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Immune system sensitivity in tobacco and psychoactive substance users: a study at Cisa-Boukhadra, Algeria.

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ABSTRACT:
Psychoactive substances (PAS) are substances that affect an individual's psyche by altering their neuropsychological functioning. They can disrupt the central nervous system's operations or stimulate immune system activity. Generally, these substances can be divided into those that have a calming effect, such as cannabis or opioids like tramadol, and those that have a stimulating effect, like tobacco, which is considered a stimulant of the central nervous system (CNS). The effects of these substances can vary depending on the dose consumed.

The objective of our study was to examine the effects of smoking and other psychoactive substances (PAS) on the immune system, specifically focusing on mental and biological changes. The study aimed to analyze the relationship between the degree of dependence on psychostimulants and antidepressants and their effects on bodily functions, and to determine the high-risk group for developing addiction and an inflammatory syndrome (IS) based on the age of initiation of smoking (starting tobacco use in childhood [9-13 years], adolescence [14-18 years], or adulthood [19-41 years]).

A self-assessment questionnaire was administered to 100 smoking subjects to gather data on the patient's demographic characteristics (age, age of smoking initiation, risk factors, etc.), mental health status (depression, anxiety, stress), and an analytical blood study on several hematological inflammatory parameters (White Blood Cells (WBC), Hemoglobin (HB), C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR)). All the data were extracted from patient records and medical files used by the Boukhadra Intermediate Addiction Care Center (CISA).

In this study, we found a strong relationship between the level of nicotine and psychoactive substance (PAS) dependence and changes in both mental and biological aspects. We suggest a high risk of personal vulnerability and a sociocultural environment for individuals with a strong cigarette addiction, particularly those who started smoking during adolescence. The inflammatory profile appears to be an interesting biomarker to consider during PAS withdrawal.

Keywords: Psychoactive substances, tobacco, dependence, inflammatory parameters.

1. INTRODUCTION :

The human nervous system (NS) is responsible for sending, receiving, and processing nerve impulses, which are essential for the function of muscles and organs. Understanding the interdependence within the NS is crucial (**Abou Sarr, 2008**). Homeostasis in mammals is maintained through three major communication and integration systems: the nervous, endocrine, and immune systems. Initially considered independent, recent studies reveal that these systems interact in a multidirectional and precise manner (**Chettoum, 2014 and Boumaza and Benferdi, 2019**). Each system is activated by specific factors, and deficiencies can lead to serious consequences. The immune system (IS) plays a role in brain surveillance, with excessive glial cell responses potentially harming neurons and contributing to psychiatric disorders, such as anxiety, depression, and other mood disorders (**Brochier and Olie, 1993 and Chettoum, 2014**).

Tobacco is classified as a mild stimulant of the nervous system (NS) (**Ben Amar and Légaré, 2006**). It is derived from the Nicotiana tabacum plant, which has been modified by the tobacco industry to enhance dependence and increase enjoyment of its consumption (**Boukkebous and Sabouni, 2020**). Tobacco boosts alertness, stimulates the cerebral cortex, and accelerates mental processes, leading to heightened vigilance, mood stimulation, and increased motor activity. While it enhances energy and focus, it also weakens the immune system (IS) (**Ben Amar and Légaré, 2006 and Gaiha *et al*., 2020**). Tobacco smoke contains numerous toxic, irritating, and carcinogenic compounds, with nicotine being the primary addictive and psychoactive substance. Once inhaled, nicotine directly affects the brain by binding to nicotinic receptors for acetylcholine (**Romain, 2018**). While tobacco acts as a stimulant of the NS, cannabis and tramadol are known disruptors of the system (**Ben Amar and Légaré, 2006 and Amedjekouh and Siaci, 2017**).

Cannabis (*Cannabis sativa*) is a natural substance and one of the most commonly consumed drugs globally. It induces significant psychological dependence, with its toxicity varying based on the dose of active compounds that enter the brain (**Bruneau, 2016**). Tramadol, an opioid analgesic, works by directly altering the brain's perception of pain. Chronic use, especially at high doses, can lead to dependence. It has strong analgesic properties due to its effects on the nervous system (NS) (**Bourouis and Chouki, 2021**). Over the last two decades, many studies

have highlighted the connection between smoking and the development of immune and psychiatric disorders (**Boumaza and Benferdi, 2019**). The inflammatory response refers to the body's mechanisms to fight off various types of aggression, including infectious, immunological, tumoral, physical, or chemical insults (**Chappuis, 2012**). Cigarette smoke induces a systemic inflammatory response, stimulating the hematopoietic system, particularly the bone marrow. Biologically, the inflammatory syndrome involves disturbances such as increased erythrocyte sedimentation rate (ESR) and inflammatory proteins (**Audia *et al*., 2008 and Chappuis, 2012**).

To validate our study, we focused on key objectives including demographic factors (age, marital status, daily and occasional consumption doses, etc.), socio-economic factors (current profession), and the measurement of inflammatory biomarkers such as C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and Complete Blood Count (CBC) including Hemoglobin (HB) and White Blood Cells (WBC).

2. MATERIALS AND METHODS:

1- Sampling and Data Collection:

Our study targeted 100 male patients aged 14 to 64 years with tobacco use disorder and other psychoactive substance dependencies, admitted to the CISA-Boukhadra center, and categorized into three groups based on smoking initiation age: childhood (9-13 years), adolescence (14-18 years), and adulthood (19-41 years). Conducted between February 27 and May 14, 2023, during a period of high patient influx, the study involved data collection from 2021-2023 patient records and a structured questionnaire addressing demographics (age, profession, marital status), smoking initiation (age, mode of initiation), concurrent substance use, medical history (personal and family), motivations and effects of substance use (initial and current), daily consumption patterns (dose, combinations, overdoses, cessation attempts), and mental state (e.g., anxiety or stress).

2- Measurement:

A thorough medical evaluation was conducted, along with blood analyses for selected inflammatory parameters, including: **complete blood count (CBC):** White blood cells (WBC)

and Hemoglobin (HB). C - reactive protein **(CRP):** measured as an inflammatory biomarker. Erythrocyte sedimentation rate **(ESR):** To assess systemic inflammation.

Quantitative variables were expressed as means, while qualitative variables were presented as percentages **(Table 1).**

Table 1: normal values of inflammatory parameters

	WBC	**HB**	**CRP**	**ESR**
Normal values	4,000 to 11,000 cells/ µL (**Chettoum, 2014**).	Males: 14 to 18 g/dL Females: 12 to 16 g/dL. (**Chettoum, 2014**).	≤6mg/L (**Chettoum, 2014**).	Males: normal values: Less than 15 mm in the first hour. Less than 20 mm in the second hour. (**Audia *et al*.,2008**)

3- Ethical Considerations:

Our study was conducted in accordance with the ethical guidelines related to human health and the principle of confidentiality regarding patients' personal information. All procedures followed the established ethical standards, ensuring the privacy and protection of participants' data throughout the research process. Informed consent was obtained from all participants, and their participation was voluntary. Data was handled with strict confidentiality, and patients' identities were anonymized in all records and reports.

4- Data Analysis:

All the anamnesic parameters studied were collected using pre-established data sheets (Anamnesis). The data were then entered into Microsoft Excel for processing and analysis. The results are presented as both numerical values and percentages to provide a clear overview of the findings. Statistical methods were applied to determine relationships and significance, ensuring accurate interpretation of the collected data.

3. RESULTS:

1. Demographic and socio-economic data:

1.1. Distribution of patients based on their real age and professional activity:

The results reveal that the predominant age group among patients using tobacco in combination with other psychoactive substances is the 20 to 64 year old group, representing 88 patients of the total sample. In addition, the 14 to 19 year old group constitutes 12 patients using tobacco in combination with other psychoactive substances. Of the 100 patients included in our research, 43 are functional, 39 are unemployed, which represents a significant share, while 18 are students, a relatively small proportion.

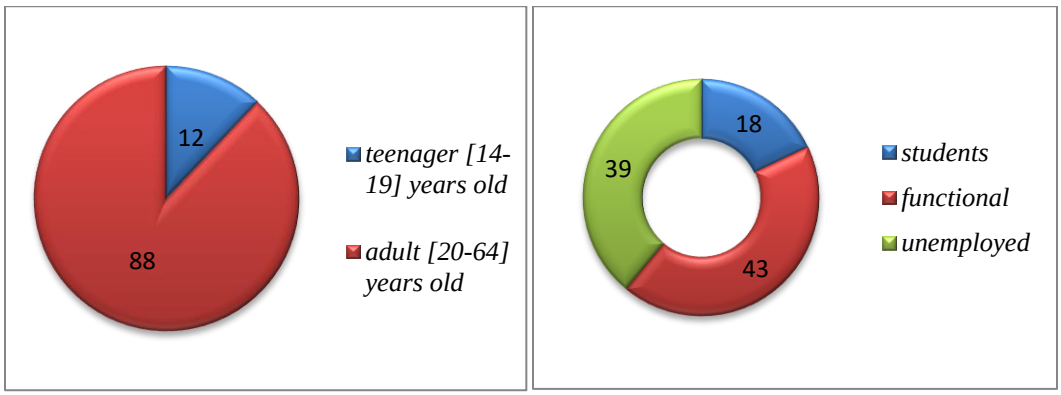

Figure1: *distribution of patients based on their real age and professional activity.*

1.2. Distribution of patients by marital status and their consumption of tobacco associated with psychoactive substances:

The data reveals that among the patients consuming tobacco combined with other psychoactive substances, 79 are single, representing the majority of cases, while 21 are married. This distribution highlights a higher prevalence of consumption among single patients. The 2nd pie chart highlights that 54% of patients consume cannabis combined with tobacco, which is the largest proportion. On the other hand, the consumption of tramadol combined with tobacco is much lower, representing only 4%. Furthermore, 42% of patients simultaneously consume tobacco with both psychoactive substances, namely cannabis and tramadol.

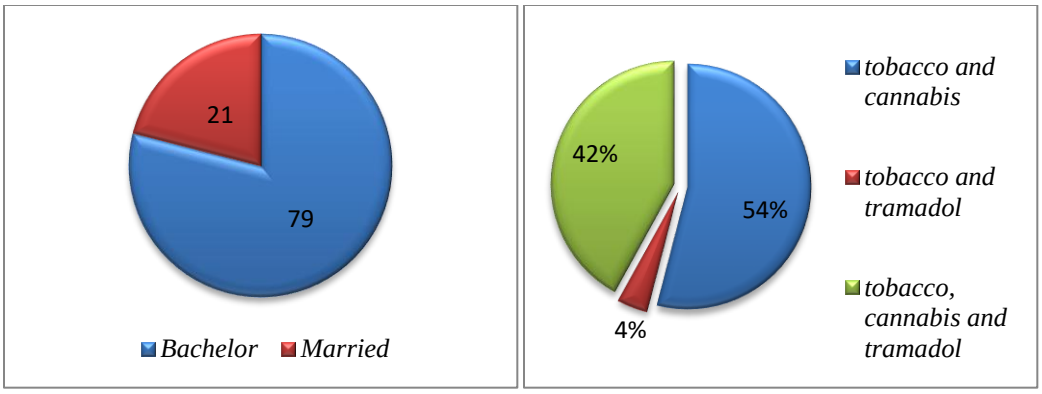

Figure2: *distribution of patients by marital status and their consumption of tobacco associated with psychoactive substances.*

1.3. Initiation modes of tobacco consumption associated with psychoactive substances:

Among the 100 patients studied, 41 began their consumption under the influence of friends or other people, thus representing the main cause. This reason is followed by 23 patients who began for recreational reasons, 18 out of curiosity and 12 during festivals. Finally, 14 patients reported having initiated their consumption to feel anxiolytic. Other patients mentioned various reasons, such as avoiding withdrawal or therapeutic uses. These results highlight the importance of social influence and festive contexts in triggering consumption **(Table 2).**

Table 2: mode of initiation of consumption among patients:

Mode of start of consumption	Curiosity	Recreational	Influence	Festive	Therapeutic	Anxiolysis
Number of patients	18	23	41	12	01	14

1.4. Distribution of patients based on factors leading to tobacco consumption associated with psychoactive substances:

The study shows that patients consume psychoactive substances in combination with tobacco for various reasons: search for Well-being: 66 patients, euphoria: 73 patients, improvement of Work Performance: 27 patients and facilitation of Social Interactions: 24 patients.

The results highlight that the primary motivations for patients consuming tobacco combined with psychoactive substances are the search for positive sensations**,** such as euphoria and well-being. These desires are driving factors in substance use and are prevalent in the majority of patients **(Table 3).**

Table 3: distribution of patients according to motivations for consuming tobacco associated with psychoactive substances.

Desired effect	Search for well-being	Feeling of euphoria	Improved work performance	Facilitation of social interactions
Number of patients	66	73	27	24

1.5. Doses of psychoactive substances and tobacco consumed daily, previous attempts at withdrawal and overdoses**:**

The results obtained show that 24 patients were exposed to significant amounts of smoke and psychoactive substances, leading them to consult the hospital **(Table 4).** While about 46 patients tried to stop smoking and consuming psychoactive substances, demonstrating their willingness to break with these habits despite the difficulties encountered.

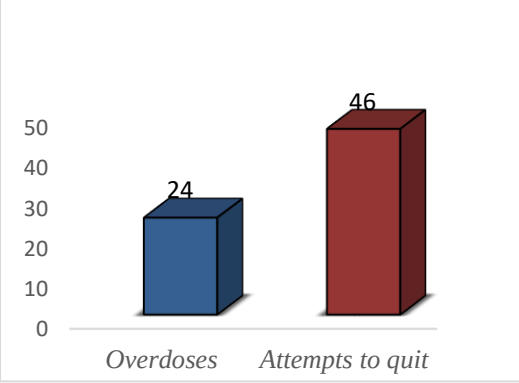

Figure3: *previous quit attempts and overdose.*

Table 4: daily doses of psychoactive substances and tobacco consumed

The doses	Average	Maximum

Substances	tobacco	cannabis	tramadol	tobacco	cannabis	tramadol
The quantities	1p/d	2-3c/d	2co/d	2 p/d	10-15 c/d	10co/d

Noticed: p/d=package/day, c/d =capsule/day, co/d=compressed/day. The tobacco pack contains 20 cigarettes.

1.6. Mental state and psychological disorders of patients**:**

Among the 100 patients who used the drug, 45 suffered from anxiety disorders, while 31 had depressive disorders. Other mental disorders were also observed, including schizophrenia, panic disorders, phobias, hallucinations and episodes of aggression **(Table5).**

Table5: mental state and psychological disorders of patients

Mental state	Anxious	Stressed	Depression	Schizophrenia
Number of patients	45	11	31	4

2. Hematological data:

2.1 Distribution of patients according to age of initiation into tobacco use:

Figure 4 illustrates the age of initiation to tobacco use, divided into three age groups: child (Chd), adolescent (Ads), and adult (Adt), with initiation ages ranging from 9 to 41 years. Among patients who use tobacco, the most represented age group is [14-18] years (Ads), comprising 58 patients from the total sample. The [9-13] years group (Chd) follows with 31 patients, also representing a significant portion of the studied population. Finally, the [19-41] years group (Adt) includes 11 patients, accounting for a smaller percentage compared to the other two groups.

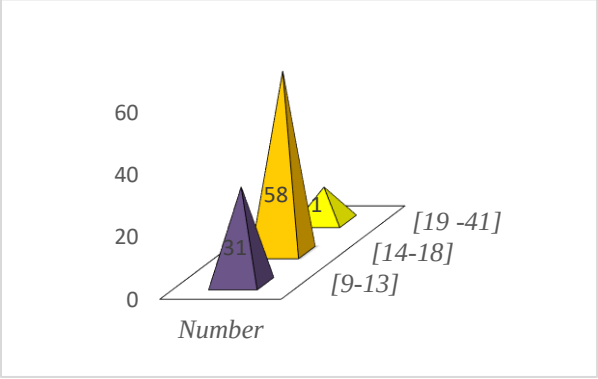

Figure 4 : *Répartition des patients selon l'âge d'initiation au tabac.*

2.1. Analysis of averages of white blood cells and total Hemoglobin according to age of initiation of smoking:

The analysis of white blood cell counts reveals a variation based on the age of initiation to tobacco use. Patients who began smoking at an early age [9-13 years] exhibit the lowest average white blood cell count, at 7779 mm³. Conversely, adolescents [14-18 years] and adults [19-41 years] have higher average white blood cell counts, reaching 13,000 mm³ and 15,576 mm³, respectively. Regarding the average hemoglobin levels, significant variations are observed across the age groups: in the (Chd), the average hemoglobin level is 15.04 g/dl. Among (Ads), it is slightly higher, reaching 16.48 g/dl. The (Adt) shows a significantly higher average hemoglobin level compared to the other two groups, at 18.89 g/dl.

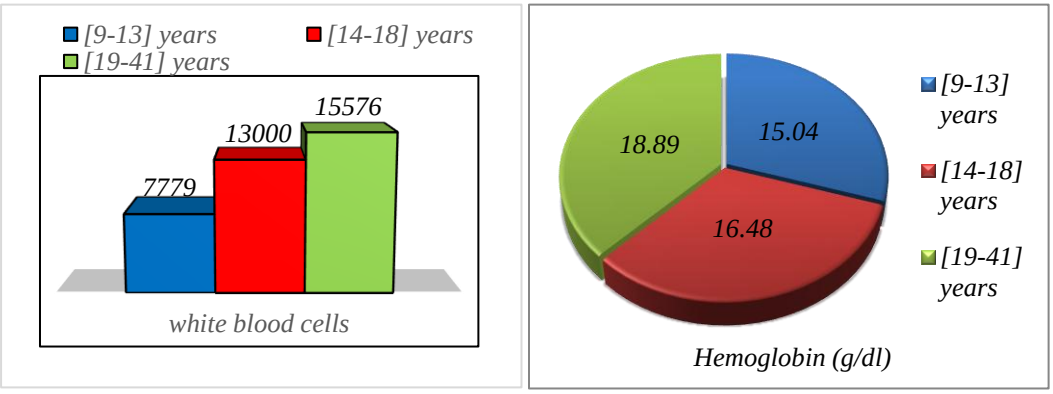

Figure 5 : *Moyenne des Globules Blancs et de l'Hémoglobine totale en fonction de l'âge d'initiation au tabac.*

2.3. Variation of C-reactive protein (CRP) according to age of smoking initiation:

In the study, among children (9-13 years, n = 31), 22 patients had a positive CRP (≥ 6 mg/L) with a mean of 23.4 mg/L, while 9 patients had a negative CRP (≤ 6 mg/L) with a mean of 1.67 mg/L. Among adolescents (14-18 years, n = 58), 46 patients had a positive CRP (≥ 6 mg/L) with a mean of 15.52 mg/L, and 12 patients had a negative CRP (≤ 6 mg/L) with a mean of 1.41 mg/L. In adults (19-41 years, n = 11), 10 patients had a positive CRP (≥ 6 mg/L) with a mean of 7.36 mg/L, while 1 patient had a negative CRP (≤ 6 mg/L) with a value of 1.83 mg/L.

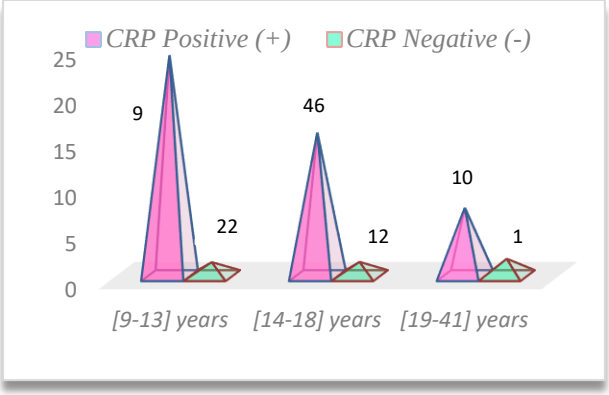

Figure 6: *Variation of C-reactive protein according to age of smoking initiation.*

2.4. Variation in erythrocyte sedimentation rate (ESR) according to age of smoking initiation:

In the study, among children (Chd), 54% had an ESR > 15 mm at the first hour, and 42% had an ESR ≥ 20 mm at the second hour. Among adolescents (Ads), 33% had an ESR ≥ 15 mm at the first hour, and 27% had an ESR ≥ 20 mm at the second hour. In adults (Adt), 63% had an ESR ≥ 15 mm at the first hour, and 36% had an ESR ≥ 20 mm at the second hour.

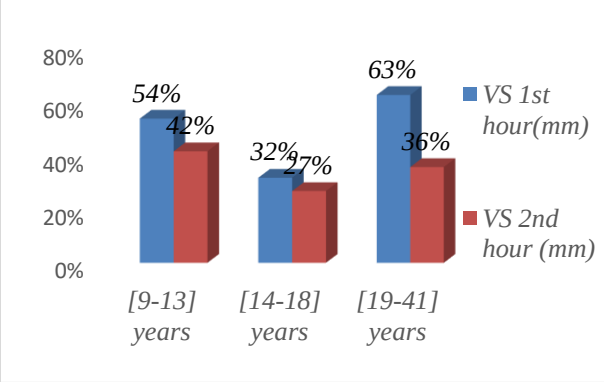

Figure 7: *Variation in erythrocyte sedimentation rate (ESR) according to age of smoking initiation*

4. DISCUSSION:

Psychoactive substances (PAS) are compounds that alter states of consciousness by affecting perception, emotions, thought processes, and behaviors. Defined as any psychotropic or psychoactive substance disrupting the central nervous system, they include opioids,

psychostimulants, antidepressants (e.g., tramadol), and substances like tobacco and cannabis. Their consumption often leads to dependence, characterized by a compulsion to consume the substance for its psychological effects or to avoid withdrawal discomfort (**Ben Amar and Légaré, 2006**).

Our study examined users aged 14 to 64, with 88% in the [20-64 years] range and an average age of 28.6 years. These findings are consistent with studies such as **Al-Husseini *et al.*, (2018)**, which reported an average age of 21.7 years in the [18-40 years] group, and **Mbongo'o *et al.*, (2021)**, which observed an average age of 27.5 years with extremes of 19 to 32 years.

Tobacco and psychotropic substance use were more prevalent among civil servants and unemployed individuals compared to students, likely influenced by age distribution. This is consistent with studies showing the impact of work conditions and unemployment on substance use. A 2010 French public health survey reported increased tobacco and cannabis consumption among one-third of regular smokers and 13% of cannabis users due to work-related stress. Unemployment is also strongly linked to higher smoking rates, particularly among men (**Khlat *et al.*, 2000**). Conversely, higher education tends to reduce substance use (**Mbongo'o *et al.*, 2021**). Furthermore, 79% of participants in our study were single, reflecting the established link between marital status and substance use behaviors (**Diakité, 2015 and Traoré, 2018**). Our research on psychoactive substances (PAS) found that most users began consumption influenced by family or friends, often for recreational reasons. Studies confirm that a family history of substance abuse significantly increases the risk of early misuse, particularly in childhood and adolescence (**Blum, 1987**). Family tolerance for alcohol or drugs, as well as parental substance use, is critical risk factors for young people (**Bailly, 1999 and Nikiéma *et al.*, 2011**). Alcohol and cannabis use among students is often tied to familial alcoholism or peer influence. Cannabis emerged as the second most consumed substance after tobacco, with most users consuming both, aligning with studies indicating that 80% of regular cannabis users also smoke tobacco (**Nikiéma *et al.*, 2011**). Initial substance use is frequently driven by curiosity, transgressive behavior, or the perceived social benefits, particularly in group settings where individuals seek belonging (**Quentin and Johana, 2022**).

Studies on smoking and psychoactive substance (PAS) use highlight the significant impact of family issues and personal struggles. Research such as **Senga *et al*., (2005)** in Brazzaville found a link between alcoholism and being orphaned, supporting the idea that family and personal history are key influencers of PAS use. Additionally, personality traits like sensation-seeking and impulsivity contribute to substance consumption (**El-Guebaly and Hodgins, 1992**). Tobacco is often used to manage stress and promote relaxation (**Laure *et al*., 2001and Houemenou, 2012**), while cannabis is consumed for relaxation, socializing, and partying. Tramadol, a sedative opioid analgesic, has seen rising use, particularly among younger populations. Polydrug use in youth is a significant risk factor for dependency and health issues (**Devaux, 2022**). Some studies on psychoactive substance (PAS) use among children and adolescents emphasize the need to consider additional factors to better understand its effects. These factors include excessive substance use in terms of both frequency and quantity, as well as the simultaneous use of multiple substances. (**Vitaro *et al*., 2000 and Laventure *et al*., 2006**). Our study corroborates these findings, particularly observing that cannabis is commonly consumed as resin mixed with tobacco (joint), consistent with earlier European studies (**Guessad, 2021**).

The consumption of psychoactive substances (PAS) has a long history and follows diverse trajectories: recreational (without significant health impacts), risky (posing dangers to users or others), or addictive (when consumption dominates the user's life). Addiction is marked by the emergence of physical and psychological withdrawal symptoms when substance use decreases or ceases. In our study, 46% of patients attempted to quit following prolonged, high-dose use, while 24% reported overdoses of tramadol or tobacco (**Didier, 2016**). The study also examined the connection between PAS use and mental health disorders, including anxiety, depression, schizophrenia, and hallucinations. A high prevalence of psychological disorders was observed among users of tobacco and other PAS, consistent with findings from **Glassman *et al*., (1990),** who noted increased smoking rates in individuals with a history of depression. Additionally, cannabis use has been linked to heightened anxiety (Leadbeater *et al*., 2019).

Our analysis focused on 100 patients, categorized into three groups based on their age of initiation to tobacco (9 to 41 years): children (Chd), adolescents (Ads), and adults (Adt). The most represented age group among tobacco users was 14 to 18 years (58%), followed by 9 to 13 years (31%). These findings align with **Holligan *et al*., (2019)**, who demonstrated that early

alcohol initiation during adolescence predicts increased alcohol use, binge drinking, and mixing alcohol with energy drinks by grade 12. These insights highlight the critical need for bolstered prevention efforts targeting alcohol and PAS consumption to mitigate their mind-altering effects and the risk of dependence.

Our study hypothesizes that psychoactive substances (PAS) induce qualitative and quantitative effects on the immune system, resulting in an inflammatory syndrome, particularly through chronic inhalation of cigarette smoke, which disrupts innate and adaptive immunity and leads to immunosuppression, hypersensitivity reactions, and immune dysregulation, increasing susceptibility to infections, tumors, allergies, asthma, and autoimmune syndromes (**Sopori, 2002**). Analysis revealed significant changes in inflammatory markers, including elevated CRP levels (7.36–23.4 mg/L) among tobacco, cannabis, and tramadol users, driven by nicotine, THC, and opioid effects (**Benoit, 2019**). These substances trigger inflammatory responses measured by CRP and erythrocyte sedimentation rate (ESR), with CRP elevations sometimes exceeding 10 mg/L for more than three weeks, indicative of chronic inflammation (**Chappuis, 2012**). While CRP levels can rise sharply during severe infections, ultra-sensitive CRP testing also highlights cardiovascular risk at levels above 3 mg/L. Immune alterations include reduced functionality of neutrophils, macrophages, and dendritic cells, along with impaired cytokine production and increased white blood cell counts. These findings underscore the need for further validation and highlight the importance of monitoring inflammatory and immune impacts of PAS to mitigate health risks (**Mar *et al*., 2005**).

Tobacco significantly impacts innate immunity, as evidenced by increased neutrophil counts (polymorphonuclear neutrophils, PNN) in smokers, whose functionality, including inflammatory activity, migration, and chemotaxis, is impaired due to nicotine and acrolein in cigarette smoke (**Sopori, 2002 and Oberti, 2017**). Similarly, macrophages, essential for phagocytosis and pathogen elimination, become less mature and lose bactericidal and phagocytic efficiency, alongside diminished secretion of pro-inflammatory cytokines, further compromising immune defense. Cigarette smoke also inhibits macrophage endocytosis and phagocytosis, while Natural Killer (NK) cells show reduced cytotoxic activity and cytokine production under tobacco exposure, impacting antimicrobial defense and tumor surveillance (**Gonçalves *et al*., 2011**). Elevated white blood cell counts, ranging from 7779 mm^3 to 15576 mm^3 in our study,

corroborate these immune alterations. Dendritic cells, crucial for initiating immune responses, experience reduced numbers and inhibited functions such as endocytosis, phagocytosis, and priming in smokers (**Gonçalves *et al.*, 2011 and Oberti, 2017**). A study involving 2,920 men further confirmed that active smokers exhibit higher C-reactive protein (CRP) and white blood cell levels compared to non-smokers, emphasizing the inflammatory effects of tobacco (**Romo *et al.*, 2013**).

Hemoglobin levels in our study fall within the reference range of 14-18 g/dL for males, with a median value of 15.49 g/dL. Children exhibit an average of 15.04 g/dL, adolescents 16.48 g/dL, and adults 18.89 g/dL. Carbon monoxide (CO), a product of cigarette combustion, binds more strongly to hemoglobin than oxygen, forming carboxyhemoglobin (COHB), which leads to tissue hypoxia. This affects arterial cells and promotes atherosclerosis, consequently accelerating the heart rate and increasing blood pressure (**Chevalier and Nguyen, 2016 and Oberti, 2017**). Additionally, the erythrocyte sedimentation rate (ESR), used as a marker of inflammation, can be influenced by various physical or pathological factors, and in our study, we observed an acceleration of the ESR. Factors such as age, female sex, pregnancy, anemia, and elevated immunoglobulin levels can impact ESR without indicating actual inflammation. We excluded female sex, pregnancy, and anemia from consideration since our study population consisted exclusively of males with consistently high average hemoglobin levels (**Cacoub and Terrier, 2015**). The ESR results at 1 hour and 2 hours were found to be above the classical reference range for a significant portion of the cases across all age groups, suggesting the presence of chronic inflammatory processes in some individuals. Furthermore, studies have shown that ESR increases with age, which may be linked to lower albumin levels and elevated gamma-globulins and fibrinogen, partially explaining the observed increase in sedimentation rate (**Chappellier, 2002**).

5. CONCLUSION:

The consumption of tobacco and psychoactive substances (PAS) follows various trajectories, ranging from recreational use to dependence with negative health consequences. This study, conducted on 100 patients admitted to the CISA-Boukhadra center, explored the neuroimmune effects of tobacco and PAS, specifically cannabis and tramadol. We identified key characteristics

of the patients, with a significant proportion falling between 20 and 64 years of age. The study also assessed their functional and family status, as well as the initiation process of tobacco and PAS consumption. Our findings revealed that most patients started using PAS under the influence of close ones, seeking euphoria and well-being. Prolonged and excessive use led to dependence, with the appearance of withdrawal symptoms, particularly after overdoses. The study also highlighted a strong correlation between PAS use and mental health, with a high prevalence of PAS consumption among patients with mental disorders. In addition, we observed a significant inflammatory response, marked by elevated levels of biological indicators such as white blood cells (WBC), hemoglobin (HB), C-reactive protein (CRP), and sedimentation rate (ESR). Furthermore, the majority of patients were civil servants, with most being single. These results underscore the socio-demographic factors influencing PAS consumption and emphasize the need to address both psychological and immunological aspects in managing addiction.

In conclusion, this study highlights the importance of understanding the neuro-immune effects of tobacco associated with psychoactive substances in patients at CISA. The results obtained can serve as a foundation for the development of targeted prevention and intervention programs aimed at reducing the risks associated with the consumption of these substances. It is crucial to continue research in this area and implement awareness and education strategies for both patients and healthcare professionals, in order to improve overall care and provide a better quality of life for those affected.

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