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Version of Record: https://www.sciencedirect.com/science/article/pii/S0022395621002259
Manuscript_334512b57027aaa5977fad01506cc61a

A pharmacoepidemiological study of the impact of psychotropic drugs on suicide reattempts.

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Running title: Pharmacoepidemiology of suicidal behaviour.

Abstract: 220 words

Main text: 3129 words

Tables and Figures: 3 tables and 1 figure

Acknowledgements: The authors acknowledge the support of the French WHO Collaborating Center in Mental Health and the French “Groupement d’Etude et de Prevention du Suicide” (GEPS).

Sources of Funding: The first author of this study received a financial support from the “Groupement d’Etude et de Prevention du Suicide” (GEPS) for this research.

Disclosures: The authors have no conflict of interest to disclose.

Abstract

INTRODUCTION: Recent pharmacoepidemiological studies have suggested that certain classes of psychotropic drugs could be considered protective or risk factors for suicidal behaviour. However, very few studies have explored the association between certain classes of psychotropic drugs and the risk of suicide attempt (SA) or death by suicide for patients who previously attempted suicide.

METHOD: The association between the different classes of psychotropic drugs and suicide reattempt within 6 months was assessed in a prospective observational cohort of 972 subjects from the ALGOS study from January 2010 to February 2013. Secondary outcomes were the role of psychotropic drugs on suicide reattempt within 14 months, the impact of combination pairs and treatment efficacy for suicide reattempt.

RESULTS: Our main results did not show an association between psychotropic drug use and suicide reattempt after 6 months of follow-up. We demonstrated that the use of benzodiazepines (HR=1.87 [1.25;2.81], p<0.01) and hypnotics (HR=1.49 [1.03;2.17], p=0.04) or a combination of both (HR=1.80 [1.17;2.72], p=0.01) were associated with suicide reattempt within 14 months after a previous SA.

CONCLUSION: The early identification of the positive association between psychotropic drugs and the risk of suicidal behaviour is of high importance for the prevention of suicide reattempts. Special precautions should probably be taken when prescribing psychotropic drugs for these subjects particularly at risk of suicide reattempt.

Keywords: Suicide, suicide attempt, pharmacoepidemiolgy, psychotropic drug.

Key points:

- Certain classes of psychotropic drugs have already been considered as potential protective or risk factors for suicidal behaviour
- Benzodiazepines and hypnotics consumptions presented an increased risk of suicide reattempt within 14 months after a suicide attempt
- Special precautions should probably be taken when prescribing benzodiazepines or hypnotics after a non-fatal suicide attempt

Introduction

For several decades, despite a decrease in the number of deaths, suicide remains one of the leading causes of avoidable death worldwide, especially among individuals aged 15 to 24 years old (Fazel and Runeson, 2020). Moreover, a high number of individuals present to health care services for suicide attempts (SAs) in France every year (Chan Chee and Jezewski Serra, 2014). Among patients who have previously self-harm, 12.4% reattempted and 2.6% died within a year (Vuagnat et al., 2019). According to various studies, the period with the highest risk of reattempt or death by suicide seems to occur during the first 6 months after an SA (Owens et al., 2002; Vuagnat et al., 2019).

Several study designs have explored the relationship between drugs and suicidal events, such as pharmacoepidemiologic studies evaluating drug use, efficacy, risk of adverse effects and mortality in large populations (Thaker et al., 2015). Interestingly, it has been shown that patients who died by suicide were dispensed more psychotropic medication than the general population, including antidepressants, anxiolytics and hypnotics (Reneflot et al., 2019). The increasing number of psychotropic prescriptions before death by suicide can be easily explained by the increased severity of depression that may be experienced prior to dying by suicide. However, in recent years, pharmacoepidemiological studies have suggested that certain classes of drugs may have effects on suicidal behaviour and can thus be considered protective or risk factors (Courtet, 2016; Demotes-Mainard et al., 2006; Gibbons and Mann, 2011). Indeed, the protective effects on suicidal behaviour of lithium in patients suffering from mood disorders and clozapine in schizophrenia patients have been demonstrated for many years (Cipriani et al., 2013; Hennen and Baldessarini, 2005). Nevertheless, an increase in suicidal risk has been associated with several drugs, such as antidepressants, anticonvulsants, and medications used for smoking cessation (Fergusson et al., 2005; Moore et al., 2011; Patorno et al., 2010). Moreover, the same psychotropic treatment may be a protective factor or a risk factor depending on the patient's clinical features, such as age. For instance, antidepressants lead to an increased risk of deliberate self-harm for patients under 24 years of age and a decreased risk for adults older than 24 years (Miller et al., 2014).

It has also been suggested that an adequate psychotropic drug prescription for a mental illness may decrease the risk of suicide (Gianatsi et al., 2020; Oquendo et al., 1999).

For example, while depression is a common risk factor for suicidal behaviour, treatment with antidepressants may reduce the risk of suicide (Hawton et al., 2013; Zalsman et al., 2016). However, among patients suffering from major depressive disorder, only 21.2% are treated with an antidepressant and 18.4% with only anxiolytics (Bryson et al., 2004). The same findings were observed in subjects suffering from schizophrenia for whom treatment with antipsychotics reduced the risk of death by suicide (Lester, 2009). In contrast, among subjects who died by suicide, 24% did not receive any treatment even though a psychiatric diagnosis had been established (Gianatsi et al., 2020).

To our knowledge, patients with a history of previous SA present a higher risk of suicide reattempt (Christiansen et al., 2007; Large et al., 2011; Vuagnat et al., 2019), and the role of psychotropic drugs on the risk of suicide reattempt is unclear. In addition, most studies about psychotropic drug prescriptions did not take into consideration the psychiatric diagnosis for which the treatment has been prescribed, while psychiatric disorders increase to the risk of suicidal behaviour (Fazel et al., 2019). Furthermore, the use of appropriate prescriptions in accordance with the patient's mental disorder seems to be central for preventing suicide among these high-risk patients.

The objective of the present study is to determine the prescription patterns of psychotropic drugs and the association between certain classes of drugs or the concurrent use of these classes and the risk of suicide reattempt within 6 months after a previous SA.

Method

Study Design

A prospective observational cohort of 972 subjects from the ALGOS study was used for the analysis. The ALGOS study is a multicentric, prospective, single-blind, randomized and controlled clinical trial with two parallel groups. Participants in the intervention group received a brief contact intervention for 6 months (Vaiva et al., 2011), and control participants did not receive any intervention. Both groups were used in the present study. This study was conducted in 23 French emergency services. Patients included were men and women of legal age with a previous SA in the 7 days prior to inclusion, regardless of the method used for the SA. Patients with no suicidal intent, those who were homeless, those who were under guardianship, or patients with more than 4 SAs in the last 3 years were excluded from the study. All participants of the ALGOS study provided signed consent.

This study received authorization from AFFSAPS (number NCT01123174) and was approved by the Committee for the Protection of Persons in the North-West Region (CPP North-West decision 09/63). The ALGOS study was registered in ClinicalTrials.gov (NCT01123174).

Collected data

At inclusion, sociodemographic characteristics (age, gender, family and work status), the number of previous SAs, the method of SA (drug overdose, acute alcohol use) and a questionnaire based on Beck's intentionality scale were collected for all subjects.

At 6 and 14 months, the psychotropic drugs taken by the patients since inclusion, the psychiatric diagnosis by using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), the number of suicide reattempts and the date of the first reattempts were assessed for all participants through a standardized telephone interview.

Primary and secondary outcomes

First, the primary outcome focused on the association between the different classes of psychotropic drugs and the occurrence of suicide reattempt within 6 months. The same association within 14 months was assessed as a secondary outcome. Moreover, the role of the adequacy between the medication and the psychiatric diagnosis was assessed. A drug

prescription was found to be adequate when it was prescribed for the appropriate mental illness according to the current guidelines (e.g., antidepressants prescribed for patients suffering from major depressive disorder).

Statistical analysis

Descriptive analysis

Descriptive statistics were calculated for sociodemographic characteristics, psychiatric diagnoses, psychotropic drug classes consumed and treatment combinations. Continuous variables are presented as the means and standard deviations (SD). Variables with nonnormal distributions are reported as the median and first and third quartiles (Q1-Q3). The 95% confidence intervals (95% CIs) were calculated using the central limit theorem. Discrete variables are expressed as frequencies and percentages. Finally, for patients whose status regarding suicide reattempt and drug consumption were known, the Kaplan-Meier estimate enabled us to draw survival curves and to estimate SA-free survival. Curves were stratified according to psychotropic drug consumption.

Analysis of primary and secondary outcomes

First, missing data were imputed using the multiple imputation method, assuming the data were missing at random. Thus, 50 imputed datasets were generated and combined according to Rubin's rules using the MICE package of the R software (Van Buuren and Groothuis-oudshoorn, 2011). After imputation for missing data, the relationship between the different drug classes, psychiatric diagnosis, randomization group, sociodemographic factors, and suicide reattempt within 6 months was assessed using a bivariate Cox model. Then, variables with a p value under 0.2 in the previous analysis were studied using a multivariate Cox model with a descendant stepwise variable selection, and p values were considered significant under 0.05. The secondary outcomes were evaluated with the same method. R software version 3.6.1 was used for all analyses.

Results

Patients at inclusion

A total of 972 participants were included in the study (cf. **Table 1**). More than half of the subjects included were women (63.6%) and first-time attempters (53.3%), with an average age of 38 years old. The most common method of SA prior to inclusion was medication overdose (94%).

Insert table 1 about here.

Psychotropic drug consumption

Since inclusion, half of the patients benefited from antidepressants (48.1% at 6 months and 50.5% at 14 months) and anxiolytics (47.2% at 6 months and 48.4% at 14 months) (cf. **Table 2**). Approximately one-fifth of the patients consumed hypnotics (20.7% at 6 months and 25% at 14 months). Concomitant use of antidepressants and benzodiazepines was relatively frequent at 6 and 14 months after SA (28.4% and 30.9%, respectively), such as the concurrent use of antidepressants and hypnotics (14.2% at 6 months and 17.4% at 14 months) or benzodiazepines and hypnotics (14% at 6 months and 15.6% at 14 months).

Insert table 2 about here.

Of 880 participants re-contacted at 6 months after inclusion, 117 (13.3%) had reattempted suicide. At 14 months after inclusion, 173 (21.1%) had reattempted suicide. The most common psychiatric diagnosis corresponded to mood disorders (198 (29.2%) at 6 months and 152 (24.4%) at 14 months), anxiety disorders (193 (28.5%) at 6 months and 114 (18.2%) at 14 months) and alcohol use disorders (124 (18.3%) at 6 months and 103 (16.3%) at 14 months).

Missing data

The patient's status regarding suicide reattempt was missing for 9.5% of participants at 6 months and 15.8% at 14 months. Psychotropic drug consumption was only known for

670 patients at 6 months and 628 patients at 14 months. Additionally, only 678 and 630 patients agreed to complete the MINI at 6 months and 14 months, respectively.

Survival curve analysis

The SA-repeat-free survival curves within 14 months were stratified according to psychotropic drug consumption and are presented in **Figure 1**. Within 6 months after SA, survival probability seems similar for the different psychotropic classes except for lithium, anticonvulsants and maintenance treatment of alcohol dependence. Treatment with lithium seems to provide a higher survival probability, whereas anticonvulsants and maintenance treatment of alcohol dependence show lower survival probabilities. The lowest survival probability within 14 months after SA was found for the consumption of sedative antipsychotics, anticonvulsants and maintenance treatment for alcohol dependence.

Insert Figure 1 about here.

Association between psychotropic classes and the risk of suicide reattempt within 6 months (primary outcome)

None of the psychotropic drug classes or combination pairs were associated with suicide reattempt within six months after SA in the multivariate Cox model (cf. **Table 3**). However, a history of previous SA before the index SA (hazard ratio with 95% CI (HR)=1.63 [1.12;2.37], p=0.01), mood disorders (HR=1.58 [1.12;2.37], p=0.01) and anxiety disorders (HR= 1.96 [1.30;2.96], p<0.01) were risk factors for suicide reattempt within 6 months.

Insert table 3 about here.

Association between psychotropic classes and the risk of suicide reattempt within 14 months

Within 14 months after SA, the use of benzodiazepines was statistically associated with suicide reattempt (HR=1.87 [1.25;2.81], p<0.01), such as the use of hypnotics (HR=1.49 [1.03;2.17], p=0.04), a history of more than 1 previous SA (HR=1.65 [1.22;2.23], p<0.01) and

substance use disorder (HR=1.74 [1.20;2.53], p<0.01) after adjustment for confounding variables.

Concurrent use of classes and the risk of suicide reattempt within 6 and 14 months

None of the combination pairs of psychotropic drug classes were associated with suicide reattempt within 6 months. Nonetheless, concomitant use of benzodiazepines and hypnotics was also associated with an increased risk of suicide reattempt within 14 months (HR=1.80 [1.17;2.72], p=0.01).

Adequacy between psychiatric diagnosis and psychotropic drug consumption

Patients suffering from anxiety disorder and major depressive disorder seem to benefit from appropriate drug prescriptions (73.3% and 65.3% at 6 months, respectively; 81.2% and 81.6% at 14 months, respectively), whereas half of patients suffering from bipolar disorder or psychotic disorder had inadequate consumption (55.6% and 50% at 6 months, respectively; 59.5% and 40% at 14 months). Adequacy between mental disorders and psychotropic drug prescriptions was not significantly associated with the risk of suicide reattempt within 6 and 14 months.

Discussion

Here, we present the first pharmacoepidemiological study exploring the risk of re-offending associated with the use of psychotropic drugs in patients who have already attempted suicide. While our main results did not show an association between psychotropic drug use and suicide reattempt after 6 months of follow-up, we demonstrated that the use of benzodiazepine and hypnotics or a combination of both were associated with suicide reattempt within 14 months after a previous SA. We also found good adequacy between mood and anxiety disorders and psychotropic drug consumption but poor adequacy for bipolar or psychotic disorders. However, treatment efficacy does not seem to be associated with suicide reattempt at 6 or 14 months.

We found that the use of benzodiazepines was a risk factor for suicide reattempt within 14 months after an SA, with an almost two-fold increase in the risk of reattempt (HR=1.87 [1.25;2.81], p<0.01). This result seems to be important given the widespread prescription of benzodiazepines in France (Benard et al., 2017). A recent review of placebo-controlled trials and case-control studies in a variety of populations also found that benzodiazepine use is associated with an increased risk of SA or death by suicide (Dodds, 2017). The authors of this review hypothesized that benzodiazepine consumption is increasing aggression and impulsivity or that discontinuation or reduction in dosage may be responsible for withdrawal or rebound in symptoms. Nevertheless, in 2002, a study no longer found an association between benzodiazepine use and SA after adjustment for borderline personality disorder (BPD) (Lekka et al., 2002).

According to our results, hypnotic use also appears to be a risk factor for suicide reattempt within 14 months after an SA (HR=1.49 [1.03;2.17], p=0.04). A review of the scientific literature similarly highlighted that most studies found an association between the use of hypnotics and the risk of suicide (Wang et al., 2016). More specifically, a recent epidemiological study found a higher risk of suicide with Zolpidem use after 80 months of observation (HR=2.01 [1.58;2.56], p < 0.001). However, the main limitation of these studies was that none of them adjusted the analyses for possible confounding factors such as depression or sleep disorders. While our analysis was adjusted for mood disorders, the involvement of sleep disorders in suicidal behaviour has also been demonstrated and was not assessed in our study (Malik et al., 2014; Pigeon et al., 2012). The analysis of the

National Comorbidity Survey Replication also highlighted that hypnotic use in the past year was significantly associated with SA (adjusted OR = 3.4; $p < 0.01$) after adjustment for sleep disturbances and was a stronger predictor than insomnia for SA (Brower et al., 2011). The causal effect of hypnotic medication on suicidal behaviour is not clear. It has been suggested that hypnotics may cause parasomnias or an impairment of judgement and promotion of violent and risky behaviours that may lead to suicidal ideations (McCall et al., 2017).

An analysis of drug class combinations taken during the 14 months following inclusion showed an almost two-fold higher risk of SA with concomitant use of benzodiazepines and hypnotics (HR=1.80 [1.17;2.72], p=0.01). The study of the relationship between drug class combinations and the risk of SA seems to have rarely been explored in the current scientific literature. A Korean case–control study based on the National Health Insurance Service found a 2.80-fold higher risk of suicide among patients taking benzodiazepines and antidepressants with zolpidem than in those taking zolpidem alone (adjusted OR= 2.80 [1.38;5.70])(Sung et al., 2019). Regarding elderly individuals, a Swedish case-control study found a four-fold increased risk of suicide among seniors who used sedative or hypnotic treatments after adjustment for psychiatric diagnosis (Carlsten, 2009).

Interestingly, different studies have assessed the association between the different classes of psychotropic drug consumption and the risk of suicidal behaviour in other specific populations. Among schizophrenia patients, the use of benzodiazepine was also associated with an increased risk of death by suicide (HR=3.83 [1.45;10.12])(Tiihonen et al., 2012). Concerning elderly individuals, the same results were found in a population-based study with an association between benzodiazepine use and a higher suicide risk (Voaklander et al., 2008).

Strengths and limitations

One of the strengths of this study is the relatively high number of participants included with a distribution of sociodemographic and clinical characteristics that are typically found in a natural cohort of individuals who attempted suicide. Moreover, studies on psychotropic drugs and suicide are challenged by confounding by indication bias, whereby suicidal patients are prescribed psychotropic medications because they are seeking treatment due to increased distress. To counter this bias, the analysis was adjusted for psychiatric diagnosis to improve the interpretation of the results. For instance, we did not

find any association between maintenance treatment for alcohol dependence and suicide risk after adjustment for substance use disorder, which is a main risk factor for suicidal behaviour (Yuodelis-Flores and Ries, 2015).

This study also has some limitations. First, there was a large amount of missing data, sometimes as much as 35% of the data depending on the variable studied. Nevertheless, this bias was reduced by using multiple imputation for missing data, thus generating 50 imputed tables that were combined for the analyses. Second, the retrospective information collection during telephone interviews at 6 and 14 months after inclusion also exposes to the risk of loss of information. Then, we a priori set the alpha threshold at 0.05 despite multiple testing. Indeed, only one multivariate model was used for primary outcome assessment, and secondary outcomes are exploratory results and do not pretend to demonstrate a causal link. Finally, this study analysed classes of psychotropic drugs, but the study design does not permit an assessment of more specific effects of certain subclasses or drugs such as lithium (too few patients were benefiting from it) or the effect according to the daily dose prescribed.

Perspectives

The objective of the ALGOS study was to assess a post-hospital monitoring device for suicidal patients by following the ALGOS algorithm. The analysis of the drug consumption of participants during the telephone interviews brought a new dimension to this study through a pharmacoepidemiological approach. Nevertheless, the evaluation of drug prescriptions on a larger scale in national registries could allow for more specific analyses of certain subclasses of psychotropic drugs or certain medications. In addition, sleep disorders, the impulsivity dimension and borderline personality disorders are widespread in the psychiatric population and in suicidal patients. Their consideration in a future study would allow for better adjustment of these confounding factors and more specific analyses of the pharmacological effect of drug classes.

Conclusion

This study investigated the psychotropic drug prescription patterns and the association between the prescription of certain classes and a higher risk of suicide reattempt within 14 months. Therefore, benzodiazepine and hypnotic uses were found to be risk factors for suicide reattempt within 14 months. The early identification of the positive association between psychotropic drugs on this risk of suicidal behaviour is important for the prevention of suicide reattempt. Special precautions should probably be taken when prescribing psychotropic drugs for individuals with a previous SA, particularly those at risk of suicide reattempt, such as prescribing with greater vigilance and prescribing appropriate treatments based on the psychiatric diagnosis. A more personalized pharmacological approach to patients who attempted suicide is necessary to prevent suicide reattempts or deaths by suicide.

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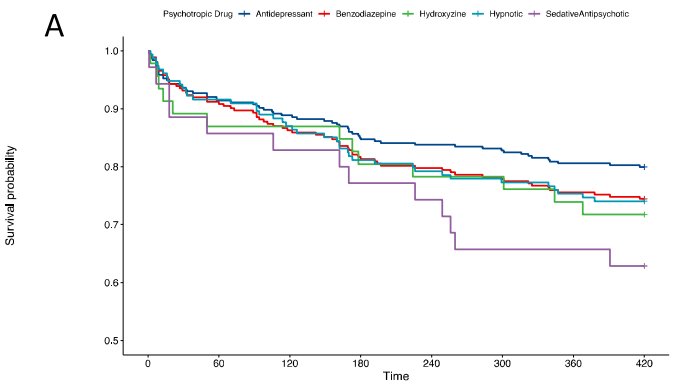
Table 1. Baseline Characteristics of Participants.

Characteristics	All Patients (N = 972)
Intervention group	
ALGOS	480 (49.4)
Control	492 (50.6)
Age, mean ± SD	38 ± 13.3
18–35 y	226 (23.3)
36–55 y	558 (57.4)
> 55 y	188 (19.3)
Sex	
Men	354 (36.4)
Women	618 (63.6)
Marital status	
Single	515 (53.1)
In couple	455 (46.9)
Working status	
Employed	619 (63.9)
Unemployed	349 (36.1)
First attempt	518 (53.3)
Suicide attempt by medication overdose	912 (94)
Suicide attempt with acute alcohol use	417 (43.7)

Table 2. Psychotropic drug classes and combination pairs used since inclusion evaluated at 6 and 14 months. *(*1 number of patients having at least this treatment, irrespective of other treatments; 2 number of patients having at least this pair of treatments, irrespective of other treatments)

Psychotropic drugs	**6 months (N= 670)**	**14 months (N= 628)**
Antidepressants[1]	322 (48.1)	317 (50.5)
Anxiolytics[1]	316 (47.2)	304 (48.4)
Benzodiazepines[1]	267 (39.9)	263 (41.9)
Hydroxyzine[1]	45 (6.7)	46 (7.3)
Sedative antipsychotics[1]	26 (3.9)	35 (5.6)
Hypnotics[1]	139 (20.7)	157 (25.0)
Analgesics[1]	58 (8.7)	66 (10.5)
Anticonvulsants[1]	42 (6.3)	35 (5.6)
Antipsychotics (others) [1]	30 (4.5)	33 (5.3)
Lithium[1]	5 (0.7)	10 (1.6)
Maintenance treatment of alcohol dependence[1]	25 (3.7)	27 (4.3)
Opioid maintenance therapy[1]	2 (0.3)	3 (0.5)
At least one psychotropic drug	451 (67.4)	442 (70.4)
Combination pair		
Antidepressant - Benzodiazepine[2]	190 (28.4)	194 (30.9)
Antidepressant - Hydroxyzine[2]	31 (4.6)	32 (5.1)
Antidepressant - Hypnotic[2]	95 (14.2)	109 (17.4)
Benzodiazepine – Hypnotic[2]	94 (14.0)	98 (15.6)
Benzodiazepine – Analgesics[2]	23 (3.4)	33 (5.3)


A
Psychotropic Drug
Antidepressant
Benzodiazepine
Hydroxyzine
Hypnotic
SedativeAntipsychotic
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0
60
120
180
240
300
360
420
Time

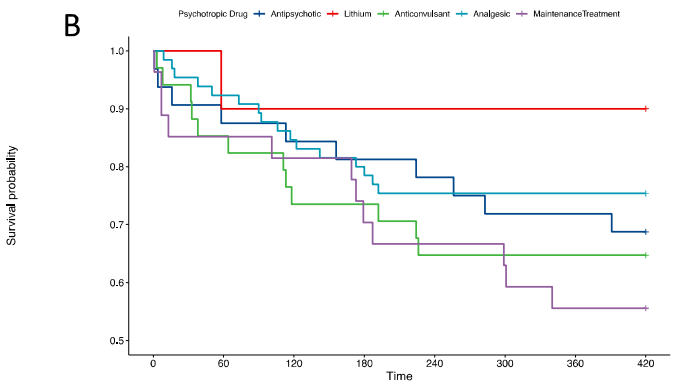

B
Psychotropic Drug
Antipsychotic
Lithium
Anticonvulsant
Analgesic
MaintenanceTreatment
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0
60
120
180
240
300
360
420
Time

Table 3. Association between classes of psychotropic drugs and SA reattempt within 6 and 14 months.

Factor	6 months				14 months			
	HR (95CI)*	p*	adjusted HR (95CI)**	p**	HR (95CI)*	p*	adjusted HR (95CI)**	p**
Randomization group (ref.=ALGOS)								
Control	1.34 [0.94;1.92]	0.10			1.27 [0.94;1.70]	0.12		
Sex (ref.=male)								
Female	0.82 [0.57;1.18]	0.29			0.88 [0.65;1.18]	0.39		
Age (ref.= 18-26)								
26-50	1.85 [1.09;3.13]	0.02			1.66 [1.07;2.57]	0.02		
> 50	1.72 [0.94;3.17]	0.08			1.53 [0.92;2.54]	0.10		
Non-First-time attempter	1.79 [1.23;2.59]	<0.01	1.63 [1.12;2.37]	0.01	1.83 [1.36;2.47]	<0.01	1.65 [1.22;2.23]	<0.01
Marital status (ref.= single)								
In couple	0.79 [0.55;1.15]	0.22			0.78 [0.58;1.06]	0.11		
Working status (ref.= employed)								
Unemployed	1.31 [0.92;1.88]	0.14			1.31 [0.97;1.76]	0.07		
<u>Psychiatric diagnosis</u>								
Mood disorder	2.18 [1.47;3.24]	<0.01	1.58 [1.12;2.37]	0.01	1.72 [1.25;2.38]	<0.01		
Anxiety disorder	1.50 [1.03;2.18]	0.04			1.95 [1.41;2.70]	<0.01		
Psychotic disorder	1.27 [0.8;2.02]	0.30			1.88 [1.33-2.65]	<0.01		
Substance use disorder	2.42 [1.67;3.52]	<0.01	1.96 [1.30;2.96]	<0.01	2.38 [1.73;3.29]	<0.01	1.74 [1.20;2.53]	<0.01
Eating disorder	1.13 [0.72;1.77]	0.59			1.70 [1.21-2.40]	<0.01		
<u>Psychotropic drug</u>								
Antidepressant	1.69 [1.09;2.61]	0.02			1.44 [1.01;2.06]	0.05		
Benzodiazepines	1.86 [1.19;2.89]	0.01			2.48 [1.67;3.67]	*<0.01*	1.87 [1.25;2.81]	<0.01
Sedative antipsychotics	1.47 [0.96;2.26]	0.07			2.07 [1.47;2.94]	*<0.01*		

Hydroxyzine	1.53 [1.05;2.23]	0.03			1.81 [1.24;2.63]	*<0.01*		
Hypnotics	1.47 [0.99;2.18]	0.06			2.26 [1.64;3.13]	<0.01	1.49 [1.03;2.17]	0.04
Other antipsychotics	1.44 [0.96;2.15]	0.08			1.96 [1.40;2.74]	<0.01		
Lithium	1.37 [0.88;2.14]	0.16			1.74 [1.23;2.45]	<0.01		
Anticonvulsants	1.52 [1.04-2.21]	0.03			2.19 [1.61;2.98]	<0.01		
Analgesics	1.37 [0.94;2.01]	0.10			1.90 [1.38;2.62]	<0.01		
Maintenance treatment of alcohol dependence	1.62 [1.05;2.50]	0.03			2.08 [1.47;2.94]	<0.01		
<u>Combination pair</u>								
Antidepressant and Hypnotic	1.38 [0.92;2.07]	0.12			2.06 [1.46;2.91]	<0.01		
Antidepressant and Benzodiazepine	1.48 [0.97;2.26]	0.07			2.10 [1.42;3.10]	<0.01		
Antidepressant and Hydroxyzine					1.77 [1.23;2.53]	<0.01		
Benzodiazepine and Hypnotic	1.57 [1.03;2.38]	0.04			2.42 [1.69;3.46]	<0.01	1.80 [1.17;2.72]	0.01
Benzodiazepine and Analgesic					2.02 [1.43;2.85]	<0.01		
<u>Treatment adequacy</u>								
Major depressive disorder	1.14 [0.58;2.28]	0.70			0.92 [0.48;1.78]	0.80		
Anxiety disorder	1.37 [0.59;3.21]	0.46			1.27 [0.55;2.93]	0.56		
Bipolar disorder	0.94 [0.45;1.97]	0.88			0.94 [0.43;2.04]	0.87		
Psychotic disorder	1.21 [0.62;2.38]	0.58			1.09 [0.54;2.21]	0.81		
Alcohol use disorder	1.08 [0.40;2.93]	0.88			1.28 [0.68;2.41]	0.44		

** Hazard ratio and p-value estimated by bivariate Cox model*

*** Adjusted hazard ratio and p-value estimated by multivariate Cox model*

p = p value