CLINICAL-EPIDEMIOLOGICAL PROFILE OF SUICIDE ATTEMPTS BY TRICYCLC ANTIDEPRESSANTS VERSUS SELECTIVE SEROTONIN REUPTAKE INHIBITORS RECORDED IN A TOXICOLOGICAL CENTER IN THE STATE OF SANTA CATARINA, BRAZIL, 2015-2019

Perfil clínico-epidemiológico das tentativas de suicídio por antidepressivos tricíclicos versus inibidores seletivos da recaptação de serotonina dos casos registrados no Ciatox/Sc de 2015 A 2019

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ABSTRACT

Background: The high prevalence of poisoning by antidepressants in suicide attempts is related to the overall increase in prescriptions of these drugs.

Objective: To analyze and compare the clinical and epidemiological profile of patients who attempted suicide using tricyclic antidepressants (TCAs) versus selective serotonin reuptake inhibitors (SSRIs), treated at the Santa Catarina Toxicological Assistance and Information Center (CIATox/ SC).

Methods: We conducted a descriptive, retrospective, cross-sectional study with data from records of suicide attempts using only TCAs and SSRIs from the CIATox/SC database from January 2015 to December 2019.

Results: We recorded 1593 exposures, of which 54.68% involved SSRIs, 40.18% involved TCAs and 5.15% involved both. Most exposures occurred in women, aged between 20 and 29 years, and in most cases, the intake reached the toxic dose. The majority of TCA overdoses led to hospitalization and 11.72%

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required admission to Intensive Care Unit (ICU). Five deaths were recorded with the use of tricyclics.
Conclusion: Suicide attempts involving TCAs had a greater deleterious impact on patients' health when compared with intentional exposures by SSRIs.

Keywords: Poisoning. Attempted suicide. Tricyclic antidepressants. Serotonin reuptake inhibitors.

RESUMO

Introdução: A alta prevalência de intoxicações por antidepressivos em tentativa de suicídio está relacionado ao aumento global das prescrições desses medicamentos.
Objetivo: Analisar o perfil clínico-epidemiológico dos pacientes que sofreram intoxicação em tentativa de suicídio por antidepressivos tricíclicos (ADTs) *versus* inibidores seletivos da recaptação de serotonina (ISRSs), atendidos no Centro de Informações e Assistência Toxicológicas de Santa Catarina (CIATox/SC).
Métodos: Trata-se de um estudo descritivo, retrospectivo, transversal no qual foram utilizadas as informações das fichas geradas dos atendimentos com ADTs e ISRSs do CIATox/SC do período de janeiro de 2015 a dezembro de 2019.
Resultados: Foram registradas 1593 exposições, sendo 54,68% com ISRSs, 40,18% com ADTs e 5,15% com ambos. A maioria das exposições ocorreu no gênero feminino, na faixa etária de 20 a 29 anos. Os medicamentos mais utilizados foram a amitriptilina e a fluoxetina. Grande parte das exposições atingiu a dose tóxica. A maioria dos atendimentos apresentou manifestações clínicas leves, sendo a sonolência o sintoma mais prevalente em ambos os grupos. As intoxicações por ADTs apresentaram maior taxa de internação em enfermaria e em Unidade de Terapia Intensiva (UTI), com maior tempo de hospitalização. Houve registro de cinco óbitos com a overdose de tricíclicos.
Conclusão: As tentativas de suicídio por ADTs geraram maior impacto na saúde dos pacientes quando comparadas às exposições por ISRSs.

Palavras-chave: Antidepressivos tricíclicos. Antidepressivos de segunda geração. Envenenamento. Tentativa de suicídio.

RESUMEN

Introducción: La alta prevalencia de intoxicación por antidepresivos en intentos de suicidio está relacionada con el aumento global de la prescripción de estos medicamentos.

Objectivo: Analizar el perfil clínico-epidemiológico de pacientes que sufrieron intoxicación en intento de suicidio por antidepresivos tricíclicos (ATC) versus inhibidores selectivos de la recaptación de serotonina (ISRS), atendidos en el Centro de Información y Asistencia Toxicológica de Santa Catarina, Brasil (CIATox/SC).

Métodos: Se trata de un estudio descriptivo, retrospectivo y transversal, en el que se utilizó información de formularios generados a partir de las consultas con ATC e ISRS en el CIATox/SC desde enero de 2015 hasta diciembre de 2019.

Resultados: Se registraron 1.593 exposiciones, 54,68% con ISRS, 40,18% con ATC y 5,15% con ambos. La mayoría de las exposiciones ocurrieron entre mujeres, de edades comprendidas entre 20 y 29 años. Los medicamentos más utilizados fueron amitriptilina y fluoxetina. La mayoría de las exposiciones alcanzaron la dosis tóxica. La mayoría de las consultas presentaron manifestaciones clínicas leves, siendo la somnolencia el síntoma más prevalente en ambos grupos. Las intoxicaciones por TCA tuvieron una mayor tasa de hospitalización en sala y Unidad de Cuidados Intensivos (UCI), con tiempos de hospitalización más prolongados. Se registraron cinco muertes por sobredosis de tricíclicos.

Conclusión: Los intentos de suicidio por ATC generaron un mayor impacto en la salud de los pacientes en comparación con las exposiciones por ISRS.

Palavras-clave: Antidepressivos tricíclicos. Antidepressivos de segunda generación. Envenenamiento. Intentos de suicídio.

1 INTRODUCTION

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are among the main classes of antidepressants in suicide attempts (GUMMIN *et al*., 2022). These drugs are frequently present in intoxications and are commonly prescribed to patients with psychiatric disorders, who are at high risk of committing a suicide attempt (KIM *et al*., 2015).

SSRIs are considered the first choice in the treatment of depression (PARICK *et al*., 2009). They are well tolerated by patients and exhibit a good safety profile, as they present low toxicity and few adverse effects. TCAs are potentially more toxic in overdose and have a higher rate of discontinuation due to notable side effects (CIPRIANI *et al*., 2018; MOTTRAM; WILSON; STROBL, 2006). Despite that, they are still widely prescribed for refractory depressive disorders, neuropathic pain, migraines and other psychiatric disorders (SALHANICK, 2018).

Intoxication with tricyclic antidepressants is a serious clinical condition characterized by cardiovascular and neurological manifestations, with potential risk of seizures and cardiac arrhythmias. Most patients present sedative and anticholinergic symptoms and recover with supportive care. However, a subset may experience a rapid deterioration of their clinical status, which increases the risk of death and requires more invasive medical procedures (OLSON, 2014).

Due to their wide therapeutic window, isolated overdoses of SSRIs usually trigger mild clinical signs of intoxication. Nevertheless, more severe symptoms may be observed in some cases, such as serotonin syndrome, seizures and cardiac arrhythmias (BARBEY; ROOSE, 1998). Cases of death usually occur in suicide attempts in which the ingested dose exceeds the therapeutic threshold by 150 times or in scenarios of concomitant ingestion with alcohol and benzodiazepines (ISBISTER *et al*., 2004).

2 OBJECTIVES

We aimed to analyze and compare the clinical and epidemiological profile of suicide attempts by SSRIs *versus* TCAs registered at Santa Catarina Toxicological Assistance and Information Center (CIATox/SC) between 2015 and 2019.

3 METHODS

We performed a descriptive, retrospective and cross-sectional study. We extracted data from the medical care forms of CIATox/SC from January 2015 to December 2019 to analyze and compare the epidemiological profile of suicide attempts by SSRIs and TCAs.

We included suicide attempt registries containing confirmed cases involving exposure to the following agents: amitriptyline, nortriptyline, imipramine, clomipramine, fluoxetine, sertraline, escitalopram, citalopram, fluvoxamine, paroxetine and undetermined tricyclic. We excluded cases in which exposure was not confirmed or involved ingestion of multiple toxic agents.

We conducted a survey using data from the Brazilian Poisoning Registration System of Toxicological Information and Assistance Centers (DATATOX) to quantify cases of poisoning by TCAs and SSRIs. The variables extracted from the database included: year and month of registration, gender, age group, pharmacological class, medication, reported intake dose, initial clinical manifestations, need for hospitalization, duration of hospital stays, and clinical outcomes.

We performed data analysis using EXCEL® Microsoft and TABWIN® software to generate graphs and tables. SIGMAPLOT® program was used for descriptive statistical analysis with frequency distribution and for statistical tests (chi-square and Mann-Whitney) according to the studied variable. The ingested medication (TCA, SSRI, TCA and SSRI) was designated as an independent variable, classifying the groups for analysis. P values of <0.05 were considered statistically significant.

We referenced the toxic dose values of each medication according to the UK Clinical Toxicology Database (TOXBASE, 2019).

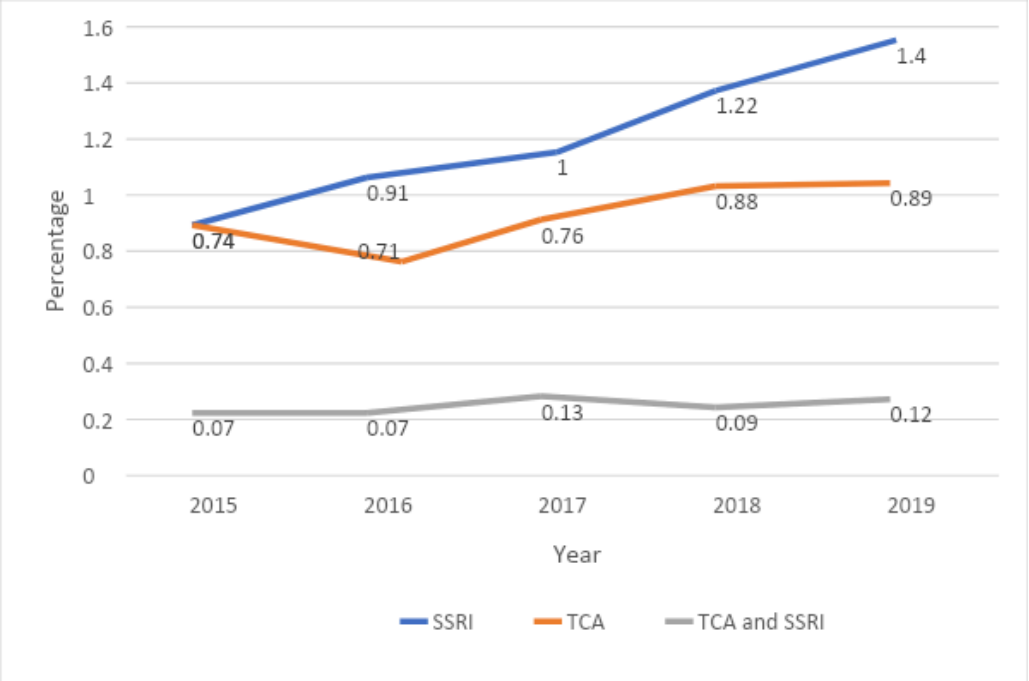
The study was approved by the Ethics Committee for Research with Human Beings of the Federal University of Santa Catarina under the number: 4.279, 311. The study did not receive any funds and authors declare no conflicts of interest.

4 RESULTS

We assessed 1593 records of exposure to antidepressants with suicidal intent and classified them into three groups according to the toxic agent. In total, 871 (55%) cases exclusively involved SSRIs, 640 (40%) involved TCAs, and 82 (5%) were due to concomitant exposure of both types of antidepressants.

When comparing the percentage of cases of suicide attempts relative to the total yearly records in CIATox/SC, we noticed an increase in suicide attempts with SSRIs and a more stable trend of cases with TCAs, as described in Figure 1. From 2015 to 2019, registrations by SSRIs and TCAs showed a relative increase of 89.18% and 20.27%, respectively.

Figure 1. Percentage of the number of suicide attempts by TCAs and SSRIs over the total records in CIATox/SC from 2015 to 2019 (n=1593).



Source: Author (2020).

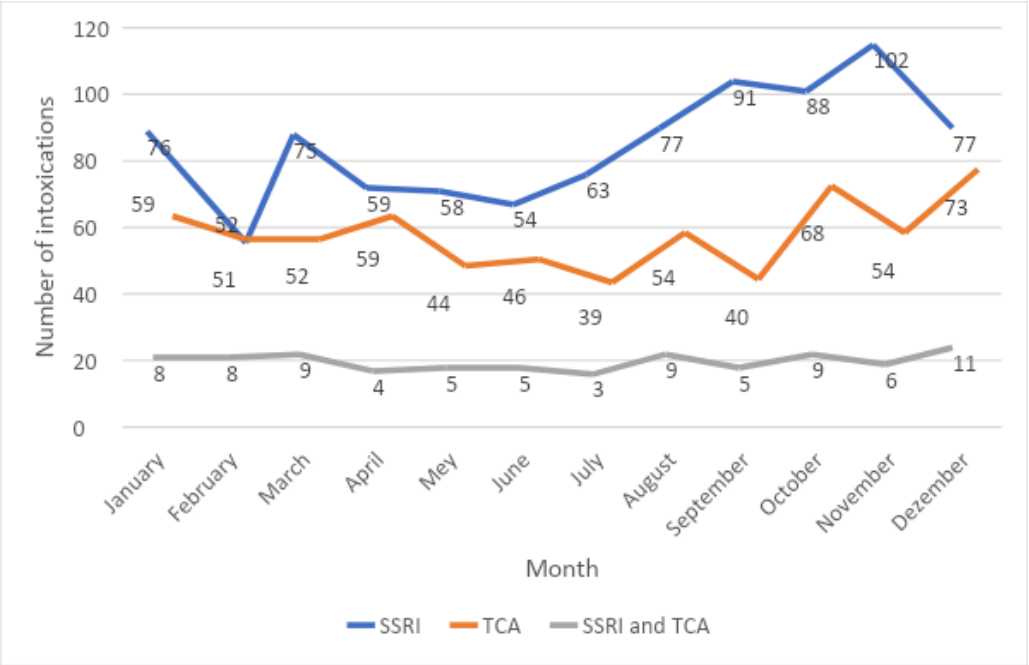
The female gender was more frequently common in the three groups, accounting for 82.32% of intoxications by SSRIs, 84.69% by TCAs and 81.71% in cases of simultaneous ingestion of both drugs. There was no statistically significant difference in gender distribution between groups (p=0.25).

Young adults aged 20 to 29 years were the most affected in the three groups analyzed. However, we observed that intoxications by SSRIs were more

frequent among younger patients when compared with exposures by TCAs (p<0.001).

The incidence of intoxications for the three groups was higher during the hottest months of the year, as shown in Figure 2. There was no statistically significant difference between the three groups (p=0.33).

Figure 2. Distribution according to the month of occurrence of poisonings by SSRIs and TCAs registered at CIATox/SC from 2015 to 2019 (n=1,593).



Source: Author (2020).

The 1593 records encompassed a total of 1675 medications, as some patients took more than one simultaneously. Amitriptyline was the most frequent toxic agent in overdoses with TCAs, accounting for 615 cases (85.18%). Among SSRIs, fluoxetine was the most commonly used drug leading to intoxications (332 cases [34.84%]), followed by sertraline (312 [32.74%]).

When calculating the intake doses reported by patients and/or family members in mg/g, it became evident that the majority of cases involving both SSRIs and TCAs surpassed the toxic threshold for the drug. However, patients who ingested TCAs reached the toxic dose (87.97%) more frequently when compared with the SSRI group (81.40%) (p<0.001). It is noteworthy that, in

3.26% of all cases, it was not possible to determine the ingested dose, therefore, these cases were excluded from the statistical analysis.

Table 1 shows the frequency of clinical manifestations registered in each group. Drowsiness was the most common symptom among the three groups. Nausea and vomiting were more frequent in SSRI poisonings, whereas altered level of consciousness and coma were more common in TCA overdoses.

Table 1 – Clinical manifestations by SSRIs, TCAs, and their combined use registered in CIATox/SC database from 2015 to 2019 (n=1593).

	n=871	n=640	n=82
Clinical manifestation	SSRI (%)	TCA (%)	SSRI and TCA (%)
Psychomotor agitation	4.25	5.31	9.76
Altered level of consciousness	1.15	17.34	29.27
Asymptomatic	29.74	12.03	12.20
Headache	5.63	0.78	1.22
Coma	0.34	8.13	25.61
Seizures	0.80	0	0
Hypertension	4.02	3.28	0
Nausea	25.49	2.34	0
Other symptoms	16.65	6.41	8.54
Drowsiness	33.18	86.41	60.98
Tachycardia	11.14	10.63	8.54
Vomit	11.71	2.81	6.10

Source: Author (2020).

Overdoses by TCAs led to more hospitalizations in the ward and in the ICU when compared with the SSRI group ($p<0.001$). Only 76 patients (8.38%) with SSRI overdose were admitted in the hospital compared with 349 (54.53%) involving TCAs. Only three cases (0.34%) from the SSRI group required admission to the ICU, in contrast to 75 patients (11.72%) in the TCA group.

In cases of combined ingestion of both classes of antidepressants, 49 patients (59.76%) required hospitalization, of whom 11 were admitted to ICU (13.41%), with a statistically significant difference when compared with SSRI alone ($p<0.001$), but with no statistically significant difference compared with the TCA group ($p=0.081$). Period of hospitalization for TCA poisonings were longer when compared with SSRI ($p<0.001$). The mean periods of hospitalization (ward and ICU) in the TCA and SSRI groups were 2.8 days (1 to 30 days) and 1.2 days (1 to 4 days), respectively.

TCA-related overdoses led to greater periods of hospitalization compared with SSRI. Patients reporting TCA overdose remained hospitalized for a median of 2 days in the ward and/or emergency room and for a median of 4 days in the ICU. On the other hand, patients intoxicated by SSRIs were hospitalized in both the ward and the ICU for a median of 1 day ($p<0.001$).

In our statistical analysis comparing outcomes between the two groups, we excluded 80 exposures due to loss of follow-up. The remaining sample was distributed using the quartile method. Although the majority of exposures presented with mild clinical manifestations, TCA intoxications were associated with more severe outcomes ($p<0.001$). Within the SSRI group, 67.92% of patients had mild clinical manifestations and 23.45% were asymptomatic. Only one case (0.13%) evolved with severe clinical manifestations and no deaths were recorded. In the TCA group, 61.63% of patients had mild clinical manifestations, 11.48% had severe clinical manifestations, with 4 fatal records. Most patients who ingested TCAs and SSRIs simultaneously presented mild clinical manifestations (62.65%), 14.46% had severe symptoms, including one death.

The five deaths occurred in female patients with a mean age of 38.8 years (14 to 67). Amitriptyline was ingested alone in three cases, with a reported dose of 12, 15 and 19.2 mg/kg. One patient ingested 12 mg/kg of sertraline associated with 24 mg/kg of amitriptyline, while another patient ingested 37.5 mg/kg of nortriptyline. The five patients evolved with hypotension and altered level of consciousness. The mean time from drug intake to death was 58.8 hours (6 to 132 hours). All deaths were preceded by arrhythmias and electrocardiographic changes, such as widening of the QT interval and QRS complex. Table 2 summarizes the main differences assessed in the study.

Table 2 – Comparison of exclusive exposures with TCAs and SSRIs registered by CIATox/SC from 2015 to 2019 (n=1593).

Category	Variables	SSRI	TCA	P value
Gender	Female	82.32%	84.69%	0.250
	Male	17.68%	15.31%	
Toxic dose	Yes	81.40%	87.97%	<0.001
	No	18.60%	12.03%	
Need for hospitalization	Yes	8.72%	54.53%	<0.001
	No	91.28%	45.47%	
Infirmary admission	Yes	8.38%	43.13%	<0.001
	No	91.62%	45.47%	
ICU admission	Yes	0.34%	11.72%	<0.001
	No	99.66%	88.28%	
Severe clinical manifestations	Yes	0.11%	11.41%	<0.001
	No	99.89%	89.59%	

Source: Author (2020).

5 DISCUSSION

In our study, there was an annual increase in the incidence of suicide attempts with SSRIs from 2015 to 2019. In a similar fashion, this trend is also reported in other studies in the literature (GILLEY *et al*., 2020; GUMMIN *et al*., 2022; MCKENZIE; MCFARLAND, 2007; TOWNSEND *et al*., 2001). The potential reasons for this increase are the higher number of prescriptions of this class of drug, the rise in the incidence of suicide attempts and the replacement of TCAs by SSRIs in the treatment of depression (GRAUDINS; DOWSETT; LIDDLE, 2002; MASON; FREEMANTLE; ECCLES, 2000; PHILLIPS *et al*.,

1997).

The stability in the number of intoxications by TCAs found in our study diverges from the international literature, which suggest a decline in intoxication rates caused by this class of drugs (GIBBONS *et al*., 2005; GRAUDINS; DOWSETT; LIDDLE, 2002). This stability may be attributed to the persistent use of tricyclic antidepressants in medical practice within the state of Santa Catarina, especially among patients with psychiatric disorders at high risk of suicide.

Most suicide attempts occurred in females aged 20 to 29. This demographic is predominant in drug poisoning in general, (GILLEY *et al*., 2020; GUMMIN *et al*., 2022) and this pattern is in line with other descriptive studies on suicide attempts resulting from overdose of antidepressants (MATHIAS; GUIDONI; GIROTTO, 2019; TOWNSEND *et al*., 2001).

We observed that poisoning with TCAs and SSRIs was more frequently reported in December and November, respectively. The 2019 CIATox/SC report highlights that the total number of records from all causes is higher during the warmer months of the region (i.e. November, December and January). Similarly, the highest rates of poisoning and suicide attempts occur in the hottest months of the year (UFSC, 2019).

Unverir *et al*. (2006), when analyzing the seasonality of antidepressant overdoses in Turkey, noticed a greater incidence of hospital admissions in the month of July, coinciding with elevated temperatures in the country. In contrast to overall mortality trends, suicide rates increase during the summer and decreases in the winter. Studies suggest that this phenomenon might be explained by the intricate interaction between biological factors, such as climate and temperature, which could alter the functioning of the nervous and endocrine systems. Such changes may influence the stability of patients with mood disorders, thus triggering suicide attempts. Nevertheless, it is also paramount to acknowledge the influence of sociological factors in order to understand the changing social dynamics associated with seasonal transitions (BURKE *et al*., 2018; OLIVEIRA *et al*., 2020).

Amitriptyline and fluoxetine were the most commonly used drugs in overdoses. Other Brazilian studies have highlighted amitriptyline as the most frequent TCA in suicide attempts (BERNARDES; TURINI; MATSUO, 2010;

FERNANDES *et al*., 2006). Amitriptyline was the main TCA used in poisoning in toxicological care managed by the São José do Rio Preto Toxicological Assistance and Information Center (FERNANDES *et al*., 2006). Fluoxetine is cited in the literature as the most used SSRI in overdoses (GUMMIN *et al*., 2022; MATHIAS; GUIDONI; GIROTTO, 2019; UFSC, 2019). This trend probably arises due to its status of being the first approved SSRI, for having a good safety profile and a wide range of clinical indications (GANETSKY, 2017).

The most frequent clinical manifestation in the TCA group found in our study is in accordance with the literature, which highlights symptoms caused by neurotoxicity and cardiotoxicity, such as drowsiness, altered level of consciousness, comaand arrhythmias (FERNANDES *et al*., 2006; SALHANICK, 2018; UNVERIR *et al*., 2006). Anticholinergic signs and symptoms (flushing, mydriasis, dry skin, urinary retention, hyperthermia) were not among the most frequent in our findings, despite reports in the literature (SALHANICK, 2018). The minor severity of these alterations might have led to fewer reports and thus come unnoticed by the physician providing information to CIATox/SC.

In the SSRI group, the most common clinical manifestations were drowsiness, nausea, tachycardia and vomiting. According to the literature, nausea and vomiting are frequent when the ingestion of this class of drugs is 30 times above the daily dose, while changes in the level of consciousness and electrocardiographic findings are expected when the dose exceeds 75 times the daily dose (GANETSKY, 2017). In our study, 29.74% of SSRI exposures were asymptomatic, although 83,58% of patients reached the toxic dose. This finding suggests that patients who exceed the toxic threshold will not necessarily present noticeable clinical changes during the initial medical evaluation.

A similar rate of tachycardia was reported in the SSRI (11.14%) and TCA (10.63%) groups, which differs from literature data. Multiple studies have shown a higher incidence of tachycardia in poisoning by TCAs compared with SSRIs (FERNANDES *et al*., 2006; ISBISTER *et al*., 2004; UNVERIR *et al*., 2006). Sinus tachycardia is a commonly reported manifestation in TCA overdoses, probably due to anticholinergic effects and reflex tachycardia caused by hemodynamic decompensation. On the other hand, SSRIs are weak antagonists for muscarinic and adrenergic receptors and usually do not cause anticholinergic symptoms or hypotension (SALHANICK, 2018). The conflicting

data found in our study may be biased, since the majority of cases did not present an electrocardiogram record.

Intoxications by TCAs lead to higher rates of hospital admissions and more prolonged hospitalizations when compared with with SSRIs. Previous studies have shown that 68 to 78% of patients intoxicated with TCAs are eventually hospitalized, (FERNANDES *et al*., 2006; MCKENZIE; MCFARLAND, 2007) whereas in our study we found an admission rate of 54.53%. This lower incidence might be partially explained by the inclusion exposures to TCA that did not reach the toxic dose (7.97%).

Patients presenting with TCA overdoses are more likely to progress with severe clinical manifestations as compared with SSRIs, therefore requiring more admissions to ICUs. This finding is in line with other studies, which also report a greater need for invasive procedures, such as orotracheal intubation (GRAUDINS; DOWSETT; LIDDLE, 2002; UNVERIR et al., 2006). Two international studies demonstrate that the mortality rate in overdoses with SSRIs is significantly lower compared with TCAs (MASON; FREEMANTLE; ECCLES, 2000; PHILLIPS *et al*., 1997).

6 STUDY LIMITATIONS

The results from this study are prone to limitations inherent to retrospective research. We collected data from secondary sources, filled in and validated by trained professionals. The assessment of patients' electrocardiograms and the need for invasive procedures was not possible due limited information available in the records. Additionally, the contact initiated by health professionals with CIATox/SC is voluntary, therefore our data may not reflect the total number of exposures by TCAs and SSRIs during the analyzed period.

7 CONCLUSION

TCA intoxication poses a high morbidity and mortality risks, primarily attributed to its cardiotoxic and neurological effects that frequently require monitoring, hospitalization and invasive procedures. These events significantly impact the health of affected patients, mainly because of the absence of effective antidotes. Consequently, investments in preventive measures are

paramount, particularly through a comprehensive understanding of the epidemiological profile of this population, given that a history of previous attemps is the major risk factor for fatal suicide attempts (WHO, 2019).

SUS is tasked with conducting awareness campaigns that address the concepts of psychological distress, depression and suicide. The main goal is to prevent social marginalization of this population and promote family support. Furthermore, the health care system should allocate resources for the comprehensive care of these patients, empowering physicians to carefully weigh the benefits and risks of prescribing TCAs. Whenever feasible, opting for safer medications is highly recommended.

Finally, further studies are warranted to assess the impact of intoxication and suicide attempts by tricyclic antidepressants and selective serotonin reuptake inhibitors. It is important to evaluate the association of these overdoses with prescription rate of these drugs in order toassess whether the frequent use of TCAs in patients with psychiatric disorders at high risk of suicide is truly necessary, especially when other safer medication options are avaliable.

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