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Review Article

Epigenetic control of drugs of abuse: new contribution to mental health?*

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Objective: to map the production of knowledge on the role of epigenetics in response to drugs of abuse, as well as the epigenetic changes observed in addiction and mental health. **Methodology**: a scoping review was conducted. The search was carried out in the bibliographic databases: PubMed/Medline, Science Direct, Scopus, Bentham Science, Embase, Web of Science, and Gale Academic OneFile. The data generated were analyzed thematically in three stages: a) selection and analysis of articles; b) analysis of textual data; and c) generation of bibliographic maps. **Results:** the search identified 21 articles related to the epigenetic effects of drugs of abuse on the mechanisms that generate chemical dependence. **Conclusion:** the results obtained allowed us to identify and verify that epigenetic mechanisms occur in response to the use of drugs of abuse, thus resulting in changes in genetic expression. It's pointed out that epigenetics aims to offer an additional mechanism of control over transcription and how genes are expressed, seeking to mitigate the impact of drugs of abuse in the treatment of mental disorders and chemical dependency.

Descriptors: Health Vulnerability; Substance-Related Disorders; Epigenomics; Mental Health.

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Controle epigenético das drogas de abuso: novo aporte à saúde mental?

Objetivo: mapear a produção de conhecimento sobre o papel da epigenética na resposta às drogas de abuso, bem como as alterações epigenéticas observadas na dependência e na saúde mental. **Metodologia:** foi realizada uma revisão de escopo. A busca foi realizada nas bases de dados bibliográficas: *PubMed/Medline*, *Science Direct*, *Scopus*, *Bentham Science*, *Embase*, *Web of Science* e *Gale Academic OneFile*. Os dados gerados foram analisados tematicamente em três etapas: a) seleção e análise dos artigos; b) análise de dados textuais; c) geração de mapas bibliográficos. **Resultados:** a busca identificou 21 artigos relacionados aos efeitos epigenéticos das drogas de abuso sobre os mecanismos geradores da dependência química. **Conclusão:** os resultados obtidos permitiram identificar e verificar que mecanismos epigenéticos ocorrem em resposta ao uso de drogas de abuso, resultando em alterações na expressão genética. Aponta-se que a epigenética visa oferecer um mecanismo adicional de controle sobre a transcrição e a forma como os genes são expressos, buscando mitigar o impacto das drogas de abuso no tratamento de transtornos mentais e dependência química.

Descritores: Vulnerabilidade em Saúde; Transtornos Relacionados ao Uso de Substâncias; Epigenômica; Saúde Mental.

Control epigenético de las drogas de abuso: ¿nueva contribución a la salud mental?

Objetivo: mapear la producción de conocimiento sobre el papel de la epigenética en respuesta a las drogas de abuso, así como los cambios epigenéticos observados en la adicción y la salud mental. **Metodología:** se realizó una revisión del alcance. La búsqueda se realizó en las bases de datos bibliográficas: *PubMed/Medline*, *Science Direct*, *Scopus*, *Bentham Science*, *Embase*, *Web of Science* y *Gale Academic OneFile*. Los datos generados fueron analizados temáticamente en tres etapas: a) selección y análisis de artículos; b) análisis de datos textuales; c) generación de mapas bibliográficos. **Resultados:** la búsqueda identificó 21 artículos relacionados con los efectos epigenéticos de las drogas de abuso sobre los mecanismos que generan dependencia química. **Conclusión:** los resultados obtenidos permitieron identificar y verificar que los mecanismos epigenéticos ocurren en respuesta al uso de drogas de abuso, resultando así en cambios en la expresión genética. Se señala que la epigenética pretende ofrecer un mecanismo adicional de control sobre la transcripción y cómo se expresan los genes, buscando mitigar el impacto de las drogas de abuso en el tratamiento de los trastornos mentales y la dependencia química.

Descriptores: Vulnerabilidad en Salud; Trastornos Relacionados con Sustancias; Epigenómica; Salud Mental.

Introduction

The completion of this study arises from the search for learning and contribution to the field of study of drug policies, especially in the area of drug consumption prevention. The expectation of prevention as an effective field to manage the relationship between man and drugs is fundamental for public health actions(1-2). Here we review how drugs of abuse act at the epigenetic level and the importance of these epigenetic changes in addiction. Research reveals and updates scientific knowledge that translates into interventions to reduce health disparities, including individual behaviors, lifestyles, biological processes, genetics, and epigenetics, which are potentially affected by chemical dependence(3).

Addiction develops in several stages: the beginning of drug use, intermittent to regular use, and, finally, addiction and relapse(4). The characteristics of addiction are the development of dependence on the drug, such that there is a physiological need for the drug for the individual to function properly; the development of tolerance, so higher doses of the drug are required to achieve the same effect; and the development of withdrawal, symptoms that occur once its use is stopped(4-5). Drugs of abuse alter physiological systems, contribute to the maintenance of the addictive state, and influence abstinence and relapse(4).

The biological factors, social, environmental, and convergent genetics, influence vulnerability to addiction, and chronic addiction(6). Twin studies have revealed that standard inherited genetic components predispose an individual to drug addiction. These genetic factors contribute 20 to 50% of the variance in the development of drug addiction and the rest is due to non-genetic factors(7-9). Recent studies have elucidated the interrelated nature of these determinants, clarifying the idea that individual biological factors and broader biosocial influences interact(10-17).

Although the effects of gene-environment interactions are still unclear, there may be a greater genetic influence on the phenotypes exhibited than traditional studies would indicate(18-21). In the context of drug addiction, interactions between genotype and environmental factors point to a significant role of epigenetic mechanisms in the acute response to drugs and the development of addiction(22). This epigenetic perspective is consistent with the longevity of psychiatric conditions, and the difficulty in effectively developing pharmacotherapeutic interventions to treat chronic behavioral disorders(23).

Epigenetics is the study of changes in genetic expression that are transmitted from generation to generation and has a place without an alteration in the sequence of deoxyribonucleic acid (DNA), but it is due to the modulation of factors associated with chromatin by effects environmental. Drug addiction continues to be a serious medical and social problem(24-26). The vulnerability to developing drug addiction depends on genetic, environmental, social, and biological factors(27), in particular, the interactions of environmental and genetic factors. The knowledge of research at a genetic and epigenetic level potentially provides spaces that allow us to translate the biology of drugs of abuse to new means to treat the disorder caused by the use of drugs of abuse using pharmacotherapeutic tools(28).

This research aimed to map the production of knowledge on the role of epigenetics in the response to drugs of abuse, as well as the epigenetic changes observed in addiction and mental health. In this way, it analyses the role of epigenetics in response to drugs of abuse, as well as the epigenetic changes observed in addiction and mental health.

Methodology

The study was designed as a comprehensive review. This type of review (Scoping Study or Scoping Review) provides a map of the main concepts that underlie an area of knowledge, in addition to examining the scope and nature of the investigation, allowing the dissemination of the research data, clarifying gaps in existing investigations, and therefore, tends to obtain integral results(29). Given the relevance of the content covered, the selection of this methodology is powerful because it can encompass all types of scientific literature, and there are more questions related solely to the effectiveness of an intervention or experience with treatments or care(30).

To carry out the study, developed according to the methodology of the Joanna Briggs Institute (JBI) protocol, the nine proposed steps were followed: 1) definition and alignment of objectives and questions; 2) development and alignment of inclusion criteria with the objective and question; 3) description of the planned approach to searching for evidence, 4) selection, data extraction and presentation of evidence; 5) search for evidence; 6) test selection; evidence extraction; test evaluation; 7) presentation of results; 8) summarize the evidence to the purpose of the review, 9) draw conclusions and point out any implications of the findings(31).

Data collection

The nature of the Scoping Review carries out extensive research. In this way, it includes databases with a wide range of coverage, intending to provide research with a greater scope of scientific productions on the topic(32). For this review, electronic databases were used as a source of evidence search, using the descriptors found in the Medical Subject Headings (MeSH). The study selection process was carried out in April/July 2023.

To guide the search, the research question was formulated using the PICO(33) strategy (P: population/ patients; I: intervention; C: control; O: outcome), defining "Dependents of drugs of abuse" as the population, " Epigenetic mechanisms that generate chemical dependence" as a phenomenon of interest, "Epigenetic mechanisms that generate chemical dependence" as a phenomenon of interest and "public health" as a context. Thus, the structured question was: What damages to the mental health of drug users are related to the occurrence of epigenetic modifications and their relevance in the characterization of drug dependence?

A bibliographic search was carried out in the following databases, covering an open period: PubMed/ Medline, Science Direct, Bentham Science, Embase, Scopus, Web of Science, and Gale Academic OneFile. The following research terms (search strategy) were entered into the aforementioned databases: "epigenetics AND drugs of abuse AND mental health OR addiction AND health vulnerability AND substance-related disorders").

Operational procedures for analysis of selected articles in the bibliographic search

The operational procedures were carried out in two stages:

1. Open access articles in English were selected, using the JBI protocol(31), and the articles that comprise this study's sample were selected and organized.
2. To access the discursive elements of the articles concerning the topic (epigenetic evidence and impact on mental health due to the use of drugs of abuse), extracts from the summaries of the articles selected in stage 1 were used. The summary was chosen because it summarizes the theoretical proposal of the author's objectives, methods, and reflections regarding the results found, thus creating conditions to analyze its discursive line more succinctly and objectively than the analysis of the entire article. This favors the acquisition of results that highlight the academic findings produced on the topic, with subsequent quality analyses necessary to evaluate the results' equity.

   To form the textual *corpus*, fifty-six extracts from the summaries were selected. These contained information about the theoretical framework, objective, method, and discussion of the results in their structure. The abstracts were then classified according to the type of study, area of knowledge, and published journal. After this process, they were subjected to the IRAMuTeQ® program (*Interface de R pour les Analyses Multidimensionnelles de Textes et de Questionnaires*)(34-35).

   The analysis of textual data, or lexical analysis(36-37), proposes overcoming the classic dichotomy between quantitative and qualitative data analysis since it allows us to quantify and use statistical calculations on qualitative variables: the texts. From textual analysis, it is possible to describe material produced by a certain producer, either individually or collectively (an individual or a group), and textual analysis can also be used for comparative and relational purposes, comparing different productions based on specific variables. that describe who produced the text.
3. Thus, the collected material was sent to the VOSviewer software version 1.6.16 to generate bibliographic maps and present scientometric networks in scientific landscape formats capable of revealing the relationships between specific elements.

VOSviewer is a software tool that allows the construction and visualization of bibliometric networks. According to guidelines defined for the descriptive presentation of the data, bibliometric maps were extracted (software output)(38), whose items are connected through couplings or bibliographic links, forming networks (elements and links between themselves) of citation, co-citation, co-authorship, and bibliographic coupling.

Finally, elements can be placed in groups, with each group represented by a set of elements gathered on a map, a graphical representation.

Results

The search identified 134 articles related to the use of drugs of abuse, of which 21 were excluded because they were repeated in the databases. After analysis of the titles and abstracts, 36 articles were excluded for not meeting the research eligibility criteria. The remaining 77 articles were read and analyzed in their entirety. Of them, 38 were excluded for not meeting the inclusion criteria. The remaining 39 articles were analyzed according to the Checklist SRQR procedure (Standards for Reporting Qualitative Research)(39), excluding 18 for not meeting the minimum score of 80% of the items, leaving 21 articles. Figure 1 shows the article selection process.

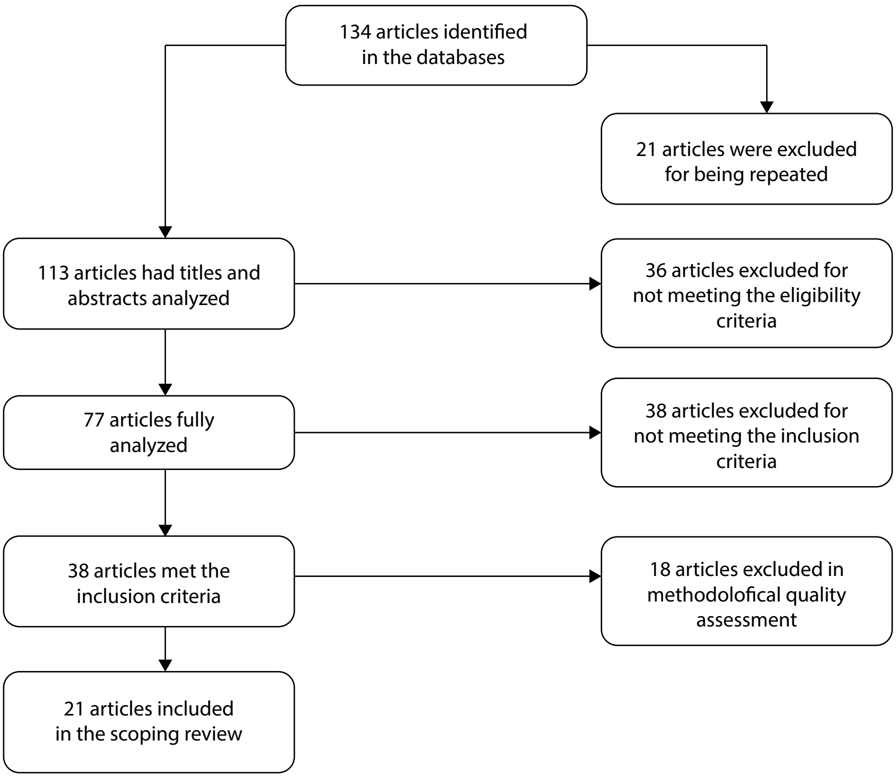

Figure 1 - PRISMA flow diagram for the scoping review process(31)

Figure 2 presents the typical characteristics of the articles selected for this research, which were identified and categorized into the themes of epigenetics and chemical dependence. The distribution of results is presented according to authors, year of publication, journal, description of the research object, and result. It was observed that 95.24% of the articles were published after 2010.

References	Year	Journal	Objective	Result
Nestler E(40)	2008	Philosophical Transactions of the Royal Society B	To investigate the detailed molecular mechanisms by which Delta FosB regulates focal genes and produces its behavioral effects.	Among the many transcription factors known to influence the drug addiction process, one of the best characterized is Delta FosB, which is induced in reward regions of the brain by chronic exposure to virtually all illicit drugs and media. sensitization responses to drug exposure.
Deng JV, Rodriguiz RM, Hutchinson AN, Kim IH, Wetsel WC, West AE(41)	2010	Nature Neuroscience	To demonstrate that the expression of $MeCP_2$ (mutations in patients with mental retardation) in the *nucleus accumbens* (NAcC) bidirectionally modulates Amphetamine-Induced Place Preference (AMPH).	The data reveal new functions for $MeCP_2$ both in the development of the mesocorticolimbic circuit and in the regulation of psychostimulant-induced behaviors.
Koob G, Volkow N(42)	2010	Neuropsychopharmacology	To investigate the psychiatric motivational structure that provides sources of positive and negative reinforcement for drug use.	Drug addiction has been conceptualized as a disorder that involves elements of impulsivity and compulsivity that generate a cycle of addiction composed of three stages: “compulsion/intoxication,” “withdrawal/negative affect,” and “preoccupation/anticipation” (craving).

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References	Year	Journal	Objective	Result
Bali P, Im HI, Kenny P[25]	2011	Epigenetics	To discover how epigenetic regulation at remote cortical brain sites may be driven by memory-related plasticity in the hippocampus and how it may be essential in long-term memory storage.	Drug addiction has been conceptualized as an aberrant form of learning and memory. Interestingly, DNA methylation has also emerged as a key mechanism governing synaptic plasticity induced by drug abuse, such as cocaine, and may therefore play a key role in the transition from controlled use of drug treatment to compulsive drug use that characterizes addiction.
Wong C, Mill J, Fernandes C[43]	2011	Addiction	To demonstrate the potential role of dynamic epigenetic changes in mediating addictive behaviors through long-lasting changes in gene expression.	Current evidence shows that epigenetic changes in the genome, including DNA methylation and histone modifications are important mechanisms underlying addiction and the neurobiological response to addictive substances.
Volkow N, Wang GJ, Fowler J, Tomasi D[44]	2012	Annual Review of Pharmacology and Toxicology	To understand illicit drug use disorders and discover why some people become dependent when exposed to drugs.	Several brain circuits are relevant to the neurobiology of addiction and result in increased motivational value of the drug at the expense of other reinforcers and an impaired ability to inhibit intentional actions associated with strong desires to use the drug that result in compulsive use.
Boyadjieva N, Varadinova M[45]	2012	Journal of Pharmacy and Pharmacology	To highlight epigenetic mechanisms in reference to the heritable but reversible regulation of various biological functions, such as DNA methylation and chromatin structure derived from modifications in histones involved in brain development, pathogenesis, and pharmacotherapy of brain disorders.	Analysis of epigenetic aberrations in the mechanisms of psychoactive drugs helps determine dysfunctional genes and pathways in the brain, predict drug side effects in the human genome, and identify new pharmaceutical targets for the treatment of psychiatric diseases.
Tuesta LM, Zhang Y[46]	2014	The EMBO Journal	To examine the epigenetic regulation of illicit drug addiction and look to the future to discuss its implications for reward memory and the development of drug addiction.	Epigenetic mechanisms may regulate the ability to store long-term memories. The maintenance of these memories can last an individual's entire life, and it is intriguing to speculate how illicit drugs could induce similar long-lasting changes in reward pathways that could predispose a person to addiction.
Umesh S, Khess CRJ, Simlai J, Bose S[47]	2015	Hereditary Genetics	To provide an overview of the diverse types of epigenetic modifications and their application to drug abuse disorders.	Based on current research, it is evident that there is exponential growth in epigenetic research to understand the mechanisms underlying illicit drug use disorder and its related behaviors. Thus, much is anticipated in the future of epigenetics in psychiatric disorders and, more specifically, in disorders caused by using drugs of abuse.
Farris SP, Harris RA, Ponomarev I[48]	2015	Frontiers in Neuroscience	To reveal the cause of the pronounced effects on neurobiological systems within the hippocampus in a manner specific to the action of drugs of abuse.	Epigenetic modifications of histones can regulate long-lasting changes in gene expression. Although addiction to different substances may converge on some common genes, some mechanistic networks on which it acts may be different between different brain regions and different drugs.

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References	Year	Journal	Objective	Result
McCowan TJ, Dhasarathy A, Carvelli L(49)	2015	Addiction & Prevention	To examine epigenetic changes induced by chronic and acute Amphetamine (AMPH) treatments.	AMPH is a psychostimulant and the most prescribed drug to treat Attention Deficit Hyperactivity Disorder (ADHD). Although the doses used therapeutically are well tolerated, numerous side effects can still occur, such as nervousness, loss of appetite, and psychosis.
Szutorisz H, Hurd YL(50)	2016	Biological Psychiatry	To examine the epigenetic effects of cannabinoids.	Epigenome perturbations have been hypothesized to be the molecular machinery underlying the persistent, often tissue-specific, transcriptional, and behavioral effects of cannabinoids that have been observed throughout life and even in cannabinoids.
Gajewski P, Turecki G, Robison A(51)	2016	PLoS One	To identify the differential expression of FosB proteins and potential target genes in selected brain regions of patients with addiction and depression.	Chronic exposure to stress or illicit drugs has been linked to altered gene expression throughout the body, and changes in gene expression in different regions of the brain are thought to underlie many psychiatric diseases, including major depressive disorder and drug dependence.
Walker D, Nestler E(52)	2018	Nature Reviews Genetics	To reveal potential genes involved in addiction risk through genome-wide association studies.	Drug addiction is a multifactorial syndrome that involves a complex interaction between genes and the environment. Evidence suggests that the underlying mechanisms regulating these persistent behavioral abnormalities involve changes in gene expression throughout the brain's reward circuitry, particularly in the mesolimbic dopaminergic system.
Mason B, Donaldson ST, Hunter RG(11)	2018	Journal of Drug and Alcohol Research	To identify advances in technology that have expanded the field of epigenetics, providing a deeper understanding of gene-environment interactions.	Epigenetic mechanisms underlie drug-induced modifications in brain morphology, synaptic plasticity, and behavior. Epigenetic marks mediate long-lasting and potentially transgenerational changes in neuronal chromatin and subsequent gene expression that can lead to persistent vulnerability to relapse and/or children's vulnerability to addiction.
Hamilton D, Nestler E(22)	2019	Current Opinion in Neurobiology	To target epigenetic changes to increase understanding of the biological basis of addiction and produce more effective addiction therapies.	When an individual becomes addicted to a drug of abuse, nerve cells within the brain's reward circuits adapt at an epigenetic level during repeated exposure to the drug. These drug-induced epigenetic adaptations mediate long-lasting changes in brain function that contribute to the drug-related behavioral abnormalities that define addiction and last a lifetime.
Stewart AF, Fulton SL, Maze I(53)	2021	Cold Spring Harbor Perspectives in Medicine	To examine the implications of basic epigenetic concepts such as chromatin architecture, histones and their post-translational modifications, methylation of DNA and non-coding RNA, with special attention to neuro epigenetic-mediated plasticity in multiple behavioral models of addiction.	Illicit drug use disorders are chronic brain diseases characterized by transitions from recreational drug use to compulsive use. Thus, epigenetic mechanisms represent a convergent regulatory structure through which the plasticity necessary to achieve an addictive state can emerge and persist long after drug use has ceased.

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References	Year	Journal	Objective	Result
Cadet JL, Jayanthi S(12)	2021	Neurochemistry International	To evaluate the current literature on the effects of drugs of abuse on epigenetic markers that support the idea that these drugs may have acute and persistent effects on the expression of several enzymes involved in causing post-translational histone modifications and deoxyribonucleic acid methylation/ hydroxymethylation in the brain.	Epigenetic changes were reported in models of cocaine, methamphetamine, and opioid use disorders. Accumulating data suggest that future therapeutic interventions should focus on the development of epigenetic drugs against addictive diseases.
Salmanzadeh H, Ahmadi-Soleimani SM, Azadi M, Halliwell RF, Azizi H(13)	2021	Current Neuropharmacology	To provide an evaluation of transgenerational and multigenerational phenotypes derived from parents exposed to drugs of abuse only during adolescence.	There has emerged a growing set of tests that demonstrate that drugs of abuse induce epigenetic changes that can have markedly multigenerational effects.
Werner CT, Altshuler RD, Shaham Y, Li X(14)	2021	Biological Psychiatry	To examine epigenetic mechanisms (e.g., histone modifications, chromatin remodeler-associated modifications, and DNA methylation) that contribute to drug-seeking relapse.	Preventing relapse is the main challenge in drug addiction treatment. Evidence suggests that exposure to addictive drugs causes epigenetic changes in multiple areas of the brain, but most preclinical studies have focused on epigenetic changes observed during acute withdrawal (<24 h after drug exposure) and Epigenetic mechanisms underlying psychomotor sensitization and drug reinforcement.
Mazzeo F, Meccariello R(54)	2023	International Journal of Environmental Research and Public Health	To summarize the main advances in epigenetic inheritance through the use of *Cannabis* in this field, suggesting the need to pay attention to possible long-term epigenetic risks for the reproductive health of cannabis users and the health of their descendants.	Cannabis is the most widely consumed illicit drug in the vast majority of countries and its consumption is exceptionally high among adolescents and young adults. Its main psychotropic component, the cannabinoid delta-9-tetrahydrocannabinol (THC), interferes with the endogenous endocannabinoid system. This signalling system is involved in the control of many biological activities, including the formation of high-quality male gametes. Direct adverse effects of THC on male reproduction, and the possibility of long-term effects due to epigenetic mechanisms, have recently been reported.

Figure 2 - Descriptive characteristics of the 21 selected studies that examined the epigenetic mechanisms of drugs of abuse that generate chemical dependence

Through the Descending Hierarchical Classification (DHC), four related semantic classes were revealed, which were generated from the processing of the *corpus* by the IRAMuTeQ® software (*Interface de R pour les Analyses Multidimensionnelles de Textes et de Questionnaires*), which enables different types of analysis: classical textual statistics; specificities of groups; descending hierarchical classification; analyses of similarity and word cloud. The DHC, in the form of a dendrogram, is an important visualization and analysis tool, since it allows groups to be identified and their descending hierarchical ordering, based on the most frequent words within the respective descriptors.

To construct the dendrogram (Figure 3), words with a frequency equal to or greater than the average frequency were considered. Each class is described by the most significant (most frequent) words and their respective associations with the class. With the dendrogram, it was possible to visualize the words that had the highest percentage in terms of average frequency among themselves and different from each other. This word dictionary allowed, using chi-square (χ2), the analysis of words that presented a value greater than 2.78 and p<0.0001.

Thus, it is possible to identify the words that had the highest average frequency within the classes. In class 1, the consequences of drug addiction are explained. Class 2 explains chemical dependency disorders. Class 4 demonstrates the (irreversible) epigenetic impacts caused by the systematic use of drugs of abuse.

In this way, the analyzable words were distributed in the four classes of this research, as follows: class 1, with 18 text segments, corresponding to 33.4%; class 2, with 14 text segments, corresponding to 38.9%; class 3, with 7 text segments, totaling 6.8%; class 4, with 7 text segments, a score of 20.9%.

The constructed dendrogram illustrates the partitions made in the *corpus*, until obtaining the final classes. When reading from left to right, as recommended by IRAMuTeQ®, we identified that *a priori,* there was a division of the main corpus with the emergence of a segment, that is, class 1 generated class 4, which was divided into two classes (2 and 3).

In effect, the factorial representation provided by the software confirmed the interconnection of the classes, compared to those carried out in the research during the analysis of the qualitative data, and made it possible to recover the context in which the words were associated. with statistical significance.

The information prepared through bibliometric studies measures the contribution of scientific knowledge derived from publications in a given field. Production indicators are beneficial for the scientific community's knowledge of the system in which it operates. The bibliometric methodology encapsulates the application of quantitative techniques (i.e., bibliometric analysis - e.g., citation analysis) on bibliometric data (e.g., units of publication and citation), observing the state of science through scientific production recorded in a specific data repository. In this way, with the VOSviewer software's help, it was possible to detect the main keywords in the titles and summaries of the articles of the selected journals. The keywords were detected based on a co-occurrence network, as can be seen in Figure 3. Using the VOSviewer clustering technique, it is observed that three groups were formed from 68 keywords algorithmically identified by the software. It was also found that the keywords presented in each group were strictly related to the research topic.

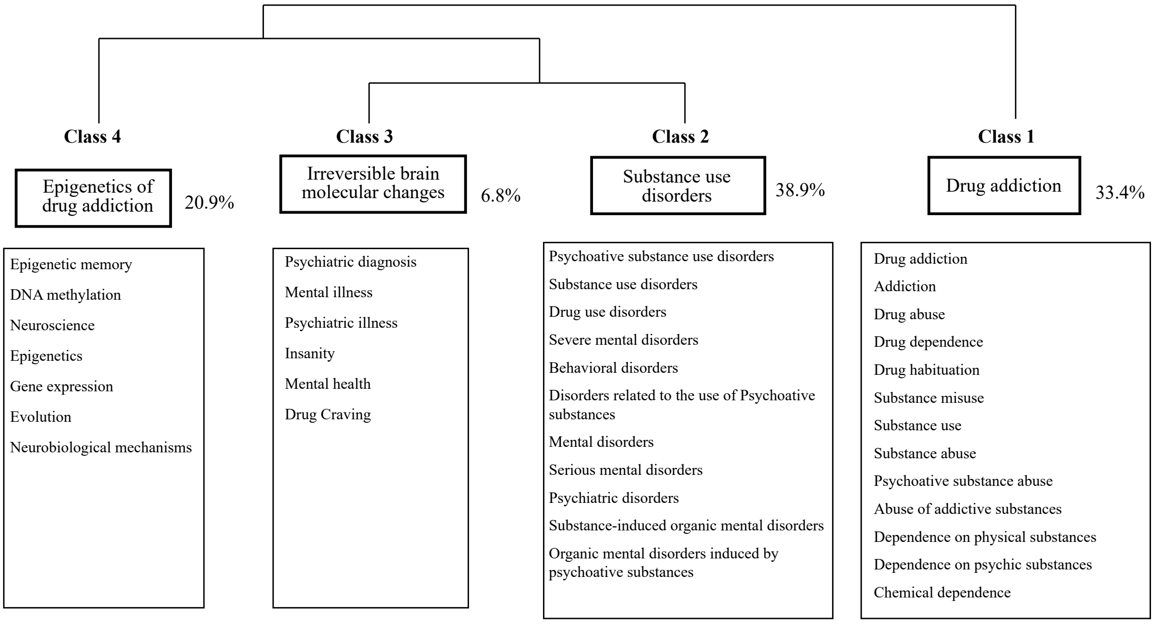

Figura 3 - Descending Hierarchical Classification, organized based on the IRAMuTeQ® software

Figure 4 shows the map of the main words present in the titles and abstracts of the sample. The colors displayed are random, separating only the groups of words. Each circle represents a term and only part of them have their name presented, as the software, to avoid overlaps, identifies only some. The size of the circle refers to the number of occurrences of the term. The words present in the clusters have a direct relationship with each other, corresponding to their separation factor. The size of each word in the cluster is related to its weight, that is, its co-occurrence in publications.

In the map shown in Figure 5 the group related to the epigenetic effects of drugs of abuse is found in the same cluster that contains the most recent publications. The year of publication affects the colour of the group.

The groups refer to words extracted from articles published with greater emphasis between 2010 and 2013, which, according to the table, demonstrate greater quantity and concern for the mechanisms that generate chemical dependence, pointing to epigenetic effects.

Therefore, it is understood that the number of articles on the topic has increased in recent years, indicating that it is an emerging topic in the field of scientific research.

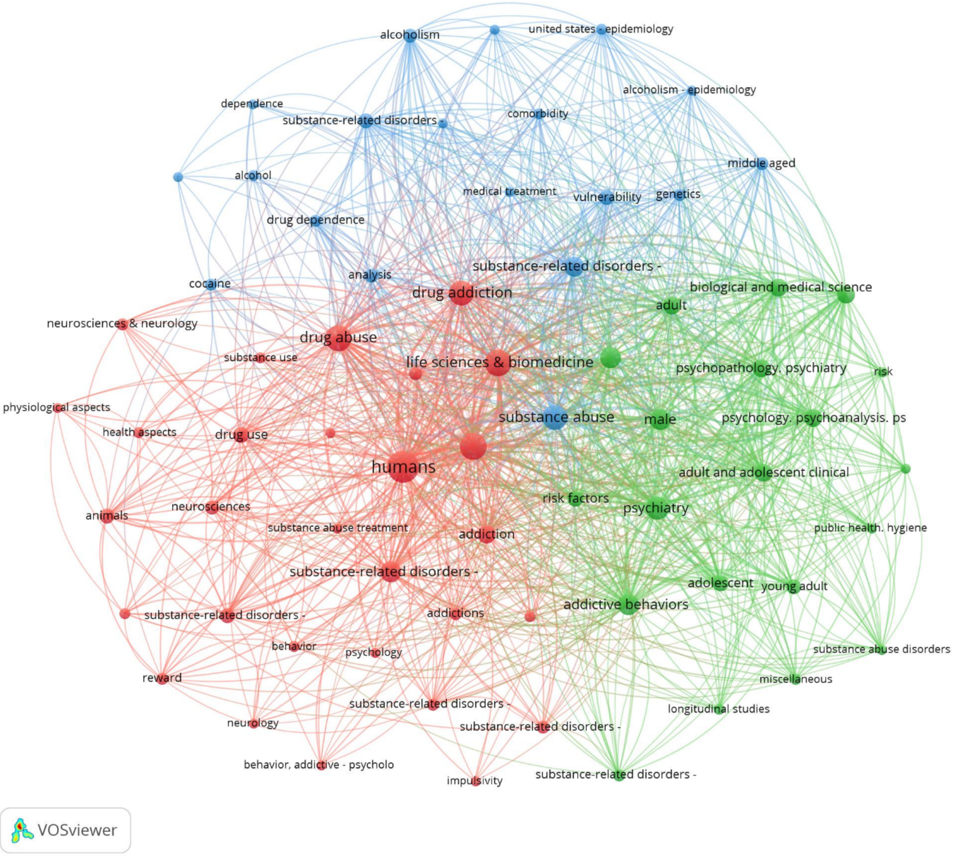

Figure 4 - Map of the main words present in the titles and summaries of the sample

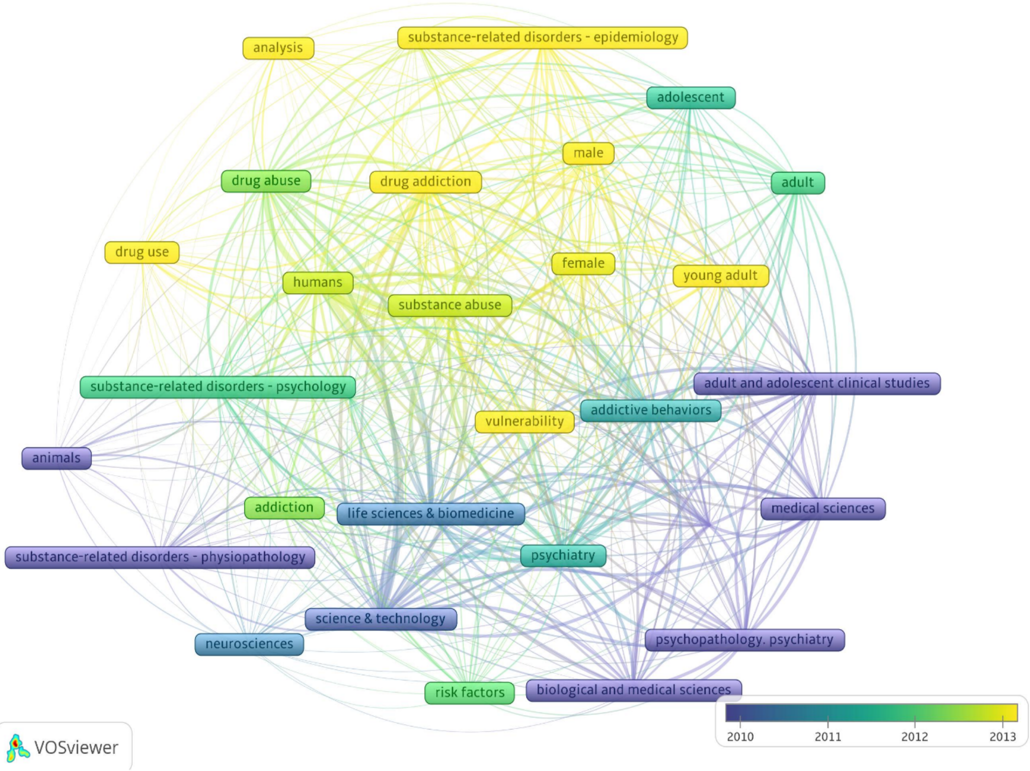

Figure 5 - Map of the main keywords present in the titles and abstracts of the sample, classified by year of publication

Discussion

Although the intergenerational effects of drug use represent an important line of study to understand how susceptibility to addiction is determined, this review focused on the mechanics of epigenetic changes, from initial drug exposure to the persistent effects that occur; since, in general, they culminate in drug dependence and mental disorders(14-16).

Neuroepigenetic mechanisms regulate coordinated transcriptional responses to transduce environmental stimuli into functional changes in cellular output. The standard use of epigenetics is the set of mechanisms that lead to stable heritable functional changes in gene expression caused by modulation of gene expression rather than changes in DNA sequence(55-57). This definition includes effects transmitted between generations or between multiple generations of descendants. For example, in the case of cocaine, several studies have confirmed that paternal exposure to cocaine influences reward-based behavior in offspring through epigenetic processes, including increased susceptibility to motivated drug-related behaviors, dependence, memory/cognition, and measures affectiveness, such as mood or anxiety(4-7,40-46).

The drug problem is associated with social and economic indicators. If countries maintain public policies that favor the repression of excess supply, organizations that profit from the consumption of drugs of abuse use aggressive market strategies that deepen consumption and social vulnerability. Therefore, a drug policy that seeks to help public health must focus on understanding the conditions that determine drug-related effects on well-being and development and the different manifestations of the problem of psychoactive substances, supporting efforts to acquire knowledge about the more effective means of interventions, such as epigenetics, which is currently crucial to this demand(5,26).

The data shown in the results denote that illicit drugs are effectors of the epigenome, with impacts on DNA methylation, histone modification and the expression of small RNA molecules present in pathways as diverse as reward, memory, and aging. and cardiovascular diseases(17,26,29,42-45). However, the number of drugs and phenotypes with epigenetic effects measured is relatively small so far, and further investigation of these effects will be vital for a full understanding of the developmental consequences of exposure to illicit drugs and other toxic substances. Directly linking epigenetic changes with tissue-specific messenger RNA (mRNA) and/or protein levels to candidate genetic networks is also vital to identify specific causal or contributory epigenetic changes associated with a given phenotype(56-57).

The different software that was used in the research, to a high degree, denoted the consequences and impacts of the consumption of drugs of abuse, in line with mental disorders and drug addiction. Both the lexical strata and the groups of keywords as a result of the research clearly showed the exchange of the harmful actions of drugs, as well as the genetic damage they cause to DNA. Thus, epigenetics demonstrates its strength and importance and provides a new field of research, given the complexity of the treatment of drug-dependent people.

Conclusion

The main mechanisms controlling epigenetic inheritance are DNA methylation and chromatin remodeling. Epigenetic modifications can be immediate or accumulate slowly and can be transmitted to daughter cells or successive generations through mitotic or meiotic inheritance. These epigenetic alterations may be due to inheritance through genomic imprinting, previous life events, chronic drug use, or pharmacotherapies for addictions.

The studies discussed throughout this review highlight the enormous complexity of epigenetic regulation in drug addiction, and most articles point out that substance use disorder is characterized by an aberrant transcriptional increase, with plasticity in regions of brain reward key. This plasticity appears to be dictated, in large part, by chromatin-mediated transcriptional initiation effects that act to maintain persistent cellular and behavioral phenotypes associated with the long-lasting nature of addiction.

As the field advances, it will be important to continue to use the power of operant models of drug use to more fully delineate the epigenetic changes that are in fact causal in mediating substance use disorder endophenotypes.

Additionally, it will be critical for future research to continue to leverage currently available genomic sequencing methods to profile more comprehensive gene expression patterns along with additional epigenetic assessments. It is important to note that now these types of experiments can also be performed on human brain tissue (*post-mortem*) from drug addicts. These efforts promise to significantly improve the translatability of the identified key regulators and assist in the identification of genuine targets for the future development of effective clinical procedures aimed at the treatment of drug addiction and related disorders.

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