric disorder which is most frequently diagnosed is major depression. The suicidal phenomenon has been analysed by researchers from every scientific paradigm. Biological investigations have been carried out: genetic studies of various types or neurobiochemical, mainly related to serotonin; psychoanalytic which focus on unconscious aggressiveness; or psychosocial, above all Durkheim’s influential theories. Nowadays the tendency is to

consider ‘multidimensional’ models which try to integrate several theories. In the evaluation of a suicidal patient it is basic to control the anguish that these patients frequently provoke to avoid taking wrong steps. It is necessary to have a complete clinical history, analyse a possible psychopathology previous to the attempt, know the details of the suicidal act if it has been produced and carry out a good psychopathological exploration, paying special attention to the presence and dangerousness of the suicidal ideation. In order to assess and prevent suicidal risk, the doctor will have to evaluate sociodemographic and behavioural data that are statistically associated with a high risk, but without forgetting the lethality of the ideation or the attempt in accordance with the intrapsychic factors of the patient. For this purpose, health professionals should look out for the signs of a possible suicide offered by the patient, the degree of suicidal intent or the existence of the typical psychological characteristics of the suicidal ideation. Family participation is key when it comes to assessing and dealing deal with the patient (Kposowa AJ, 2001). The attitude of the therapist must be empathic, understanding and firm. Once the organic damage, if it exists, has been treated, the main goal is the patient’s safety. Many self-harm acts are not real psychiatric

emergencies and should not be treated as such. If there is a psychiatric disease, it should be treated in the mid and long term. In suicide attempts of high lethality, it is the psychiatrist who should decide if hospitalisation or outpatient treatment is recommended (Stenager EN et al., 1994).

### *8.3. Clinical history*

The development of information systems in health care is modifying certain aspects of the clinical practice, causing changes which will require the participation and consensus of all health care professionals in the future. There is no doubt that the clinical history is a central element of the patient's medical information and a communication channel among the different health professionals caring for the patient. For a number of years, most hospitals have had a very useful tool, a computer-based or electronic clinical history. It is important that the collection of the terminological information in the computer-based clinical history is previously defined in order to process it and make the most of it later on. For the processing of terminological information in the electronic clinical history, there are documentary-based languages which allow to classify and codify every illness. The future tendency is the compilation of

the different documentary-based languages allowing the professional not only to navigate through the clinical history, but also access bibliographical databases and help tools for the decision making. The role of the electronic clinical history for the quality of health care has been the topic of numerous pubications with different results because of methodological problems. The most important beneficial effects are connected with a greater adhesion to the clinical practice guidelines and the decrease of mistakes made in the control of the medication (González E et al., 2007). In a recent study comparing the information collection between the paper histories and the computerised ones, it was observed that, in terms of precision and comprehensiveness, the most complete information was obtained from the electronic records in comparison with the paper records. However, in both types of systems deficiencies were observed in the documentation systems for the studied pathology (Tubaishat A, et al, 2015).

In our study, the computer-based clinical history had all the information relative to the hospital admissions not only in the Psychiatry Unit but also in other medical departments. Besides, it also included the outpatient visits to the specialised assistance practices and a number of visits to Emergency that the patients

had made. Also, not only were the clinical diagnoses included, but also the pharmacological treatments prescribed to every patient. In the case of the patients who had committed a suicide attempt prior to 2005, the paper histories were used. These histories practically included the same information, although the data collection was more laborious.

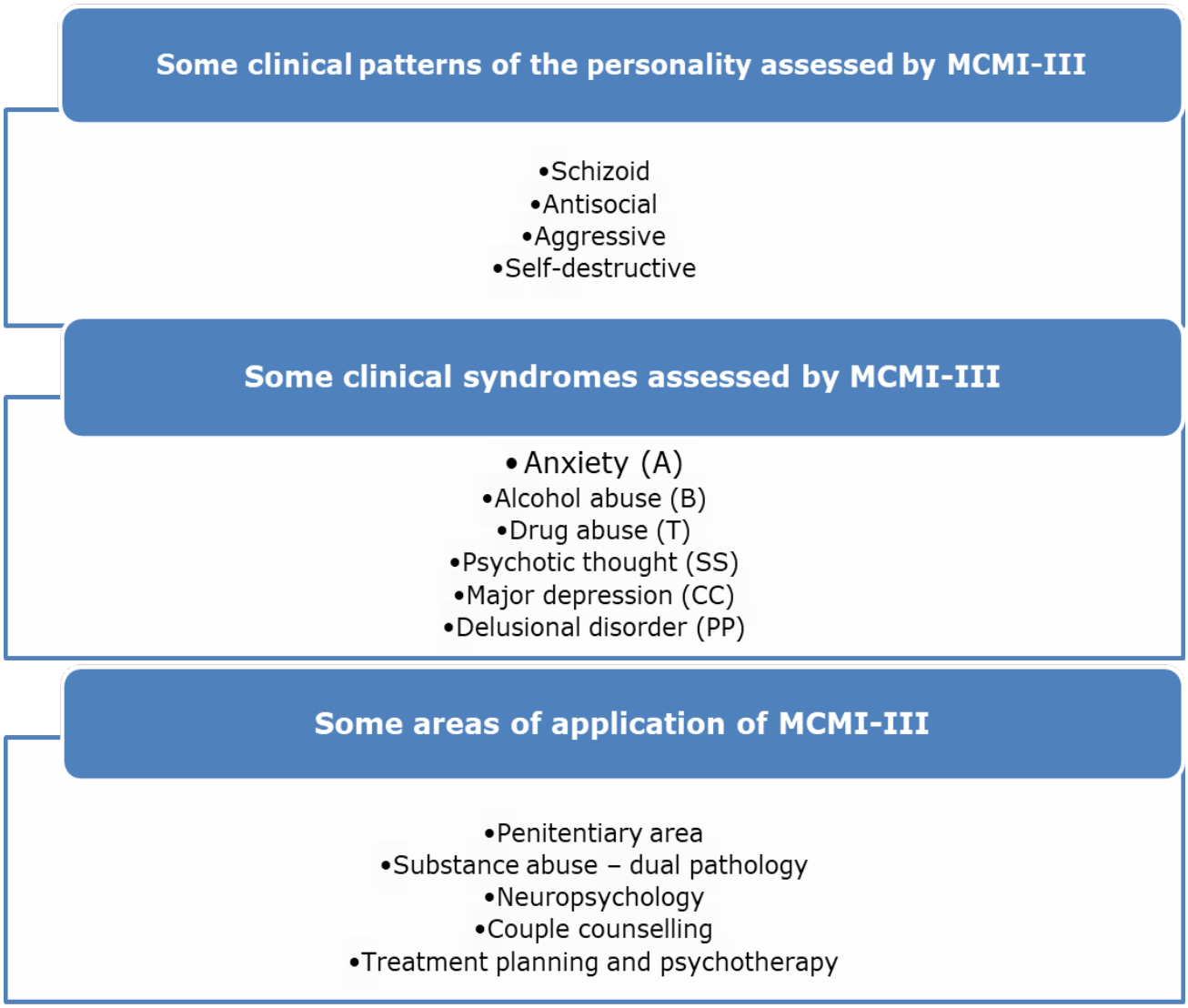
### *8.4. MCMI-III (Millon Multiaxial Clinical Inventory III)*

Theodore Millon (1928-2014) contributed to the study of personality disorders in the DSM-III, a structure which has evolved into the DSM-5. His 1969 book, *Modern Psychopathology,* created a theoretical framework which facilitated the understanding of the known personality prototypes. His theoretical work soon led to the creation of several psychological inventories, Millon Multiaxial Clinical inventory (MCMI), being the best known and most used (Choca JP, et al., 2015). For more than 35 years, the personality model and the MCMI have been very useful resources, used by professionals to understand and assess personality disorders and clinical syndromes in psychiatric patients (Strack S, et al., 2007). The original inventories (MCMI-I; Millon, 1977 and MCMI-II), were gradually refined through theoretical

investigations. The new Millon Clinical Multiaxial Inventory-III (MCMI-III; Millon, 1994) was coordinated even more with the diagnostic scheme of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in an even more explicit way.

The current version of MCMI, the MCMI-III, reinforces these theoretical correspondences, making use of many of the diagnostic criteria of DSM-IV (and current DSM-5) to serve as a basis in the drafting of the inventory articles (Millon T., et al, 1997). MCMI-III provides empirically validated information, relevant and reliable to support the diagnosis of psychiatrists and other mental health professionals in different areas; clinical, medical, forensic, etc.

This questionnaire consists of 4 indices that enable the assessment of the protocol validity and 24 clinical scales grouped in accordance with the level of severity: clinical patterns of the personality, serious pathology of the personality, clinical syndromes and serious clinical syndromes. MCMI-III is not a general personality instrument to be used with healthy individuals or with a different purpose other than psychological evaluation. Neither is it advisable to be used among the adolescent population.




*Source: adapted from MCMI-III, 2014

## *8.5. Additional tables*

Table 11. Previous suicide attempts among the cases

| | | Gender | | | | Total | |
|---|---|---|---|---|---|---|---|
| | | Male | | Female | | | |
| | | N | % | N | % | | |
| Previus attempt yes/no | No | 144 | 79,6% | 89 | 23,5% | 233 | 41,6% |
| | Yes | 37 | 20,4% | 290 | 76,5% | 327 | 58,4% |
| Total | | 181 | 100,0% | 379 | 100,0% | 560 | 100,0% |

Table 12. Personality of the cases (percentage for men and women).

| | | Gender | | | | Total | |
|---|---|---|---|---|---|---|---|
| | | Male | | Female | | | |
| | | N | % | N | % | N | % |
| Personality | Antisocial | 4 | 2.2% | 7 | 1.8% | 11 | 2.0% |
| | Dependent | 29 | 16.0% | 55 | 14.5% | 84 | 15.0% |
| | Schizoid | 10 | 5.5% | 22 | 5.8% | 32 | 5.7% |
| | Schizotypal | 10 | 5.5% | 15 | 4.0% | 25 | 4.5% |
| | Avoidant | 3 | 1.7% | 6 | 1.6% | 9 | 1.6% |
| | Histrionic | 10 | 5.5% | 7 | 1.8% | 17 | 3.0% |
| | Borderline | 107 | 59.1% | 250 | 66.0% | 357 | 63.8% |
| | Narcissist | 1 | 0.6% | 5 | 1.3% | 6 | 1.1% |
| | Obsessive | 3 | 1.7% | 2 | 0.5% | 5 | 0.9% |
| | Paranoid | 4 | 2.2% | 10 | 2.6% | 14 | 2.5% |
| | Total | 181 | 100.0% | 379 | 100.0% | 560 | 100.0% |

Table 13. Suicide methods used by the cases.

| | | Gender | | | | Total | |
|---|---|---|---|---|---|---|---|
| | | Male | | Female | | | |
| | | N | % | N | % | N | % |
| Type of autolythic attempt | Medication Intox. | 84 | 46.4% | 229 | 60.6% | 313 | 56.0% |
| | Defenestration | 12 | 6.6% | 16 | 4.2% | 28 | 5.0% |
| | Self-injury | 56 | 30.9% | 112 | 29.6% | 168 | 30.1% |
| | Gas Intox. | 6 | 3.3% | 11 | 2.9% | 17 | 3.0% |
| | Hanging | 13 | 7.2% | 5 | 1.3% | 18 | 3.2% |
| | Drowning | 2 | 1.1% | 2 | 0.5% | 4 | 0.7% |
| | Others | 8 | 4.4% | 3 | 0.8% | 11 | 2.0% |
| | Total | 181 | 100.0% | 378 | 100.0% | 559 | 100.0% |

## *8.6. Publications related to the study*

- *Fármacos anticonvulsionantes analgésicos y conducta suicida.* Trabajo final de máster en Investigación en Ciencias de Salud. Universidad de Valladolid. Facultad de Medicina, 2012.

- Premio Sancho Valázquez Cuéllar por la comunicación formato póster: "*Psicotropos y comportamiento suicida*" presentada en la VXII Reunión Asociación Castellano Leonesa de Psiquiatría el 19 de octubre de 2012

- *Fármacos y conducta suicida: Estudio de Casos y Controles;* comunicación oral presentada en la VXII Reunión Asociación Castellano Leonesa Psiquiatría del 18 al 20 de octubre de 2012.

- *Fármacos y conducta suicida: un estudio de casos y controles*; Autores: Ana Fructuoso Castellar, Manchón Asenjo MJ, Alfonso Carvajal García-Pando; Antonio Escudero García; Natalia Jimeno Bulnes; Encuentros en psiquiatría, 12 y 13 de abril de 2013.

- *Psychotropics and suicidal behaviour- a case-control study*; European Psychiatry; Volume 28, Supplement 1, 2013, Pages 1; Abstracts of the 21th European Congress of Psychiatry.

- *Personalidad, consumo de fármacos y conducta suicida: un estudio de casos y controles;* Ana Fructuoso Castellar; Alfonso Carvajal García-Pando; Antonio Escudero García; Natalia Jimeno Bulnes; X Congreso Nacional de Personalidad, 23-25 de abril de 2014, Barcelona.

- *Analgesics and suicidal behavior: a case-control study*; Autores: A. Fructuoso Castellar, A. Carvajal García-Pando, A. Escudero García, N. Jimeno Bulnes; XVI World Congress of Psychiatry, 14-18 de septiembre de 2014, Madrid.

- *Suicide attempt and medications. A retrospective case-control study*; Autores: Fructuoso A, Fierro I, Jimeno N, Carvajal A. Centro de estudios sobre la seguridad de los medicamentos (CESME), Universidad de Valladolid (Sevilla, 3 y 4 de octubre de 2014).