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Repeated self-poisoning: an addictive rather than a suicidal behaviour?

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UNIVERSITE GRENOBLE ALPES
FACULTE DE MEDECINE DE GRENOBLE

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N°

Intoxications médicamenteuses volontaires répétées :
Une conduite addictive plutôt que suicidaire ?

THESE

PRESENTEE POUR L'OBTENTION DU DOCTORAT EN MEDECINE

ASMA FARES

[Données à caractère personnel]

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE MEDECINE DE GRENOBLE*

Le Mardi 23 Mai 2017

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Résumé

Contexte

L'intoxication médicamenteuse volontaire (IMV) est le mode le plus fréquent de tentative de suicide. Les mécanismes et la prévention optimale de sa récurrence demeurent méconnus.

Méthodes

Une étude rétrospective sur dossiers médicaux au CHU de Grenoble en 2012 a identifié les facteurs de risque d'une première IMV, seconde et troisième ou plus (3+), les taux de réadmission et les coûts.

Résultats

730 IMV pour 645 patients ont été analysées et 57% étaient une récurrence. Un antécédent de scarification et un suivi médical en cours ou interrompu étaient associés à la récurrence. Les sujets 3+ étaient plus à risque d'être sans emploi, de trouble de la personnalité, d'usage du tabac, de mésusage de l'alcool, d'ingérer des benzodiazépines pour leur IMV et d'être réadmis à un an pour le même motif (9%, 15% et 30% en cas de première, seconde et 3+ IMV). L'idéation suicidaire (49%) et la préméditation (10%) étaient similaires entre les groupes. Le coût des IMV répétées s'élevait à 902 mille euros, représentant 54% du coût total des IMV en 2012.

Conclusion

Une vulnérabilité à l'usage du tabac et au mésusage de l'alcool, l'usage de benzodiazépines pour l'IMV, un binge-drinking associé, la chronicité des IMV, l'absence d'idéation suicidaire dans 51% des IMV et la grande part d'actes impulsifs (10% d'IMV préméditées) chez les sujets 3+ peuvent évoquer un mésusage des psychotropes, à l'origine des récurrences.

Les IMV répétées s'apparenteraient à des prises médicamenteuses massives sur un temps restreint (binge-drugging). L'évaluation de la consommation des benzodiazépines (abusives, répétées, impulsive-compulsive-automatique) est déterminante afin de proposer des soins adaptés. L'évolution des politiques restreignant l'accès aux benzodiazépines doit être poursuivie.

Mots-clés: Intoxications médicamenteuses volontaires, répétition, addiction, tentative de suicide, facteurs de risque, réadmission, coût, économie

Repeated self-poisonings with benzodiazepines: an addictive rather than a suicidal behaviour?

Abstract

Background

Self-poisoning (SP) is the leading self-harm method. Mechanisms of SP repetition (SP-r) are poorly understood and questions remain regarding its optimal prevention.

Methods

A chart review was undertaken to compare admissions for a first, a second, or a third and more (3+) SP in 2012 in a French university hospital. Risk factors for SP-r were identified using multinomial logistic regressions. Readmission rates and hospital costs were assessed.

Results

730 SPs for 635 patients were analysed and 418 (57%) SPs corresponded to a repetition. A cutting self-harm history, a specialised or an interrupted mental follow-up were associated with the SP-r. Multiple repeaters (3+) were more likely to be unemployed, suffering from personality disorders, tobacco use and alcohol misuse, ingesting benzodiazepines, and being readmitted for a SP within one year (9%, 15%, and 30% in non-, first- and multiple repeaters respectively). The suicidal ideation (49%) or premeditation (10%) were similar between the groups. SP-r contributed 54% (EUR 902 k) of the hospital costs related to SPs.

Conclusion

The vulnerability to tobacco use and alcohol misuse, the use of benzodiazepines, the associated binge-drinking, the SP chronicity, the absence of suicidal ideation in 51% of SPs, and the great prevalence of impulsivity (10% of premeditated SPs) in multiple repeaters are consistent with the hypothesis of a psychotropic prescription drugs misuse, leading to SP-r. Repeated SPs presented characteristics of binge-drugging and benzodiazepines consumption (repetition, abuse-binge, and impulsive-compulsive-automatic) should be examined systematically to address these patients to specialised care. Policymakers should keep on restricting the access to benzodiazepines.

Key-words: Self-poisoning, self-harm, suicide attempt, addiction, repetition, risk factor, readmission, cost, economics

Introduction

Suicide attempts outnumber suicides by ten to twenty globally.¹ Self-poisoning (SP) is the leading method and results in a strong demand of care in high-income countries. French emergency wards manage 200,000 self-harm episodes every year and SP leads to 72,000-87,000 hospital admissions.² SP repetition (SP-r) is common (26% within one year)³ and a substance misuse double this risk.⁴ Underlying mechanisms are poorly understood, but an increased suicidal ideation or impulsiveness among misusers could trigger the SP-r.⁵⁻⁸

Benzodiazepines are mainly involved in SPs (80% in France).⁹⁻¹⁵ These drugs are widely prescribed against anxiety and insomnia^{16,17} and long-term use contributes to the development of a dependence. Interestingly, both a history of SP and benzodiazepine therapy are risk factors for a SP.¹⁸ This raises the hypothesis of a psychotropic prescription drugs misuse being the root-cause of repeated and impulsive SPs. Thus, the underlying mechanisms of the SP-r need to be reconsidered.

As highlighted by Ness et al., previous studies usually gathered repeaters in a single group.¹⁹ Few ones took into account the number of previous episodes to assess the risk factors for self-harm repetition. Haw et al. classified patients as “high-repeaters” beyond four self-harm episodes, with no detail about the methods being used.²⁰ To our knowledge, no study compared non-repeaters (first SP) versus first-repeaters (second SP) versus multiple repeaters (third and more SP). This classification is clinically relevant though to involve the patient quickly in tailored care, as the intensity and the appropriate time of secondary prevention are still debated. Finally, no study assessed the financial costs of the SP-r in France, when this data could help in the allocation of resources for secondary prevention.

The aim of this study was to identify the risk factors for SP-r distinguishing non-, first-, and multiple repeaters. The secondary aims were to compare the recurrence rates on the three following years and the associated hospital direct costs between the three groups.

Methods

Setting

A retrospective cross-sectional study was undertaken in a French university hospital, with an average admission rate of 130,000 per year. The time scale under review spanned from the 1st of January to the 31st of December 2012.

Definitions and identification of SPs

Admissions related to a SP in adult patients (≥ 18 years old) were identified in the Hospital discharges databases. Self-harm was defined as an “intentional SP or self-injury carried out by an individual, irrespective of motivation”,²¹ according to the definition of the National institute for health and care excellence. Admissions were first targeted thanks to the Tenth revision of the International classification of diseases (ICD10) codes, where intentional SPs were coded [X60 - X64] according to the drug class involved and intentional self-harm with other methods, [X65 - X84]. The code Z91.5 only indicates a self-harm history. Thus, miscoded admissions were excluded and the number of previous episodes was searched in the medical records. Finally, SPs were classified among three groups: the group of non-repetition, of first-repetitions (2 SPs), and of multiple repetitions (3+ SPs).

Data collection

Medical records were reviewed to collect the following data:

- 1) *Individual factors of vulnerability*: history of mental disorders, self-harm with other methods, tobacco use and substance misuse.

The investigation of mental disorders included depressive, anxiety, personality, compulsive eating, and bipolarity disorders. Diagnosis made by psychiatrists at the moment of the SP or during a prior admission were searched. Diagnosis of substance misuse made by all physicians were searched according to an identical procedure.

2) *Context factors surrounding the SP:*

- Preceding the SP: the current mental follow-up, the socioeconomic issues, the triggers, the suicidal ideation and intent (the will to die).

The retrospective study design did not permit the use of instruments available for the assessment of the suicidal ideation and intent.²² To overcome this issue, a suicidal ideation was admitted if “dark thoughts” or explicit suicidal thoughts were reported. Concerning the intent, elements of premeditation (or planning) were collected: final arrangements, definite plans, a suicide note or a letter, and a contemplation of suicide in the previous days. It was assumed that premeditation was well-reported in the medical records, as it is indicative of a high suicidal intent (high will to die). Inversely, if the intent was assessed by physicians with no mention of premeditation, the SP was assumed to be impulsive. A contact to emergency services by the patient himself before, during, or after the act was an indicator of a lower intent. A missing data was recorded if the assessment of the suicidal intent was not reported.

- During the SP: the drugs and other substances used, the association with other methods.
- Following the SP: the lethality of the SP (death or lowest Glasgow coma scale observed under eight), the examination by of a physician or a social worker, and the referral.

3) *Further self-harm*

A readmission for a self-harm in the three following years was searched. Patients who declared a postcode of permanent home residence in the French department of the hospital were considered for this analysis. Non-permanent residents were excluded, as they were considered as being lost-to-follow-up.

Cost analysis

The annual hospital costs of the SP-r were estimated. Local data of the national hospital costs study (Etude nationale de coûts à méthodologie commune) was used. This study aims at adjusting national hospital tariffs. Detailed direct costs are provided for each admission thanks to a top-down “cost accounting model”, where the consumption of financial resources is distributed into hospital stays. We calculated the total cost of the SP-r and the cost per patient per group.

Statistical analyses

Qualitative variables were described by numbers and percentages and quantitative ones, by means and standard deviations (SDs). Pearson χ^2 and Fischer exact tests were used as appropriate to test associations of two qualitative variables. Missing data was excluded and the significance threshold was set at 0.05. The analyses were performed with Stata software V12.

Individual factors and readmission rates were compared at a patient-level between the three groups (non-repeaters, 2 SPs, and 3+ SPs). This patient-level analysis was done to not overestimate the associations of individual factors with the SP-r: if several admissions were observed for a same patient, only the first one was kept. Then, a SP-level analysis including all the SPs compared context factors described previously.

Last, a multinomial logistic regression model identified risk factors for SP-r. Non-repeaters were the reference group. Factors found to be significant in the bivariate analysis ($P \leq 0.20$) were considered in the model and backward stepwise elimination was then applied. Modelling was performed at the patient-level to grant the independence of observations. Non-adjusted and adjusted multinomial odds ratios with their 95% confidence intervals were reported.

Results

Presentations of SPs

A total of 730 SPs for 645 patients were identified for 2012 and 418 (57%) SPs corresponded to a repetition (Figure 1). Individual characteristics are described in Table 1. Self-poisoners were mainly aged 35-54 years old and women (68%). Depressive (51%) and anxiety disorders (23%) were the most reported psychiatric diagnosis and 52% of self-poisoners had a diagnosis of one substance use at least. Polysubstance use was observed in 25% of the sample, and the association of tobacco use and alcohol misuse was the main one observed (18%). Behavioural addictions were diagnosed in 11 (2%) self-poisoners. Self-harm history was declared by 66 (10%) patients for cutting, and by 49 (8%) for more lethal methods. SP repeaters were more likely to be aged 35-54 years old and to have a history of psychiatric disorders, substance misuses, and cutting self-harm.

Context factors are described at a SP-level in Table 2. At the moment of the SP, a mental health follow-up was present in 57% of SPs and deliberately interrupted by the patient in 11% of them. Socioeconomic issues were usually experienced by self-poisoners with an unemployment rate of 51%. Interpersonal issues (66%) were mainly reported as triggers factors. Preceding the acting, suicidal ideation and premeditation were found in 49% and 10% of SPs, with no difference between the groups. A higher proportion of SP repeaters were involved in a medical mental specialised follow-up or in a situation of deliberate interruption of care. SP repeaters were also more likely to experience all the socioeconomic issues investigated excepted living alone before their SP (49% reported precarious living conditions or financial difficulties, 68% unemployment, and 31% interpersonal isolation). Significant decrease in interpersonal triggers and increase in substance misuse ones were observed by SP repeaters.

Type of medication used

Molecules and methods used for the SP are reported in Table 3. Benzodiazepines (including Z-drugs) were involved in 71% of SPs and paracetamol in 14%. An alcohol intake was reported in 44%. The average blood alcohol concentration was 1.62 (SD: 0.92) gram/litre. SPs were combined with illicit substances in 5% of cases, with a cutting self-harm in 5%, and a more lethal method in 3%; and no difference was observed between the groups. Non-repeaters were more likely to ingest paracetamol and repeaters, benzodiazepines (significant differences).

Outcomes, hospital evaluation, and referral

No death related to a SP was observed in the whole sample and an admission in an intensive care unit was indicated for 111 (15%) SPs. Table 4 shows no difference in the clinical outcome (similar rates of Glasgow coma scale under 8, 11%). An examination by a psychiatrist was usually performed (94%) and few SPs led to an interview with an addiction specialist (7%). Psychiatric admissions (43%) and psychiatric referrals (29%) were the main care strategies proposed afterwards the SPs overall. Multiple repeaters (3+ SPs) were more likely to call themselves emergency services (26%) at the moment of the SP, to be admitted in a psychiatric unit afterwards (49%), to be referred to addiction services (8%), and to refuse any referral or to abscond from emergency wards (12%).

Risk factors for SP-r

Table 5 reports the final model explaining the repetition extent status. First-repeaters (2 SPs) were more likely to have a history of cutting self-harm, a specialised or an interrupted mental follow-up in comparison with non-repeaters. These characteristics were also the strongest risk factors for multiple SP-r (3+ SPs), with the combination of tobacco use and alcohol misuse. No interaction with age was observed. Having a previous diagnosis of personality disorder,

unemployment, and the ingestion of benzodiazepine anxiolytics were associated with multiple SP-r. Gender and illicit drugs misuses were not risk factors.

SP-r hospital costs

The hospital direct costs incurred by SPs amounted to EUR 1.679 million in 2012: EUR 777k (46%) by first SPs, EUR 317k (19%) by second ones, and EUR 585k (35%) by multiple repetitions. A first SP costed on average EUR 2,604 and a SP-r (first and multiple), EUR 2,760.

Further readmissions

The analysis of readmissions for a SP-r within three years included 621 (96%) patients and 23 (4%) patients were considered as lost-to-follow-up. The one-year risk was highest: 9%, 15%, and 30% for non-repeaters, first-repeaters, and multiple repeaters respectively. The three-year risk was 17%, 27%, and 39%. The average number of readmissions per patient increased with the repetition extent status: 1.2 (SD: 0.5), 1.8 (SD: 1.2), and 3.0 (SD: 5.3) respectively.

Twenty-four (4%) subjects were readmitted for a cutting self-harm and 22 (4%) for a self-harm using more lethal methods, with no difference between the groups.

Figure 2 summarises the characteristics of self-poisoners (individual vulnerability) and self-poisonings (context factors), the readmission rates and the costs related to the SP-r

Discussion

Main findings

A self-harm history is the main risk factor for SP-r. Multiple repeaters were little studied as a distinct group and our study aimed to compare the profiles of non-repeaters, first-repeaters (2 SPs), and multiple repeaters (3+ SPs). A first repetition was associated with a cutting self-harm history and took place in a context of a specialised or an interrupted mental follow-up by the patient. These associations remained beyond the second SP. Those with 3+ SPs were also at higher risk of combined tobacco use and alcohol misuse, personality disorders, and precariousness by comparison with non-repeaters. Overall, the SP-r was associated with an increased severity in the clinical and contextual backgrounds and several findings suggested that repeated SPs would correspond to addictive rather than to suicidal behaviours.

First, multiple repeaters (3+ SPs) of our study presented an individual vulnerability to addictive behaviours, as shown by the over-representation of tobacco use and alcohol misuse among this group. Compared with non-repeaters, polysubstance use was increased by a factor 3. Substance use disorders are well-known risk factors for SP-r or self-harm repetition^{4,23,24} and alcohol misuse was mainly examined.^{10,25–29} Their use reflected their large availability and use in France,³⁰ but could also correspond to self-medication practices for negative affect regulation.³¹ Despite an unexpected similar distribution of anxiety disorders between the groups, the parallel increased use of benzodiazepines anxiolytics among multiple repeaters for their SP strengthened the hypothesis for a self-medication purpose.

While a single alcohol misuse was not associated with SP-r, a single or an associated tobacco use were risk factors for multiple repetitions. Misusers of any substance are seven times more likely to suffer from any other substance misuse.³² However, sex and age differences could explain the absence of a single alcohol misuse as a risk factor for SP-r. Alcohol and benzodiazepines are both anxiolytics, sharing common neurobiological pathways. Regular

alcohol use is mainly declared by men among general population and psychotropic drugs use by women, especially by those aged 35-65 years old. Daily use of tobacco is also greater among men, but with a slighter gender gap.³⁰ This difference is explained by a higher demand of mental care in women^{30,33} and this fact was observed in our SPs hospital sample, which was mainly female and aged 35-54 years old.

However, half of SPs of our study were associated to an acute alcohol poisoning^{15,34} and a blood alcohol concentration greater than 0.80 gram per litre was found in three quarters of them at hospital. Interestingly, the French definition of binge-drinking equates to the consumption of 60 grams of pure ethanol for women (6 glasses) and to 70 grams for men (7 glasses), in less than 2 hours to reach a blood alcohol concentration of 0.80 gram/litre. Thus, alcohol poisonings associated to SP-r could correspond to binge-drinking behaviours. Both simultaneous and successive ingestions of alcohol and drugs were declared. Alcohol was identified as the root cause of SP in previous studies, because of its disinhibiting effect. The existence of simultaneous poisonings in our study could suggest a similar pattern of use, and so on, a binge-drugging behaviour.

Smoking is a risk factor for suicide attempts,³⁵ but also the addiction which kills most in France.³⁶ Patients of our study were never quizzed about their tobacco use at the moment of their self-harm. Focus was done on alcohol and illicit substances poisonings, probably because of severe immediate adverse effects. A previous French study reported the insufficient assessment of tobacco use among suicide attempters, despite a positive association between nicotine dependence and multiple repetition of attempts. Authors suspected impulsive acts among nicotine dependent subjects.³⁷

Second, no increase in the suicidal ideation and severe intent rates were observed in repeaters of this study.³⁸⁻⁴¹ The SP-r was not associated with depressive disorders or bipolarity. In addition, SPs were little planned (10% overall^{10,38}). Most of the SPs were

impulsive, regardless the status toward SP-r (2 and 3+ SPs). A higher use of sedatives and tranquilizers was reported for repeated SPs in previous studies.^{10,14,22,31-33} The higher use of benzodiazepine anxiolytics by multiple repeaters in our study could reflect the need of a tension relief in stressful situations with compulsive components, not related to a higher suicidal ideation or intent.

Third, no increase in lethality or admission rates in intensive care units was observed with SP-r in our study.^{11,15} Novack et al. identified the admission in an intensive care unit as a protective factor for SP-r.⁴⁵ It has also been shown that repeaters ingested higher doses of benzodiazepines.¹⁵ A tolerance to drugs developed by SP repeaters could explain these findings. Amounts of drugs ingested by self-poisoners of our sample were collected on the basis of the patients' or the first-aiders' declarations. Their accuracy was questioned. Toxicological assays were costly and mainly demanded in case of diagnosis uncertainties. Because of these pitfalls, this comparison was not reported.

Fourth, the risk of readmission was higher in repeaters.³ SP as a sole method was favoured and few patients turned to more lethal ones afterwards. Lilley et al. and Owens et al. observed lower switching in self-harm methods in self-poisoners too.^{46,47} Interestingly, those with 3+ SPs were more likely to repeat afterwards, taking into account the number of episodes or the recurrence rate, as reported by Perry et al..³ In addition to the increased risk of recurrence, Crane et al. reported a decreased sensitivity to life events and a lower intent as determinants of SP-r, highlighting mechanisms of sensitisation and automatization among the subgroup of SP repeaters.³⁹ Thus, repeaters had a chronic and dangerous use of prescription drugs coexisting with other substances use, continuing their misuse despite previous and serious health adverse effects. According to the fifth edition of the *Diagnosis and statistical manual of mental disorders*, these characteristics constitute criteria of the diagnosis of a psychotropic prescription drug use disorder. All these elements are consistent with the

hypothesis of an addictive behaviour, especially a binge-drugging, coexisting with other polysubstance use.

Psychiatric illnesses and especially personality disorders, tobacco use, alcohol misuse, and social issues (unemployment, isolation) were identified as risk factors in the literature, irrespectively from the episode considered, given that all the repeated episodes were gathered in a unique group.^{11,15,27,28,41}

SP-r contributed 54% (EUR 902 k) of the hospital costs related to all SPs. Vinet et al. amounted the yearly societal cost of suicide attempts to EUR 1.2 billion in France, including direct and indirect costs.⁴⁸ To our knowledge, it is the first study to assess the costs of SP-r. Our data provided an estimation of the avoidable costs by specific prevention strategies targeting first self-poisoners. The choice to use the hospital cost accounting allowed an accurate estimation of costs related to SPs, and is an easily understandable tool by hospital managements for the planning of prevention programmes. Indeed, this method estimated the actual consumption of hospital resources, contrary to costing methods based on national tariffs of hospital stays.

Limits

Our study was mainly limited by its cross-sectional design, which did not permit the follow-up of self-poisoners' behaviours for the assessment of risk factors. During the extraction of admissions in the hospital discharge database, the miscoding could not be totally controlled. False negatives (admissions related to actual self-harm episodes with no self-harm code (X-code of the ICD10) were excluded of the analysis. Thus, the cost, and the burden of the SP-r could be underestimated, but our methods were conservative. Because of the use of medical records, standard evaluations of mental and substance use disorders, suicidal ideation and intent were not possible.

Despite these limits, our methods allowed to study some of the addictive underlying mechanisms of SP-r, on both the short and long-terms. Individual and context factors could be investigated and similar trends were observed as in prospective studies. The implementation of a standardised review protocol improved the data reliability and limited the missing data. The distinction between first- and multiple repeaters was informative. As Bethell et al.,⁴⁹ we think that further studies should consider the repetition extent status, as repeaters have a particular profile beyond the second episode.

Implications for patients

SP-r corresponded to more than one in two SPs in our study.^{45,50} Repeaters were more likely to have an ongoing specialised mental follow-up (mainly by psychiatrists) and a psychiatric admission afterwards.^{4,10,51,52} Addiction specialists were little involved in the management of SP-r. Their expertise was mainly requested for alcohol or illicit substances misuse, whereas they may help for the diagnosis, the patient's referral, and the follow-up of benzodiazepines addictions.

Encouraging healthcare givers to assess the patient's regular use of all the substances, including benzodiazepines, is a simple strategy to detect misuses. Psychotropic prescription

drugs use is both under-declared and little investigated in emergency departments,⁵³ and was probably underestimated in our study. Quizzing the patient about his psychotropic drugs use (purpose, duration, etc.) is not time-consuming and is within all the healthcare professionals' reach. A diagnosis of substance use disorder, made in the emergency wards was more likely to decrease the self-harm repetition.⁵⁴ Moreover, this practice could help emergency staff members to gain confidence in their own skills, since they reported suffering from frustration towards SP repeaters.⁵⁵⁻⁵⁷ This point is relevant because negative experiences in emergency rooms can impact the repeaters' choice to seek for help afterwards.⁵⁸ In spite of a lower compliance (explicit refusal of care, absconding from emergency rooms, and deliberate interruption of mental follow-up),¹⁵ those with 3+ SPSs were also more likely to seek for help by calling themselves emergency services at the moment of the self-harm. Their ambivalence towards care reflects an intention of change, but possible inappropriate medical response. Motivational interviewing approach was developed for patient with alcohol use disorder. The Cochrane group led a meta-analysis about the motivational interviewing effectiveness for benzodiazepines misuse. Because of little evidence available, no definitive conclusion could be provided.⁵⁹ However, self-harm behaviours were excluded in the interest of clarity, while this technique could meet SP repeaters' needs, improve their initiation in a care process and maintain their desire to change.

Implications for decision-makers

There is a benefit in enhancing the knowledge of SP-r, since suicidal behaviours impact the whole society. Our results highlighted the necessity to keep on restricting the access to benzodiazepines and Z-drugs through specific policies, as they are involved in three quarters of SP recurrences. Despite regulation policies, 14% of prescriptions still exceeded recommended durations in 2015 in France.¹⁷ Durations of prescriptions are key indicators of benzodiazepines use at a population-level. However, Kroll et al. showed an increased risk of

benzodiazepines prescriptions at high-doses among patients with a current tobacco use and alcohol abuse.⁶⁰ Patients with pre-existing addictive behaviours are vulnerable to benzodiazepines dependence. Raising the awareness about this vulnerability is a same priority as fighting against long durations of prescription.

Limiting the building-up of stocks at home has a key preventive role, as most of self-poisoners use their own therapies for the act.⁶¹ French pharmacists are allowed to dispense one-month treatment at one time for a patient to be eligible for reimbursement. In a pilot study performed in our hospital (data not published), a weekly compared to monthly drug dispensing reduced by a factor of 7 the number of repetitions and increased by a factor of 4 the period between two episodes at three months of follow-up.⁶² This intervention was based on the principles of the dispensing of opioid substitution treatment, whose main purpose was to limit the risk of overdose. Although it needs to be replicated in a larger sample, the implementation of this low-cost prevention strategy could reduce the risks associated to benzodiazepines. Such a system associated with secure prescriptions requires collaborations between physicians and pharmacists, in agreement with the patients.

Conclusion

SP repeaters challenge practices, despite more intensive care. Our study brought an original interpretation of data: SP-r can correspond to suicidal behaviours, especially when the act is planned, but also to addictive behaviours with benzodiazepines beyond a second episode. At a patient-level, efforts should be done in the evaluation of the pathological relationship between the individual and the substance, taking into account the other addictive behaviours. At a hospital-level, the collaboration with addiction specialists, who practice motivational interviewing techniques, could help in the management of multiple repeaters presenting compliance issues. At a population-level, the regulation systems of benzodiazepines must keep on progressing to protect repeaters, who were medically and socioeconomically

disadvantaged. In research, further studies are urgently needed to examine the development of mechanisms of “binge-drugging” disorders, opening the way to innovative and tailored care adapted to impulsive, compulsive, and automatic substance intake.

Conclusion de thèse signée par le doyen

Repeated self-poisoning with benzodiazepine: an addictive rather than a suicidal behaviour?

Thèse soutenue par Asma FARES

CONCLUSION

L'intoxication médicamenteuse volontaire (IMV) est le mode le plus fréquent d'auto-lésion infligée, et est généralement interprétée comme une tentative de suicide. Les mécanismes de sa répétition sont peu compris à ce jour malgré sa fréquence élevée (20 à 30% de récurrence à un an).

Nous avons mené une étude rétrospective sur dossiers médicaux au sein du centre hospitalier universitaire de Grenoble en 2012 afin d'identifier les facteurs de risque liés à une admission pour une première IMV, une seconde et une troisième ou plus. Les taux de réadmission et les coûts associés ont été estimés secondairement.

L'analyse a finalement porté sur 730 IMV pour 645 patients. Un antécédent personnel de scarification et un suivi médical spécialisé en cours (par un psychiatre ou un addictologue) ou interrompu étaient associés à une seconde IMV, ainsi qu'à une troisième IMV ou plus. Les récidivistes multiples (≥ 3 IMV) étaient également plus à risque d'être sans emploi, d'ingérer des benzodiazépines pour leur passage à l'acte et de présenter un antécédent personnel de trouble de la personnalité et d'usage problématique du tabac et de l'alcool. Les fréquences de l'idéation suicidaire (49% des IMV) et de la préméditation (10% des IMV) étaient similaires à celles retrouvées au cours d'un premier épisode d'IMV.

Les taux de réadmission pour une IMV étaient de 9%, 15% et 30% à un an chez les sujets s'étant présentés pour une première, une seconde et une troisième ou plus IMV en 2012 respectivement. Pour finir, le coût hospitalier des IMV répétées s'élevait à 902 mille euros pour l'année 2012, représentant 54% du coût de l'ensemble des IMV prises en charge cette année (premier épisode ou récurrence).

Ainsi, les récurrences d'IMV sont caractérisées par une chronicité dans le temps, un usage de benzodiazépines à fort potentiel addictif, une absence d'idéation suicidaire majorée

en amont et par une proportion élevée d'actes impulsifs (10% des IMV étant préméditées).

Ces IMV répétées semblent donc présenter les caractéristiques de prises médicamenteuses massives et compulsives sur un temps restreint, et pourraient correspondre en cela à des conduites addictives, plutôt que suicidaires. L'évaluation des modes de consommation des benzodiazépines par les soignants (abusives ou non, répétées ou non dans le temps, compulsives ou automatiques) est déterminante puisqu'elle permettrait d'orienter les patients récidivant les IMV vers des soins adaptés. A l'échelle populationnelle, l'évolution des politiques du médicament restreignant l'accès aux benzodiazépines devrait être poursuivie afin de protéger les patients récidivistes, plus défavorisés sur le plan clinique et socio-économique.

VU ET PERMIS D'IMPRIMER
Grenoble, le 11/05/17

LE DOYEN

Pour la Présidente
et par délégation
Le Doyen de Médecine
Pr. Jean-Paul ROMANET

J.P. ROMANET

LE PRESIDENT DE LA THESE

PROFESSEUR P. FRANCOIS

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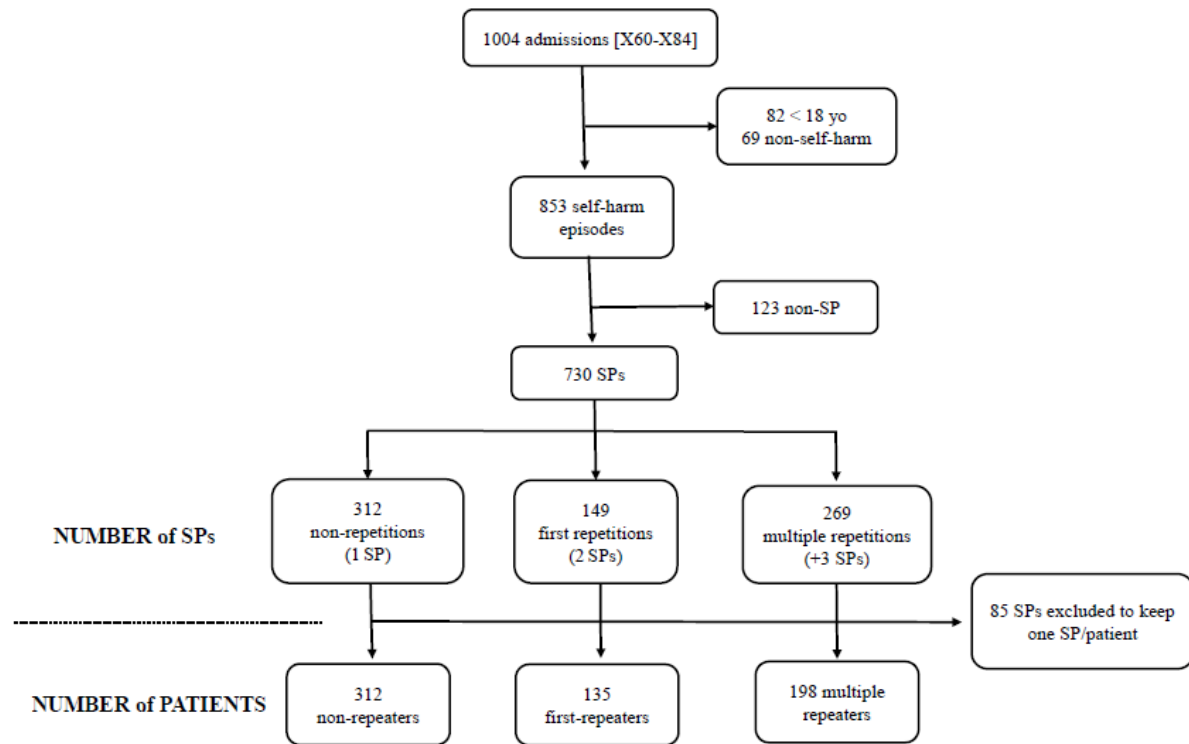
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Figures and tables

Figure 1: Flowchart summarising the selection of hospital admissions related to self-poisoning episodes in 2012



Note: SP for self-poisoning.

Admissions with a [X60-X84] code were retrieved from the hospital information systems. Medical records were reviewed for the further selection of admissions related to SPs.

Table 1: Characteristics of repeaters and non-repeaters

Characteristics	All patients N=645 (%)	Non-repeaters N=312 (%)	2 SPs N=135 (%)	≥ 3 SPs N=198 (%)	p-value
Female sex	441 (68)	211 (68)	97 (72)	133 (67)	0.61
Age (years old)					
18-34	208 (32)	115 (37)	47 (35)	46 (23)	0.003
35-54	295 (46)	122 (39)	63 (47)	110 (56)	
≥ 55	142 (22)	75 (24)	25 (19)	42 (21)	
Psychiatric comorbidities					
Depressive disorder	326 (51)	144 (46)	66 (49)	116 (59)	0.022
Anxiety disorder	151 (23)	74 (24)	33 (24)	44 (22)	0.88
Personality disorder	62 (10)	16 (5)	15 (11)	31 (16)	< 0.001
Bipolarity	42 (7)	11 (4)	11 (8)	20 (10)	0.009
Psychotic disorder	48 (7)	17 (5)	9 (7)	22 (11)	0.06
Compulsive eating disorder	32 (5)	6 (2)	10 (7)	16 (8)	0.003
Substance use/misuse					
Tobacco use only	168 (26)	74 (24)	34 (25)	60 (30)	< 0.001
Alcohol misuse only	142 (7)	17 (5)	8 (6)	17 (9)	
Tobacco use & alcohol	114 (18)	35 (11)	20 (15)	59 (30)	
Cannabis misuse	62 (10)	22 (7)	14 (10)	26 (13)	0.07
Psychotropic prescription drugs misuse	29 (5)	9 (3)	8 (6)	12 (9)	0.16
All opioids misuse	27 (4)	7 (2)	7 (5)	13 (7)	0.05
Cocaine misuse	19 (3)	9 (3)	0 (-)	10 (5)	0.014
Behavioural addictions	11 (2)	2 (1)	3 (2)	6 (3)	0.11
≥ 1 substance use**	334 (52)	132 (42)	66 (49)	136 (69)	<0.001
≥ 2 substances use**	163 (25)	53 (17)	34 (25)	76 (38)	< 0.001
Self-harm history					
Cutting	66 (10)	14 (4)	17 (13)	35 (18)	< 0.001
Other (hanging, firearm etc.)	49 (8)	18 (6)	9 (7)	22 (11)	0.08

*Note: *p-value of Pearson χ^2 or Fisher exact tests*

***including tobacco use or another substance misuse*

Table 2: Context factors preceding the SPs according to the repetition extent status

	All SPs n=730 (%)	1 st SP n=312 (%)	2 nd SP n=149 (%)	≥ 3 rd SP n=269 (%)	p-value*
Mental health medical follow-up					
<i>None</i>	237 (32)	149 (48)	42 (28)	46 (17)	< 0.001
<i>General practitioner</i>	125 (17)	60 (19)	27 (18)	38 (14)	
<i>Psychiatrist / addiction specialist</i>	290 (40)	83 (27)	59 (40)	148 (55)	
<i>Interrupted by the patient</i>	78 (11)	20 (6)	21 (14)	37 (14)	
Socioeconomic issues					
<i>Precarious living condition or financial difficulties</i>	279 (65)	87 (28)	60 (40)	132 (49)	< 0.001
<i>Unemployment</i>	355 (51)	114 (38)	67 (48)	174 (68)	<0.001
<i>Living alone</i>	249 (34)	95 (30)	47 (32)	107 (40)	0.05
<i>Interpersonal isolation</i>	173 (24)	53 (17)	37 (25)	83 (31)	< 0.001
Triggers					
<i>Interpersonal</i>	464 (66)	217 (72)	92 (62)	155 (61)	0.013
<i>Psychiatric cause</i>	136 (19)	52 (17)	37 (25)	47 (19)	0.15
<i>Substance misuse**</i>	45 (6)	6 (2)	8 (5)	31 (12)	< 0.001
<i>Socioeconomic issue</i>	33 (5)	11 (4)	7 (5)	15 (6)	0.46
<i>Physical pain***</i>	23 (3)	12 (4)	3 (2)	8 (3)	0.60
Suicidal ideation	320 (49)	148 (52)	67 (50)	105 (44)	0.31
Premeditation (planning of the SP)	66 (10)	27 (9)	18 (13)	21 (9)	0.37

*Note: *p-value of Pearson χ^2 or Fisher exact tests*

*** A trigger involving a substance misuse could correspond to a relapse of a misuse, withdrawal symptoms, or to a recreational drug use of illicit/licit substances use*

**** including both acute and chronic pains*

Table 3: Methods used according to the repetition extent status

	All SPs n=730 (%)	1st SP n=312 (%)	2nd SP n=149 (%)	≥ 3rd SP n=269 (%)	p-value*
Psychotropic drugs					
<i>Benzodiazepines and Z-drugs</i>	512 (71)	199 (64)	102 (68)	211 (79)	< 0.001
<i>Anxiolytics</i>	423 (58)	153 (49)	89 (60)	181 (68)	< 0.001
<i>Hypnotics</i>	166 (23)	61 (20)	41 (28)	64 (24)	0.15
<i>Antidepressants</i>	151 (21)	55 (18)	37 (25)	59 (22)	0.17
<i>Antipsychotics</i>	122 (17)	35 (11)	25 (17)	62 (23)	0.001
<i>Antiepileptics</i>	32 (4)	11 (4)	2 (1)	19 (7)	0.014
<i>Mood stabilisers</i>	20 (3)	7 (2)	3 (2)	10 (4)	0.45
<i>Opioid substitution therapy</i>	23 (3)	7 (2)	5 (3)	11 (4)	0.42
Analgesics					
<i>Opioid analgesics</i>	62 (9)	24 (8)	10 (7)	28 (11)	0.33
<i>Paracetamol (± codeine)</i>	98 (14)	60 (19)	15 (10)	23 (9)	< 0.001
Others**	89 (12)	43 (14)	16 (11)	30 (11)	0.52
Associated substances					
<i>Alcohol</i>	321(44)	130 (42)	57 (38)	134 (50)	0.041
<i>BAC > 0.80 gram/litre (n=222)</i>	164 (74)	58 (69)	26 (68)	80 (80)	0.17
<i>Illicit drugs</i>	34 (5)	13 (4)	4 (3)	17 (6)	0.20
Associated methods					
<i>Cutting</i>	34 (5)	12 (4)	9 (6)	13 (5)	0.57
<i>More lethal self-harm</i>	20 (3)	11 (4)	3 (2)	6 (2)	0.61

Note: BAC for blood alcohol concentration

**p-value of Pearson χ^2 or Fisher exact tests*

***Non-analgesics and non-psychotropic drugs such as anticoagulants, high blood pressure medication, etc.*

Tableau 4: Hospital evaluation according to the repetition extent status

	All SPs n=730 (%)	1 st SP n=312 (%)	2 nd SP n=149 (%)	≥ 3 rd SP n=269 (%)	p-value*
Call emergency services	148 (22)	49 (16)	28 (19)	71 (26)	0.005
Glasgow coma scale < 8	78 (11)	28 (9)	16 (11)	34 (13)	0.36
ICU admission**	111 (15)	42 (13)	26 (17)	43 (16)	0.49
Emergency/ICU evaluation**					
<i>Psychiatrist</i>	684 (94)	297 (95)	144 (97)	243 (90)	0.014
<i>Addiction specialist</i>	53 (7)	17 (5)	9 (6)	27 (10)	0.09
<i>Social assistant</i>	21 (3)	12 (4)	6 (4)	3 (1)	0.08
<i>Patient's refusal</i>	8 (1)	0 (-)	0 (-)	8 (3)	0.001
Postvention					
<i>Psychiatric admission</i>	314 (43)	112 (36)	68 (46)	133 (49)	0.004
<i>Psychiatric referral</i>	211 (29)	87 (28)	50 (34)	74 (28)	0.37
<i>General practitioner referral</i>	97 (13)	59 (19)	16 (11)	22 (8)	< 0.001
<i>None (absconded or refused)</i>	56 (8)	17 (5)	8 (5)	31 (12)	0.011
<i>Addiction medicine referral</i>	45 (6)	11 (4)	13 (9)	21 (8)	0.035
<i>Psychotherapy</i>	44 (6)	28 (9)	7 (5)	9 (3)	0.013
Non cooperative patient	201 (28)	64 (21)	41 (28)	96 (36)	< 0.001

Note: No death related to a SP was observed in the whole sample

**p-value of Pearson χ^2 or Fisher exact tests*

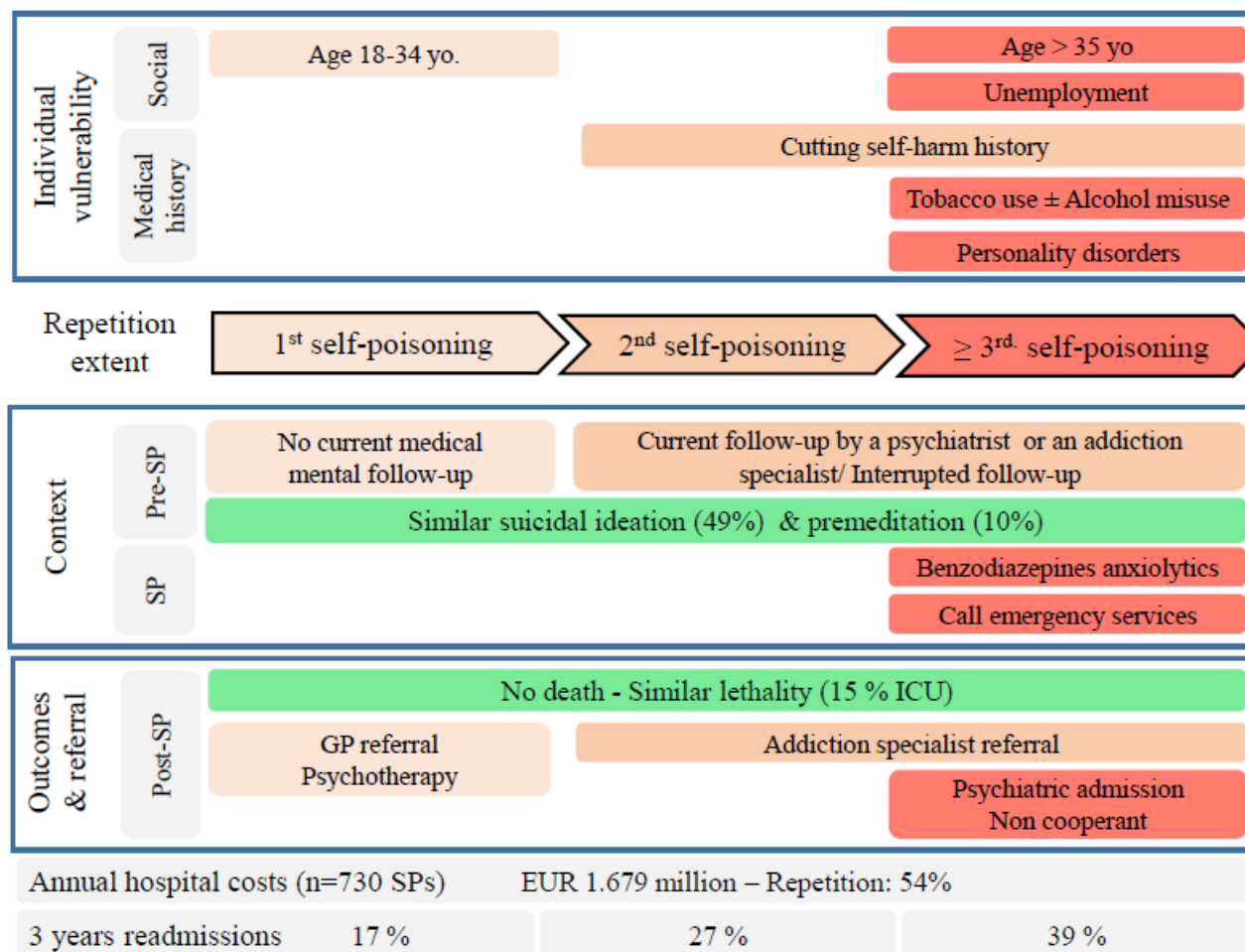
*** ICU for Intensive care units*

Table 5: Univariable and multivariable multinomial logistic regression of the SP repetition extent status (comparison group: non-repeaters)

Repetition status		2 SPs				+ 3 SPs				
		Univariable		Multivariable		Univariable		Multivariable		
Variables		NA-OR (95% CI)	p-value	A-OR (95% CI)	p-value	NA-OR (95% CI)	p-value	A-OR (95% CI)	p-value	
Individual factors	Age (years old)									
		<i>18-34</i>	ref.	ref.	ref.	ref.	ref.	ref.	ref.	
		<i>35-55</i>	1.26 (0.80-1.99)	0.31	1.51 (0.88-2.60)	0.13	2.25 (1.47-3.46)	< 0.001	2.31 (1.35-3.95)	0.002
		<i>> 55</i>	0.82 (0.46-1.44)	0.48	1.06 (0.53-2.11)	0.88	1.40 (0.84-2.33)	0.20	2.25 (1.14-4.41)	0.019
		Depressive disorder	1.12 (0.75-1.67)	0.60	.91 (0.56-1.48)	0.56	1.65 (1.15-2.37)	0.006	1.36 (0.84-2.19)	0.21
		Bipolarity	2.43 (1.03-5.75)	0.044	1.71 (0.62-4.67)	0.62	3.08 (1.44-6.57)	0.004	2.15 (0.82-5.61)	0.12
		Personality disorder	2.31 (1.11-4.83)	0.026	1.88 (0.85-4.11)	0.12	3.43 (1.83-6.46)	< 0.001	2.45 (1.18-5.05)	0.016
		History of cutting self-harm	3.07 (1.47-6.42)	0.003	3.21 (1.43-7.21)	0.005	4.57 (2.39-8.74)	<0.001	3.81 (1.78-8.17)	0.001
		Substance use problem								
		<i>None</i>	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
	<i>Tobacco only</i>	1.17 (0.72-1.91)	0.53	1.07 (0.63-1.84)	0.80	2.43 (1.56-3.80)	< 0.001	2.37 (1.40-4.03)	0.001	
	<i>Alcohol only</i>	1.20 (0.50-2.90)	0.69	.99 (0.39-2.53)	0.99	3.00 (1.44-6.23)	0.003	1.89 (0.82-4.34)	0.13	
	<i>Both tobacco & alcohol</i>	1.46 (0.79-2.69)	0.23	.90 (0.45-1.79)	0.76	5.06 (3.05-8.40)	< 0.001	3.09 (1.72-5.58)	< 0.001	
Context factors	Unemployed	1.48 (0.97-2.26)	0.07	1.31 (0.81-2.12)	0.27	2.61 (1.79-3.82)	< 0.001	2.34 (1.48-3.71)	< 0.001	
	Interpersonal isolation	1.48 (0.90-2.44)	0.12	1.44 (0.84 -2.48)	0.18	1.88 (1.23-2.90)	0.004	1.59 (0.96-2.66)	0.07	
	Mental health medical follow-up									
		<i>None</i>	ref.	ref.	ref.	ref.	ref.	ref.	ref.	
		<i>General practitioner</i>	1.70 (0.95-3.04)	0.07	1.76 (0.92-3.37)	0.09	2.00 (1.13-3.55)	0.018	1.47 (0.76-2.84)	0.26
		<i>Specialised*</i>	2.50 (1.53-4.11)	< 0.001	2.04 (1.14-3.63)	0.016	5.39 (3.39-8.56)	< 0.001	2.92 (1.68-5.06)	< 0.001
		<i>Interrupted by the patient</i>	3.53 (1.70-7.32)	0.001	3.41 (1.56-7.44)	0.002	5.17 (2.59-10.33)	< 0.001	3.26 (1.48-7.16)	0.003
	Benzodiazepine anxiolytics	1.37 (0.91-2.05)	0.13	1.17 (0.75-1.83)	0.49	2.32 (1.60-3.35)	< 0.001	1.75 (1.13-2.70)	0.012	

Note: ref. for class of reference; SP for self-poisoning, NA-OR: non-adjusted odds ratio (univariable analysis), A-OR: adjusted odds ratio (multivariable analysis), 95% CI: 95% confidence interval.

Figure 2: Individual vulnerability and context factors, annual hospital costs, and readmission rates at 3 years of follow-up related to hospital admissions for a self-poisoning according to the repetition extent status.

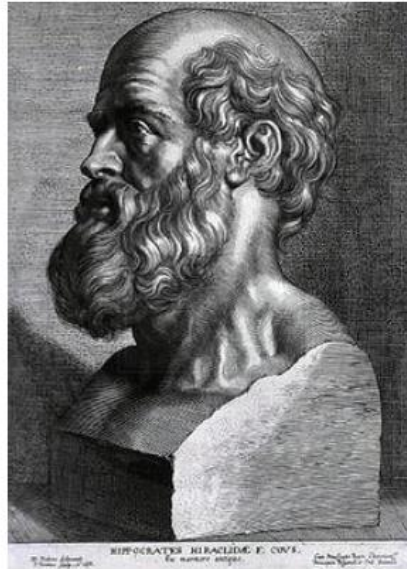


Note: SP for Self-poisoning, ICU for Intensive care unit, GP for General practitioner.

The group of admissions related to a first ever episode of self-poisoning was the reference group for the comparison of individual/context factors associated to repeated self-poisonings.

The annual hospital costs were assessed for the 730 self-poisonings admitted in 2012.

Serment d'Hippocrate



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

Repeated self-poisonings: an addictive rather than a suicidal behaviour?

RESUMÉ

Contexte : L'intoxication médicamenteuse volontaire (IMV) est le mode de tentative de suicide le plus fréquente. Les mécanismes et la prévention optimale de sa récurrence demeurent méconnus.

Méthodes : Une étude sur dossiers médicaux au CHU de Grenoble en 2012 a identifié les facteurs associés à une première IMV, seconde et troisième ou plus (3+) par une modélisation multinomiale, les taux de réadmission et les coûts.

Résultats : 730 IMV pour 645 patients ont été analysées (57% de récurrences). Un antécédent de scarification et un suivi médical en cours ou interrompu étaient associés à la récurrence. Les sujets 3+ étaient plus à risque d'être sans emploi, de trouble de la personnalité, d'usage du tabac, de mésusage de l'alcool, d'ingérer des benzodiazépines pour leur IMV et d'être réadmis à un an pour le même motif (9%, 15% et 30% en cas de première, seconde et 3+ IMV). L'idéation suicidaire (49%) et la préméditation (10%) étaient similaires entre les groupes. Le coût des IMV répétées s'élevait à 902 mille euros, soit 54% du coût total des IMV en 2012.

Conclusion : Une vulnérabilité à l'usage du tabac et au mésusage de l'alcool, l'usage de benzodiazépines pour l'IMV, un binge-drinking associé, la chronicité des IMV, l'absence d'idéation suicidaire dans 51% des IMV et la grande part d'actes impulsifs (10% d'IMV préméditées) chez les sujets 3+ évoqueraient un mésusage des psychotropes, à l'origine des récurrences. Les IMV répétées s'apparenteraient à des prises médicamenteuses massives sur un temps restreint (binge-drugging). L'évaluation de la consommation des benzodiazépines (abusives, répétées, impulsives-compulsives-automatiques) est déterminante afin de proposer des soins adaptés.

Mots-clés: Intoxications médicamenteuses volontaires, répétition, addiction, tentative de suicide, facteurs de risque, réadmission, coûts, économie

ABSTRACT

Background: Self-poisoning (SP) is the leading self-harm method. Mechanisms of SP repetition (SP-r) are poorly understood and questions remain regarding its prevention.

Methods: A chart review was undertaken in 2012 in a French university hospital to identify risk factors for an admission for a first, a second, or a third and more SP. Readmission rates and costs were assessed.

Results: 730 SPs for 635 patients were analysed and 418 (57%) SPs corresponded to a repetition. A cutting self-harm history, a specialised or an interrupted mental follow-up were associated to the SP-r. Multiple repeaters were more likely to be unemployed, suffering from personality disorders, tobacco use and alcohol misuse, ingesting benzodiazepines for the SP, and being readmitted for a SP within one year (9%, 15%, and 30% for first, second and third and more SPs respectively). The suicidal ideation (49%) or premeditation (10%) were similar between the groups. SP-r contributed 54% (EUR 902 k) of the hospital costs related to SPs in 2012.

Conclusion: The vulnerability to tobacco use/alcohol misuse, the use of benzodiazepines for the SP-r, the associated binge-drinking, the SP chronicity, the absence of suicidal ideation in 51% of SPs, and the great prevalence of impulsivity (10% of premeditated SPs) in multiple repeaters are consistent with the hypothesis of a psychotropic prescription drugs misuse, leading to SP-r. Repeated SPs presented characteristics of binge-drugging and benzodiazepines consumption (repetition, abuse, impulsive-compulsive-automatic) should be examined systematically to address these patients to adapted care.

Key-words: Self-poisoning, self-harm, suicide attempt, addiction, repetition, risk factor, readmission, cost, economics