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SUICIDE: A PHARMACOEPIDEMIOLOGICAL DATABASE STUDY IN THE REGION FRIULI VENEZIA GIULIA, ITALY

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Suicide and antidepressant use in Friuli Venezia Giulia region, Italy
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my grandfather Giovanni

ABSTRACT

Aims: The objective of this thesis is to examine the relationship between suicide and health care in Italy's Friuli Venezia Giulia (FVG) region. First, it explores the correlation between suicide rates and antidepressant sales. Second, it analyses, at the individual level, the risk of suicide associated with the main suicidal risk factors, such as non-fatal self-harm, psychiatric disorders and somatic disorders. Third, it investigates the differences in suicide risk related to qualitative parameters in the use of antidepressants, such as adherence and treatment modifications. The overall aim is to help improve interventions to prevent suicide.

Methods: All data were retrieved from the FVG Regional Social and Health Information System (SISSR), which links data using a unique anonymous key from different regional databases. Paper I analyses changes in individual-based data on antidepressant use and the rates of suicide during years 1997-2006. The other three papers are designed as case-control studies. All suicides that occurred in the region during years 2002-2008 (Paper II) and 2003-2013 (Paper III) were classified as cases, which were then age- and gender- matched to controls from the general population. In Paper IV, cases and controls from 2005 to 2014 must have had at least one prescription of antidepressant in the 730 days prior to the index date. Regression analysis was used to assess the association between suicide risk and its predictors.

Results: In Paper I, suicide rates decreased by one-third in all genders and age groups. In parallel, both the number of individual users of antidepressant and the number of Defined Daily Doses per patient increased by 5-fold and 7-fold, respectively. In Paper II, the risk of suicide was highly increased by previous self-harm (OR = 53.1 for a single episode and OR = 98. for repeated episodes), as by psychiatric disorders (OR = 19.5). In Paper III, somatic disorders were strong predictors of suicide (OR = 2.9), particularly in case of comorbid disorders (OR from 2.6 to 9.8 when the number of disorders raised from 1 to $\geq$4) and in the elderly (OR = 4.3). No significant risk of suicide was found when medically-ill patients adhere to antidepressants. In Paper IV, none of the antidepressants compounds and classes was associated to suicide except SSRI (OR = 1.6). The association to suicide tended to decrease with adherence or current use of antidepressants. In all studies, on average only 10-20% of suicide cases adhere to antidepressants and 20-40% were currently using them at the time of death.

Conclusions: Our findings support the hypothesis that treatment with antidepressant medication lowers the risk of suicide. The treatment at a proper dosage and for a proper length of time further decreased the risk, particularly in somatic-ill persons. Well-known risk factors, such as non-fatal self-harm and psychiatric and somatic disorders, were confirmed to highly increase the risk of suicide. Only a minority of suicides, however, had adhered to antidepressants or were under antidepressant treatment at the time of death.

LIST OF SCIENTIFIC PAPERS

I. CASTELPIETRA G, Morsanutto A, Pascolo-Fabrici E, Isacsson G; Antidepressant use and suicide prevention: a prescription database study in the region Friuli Venezia Giulia, Italy; Acta Psychiatr Scand, 2008, 118 (5):382-388

II. CASTELPIETRA G, Bovenzi M, Clagnan E, Barbone F, Balestrieri M, Isacsson G Diagnoses and prescriptions of antidepressants in suicides: Register findings from the Friuli Venezia Giulia Region, Italy, 2002–2008; International Journal of Psychiatry in Clinical Practice, 2016, 1-4

III.; CASTELPIETRA G, Gobbato M, Valent F, Bovenzi M, Barbone F, Clagnan E, Pascolo-Fabrici E, Balestrieri M, Isacsson G; Somatic disorders and antidepressant use in suicides: A population-based study from the Friuli Venezia Giulia region, Italy, 2003–2013; Journal of Psychosomatic Research, 2015, 79 (5):372-377

IV. CASTELPIETRA G, Gobbato M, Valent F, De Vido C, Balestrieri M, Isacsson G; Antidepressant use in suicides: A case-control study from the Friuli Venezia Giulia Region, Italy, 200 5-2014; *submitted*

CONTENTS

LIST OF ABBREVIATIONS

FVG	Friuli Venezia Giulia
SISSR	Regional Social and Health Information System
AD	Antidepressant
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic
SNRI	Serotonergic Noradrenergic Reuptake Inhibitor
ICD-9	International Classification of Diseases, 9th revision
GP	General Practitioner
ATC	Anatomical Therapeutic Chemical
DDD	Defined Daily Doses
NHS	National Health System
RR	Relative Risk
OR	Odds Ratio
95% CI	95% Confidence Interval
MPR	Medical Possession Ratio
COPD	Chronic Obstructive Pulmonary Disease
RT-FVG	FVG – Cancer Registry

1 BACKGROUND

The pain and suffering behind every suicide are the reasons why Jamison KR in the book *Night falls fast: understanding suicide*, describes it as “a tragedy”. When I decided to become a psychiatrist, I did not know what the implications of suicide were. The first suicide I had to face was shocking. He was a medical student, around my age, whom I had known for a long time. The pain of his parents and friends was heart-breaking. I was hurt too, but I had to react. I also had to react in all the following deaths by suicide I had to face afterwards. My research on suicide gave me a chance to explore my feelings on the matter. A desire to understand suicide and hopefully contribute to its prevention has driven my work during these PhD years. I am also confident this will occur in my future career.

As recently stated by the World Health Organization (WHO), suicide prevention is “a global imperative”(1). Globally, at least 800,000 individuals voluntarily die every year, but the number is certainly much higher. Registration of suicide deaths is a challenging issue in many countries, due to cultural and religious beliefs and consequent stigmatization. In some countries suicidal behaviours are even illegal. Suicide registration is also complicated, since it is a multilevel procedure that includes medical and legal concerns involving several responsible authorities. Worldwide, however, suicide is included among the main causes of death, particularly in young adults, making it a major public health problem (1).

What should be done to help prevent as many as possible of these deaths? Prevention strategies at the population level include the enforcement of mental health and alcohol use policies, improved access to health services, restricted access to the means of suicide (such as firearms), the promotion of responsible media reporting and increased awareness about mental health, substance use disorders and suicide. The efficacy of these strategies, however, is difficult to assess. Suicide prevention strategies at the individual level are usually directed at subjects with a greater suicidal risk. The main risk factors of suicidal behaviours are well identified and include previous suicide attempts, mental disorders, harmful use of alcohol, chronic somatic conditions and other factors, such as job or financial loss, family history of suicide, genetic and biological factors. Nonetheless, the majority of suicide victims suffer mental disorders (1, 2). Among these disorders, depressive disorders are highly prevalent in the general population (3, 4), and are observed to a great extent in suicide deaths (5). Studies have shown that only a minority of suicide victims receive adequate pharmacological treatment with available medications, such as antidepressants (6). On the other hand, many ecological studies in recent years have observed a decrease in suicide rates that parallels an increase in sales of antidepressants (7-9). Although these studies mainly consider high-income countries, thus preventing a definitive conclusion on a causal relationship, there is growing evidence that proper treatment of depression can be crucial for the prevention of many suicides. In spite of this clear correlation, few studies have analysed antidepressant use in

individual suicides. Fewer still have analysed the relationship between suicidal risk factors, such as psychiatric and somatic disorders, and antidepressant use. The assessment of qualitative parameters of antidepressant use prior to suicide seems also crucial.

1.1 EPIDEMIOLOGY OF SUICIDE

Globally, the total number of deaths by suicide is over 800 000 people annually, accounting for 1-4% of deaths worldwide. Both demographic factors, such as gender and age groups, and geographical variations should be taken into account when studying suicidal behaviour.

Suicide can occur at any point in a person's life, yet takes a particularly large toll on youth. Worldwide, suicide is the second most frequent cause of death among young people aged 15–24 years, though in some regions, such as South-East Asia, it is the leading cause of death in this age group. Suicide attempts are some 20 to 30 times more frequent than completed suicides.

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Males are generally at higher risk of completed suicide, while females are at higher risk of suicide attempts (10). In high-income countries, the risk of completed suicide is three times higher in males than females, while in middle and low-income countries the risk is 1.5 times higher. Nevertheless, there are large differences between regions and between countries (1). Moreover, the risk of suicide usually increases with age. Suicide is extremely rare in children under 12 years old, but suicide incidence increases every year during and after puberty. The absolute and relative rate of suicide in people older than 60 years is higher compared to the general population. The proportion of suicides in older than 75 years is three times higher than in younger. Differences may be found among high-income and low income countries. As an example, high-income countries have greater suicidal rates among young adults and old women (1).

Despite the significant public health problem that suicide poses worldwide, there is evidence to suggest that efforts to curb suicide deaths have met with some success. For example, between 2000 and 2012, the total number of suicides registered worldwide decreased by about 9%, from 883,000 to 804,000, despite the increase of 13.4% in the global population in the same period. The global age-standardized suicide rate (which adjusts for differences in the size and age structure of populations over time) also decreased by 26% (23% in men and 32%

in women) during this 12-year period (1). The WHO has stated that the goal of reducing the 2000 suicide rate by 10% by 2020 might be achievable if this trend can be maintained (11).

1.1.1 The Region Friuli Venezia Giulia, Italy

Italy is a densely populated country with close to 60 million inhabitants. Compared with most other European countries suicide rates are low (5.1 suicides per 100 000 inhabitants in 2010) (12).

Friuli Venezia Giulia (FVG) is a region in the North-East of Italy with 1.2 million inhabitants. Although it had the highest suicide rate of the whole country in 1997 (15.7 suicides per 100,000 inhabitants), a decrease in suicide rates has been observed in recent years (8.4 suicides per 100,000 inhabitants in 2015). Over this nineteen-year period (1997-2015), a decrease in suicide rates in FVG has been observed also in both genders and all age groups with the greatest decrease observed in males and individuals over 60 years of age (fig. 1 and 2). Suicide rates in the region were three times higher in males than females (fig. 1), and in older age groups than younger (fig. 2), consistent with international findings (1, 10).

The Epidemiological Register of FVG (the Regional Social and Health Information System (SISSR)), is the only health registry in Italy permitted to link administrative and healthcare data for an entire region. This enables the study of suicide and antidepressant use at both the population and individual level in FVG.

Fig. 1: Suicide rate in males and females in Friuli Venezia Giulia 1997–2015

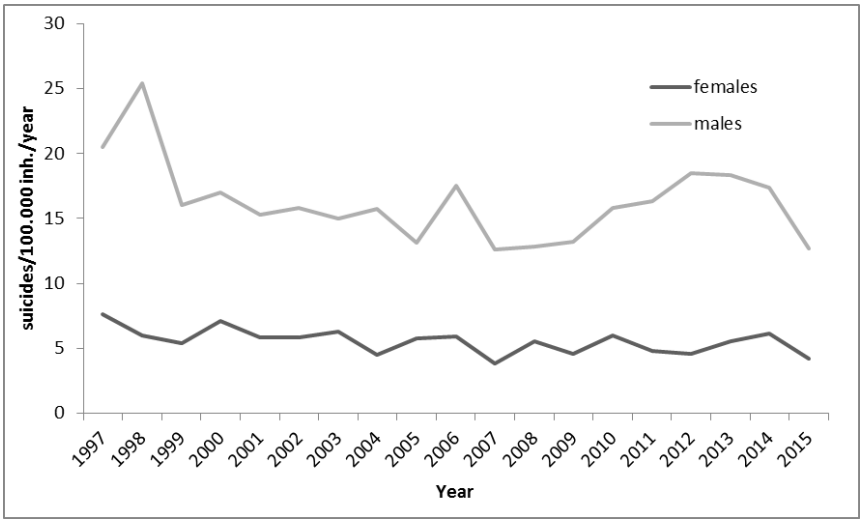
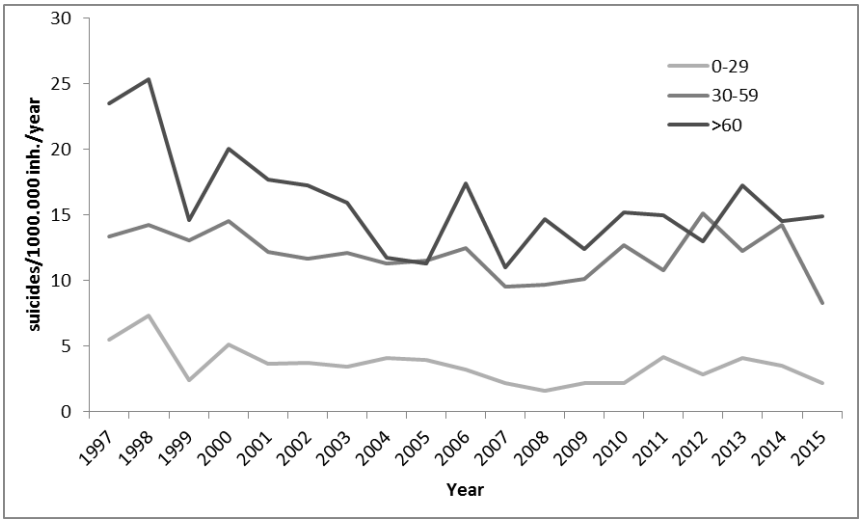


Fig. 2 Suicide rate in age groups 0-29; 30-59 and more than 60 years old in Friuli Venezia Giulia 1997–2015



1.2 MAIN SUICIDAL RISK FACTORS

Suicide is a complex phenomenon, since many factors at the individual and societal level may be implicated in suicidal behaviours. Suicide is usually explained as a convergence of genetic, psychological, social, and cultural risk factors, combined with experiences of trauma and loss (2). The WHO has divided suicidal risk factors into systemic, societal, community, relationship (social connectedness to immediate family and friends) and individual factors (1). Of these, individual factors have been more investigated and more scientific background information is available. The main individual suicidal risk factors are analysed in more detail below.

1.2.1 Self-harm

It is well established in the literature that the strongest risk factor for completed suicide is a previous history of deliberate self-harm (13). It is generally agreed that the likelihood of committing suicide after a self-harm episode increases 50 to 100 times, with 1 in 15 people dying by suicide within nine years of the self-harm episode (14). A recent study showed that for individuals who self-harmed, the risk of suicide was 131 times higher during the year following a self-harm act (15). The risk further increases in case of repeated self-harm episodes (16), especially in females (17).

1.2.2 Psychiatric disorders

Psychiatric disorders are also among the most consistently reported risk factors for suicidal behaviour (18). Psychological autopsy studies are the most frequent approach for investigating such associations (19). These have demonstrated that 90–95 % of suicide victims had been diagnosed with a psychiatric disorder prior to suicide (10, 20).

A recent review (21) confirmed the role of mental health and substance use disorders as major risk factors for suicide; in the countries considered, 84.5% of completed suicides were due to these disorders. Authors claimed that mental health and substance use disorders were also responsible of more than 60% of total suicide Disability Adjusted Life Years (DALYs), defined as years lost due to disease and disability. These disorders were therefore ranked as the third leading disease category of global health burden in 2010, with major depressive disorder having the largest health burden in this category. The attributable suicide DALYs was higher in males than females in most age groups, with the exception of females between 10 and 19 years old.

Among psychiatric disorders, depressive and bipolar disorders (affective disorders) have been demonstrated to account for the highest suicide risk (10, 22). It has been reported that 9%–15% of deaths among persons with affective disorders are due to suicide, although the proportion may be as low as 4% among persons with mild affective disorders (23). The prevalence of depression among suicide victim is the highest, since more than 50% of all people who die by suicide meet criteria for depressive disorder at the time of death (19, 24-27).

Other psychiatric disorders usually associated with a higher suicidal risk are psychotic disorders, personality disorders and alcohol use disorders. The lifetime risk of suicide in schizophrenia is about 4-5%, while the prevalence of personality disorders - particularly borderline and antisocial personality disorders - in suicide victims is around 30-40%. Many of these people, however, as well as the patients who previously had committed non-lethal self-harm, have also been shown to suffer from depressive symptoms prior to suicide (10). The lifetime risk of suicide in alcohol dependence is about 8% (28). People with eating disorders, in particular anorexia nervosa, are also at increased risk of suicide (10).

While there is no evidence that anxiety disorders alone lead to increased risk of suicide (29), when co-morbid with other mental disorders, anxiety has been shown to be a risk factor for suicide (30).

1.2.3 Somatic disorders

Somatic disorders, particularly cancer, may increase the risk of suicide (31-34). A recent study from Denmark demonstrated an increased risk in all somatic diagnostic categories (35). Other studies found a higher risk of suicide in Chronic Obstructive Pulmonary Disease (COPD) (36), in stroke (37) and myocardial infarction (38), and in neurological disorders (31). Notably, underlying depressive symptoms had been shown by patients with a variety of somatic disorders, including cancer (39, 40), stroke (41, 42), neurological disorders (43-45), myocardial infarction (46, 47), gastrointestinal diseases (48), COPD (49), endocrine disorders (50) and musculoskeletal disorders (51).

1.2.4 Economic crisis

Unemployment and financial loss may have a role in increasing suicidal risk, since these factors are associated with a higher burden of depression, anxiety and alcohol abuse (52). Economic crisis may therefore influence the individual risk of suicide, nowadays and in the past (53, 54). Nonetheless, a recent European review did not demonstrate a clear causal relationship between economic indices associated to the current economic crisis and an increase in the rates of suicide (55).

1.2.5 Familiar history of suicide

Suicidal behaviour is highly prevalent in families with a history of suicide, independent from the heredity of psychiatric disorders (56). Suicide risk, in fact, had been found to be twice as high in families of suicide victims as in comparable families (57). This may be related to both genetic dispositions as well as environmental factors (56). The negative impact of a suicide on a family can led to stress, shame, guilt, anger and anxiety. In consequence, family dynamics may change and support from others may be disrupted, due to stigma and hindered help-seeking (1).

1.3 PHARMACOLOGICAL TREATMENT OF SUICIDES

Suicide should be considered as a negative outcome of severe psychological suffering that can be mediated by the interactions of many factors. Consequently, it is not possible to identify a specific treatment for suicide. However, the proper pharmacological treatment of the underlying mental disorders may be a central component of suicide prevention strategies. Since mental disorders in most cases a probably necessary risk factor, its proper treatment may protect an individual from suicide. Moreover, psychiatric disorder is underlying many other suicidal risk factors.

Lithium is the drug that the best proven antisuicidal effect (58). This effect has been demonstrated both in monotherapy, as well as in combination with antidepressant treatment (59). Clozapine has also been shown to play a role in suicide prevention in psychotic patients (60). Other antipsychotic or mood stabilizing drugs (61, 62), have no proven effect in preventing suicide.

1.4 ANTIDEPRESSANT TREATMENT OF SUICIDES

Studies have shown that more than half of suicide victims suffered from depression prior to death (19). Antidepressant medication is the basic acute treatment of depression. An improvement in the treatment of depression in the population therefore appears to be a logical intervention in suicide prevention (6).

There is growing evidence worldwide, particularly from ecological studies, that antidepressants may play an important role in preventing suicidal behaviour (6-8, 63, 64). This evidence has

increased since the introduction of new antidepressant compounds, such as Selective Serotonin Reuptake Inhibitors (SSRI), that have fewer side-effects and a lower toxicity profile compared to older Tricyclic (TCA), possibly contributing to better patient compliance (65, 66). Nonetheless, there are official warnings that antidepressants might increase suicide risk in young subjects, particularly in the first months of treatmentas reported from meta-analyses of Randomized Clinical Trials (RCTs) (67). These findings, however, suffer from various limitations such as short study periods and the use of suicide ideation as a surrogate for suicide risk (67). Moreover, recent population-based studies failed to show such higher suicide risk (68-72), Furthermore, there are worrying indications that the official warnings have been contra-productive. From US came early signals that these warnings had led to a decrease in the use of antidepressants and an concomitant increase in young suicide (73). From Sweden was reported, from an individual-based controlled study, increasing rates of young (10-19 years) suicides in the five consecutive years from 2003(72).

1.4.1 Ecological studies

Evidence of an inverse correlation between suicide rates and antidepressant use has been cumulated from ecological studies since the first report by Isacsson in 2000, where he reported correlations of increases of antidepressant use and decreasing suicide rates 1978-1996 in Sweden, in Norway, Denmark, Finland 1990-1995 and USA from 1987 (64). Rihmer confirmed similar findings in Hungary 1984-1998 (74). In 2005, Ludwig & Marcotte (7) analysed data on suicide rates and antidepressant sales in 27 countries from 1980 to 2000. They demonstrated that an increase of one pill of antidepressant per capita (a 13% increase over 1999 levels) was associated with a 2.5% reduction in suicide rates. This relationship was more pronounced for adults than for children. In the same year, Isacsson & Rich (9) reviewed research from nine countries and found in most of them an inverse correlation between rising antidepressant use and falling suicide rates. In 2007, Baldessarini et al. (63) reviewed nineteen studies from different countries between 1980 and 2000. They found that suicide rates decreased by 14% overall while antidepressant prescriptions increased by an average of 395%. However the findings were heterogeneous, since only eight out of the nineteen selected studies found significant inverse correlations between rising sales of antidepressants after the introduction of SSRIs in the 1990s and a decrease in suicide rates not anticipated in the 1980s. Nonetheless, Isacsson & Mathè (75) argued that only three studies, among the 19 reviewed by Baldessarini et al., did not find any inverse correlation. In fact, eleven studies were positive, and five studies found an inverse correlation among the elderly. Furthermore, all three negative studies derived from small countries with a very low number of suicides per year (Iceland, Northern Ireland, Slovenia).

As summarized in Table 1, this inverse correlation was found in most of the countries where studies were published after year 2000. Data on antidepressant use and suicide rates were dated,

however, with no data available beyond 2006. The latest review conducted in 2013 (8),is based on data from 29 European countries between 1980 and 2009 and found that suicide rates tended to decrease more in countries where there had been a greater increase in the use of antidepressants, thus providing further evidence that the use of antidepressants has a positive effect on suicide prevention.

Table 1: Selected ecological studies published after year 2000 on suicide rates and antidepressant use by country (all ages and gender are considered)

Reference	Country	Period	Suicide rates	Antidepressant use	Outcome (correlation)
Isacsson (2000) (64)	Sweden	1978 - 1996	19% decrease	82% increase	Positive
Rihmer et al. (2001) (76)	Hungary	1984-1998	30% decrease	83% increase	Positive
Oravecz et al. (2003) (77)	Slovenia	1984-1997	7.1% increase	58% increase	Negative
Kelly et al. (2003) (78)	Northern Ireland	1989-1999	8% increase	467% increase	Negative (more in the ≤30 age group)
Hall et al. (2003) (79)	Australia	1991-2000	increase in 25-44 age group decrease in >44 age group	209% increase	Positive (the age group with greater increase in antidepressants use tended to have greater decrease in suicide rates)
Helgason et al. (2004) (80)	Iceland	1950-2000	unchanged	388% increase	Negative
Morgan et al. (2004) (81)	England	1993-2002	85.8% decrease	237.5% increase	Positive
Grunebaum et al. (2004) (82)	US	1985-1999	13.5% decrease	413% increase	Positive

Barak & Aizenberg (2006) (83)	Israel	1998–2002	17.6% decrease	160% increase	Positive, but significant only in men aged 55-74 years
Milane et al. (2006) (84)	US	1988-2002	14.4% decrease	1248% increase (Fluoxetine)	Positive
Reseland et al. (2006) (85)	Sweden, Norway, Denmark, Finland	1961-2003	33.6% decrease	410% increase	Positive
Nakagawa et al. (2007) (73)	Japan	1999-2003	54% increase	56% increase	Positive: inverse association between year-to-year changes in SSRI prescribing and suicide rates
Bramness et al. (2007) (86)	Norway	1980-2004	28% decrease	100% increase (non-Tricyclics)	Positive
Sebestyen et al. (2010) (87)	Hungary	1998-2006	23% decrease	113% increase	Positive

1.4.1.1 Italian studies

Two studies analysed the correlation between suicide rate and antidepressant prescriptions in Italy. The first (88) analysed data on suicide rates and antidepressant sales from 1988 to1996. Authors found a 53% increase in antidepressant sales, mainly due to the increasing use of SSRIs. During the same years, suicide rates slightly increased for men (from 9.8 to 10.2 per 100,000 inhabitants) and decreased for women (from 3.9 to 3.2 per 100,000). The second study (89) analysed data on antidepressant sales from 1983 to 2000 and suicide rates from 1955 to 2000. A 336% increase in antidepressant use was observed, while suicide rates decreased in the same period both in men (from 14.1 to 10.9) and women (from 5.4 to 3.5). In the over 65 age group the decrease was also consistent (25% in men and 33% in women), however data on antidepressant sales by age group were not available.

A study from the Veneto region (90) of antidepressant prescriptions from 2000 to 2005 found a more pronounced increase in prescriptions in males and in people aged 65 and older. Suicide rates did not change in either gender over these years. Suicide rates by age group, however,

were not available. This data gap hindered more detailed analyses on the inverse correlation between suicide rates and antidepressant prescriptions.

1.4.2 Population-based studies

Few register-based studies analysed the use of antidepressants in suicides compared to controls from the general population at the individual level (Table 2). Six (71, 91-95) out of the seven cohort studies selected found a positive outcome with regard to a preventive effect of antidepressants on suicide risk. One cohort study (68) found no increased risk of suicide along with the current use of antidepressants compared to past use. However, this finding gives no information on the possible effect of current antidepressant treatment on suicide. Nonetheless, one case-control study (69) found that a longer treatment with antidepressants was associated with lower suicide risk. Another case-control study (96) failed to demonstrate a higher risk of suicide in antidepressant users compared to controls. Two studies (70, 97) compared the risk of suicide in SSRI users to TCA or other antidepressant users. They found low or no evidence of higher risk in SSRI users. Only one study (98) found no difference in suicide risk between subjects who discontinued antidepressant treatment compared with those who did not, thus excluding a preventive effect of antidepressants on suicide. The study, however, was limited to subjects older than 50 years.

Table 2: Selected population-based studies published after year 2000 on the use of antidepressants in suicides compared to controls from the general population

Reference	Country	Period	Study design	Study sample	Age groups and gender	Main results concerning the risk of suicide and AD use	Outcome (preventing effect of AD on suicide)
Jick et al. (2004) (69)	UK	1993-1999	Case-control	17 cases (suicides) who received AD within 90 days before death (index date) 157 controls	All (10 to 69 years old)	Patients who started AD treatment within 1 to 9 days prior to index date have an increased risk of suicide 38 times higher than those who started AD ≥90 days prior to the index date	Inconsistent, but longer treatment with AD associated to lower suicide risk

Didham et al. (2005) (96)	New Zealand	1996-2001	Nested case-control	26 cases (suicides) 78 controls	All	No increased risk of suicide in AD users (SSRIs, TCAs) when adjusted for confounders (age, gender, depression/suicidal ideation)	Inconsistent
Martinez et al. (2005) (70)	UK	1995-2001	Nested case-control	69 cases (suicides) with a first prescription of AD for depression 1121 controls	All	No evidence of increased risk in SSRIs users compared to TCAs users	Inconsistent
Tiihonen et al. (2006) (71)	Finland	1997-2003	Cohort	15,390 subjects hospitalized with a diagnosis of suicide attempt (602 suicides)	All	No increased RR of suicide in TCA, SSRI and SNRI users Current use of AD was associated with decreased risk of suicide	Positive
Sondergard et al. (2006) (93)	Denmark	1995-1999	Cohort	438,625 AD users compared to 1,199,057 controls (2144 suicides)	All ≥18 years old	Suicide rates decreased both in AD users and no AD users, but the decrease in suicide rates was more pronounced in AD users	Positive
Sondergard et al. (2006) (92)	Denmark	1995-1999	Cohort	438,625 AD users compared to 1,073,862 controls (2145 suicides)	All ≥18 years old	Suicide rates decreased with the number of AD prescriptions and when patients purchased SSRIs and newer ADs	Positive (continued treatment decreases suicide risk)

						≥2-fold compared to patients who purchased once	
Simon et al. (2006) (97)	US	1992-2003 (June)	Cohort	65,103 AD users (31 suicides in the 6 months-follow-up)	All	No significant increase in suicide risk after starting treatment with new AD compared to subsequent months	Inconsistent, but did not demonstrate a higher risk in the first phase of treatment
Juurlink et al. (99)	Canada	1992-2000	Case-control	1138 cases (suicides) 4552 controls	All ≥66 years old	Increased risk of suicide in the first month of therapy with SSRIs compared with other AD, but absolute risk is low and under treatment high (68%)	Inconsistent
Sondergard et al. (2007)	Denmark	1995-2000	Cohort	31,422 patients diagnosed with depression (310 suicides)	All ≥18 years old	Suicide rates decreased with the number of AD prescriptions and when patients purchased ADs ≥2-fold compared to patients who purchased once	Positive (continued treatment decreases suicide risk)
Haukka et al. (2009) (91)	Finland	1999-2003	Cohort	258,417 AD users (886 suicides)	All	Current AD use was not associated with lower risk of suicide compared to one-prescription group, with the exception of SSRIs users	Positive only for SSRIs
Erlangsen et al. (2009)	Denmark	1995-2000	Case-control	125,426 (323 suicides) who not	All ≥50 years	No difference in suicide risk between subjects	Negative

(100)				discontinued AD treatment 91,089 (215 suicides) who discontinued treatment early	old	who discontinued AD treatment compared to whom did not	
Leon et al. (2011) (95)	US	1979-81 to 2006-09	Cohort	757 participants with affective and schizoaffective diagnoses from 5 medical centers (26 suicides)	All ≥17 years old	The risk of suicide decreased by 20% among AD users	Positive
Cheung et al. (2015) (68)	Netherlands	1994-2012	Cohort	27,712 AD users (280 suicides and suicide attempters)	All	Current use of AD (SSRIs, TCAs and other) did not increase suicide risk compared to past use of AD	Inconsistent

AD antidepressants; SSRI Selective Serotonin Reuptake Inhibitors; SNRI Serotoninergic Noradrenergic Reuptake Inhibitors; TCA Tricyclic

1.4.3 Under-treatment with antidepressants

Population-based studies observed an under-treatment with antidepressants in depressed individuals (101, 102), as well as poor adherence to antidepressant treatment, both in Italy (103, 104), as well as in other countries (105-108). Moreover, a recent review (109) observed a strong association between non-adherence to antidepressants and a worsening of patients' clinical outcomes, such as risk of relapse and recurrence of depressive episodes and consequent increase in symptom severity, decreased treatment response and remission, and a higher number of hospitalizations and visits to Emergency Departments. Economic outcomes, such as higher healthcare expenditures, have been also claimed.

Few studies based on prescription registers analysed the use antidepressants in suicide victims. A study from Jamtland county, Sweden (110), found that only seven patients out of 59 (12%) who later committed suicide were dispensed antidepressants in the last 90 days before death. Another Swedish study found that 61 (20%) out of the 295 subjects aged 10 – 19 years who had

committed suicide between 2006 and 2010 had been prescribed an antidepressant in the six months prior to death. However, only 41 of them (14%) were compliant with their prescription, as indicated by the dispensation of more than one prescription (72). A study from Funen county, Denmark (111), found that 108 suicides out of 390 were dispensed antidepressants one year before death, but only 34 suicides (8.7%) received adequate treatment one month before death. A study from Ontario, Canada (97), found that 422 out of 1329 suicides (32%), aged 66 years and older, were dispensed antidepressants in the 6 months before death.

Furthermore, studies that analysed treatment after non-fatal self-harm also indicated a low use of antidepressants. Suominen et al. (112) observed that only seven depressed patients out of 43 (17%) received an adequate treatment with antidepressants during the month before and after a suicide attempt. Another study (113) found that the proportion of patients with a diagnosis of Major Depression exposed to antidepressant treatment was significantly lower in in the group of patients who had attempted suicide than a control group (42 vs 58%).

1.4.3.1 Toxicological studies

There is evidence from studies based on forensic toxicological screening of suicide victims that they have seldom been treated with antidepressants (114-116). In Sweden, Isacsson et al. found that the number of suicides exposed to antidepressants was 16% in 1999-91(116). In a subsequent study, the authors found that the number of suicide victims exposed to antidepressants had increased to 28.9% in 2005(6). Thus the detections of antidepressants had increased 2-fold, which was a remarkably small increase since the use of antidepressants had increased 8-fold in the population. In the study of young suicides, mentioned above, the average number of suicides aged 10 – 19 years in whom antidepressants were detected in toxicological screening was 1.7 out of 407 cases per year (0.4 %) from 1992–2002 and 7.4 out of 438 cases per year (1.7 %) from 2003–2010 (72). In a study from New York City, Leon et al. (117) observed that 23.1% of the 1419 adult suicides showed evidence of antidepressants in toxicology analyses from 2001 to 2004. These toxicological data should be seen in the light of that 50-80 % of the suicide victims were depressed (19, 24-27).

2 AIMS

The overall aim of the thesis has been to explore the relation of suicide to health care in the FVG region, Italy, particularly with regard to appropriate pharmacological medication, such as antidepressants. More specifically, it explored the correlation between suicide rates and antidepressant sales, as well as the individual of risk level by the main suicidal risk factors, such as non-fatal self-harm, psychiatric disorders and somatic disorders. It further aimed to explore the differences in suicide risk related to qualitative parameters in the use of antidepressants, such as adherence and treatment modifications. By contributing to a better understanding of the relationship between suicide and health care, this thesis aimed to help improve interventions to prevent suicide, a major public health problem and among the most tragic.

The specific aims for the included papers were:

Paper I: To compare suicide trends and the use of antidepressants in the FVG region, using individual-based data on suicides and on the use of antidepressants. The hypothesis was that suicide rates decreased in parallel with an increasing trend in antidepressant prescriptions, as observed previously in several ecological studies. An under-treatment with antidepressants in the three months before death was also hypothesized.

Paper II: To explore to what extent and under which diagnoses suicides had received psychiatric in-patient care, to explore to what extent they had previously committed non-lethal self-harm, and to investigate the antidepressant treatment received by these subjects. The first hypothesis was that previous self-harm and most psychiatric diagnoses, particularly diagnoses of affective disorders, has increased the suicide risk. The second hypothesis was that current use of antidepressants was low among those who suicide attempt to or successfully commit suicide, even when previously diagnosed with an affective disorder.

Paper III: To explore the main somatic risk factors of suicide, to describe their prescription patterns, as well as adherence to antidepressants in suicides and controls, and to assess whether antidepressant treatment may play a role in decreasing the risk of suicide in patients with somatic disorders. The first hypothesis was that depression underlies several somatic disorders, while several somatic disorders, such as cancer, respiratory and cardiovascular disorders, are associated with increased risk of suicide. The second hypothesis was that the use and adherence to antidepressants was low in subjects with medical illnesses.

Paper IV: To compare the use of different antidepressant classes and compounds in individuals who committed suicide and in controls from the general population in order to assess the extent to which adherence and current use of different antidepressant classes can affect the risk of committing suicide. The hypothesis was that adherence and current use of antidepressants was associated with a lower suicide risk.

3 MATERIAL AND METHODS

3.1 THE REGIONAL "SOCIAL AND HEALTH INFORMATION SYSTEM"

All data used for this thesis were retrieved from the FVG Regional Social and Health Information System (SISSR). This is an unique individual-based health database in Italy, run by INSIEL, a major Italian Information Technology company. The SISSR had been implemented since the 1990s.

The SISSR links data using a unique anonymous key from different regional databases. For the purpose of this thesis three databases were used:

1. Death Register (used to identify suicides)
2. Hospital Discharge Register (used to identify non-fatal self-harm episodes and discharge diagnoses according to ICD-9 codes)
3. Drug Prescription Register (used to retrieve data on antidepressant prescriptions)

The anonymous key is a unique personal identifier, present in all computerised files. It identifies a patient file, which keeps a record for each resident in FVG, including gender, date of birth, general practitioner, as well as medical conditions. This enrolment file is updated daily for change of general practitioner, births, deaths, and the arrival and departure of the residents from the Region.

It gives information on:

- Age, gender, residence area.
- Visits to emergency rooms and other hospitalizations
- Admission and discharge diagnosis (ICD-9)
- Medications prescribed by a general practicioner (GP) or other public physicians, reimbursed by the National Health System. They include the prescription date, the number of packages, the volume (expressed in defined daily doses, DDD), the specific antidepressant drug name and its ATC code (118).

3.2 PAPER I

Paper I is designed as an ecological study that includes all suicides in FVG between years 1997-2006, looking at changes in both the rate of suicide and antidepressant use. Cases where the cause of death is uncertain were excluded. Data on antidepressants consumption were used for the same period, and measured as follows:

- DDDs per 1000 inhabitants per day
- Number of individuals treated per year (treatment prevalence)
- Number of DDDs per individual user (average dosage and duration of treatments)

Antidepressants were classified, following ATC codes, as Tricyclics (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs) and "others" (Table 3). SSRI data were available for the period 1999-2006, due to the fact that in 1998 these drugs were made free of charge by the National Health System (NHS).

Data on suicides and antidepressants prescriptions were analysed in men and women, as well as in age groups 0-59 and ≥60 years.

Table 3: Antidepressant classification in Paper I

Drug Class	ATC code	Antidepressant compounds
Tricyclics (TCAs)	N06AA	maprotiline and similar older
Selective Serotonin Reuptake Inhibitors (SSRIs)	N06AB	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Others	N06AX	venlafaxine, mirtazapine, oxitriptan, mianserin, reboxetin, trazodone

3.2.1 Statistical analysis

Trends were analysed using curve estimation. Spearman's Rank Correlation Coefficient was used to test correlations. Changes in suicide rates and in the use of antidepressants were calculated as Relative Risks (RR) with 95% confidence intervals (95% CI). Odds Ratios (OR) with 95 % CI were calculated in order to compare the proportions of subjects taking antidepressants (e.g., men compared to women; younger compared to older). The last year of the study (2006) was compared to the first year (1997), in all of these calculations.

3.3 PAPER II, PAPER III AND PAPER IV

3.3.1 Study design and subjects

Paper II, III and IV are designed as case-control studies.

First, we identified subjects who committed suicides in the selected study period, using ICD-9 codes E95* and E98* for intentional self-harm and events of undetermined intent. Suicides were identified as cases. Second, we selected 10 controls in Paper II and III, and 5 controls in Paper IV, from the FVG general population. In Paper II, we selected controls as subsequent to the respective case in the population register. In Paper III and IV, we selected controls by using an incidence density sampling method (119). Controls were then matched by gender and year of

birth and had to be alive at the time of suicide of their corresponding case (index date). In Paper IV, both cases and controls had to have received at least one prescription of an antidepressant in the 730 days prior to death (index date).

Table 4 shows the study period and the study population with regard to each study.

Table 4: Study period and study population of Papers II, III and IV

	Paper II	**Paper III**	**Paper IV**
Years	2002-2008	2003-2013	2005-2014
Study population	766 cases 7660 controls	1308 cases 13,080 controls	876 cases 4380 controls

3.3.2 Diagnoses

We considered, in all the three papers, the main in-patient diagnosis, recorded in the first position on the medical record on discharge from public hospitals or private hospitals covered by the Regional Health System. Diagnoses were recorded as ICD-9 codes (Table 5). Out-patients diagnoses were not available.

In Paper II, non-fatal self-harm episodes were obtained from the Hospital Discharge Register and/or emergency room admission forms where “self-harm” was annotated.

In Papers III and IV, the following diagnoses are not considered and excluded from the data analyses:

- Complications from pregnancy, childbirth, and the puerperium (codes 630–679);
- Certain conditions originating in the perinatal period (codes 760–779);
- Injury and poisoning (codes 800–999)
- External causes of injury and supplemental classification (codes E and V)

Table 5 summarizes the diagnoses and corresponding ICD-9 codes considered in each paper.

The psychiatric diagnoses at last discharge from the hospital were considered in Paper II, while the time range for diagnoses was the 365 days and the 730 days prior to the index date, in Paper III and Paper IV, respectively.

Table 5: Diagnoses and corresponding ICD-9 codes, in Papers II, III and IV

Hospital discharge diagnoses	ICD-9 codes	Paper
Psychiatric affective disorders	296, 300.4, 311	Paper II, Paper III, Paper IV
Non-affective psychiatric disorders		Paper III, Paper IV (all together)
Psychosis	295, 297, 298	Paper II
Organic	290-294	
Anxiety	300.0-300.3, 300.5-300.9	
Personality	301	
Other	306-310	
Substance Use	303-305	
Somatic disorders		Paper IV (all together)
Infectious and parasitic diseases	001–139	Paper III
Malignant neoplasms	140–208	
Benign neoplasms	210–229	
Carcinoma in situ and other neoplasms	230–239	
Metabolic and immunity disorders	240–279	
Diseases of the blood and blood-forming organs	280–289	
Neurological disorders	320–359	
Diseases of sense organs	360–389	
Heart and vascular diseases	390–459	
Diseases of the respiratory system	460–519	
Diseases of the digestive system	520–579	
Diseases of the genitourinary system	580–629	
Diseases of the skin and subcutaneous tissue	680–709	
Diseases of the musculoskeletal system and connective tissue	710–739	
Congenital anomalies	740–759	
Symptoms, signs, and ill-defined conditions	780–799	

3.3.3 Antidepressants

Data on antidepressant prescriptions included the prescription date, as well as the number of packages and the volume (expressed in DDD). In Paper IV, also the specific antidepressant drug name and the corresponding ATC code was included (Table 6). The prescriptions cover more than 90% of all antidepressant prescriptions in the region.

We assessed the use of antidepressants using different parameters in each paper:

1. Current use of antidepressants prior to death (index date) (Papers II and IV):
    a. Paper II: the last dispensation in the 90 days prior to index date with sufficient amount of pills to cover the time to index date, assuming a daily dosage of one DDD.
    b. Paper IV: the total number of DDD supplied at the second-to-last prescription sufficient to cover the time up to the last prescription, and the total number of DDD supplied at the last prescription sufficient to cover the time up to the index date.

2. Adherence to antidepressants (Papers III and IV):
   It was assesed using the Medical possesion ratio (MPR), defined as the proportion of days supplied under a specified time period (120). The total number of DDD approximated the number of days of treatment. MPR was calculated as:

$$\frac{\text{Total number of DDD during the observation period}}{\text{observation period}} \times 100$$

   Observation period: 365 days prior to the index date in Paper III and 730 days prior to the index date in Paper IV

   Subjects with an MPR $\geq$ 80% were defined as adherent to treatment, while subjects with an MPR $\leq$ 79% were defined as non-adherent.

3. Treatment modifications (Paper IV):
   a. The number of switches of antidepressants. A switch is defined as the discontinuation of an index antidepressant and the prescription of another specific antidepressant. A delay up to 31 days until the prescription of the new antidepressant as well as an overlap of the two drugs up to 31 days is allowed (121).
   b. The number of combinations of antidepressants. Combination is defined as the prescription of the index antidepressant overlapping the prescription of a second antidepressant for more than 31 days (121).

Table 6: Antidepressant classification in Paper IV

Drug Class	ATC code	Antidepressant compounds
Tricyclics (TCAs)	N06AA	amitriptiline, clomipramine, nortriptiline, trimipramine, imipramine, desipramine, dosulepine, maprotiline
Selective Serotonin Reuptake Inhibitors (SSRI)	N06AB	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonergic noradrenergic reuptake inhibitors (SNRI)	N06AX21, N06AX16	venlafaxine, duloxetine
Others	N06AX49, N06AX12, N06AX11, N06AF03, N06AX03, N06AX18, N06AX05	mirtazapine, mianserin, reboxetine, trazodone, bupropion, ademetionin, phenelzine

3.3.4 Statistical analysis

In the three papers, continuous variables were summarized using the median as a measure of central tendency and the range as a measure of dispersion, whereas dichotomous or categorical variables were tabulated into contingency tables. For categorical variables, the chi-square statistic ($\chi 2$) was used to test the differences between observed and expected frequencies.

A multivariate logistic regression analysis (Paper II) and a conditional logistic regression analysis (Papers III and IV), were used to assess the associations between outcome (suicide) and predictors, as follows:

- Paper II: psychiatric disorders, self-harm, antidepressant prescriptions, time from the first prescription of antidepressants
- Paper III: psychiatric and somatic disorders
- Paper IV: use of antidepressants

Crude and adjusted OR and 95% CI were estimated from the logistic regression coefficients and their respective standard errors. A P-value (P) < 0.05 was set as the threshold for statistical significance.

In Paper II, subjects who had never been hospitalized for psychiatric disorders and/or self-harm, as well as subjects who had not been prescribed antidepressants, were used as the reference group (OR=1.0).

In Paper III, a stratified analysis was performed according to adherence to antidepressants, comparing subjects with an MPR 0–79% to subjects with an MPR ≥ 80%. Subjects with no discharge diagnosis in the 365 days prior to index date were used as the reference group (OR=1.0).

In Paper IV, stratified analyses were performed according to adherence and current use of antidepressants. Subjects who were not prescribed the index antidepressant (i.e. SSRI, SNRI, TCA or other), were used as a reference for the conditional regression analyses (OR=1.0).

Descriptive and inferential analyses were conducted using the statistical software SAS-Enterprise Guide 4.3 (SAS Institute Inc., Cary,NC, USA), in Paper III and Stata/SE (version 13.1), in Papers II and IV.

3.4 ETHICAL CONSIDERATIONS

Given the characteristics of the SISSR as listed above, the FVG Ethical Committee did not need to be consulted for the thesis' constituting papers, as when developing other epidemiological studies in the Region, since epidemiological analyses are provided using only anonymous data.

4 MAIN RESULTS

4.1 PAPER I

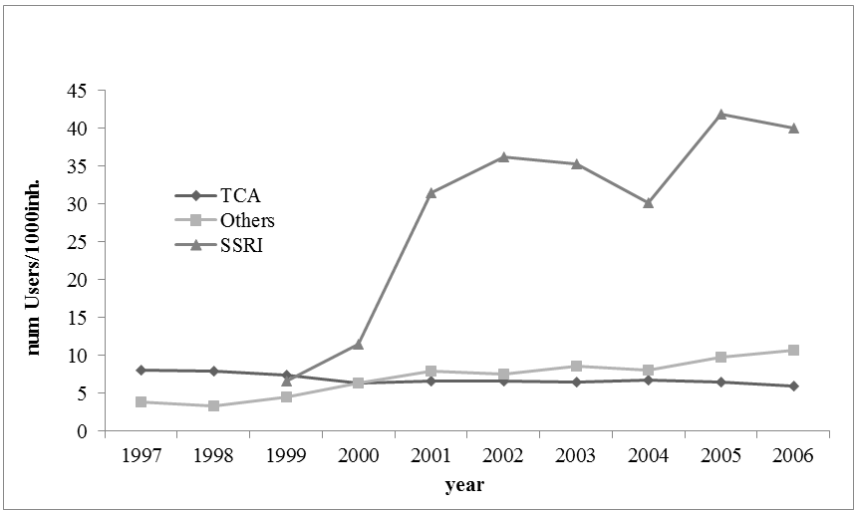
4.1.1 Suicide rates and antidepressant use

A significant decrease in suicide rates was observed in FVG during years 1997-2006, in both genders and age groups (Table 7). In parallel, an increase in the use of antidepressants was observed, with all three measures we applied. This increase was greater in the elderly and in women (Table 7). SSRI accounted for the most of the increase (71% of individual users in 2006), whilst the use of TCAs slightly decreased and the use of other antidepressants slightly increased (fig. 3). The inverse correlation between the rates of antidepressants use and the rates of suicide was confirmed by the Spearman's rank correlation ($r = 0.74$, $P < 0.01$), which fitted better to a logarithmic curve ($\log r^2 = 0.77$).

Table 7: Decrease in suicide rates and increase in antidepressants use with regard to three measures (DDD/1000 inhabitants./day; number of users/1000 inhabitants./year; DDD/number of user). Data of year 1997 are compared with those of year 2006

	Suicide rates (1997-2006)	**Use of antidepressants (1997-2006)**		
Genders	*N suicides/100,000 inh./ year*	*DDD/1000 inh./day*	*N users/1000inh./year*	*DDD/user*
Males	20.5 to 13.5	0.5 to 15.1	6.9 to 32.4	25.6 to 169.1
Females	7.6 to 5.0	1.1 to 36.9	7.6 to 79.4	25.4 to 169.1
Age groups				
0-59	10.2 to 7.0	0.5 to 17.5	11.5 to 37.9	46.6 to 168.9
≥60	23.5 to 14.3	1.8 to 48.1	25.6 to 103.0	25.2 to 170.6
Total	13.8 to 9.1 (33.8% decrease)	0.8 to 26.4 (96.9% increase)	11.9 to 56.7 (79% increase)	25.5 to 169.8 (85% increase)

Fig. 3: Number of people using antidepressants per 1000 inhabitants per year, with regard to different antidepressants classes (SSRI, TCA, Other), during years 1997-2006



4.1.2 Use of antidepressants in suicides

On average, the number of suicide victims who were dispensed antidepressants in the 90 days prior to death during years 1997-2006 was 14.8%. The main increase in the number of individuals using antidepressants was observed after year 1999, when SSRI became reimbursed by the NHS. Significant differences were found when comparing men to women and 0-59 age group to ≥60 age group (Table 8).

Table 8: Number and percentages of suicides using antidepressants in the 90 days before death, according to genders and age groups. OR with 95% CI was used to compare genders and age groups

	Suicides using AD in the 90 days before death		**Total N suicides**
	N	%	
Genders			
Males	91	9.4	963
Females	96	25.6	375
OR (95% CI)	0.32 (0.24-0.43)		
Age groups			
0-59	98	12.3	793
≥60	89	16.3	545
OR (95% CI)	0.68 (0.52-0.90)		

4.2 PAPER II, PAPER III AND PAPER IV

The proportions of male and female suicides, as well as the proportions of suicides according to age groups were similar in the three papers' population (Table 9). The mean age at which people committed suicide was around 56 years (range 12-98 years).

Table 9: Total number and percentages of suicides according to genders and age groups

	PAPER II		PAPER III		PAPER IV	
	Suicides (N = 766)		Suicides (N = 1308)		Suicides (N =1260)	
	N	%	N	%	N	%
Genders						
Males	552	72.1	957	73.2	928	73.6
Females	214	27.9	351	26.8	332	26.4
Age groups						
0-29	66	8.6	98	7.4	95	7.5
30-59	385	50.3	648	49.5	638	50.6
≥60	315	41.1	562	43.0	527	41.8

4.2.1 Previous self-harm, psychiatric and somatic disorders

The number of cases and controls who previously committed self-harm, as well as those who were hospitalised for a psychiatric disorder or a somatic disorder in Paper II and III are summarized in Table 10. In Paper II, previous self-harm episodes were found to be associated with an increased risk of suicide, as were all psychiatric disorders diagnosed at last hospital discharge. Similar findings were observed in Paper III. Somatic disorders led to a three-fold increase in suicide risk (Table 10). We also observed that the risk of suicide increased by the number of comorbid somatic diagnoses, with a ten-fold increase when subjects were diagnosed with four or more somatic disorders. Somatic diagnoses carrying the highest suicide risk were respiratory disorders (OR = 2.5). The risk of suicide in somatic disorders was further increased by more than four times in subjects older than 60 years, compared to a two times increased risk in younger subjects.

In Paper IV, affective disorders were diagnosed in 6% of suicides who received an antidepressant prescription in the 730 days prior to death. The percentage of suicides diagnosed with non-affective and somatic disorders was 12.2% and 44.4%, respectively.

Table 10: Numbers (N), adjusted odds ratio (OR) and 95% confidence intervals (95% CI) of suicide in subjects with previous self-harm, psychiatric and somatic disorders in Papers II and III

	PAPER II [a]				PAPER III [b]			
	Suicides (N=766)	Controls (N=7660)	Suicide risk, adjusted [c]		Suicides (N=1308)	Controls (N=13,080)	Suicide risk, adjusted [d]	
	N	N	OR	95% CI	N	N	OR	95% CI
Previous self-harm								
1	79	10	53.1	26.2–107.4				
≥1	31	1	98.0	12.4–775.6				
Affective	104	59	21.5	15.0-30.1	106	21	22.0	12.9–37.2
Non-Affective Psychiatric	154	123	15.3	11.6-20.2	213	53	33.1	23.9–45.8
Somatic					655	3141	2.9	2.5–3.3

[a] Psychiatric and somatic diagnoses are referred to last discharge from hospital
[b] Psychiatric and somatic diagnoses are referred to last discharge from hospital in the 365 days before the index date
[c] Adjusted for age, gender and co-morbid psychiatric diagnoses
[d] Adjusted for affective and non-affective disorders

4.2.2 Antidepressant use

Although the use of antidepressants was measured in the three studies using different methods, in only a minority of cases were suicide victims adherent to antidepressants or currently prescribed antidepressants at the time of death (Table 11).

Table 11: Number (N) and percentages (%) of suicides using antidepressants (AD)

	PAPER II [a]		PAPER III [b]		PAPER IV [c]	
	Suicides (N=766)		Suicides (N=1308)		Suicides (N=1260)	
	N	%	N	%	N	%
AD prescriptions	302	39.4	535	40.9	876	69.5
Current use of AD [d]	123	16.1			392	31.1
Adherence to AD (MPR ≥80%)			151	11.5	334	26.5

[a] Data on AD are referred to the 7-years study period
[b] Data on AD are referred to the 365 days prior to death
[c] Data on AD are referred to the 730 days prior to death
[d] Definition of "current use" differs between Paper II and Paper IV

Women were more likely to be dispensed antidepressants than men, as were subjects older than 60 years of age (compared to younger age group). We also observed that women were more likely to currently use antidepressants (Paper II) and to adhere to antidepressant treatment (Paper III). Furthermore, current use was more likely in elderly compared to younger age group (Paper II).

In Paper II, we found that only one-fifth of the cases diagnosed with a psychiatric disorders were currently using antidepressants at the time of death. A similar proportion was found also in cases with higher suicide risk, such as subjects who previously committed self-harm or had been diagnosed with an affective disorder.

In Paper III, we compared subjects with somatic disorders that were adherent to antidepressant treatment, to those either not prescribed or non-adherent to antidepressant. The risk of suicide was not increased in adherent subjects (OR = 1.0; 95% CI =0.7–1.5), while it was increased in not prescribed or non-adherent subjects (OR = 2.8; 95% CI = 2.5–3.3).

In Paper IV, we analysed antidepressant compounds and different antidepressant classes taking into account adherence, current use (Table 11), and treatment modifications. SSRI accounted for more than 90% of the total prescriptions (N = 827), while SNRI 70% (N =610), TCA 51% (N=451) and other antidepressants 52% (N=452). Combinations of antidepressants were found in more than half of the users, except users of SSRI (Table 12). When treatment modifications were not considered, only one-tenth of SSRI users was adherent to antidepressants (Table 12).

Table 12: Numbers (N) and percentages (%) of treatment modifications and adherence to antidepressants (AD) in the 730 days prior to index date, according to different AD classes. Percentages were calculated on the total number of suicides in different AD classes for treatment modifications, and on the number of suicides who neither combined nor switched AD classes when AD monotherapy was assessed.

Suicides prescribed AD								
	SSRI		SNRI		TCA		Other	
	N	%	N	%	N	%	N	%
Treatment modifications								
Switches	139	16.8	133	21.8	113	25.1	115	25.4
Combinations	359	43.4	282	62.5	341	55.9	293	64.2
AD monotherapy [a]								
Not adherent to AD (MPR 1-79%)	391	88.5	211	85.4	129	83.2	119	81.0
Adherent to AD (MPR >80%)	51	11.5	36	14.6	26	16.8	28	19.0

[a] Subjects who switched and/or combined antidepressants were not considered

The conditional regression analyses showed a higher risk of suicide only in SSRI users (OR = 1.6, 95% CI 1.1-2.2) among antidepressant classes when adjusted for treatment modifications and for psychiatric and somatic diagnoses. The adjusted risk was not significant when the analysis was applied to different antidepressant compounds. Moreover, the stratified analyses showed a decreasing trend in suicide risk when subjects with an MPR≥ 80% were compared to subjects with MPR 1-79%, as well as when subjects currently using antidepressants at the time of the index date were compared to subjects that were not. Significantly lower OR of suicide was found only in subjects who currently use TCA (OR = 0.7, 95% CI = 0.5-1.0).

5 DISCUSSION

5.1 METHODOLOGICAL CONSIDERATIONS

5.1.1 Strengths

The use of the FVG individual-based register using an unique personal identifier allowed for an analysis at the individual level, not based on aggregated data. This also avoided information and selection bias, since all studies were based on administrative data with full coverage of the regional population. The amount of information available in the register was quite comprehensive, since it included demographic data, in-patients diagnoses, detailed information on antidepressant prescriptions, such as prescription date, as well as the number of packages, the volume and the specific antidepressant drug name dispensed at each prescription. This permitted the analysis of antidepressant use with different parameters at the individual level. Moreover, the data, which referred to the 18-year period between 1997 and 2014, were exhaustive enough to describe in detail recent findings regarding suicidal behaviour and antidepressant use in the FVG Region. We were therefore able provide an overall picture of suicide risk factors using different measures that also considered antidepressant use. In particular, we used rates (suicide rates, rates of antidepressant use) and ratios (odds ratio) to analyse trends in suicide incidence and antidepressant use, as well as the suicide risk related to exposure to a variety of different risk factors (i.e. previous self-harm, psychiatric diagnoses, somatic diagnoses, qualitative parameters in antidepressant use). Since all data derived from the same regional data source, which had a consistently homogeneous population over the time period considered, it is less likely that other factors not included in this analysis affected the results.

5.1.2 Limitations

Paper I was designed as an ecological study. As a consequence, we could not assess the influence of other factors on suicide, and causality could not be inferred. Other studies, however, had been designed as case-control. The case-control design allowed analysis of causal relationships between suicide and the principal suicide risk factors, such as previous self-harm, psychiatric disorders and somatic disorders. This also allowed to study the relationship between suicide and antidepressant use at the individual level. Nonetheless, several limitations should be taken into account:

5.1.2.1 Statistical power

Suicide is a rare event. Although the study period of each paper was quite long, the sample size still hindered stratified analyses in age and gender subgroups, as in men and women younger than 30 years. Further, some stratified analyses we performed, should be interpreted with caution, due to small numbers. The odds ratio of suicide in specific diagnostic categories in

Paper II may be low powered, since the numbers are small. In Paper III, a similar limitation has to be taken into account when analyses were applied to psychiatric and somatic diagnoses in specific gender or age group, as when stratified analysis was applied in subjects adherent and not adherent to antidepressants. In Paper IV, data limitations prevented further analyses that could have yielded interesting and valuable results, such as the effect of using only one class of antidepressant or the directions and the type of treatment modifications within different antidepressant classes.

5.1.2.2 Clinical diagnoses

In Paper II, III and IV, only diagnoses at last discharge from hospital were considered. Outpatient diagnoses were not available. This may represent a misclassification of exposure, since in-patients were probably more severally ill and could be at a relatively higher suicidal risk (35, 122). On the other hand, the unavailability of outpatient diagnoses may have led to an underestimation of affective disorders (Paper II, III and IV) or anxiety disorders (Paper II), as an indication for antidepressants. Another issue is that diagnoses were clinical and not validated. Some degree of inaccuracy in the diagnostic coding, hence, should be considered.

5.1.2.3 Confounding factors

The database did not provide information on possible confounders of suicidal behavior, such as unemployment, financial loss, socio-economic status, as well as familiar history of suicide. This data gap was significant as some of these factors, for instance socio-economic conditions, have been observed to underline differences in suicide rates across Italian regions (123). Moreover, we had no information on methods of suicide, above all antidepressant poisoning. Nonetheless, we could adjust for several confounding factors, such as gender, age, affective and other psychiatric diagnoses, somatic diagnoses (Paper II, III and IV) and antidepressant treatment modifications (Paper IV).

5.1.2.4 Antidepressant prescriptions

Only publicly reimbursed prescriptions of antidepressants were included in the database. We calculated, however, that they represent more than 90% of the prescriptions filled in the Region. Furthermore, in Paper I, we had no information on the indication of antidepressants. The same limitation can be applied to the other papers, whose diagnoses was not available. This may be a minor issue, however, since other database studies indicated that antidepressants are prescribed for depression in more than half of cases (124). Another study demonstrated that Italian GPs are satisfactory in detecting moderate to severe depression (125). An additional limitation is that patients' actual adherence to antidepressant treatment could not be estimated, as in many studies based on prescription registers (92, 111, 121, 126). We tried to deal with this calculating adherence using MPR (Papers III and IV). The MPR, however, was based on DDD, that only

approximates the average recommended dose per day. A possible overestimation of drug compliance, hence, should be taken into account. Finally, we did not assess whether antidepressants were dispensed before or after hospitalizations for psychiatric or somatic disorders (Paper II and III). Nonetheless, in Paper II the current use of antidepressants was referred to the last 90 days prior to the index date and in Paper III all prescriptions were referred to the 365 days prior to the index date. Due to these limited time periods, it was not possible to assess if psychiatric and somatic disorders came before or after hospitalizations.

5.2 MAIN FINDINGS AND RELATION TO OTHER STUDIES

5.2.1 Paper I

Suicide rates in FVG decreased by 30% from 1997 to 2006, while treatment prevalence and average dosage and length of antidepressant treatment increased by 80% in the same period. The most dramatic increase was observed after SSRI became reimbursed in 1999. In 2006, 70% of individual users were prescribed SSRI. The better tolerability of SSRI, thus, may have led to higher dosages and longer duration of treatment, as previously observed in Sweden (127). Although the inverse correlation between suicide rates and antidepressant use was similar in both genders, it was more pronounced in the elderly compared to the young. Antidepressant preventive effect on suicide, thus, may be greater among elderly patients (113, 128).

Although our findings from the region were consistent with international findings (7-9, 63, 64, 73, 76, 79, 81-87), they conflicted with previous Italian studies, whose conclusions were negative towards the hypothesis that antidepressants prevent suicide (88, 89). However, more recent data from Italy up to the year 2008 (8) confirmed our hypothesis that antidepressants play a preventive role in suicides, whereas although they were based only on antidepressant sales. Data from the FVG Region permitted an analysis of the number of users of antidepressants that underestimate the DDD per 1000 inhabitants per day, and, thus, may be considered a more reliable estimate for future studies. Further, the analysis could be applied to different genders and age groups. This was of great advantage, since drug use, prevalence and incidence of depression and suicide rates greatly differ in men and women, as in older and younger subjects (79, 87, 113, 115, 129).

Finally, we observed a low use of antidepressants in suicide in the three months before death, consistent with other studies (72, 110, 111). The use of antidepressant increased from 4-6% during years 1997-1999 to 15-20% after year 2000, when SSRIs were reimbursed by NHS. Our findings therefore indicate that some of the suicide victims that were not treated, would have been saved if they had been dispensed, and taken, antidepressants.

PAPER I: IMPLICATIONS FOR SUICIDE PREVENTION

Increased individual use of antidepressants in the population may be an important factor in preventing suicide

The elderly should be considered a main target for suicide prevention with antidepressants

Suicide prevention strategies should take into account different subgroups of age and gender

5.2.2 Paper II

Findings at the individual level during years 2002-2008 indicated that 30% of suicides had been hospitalised for a psychiatric disorder, 14% had previously attempted suicide and only 16% had been currently using antidepressants at the time of death.

We found that previous non-lethal self-harm, particularly when repeated, was the strongest predictor of completed suicide, consistent with other studies (13-16). Meanwhile, psychiatric disorders, particularly affective, psychotic and personality disorders, carried the highest suicide risk, as well established in the literature (5, 24, 130-132).

It was striking that current use of antidepressants was very rare, even among cases diagnosed with affective disorders (21%) and cases who previously committed self-harm (20%). An improvement in antidepressant treatment among suicide attempters may lead to a decrease in suicide risk, as observed in Finland by Tiihonen et al. (71). Nonetheless, in FVG the number of suicides treated with antidepressants remained low, despite the drastic increase of antidepressant prescriptions in the Region (Paper I). This finding was in contrast with Swedish findings that the portion of suicides treated with antidepressants had increased to 29% in 2005 (6).

However, we found that the risk of suicide decreased by 70% as treatment duration increased from less than 20 days to 180 days and more, in line with British findings (69). We agree with Jick et al. (69) that the effect of antidepressants is greater in subjects treated for a longer period, compared to those recently diagnosed and treated. We also agree that the severity of depression may be at its worst when antidepressant treatment starts to be taken.

PAPER II: IMPLICATIONS FOR SUICIDE PREVENTION

Subjects who commit self-harm acts, particularly if repeated, and subjects with psychiatric disorders, particularly affective, psychotic and personality disorders, should be considered groups at high risk of suicide

Treatment should be improved particularly in these high risk groups

Continuous treatment with antidepressant may be an important factor in preventing suicide in depressed people

5.2.3 Paper III

Somatic disorders increased the risk of suicide by three times in FVG during years 2003-2013. This was consistent with other studies (35, 122, 133, 134). The risk was higher among subjects aged 60 years and older compared to younger, in contrast with some previous studies (35, 133), but consistent with other studies based on the elderly (135). Somatic comorbidities highly increased the risk of suicide, as also previously has been observed (35). The highest suicide risk among somatic diagnostic categories was observed in respiratory disorders. We interpreted this result assuming a possible high burden of chronic obstructive pulmonary disease (COPD) on suicidal risk, as indicated by Qin et al. (36). Further, we confirmed malignant neoplasms as an important suicidal risk factor (34). However, when stratified analysis by age groups was applied, the risk was found to increase only among the elderly.

In our data set, only 4.7% of suicides with somatic disorders had been hospitalised for affective disorders. This may indicate that depression was underdiagnosed, since concomitant depression has been found to be common in many somatic disorders (35, 39, 42, 48-51, 136). This observation is crucial, since we found that the risk of suicide in subjects who adhere to antidepressants in the 365 days prior to death was not significantly increased, while the risk increased by more than three times when subjects were not prescribed or did not adhere to antidepressants.

Forty per-cent of suicides were prescribed antidepressants one year prior to death, but only 11.5% adhered to treatment.

PAPER III: IMPLICATIONS FOR SUICIDE PREVENTION

Somatic disorders should be considered an independent risk factor of suicide, particularly in older subjects and subjects with multiple disorders

Depression is probably underdiagnosed in many somatic disorders. Antidepressants should be prescribed in case of somatic disorders with depressive symptoms, since adequate treatment with antidepressants may decrease the risk of suicide

Primary care and hospital care should be better integrated in order to identify, follow up and treat subjects at a higher suicide risk

5.2.4 Paper IV

Findings at the individual level during the years 2005-2014 confirmed that SSRI was the most frequently prescribed antidepressant class. SSRI was the only class of antidepressants positively associated to suicide risk. This association to suicide was in contrast with a previous register study (70) and a study based on toxicological screening (65). The finding is not easily explainable. It is possible that it might be an effect of confounding bias, since the prescribing of SSRIs is more frequent among GPs, who might be less able to monitor treatment and to assess and manage suicide risk when compared to psychiatrists (121, 126, 137). In Italy, however, GPs are the main antidepressant prescribers.

Our main finding, however, was that a decreasing trend in suicide risk was observed, among subjects who adhere to or currently use antidepressants, compared with those who do not currently use or adhere. Previous findings from Denmark indicated a low suicide risk in subjects continuously treated with antidepressants, using the number of prescriptions as parameter of continuous use (92, 94). However, we did not find other studies using two different qualitative parameters on antidepressant use to compare the risk of suicide in a general population.

Other interesting findings regarded the low adherence to SSRI compared to TCA when these classes were analysed separately without taking into account treatment modifications. This might be one possible explanation of TCAs lower association to suicide. It might also reflect a lower efficiency of SSRI as compared to TCA (92). Nonetheless, a low adherence was found for all antidepressant classes, consistent with our previous studies, as well as other Italian (103, 104, 137) and international findings (108, 121).

PAPER IV: IMPLICATIONS FOR SUICIDE PREVENTION

An adequate use of antidepressants (i.e. at adequate dosage and for a proper length of time) is crucial in achieving a better preventive effect

Treatment-resistant depression and lower adherence to antidepressants should be considered possible precipitating factors of suicide

Clinicians should monitor treatment in order to ascertain that antidepressants are properly used

6 CONCLUSIONS

Each suicide is a tragic event, and it is of great importance to identify risk factors that can be targets for suicide prevention. A better knowledge of suicide epidemiology in a well-defined population may contribute to developing appropriate interventions. This is crucial for health care, since most suicides suffer from mental and medical disorders. This is also crucial for stakeholders, since resources can be allocated on scientific basis.

The four papers included in this thesis provide a picture of the principal suicide risk factors related to health care in FVG, a region with a high rate of suicide. In particular, the possibility of preventing suicide through antidepressant medication was particularly analysed. Since the regional register of FVG could provide data on the individual level, this research gives unique information of great scientific value.

As previously reported at the international level, as well as in Italy as a whole, FVG has experienced a decline in suicide rates in parallel with an increase in antidepressant use. This was assessed in our research using data on individual users of antidepressant in different genders and age groups.

The present thesis has highlighted that the risk of suicide was elevated in subjects who previously had committed non-lethal self-harm and in subjects diagnosed with affective and non-affective psychiatric disorders, and in those suffering from somatic disorders. The elderly are identified as a main target for suicide prevention strategies, particularly if they have been hospitalised for somatic illnesses. When assessed at the individual level, it was observed that the use of antidepressants at a proper dosage and for a proper length of time was associated with a decreased risk of suicide. This finding indicates the importance of diagnosing underlying depression in somatic disorders. However, a general finding was that antidepressants appear underused, also in high-risk populations.

Notwithstanding the limitations, our research has supported the original *a priori* hypothesis of this research project: that treatment with antidepressant medication lowers the risk of suicide. Accordingly, more effort should be given to better identify high-risk groups of suicide and to improve antidepressant treatment in these groups. Since suicide victims were generally not hospitalised, and antidepressants in Italy mainly are prescribed in primary care settings, it appears crucial to involve primary care physicians in such efforts.

7 FUTURE PERSPECTIVES

There is a need or further investigation of suicide - it is a complex phenomenon -, and the pathways that lead to suicide should be examined in greater detail. The findings presented in this thesis can contribute to a better understanding of risk factors of suicide in relation to health care, as well as its prevention.

Our findings, however, highlighted the need to deepen the research on different genders and age subgroups. We demonstrated, for instance, that the elderly are at the highest risk of suicide, but research on suicide prevention in the elderly appears to be sparsely investigated area (138). The Regional database will enable future projects focused on the elderly. Preliminary data from the Region indicates that suicide rates in ageing population are higher in isolated areas than those in urban areas. Information available from the Regional database, such as the prevalence of psychiatric disorders, somatic disorders and antidepressant prescriptions, can be integrated with information on geographical distribution of suicides, deprivation index and distance from the closest mental health service. Spatial analysis may provide, thus, a visualization of areas with higher suicide rates and a relevant amount of information on suicide victims. As a consequence, multidisciplinary prevention strategies may be used, such as training programs for identified gatekeepers (e.g. health workers, educators, primary care providers) in order to recognize and treat vulnerable persons (139). Further, follow-up and community support may also be used for suicide attempters (140). This may enhance the development of prevention strategies that could be focused on small communities and would benefit from the collaboration between such communities and health care. Such a project may be expanded to other Italian regions that experience high suicide rates in the elderly. For instance, a preliminary project design has been developed in collaboration with the Italian Region of Sardinia.

Further research may enhance knowledge on specific somatic disorders and suicide. A first step may be developing studies on cancer, since previous Italian studies have indicated a greater risk of suicide among cancer patients (141, 142). The FVG Region has a Cancer Registry (RT-FVG), where all incident cases of malignant neoplasms in the regional population since 1995 are registered. The RT-FVG may provide information on the date of cancer diagnosis and the cancer histotype based on Anatomy Pathology Reports, in addition to other information available from Regional health database used in this project (SISSR). This may foster a better understanding of demographic factors linked to suicide and cancer, the histotypes of cancer more closely associated with suicide, the occurrence of suicides after diagnosis of neoplasms and discharge from hospital, the comorbidity with psychiatric disorders and the possible role of antidepressants in preventing self-harm among cancer patients. Future research may also investigate less studied medical illnesses here identified as predictors of suicide, such as respiratory and cardiovascular disorders.

Finally, a limitation of our studies was that data from regional outpatient services were not available in the database. In the current year, a new Informative System will be developed in the Region of FVG in order to collect epidemiological data from outpatient mental health services. When this system is in place, data will be available that can be linked with data on hospitalisations and drug prescriptions. The challenge for the future is to perform suicide research along these lines.

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