

Review Article

Challenges to Neuroscience and Public Policy Derived from New Trends and Patterns of Inhalant Misuse^{*}

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Abstract Use of inhalants (solvents, aerosols, gases, and nitrites) is a worldwide practice, mainly among children and adolescents in whom toxic effects are more detrimental than in adults. Inhalant misuse is increasing among young adults linked to new and more attractive presentations; it is more common among those coming from poor communities with high violence and delinquency levels, and also among street children and adolescents. Voluntary inhalant misuse is more frequent among males, but the gender gap is narrowing. The risk of developing dependence is well established, especially if inhalant misuse begins at an early age. Suicidality and comorbidity with psychiatric disorders are also common. Regular users are more likely to show deviant behavior, school truancy, and lower school grades. Family history of antisocial behavior has also been reported. Abuse of nitrites is associated with a higher risk of HIV. In general, abuse of inhalants increases the risk of morbidity and mortality. In spite of this evidence, these substances have received less attention than other misused drugs. This review shows results from epidemiology, psychosocial, and treatment research to draw attention to gaps of knowledge that require the involvement of neurosciences and clinical research and to propose policy options.

Keywords inhalants; underage youth; adolescents; poverty; consequences; societal responses

1. Introduction

Inhalants are a wide and diverse group of legal products that can be classified in different groups based on their chemical structure (e.g., hydrocarbons, alcohols, ethers, etc.), presentation (e.g., aerosols, gases, solvents, etc.) or commercial uses (e.g., office and school products, adhesives, spray paints, correction fluids, fuels, paint thinners, etc.). The National Institute on Drug Abuse recognizes four categories: *volatile solvents* (e.g., toluene, glue, and gasoline), *aerosols* that contain propellant gases (e.g., spray paints, deodorants, aerosols, etc.), *gases* (including anesthetic

gases, butane, propane, and refrigerants), and *nitrites* or “*poppers*” (e.g., video head cleaners, environmental deodorants, etc.) [38]. Unlike other misused substances such as opiates and psychostimulants, there is not enough evidence to classify inhalants based on their pharmacological effects and action mechanisms. However, data from molecular studies and behavioral pharmacology indicate that solvents, fuels, and anesthetic gases have some characteristics in common to support their inclusion in the same group. On the other hand, nitrous oxide (the “laughing gas”) and alkyl nitrites should be considered as categories of their own [1].

Inhalants are affordable and widely available. They are volatile at room temperature, share the same route of administration, and have fast onset of action. Moreover, inhalants have legitimate commercial uses, are legal to possess, and not easy to detect in antidoping tests. These characteristics make them attractive to different populations, including children and adolescents [44,45]. Inhalant misuse is commonly underestimated because few surveys specifically ask about this practice and those who ask do not distinguish among specific substances.

The most commonly used products in Latin America, Egypt, India, and other countries are solvents, paint thinner, adhesives, and other toluene-based products. Spray paints are the preferred products in Australia, where “chroming” is often synonymous with inhalant misuse. In the US, the intentional use of solvents and gases is also common [33]. Among the substances inhaled, there are not only the commercial products diverted from official sources, but also homemade products specifically developed to reach new markets. Some of them are prepared by adding colors and “flavors” to commercial products, which are then sold in places where illegal drugs are distributed. Variants are specific to geographical regions; this is the case of odorized

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products in Mexico [57], “agua de celeste” in the Mexico-US border cities [37], and “perfumes” in Brazil [35].

Observations derived from surveys and special studies indicate important variations in use patterns among different population groups. Most users are polydrug consumers that have included inhalants among the substances they use. They may try inhalants once or twice, quit after experimenting a few times or become regular users. A proportion of this group can develop dependence [33]. Other groups become heavily involved in inhalant misuse in specific settings. For example, inhalation can occur in parties that combine music, drug intoxication, and sex, known as “reggaeton parties (or “perreos” in Spanish) where alcohol is also consumed in big quantities [23]. A third group is formed by under-aged youth, mainly children and adolescents working or living in the streets, who have inhalants as their drug of choice [20]. Regular use is more common in this population, with few exceptions. Use patterns may vary greatly from regular use, several times a day, alternate periods of use and abstinence [34] or no use at all. Inhalant misuse has also been reported among adults, who either use these substances at work (e.g., painters, carpenters, etc.) or having developed dependence to other substances, using inhalants only when there is no other drug available. It is worth mentioning that, according to different studies, inhalant misuse is increasing among high school students in several countries [19,27,57].

In spite of the well-described deleterious consequences of inhalant misuse and the fact that children and adolescents from disadvantaged populations mainly use these substances, support to research and intervention programs is scarce. Inhalant misuse prevention and treatment require evidence-based programs capable of building bridges across social, basic, and clinical research.

Neurosciences have provided evidence that inhalant misuse, in particular compulsive inhalation of toluene-based products, is not different from other drug-related disorders. Toluene has potent psychoactive effects, interacts directly with specific molecular targets [8,14,30], and releases dopamine in the mesolimbic system [2,46,64]. As it occurs with other drugs, inhalant misuse is a medical disease modulated by the environment. Several studies have identified that exposure to environmental factors, such as violence, increases the likelihood of dependence development [3]. Persons with dependence are more prone to impulsive behaviors, are no longer able to control intake, and attribute greater importance to drugs than to traditional motivators in family, school or work environments [39].

As mentioned before, subgroups where the problem is more salient are children and adolescents coming from the most deprived environments. Limited resources can explain higher exposure to violence and other related problems, as well as increased opportunities for drug use and more harmful consequences. The World Health Organization’s

conceptual framework of social determinants of health [5] provides a base for understanding differences in how a problem derived from inequity is manifested in 5 axes: (a) socioeconomic position, (b) differential exposure to risk factors, (c) vulnerability to the effects of risks, (d) differences in access to health, and (e) consequences of abuse. This conceptual framework also suggests ways to improve societal response to this problem taking into consideration the different positions of affected individuals in society.

This paper examines epidemiological trends concerning inhalant misuse and some of the consequences associated with this practice. We address vulnerable populations who inhale while their brain is still developing, that is, during preadolescent and adolescent years, independently of social status, as well as children and underage youth coming from very poor environments that work or live in the streets. The objective is to review existing evidence and challenges for prevention, treatment, and policymaking that can be addressed on the bases of knowledge derived from epidemiology, including a discussion of findings based on what we know from neurosciences and social research.

2. What do we know from epidemiological data?

2.1. General population

The extent of inhalant misuse has been documented in several countries, but systematic and longitudinal studies are scant. Trends of inhalant use have been documented in Mexico through six national and local household surveys conducted since 1988 until the most recent ones in 2008 and 2011 [59,60,61], school surveys (1976–2012) [58,62], special population studies (1978–2012) [13,22,23,47], and statistics from patients in treatment (1987–2012) [53].

Data from the latest national household survey [61] show that inhalants are the third illegal drug of choice among the Mexican population between 12 and 65 years of age, with a lifetime prevalence of 0.9%, a rate 6.6 times lower than that observed for marihuana (6%). For those between 12 and 17 years of age, inhalants (0.9%) came second after marihuana (2.4%); that is, inhalation was only 2.6 less frequent than marihuana use in this group. The annual prevalence for the 12- to 65-year-old population was 0.1%, a rate 3 times lower than that reported in 1988 (0.3%). This decrease was due to a reduction of inhalation among males, while rates among females remained stable (0.1%). Cumulative incidence was 1.5% among males from 12 to 25 years old, increased to 2.8% for those between 26 and 34 years of age, and showed the lowest cumulative rate among those 35 or older (1.1%). Inhalant misuse is becoming more common in females because the highest rate of use among the 12–17-year-old population was 7 times higher than that reported by older groups [61].

Age of first inhalant use was low; 77% of users experimented for the first time before they were 18 years old,

20% when they were between 18 and 25 years of age, and only 3% when they were 26 or older. In contrast, approximately 50% of people who ever used marihuana and 39% of those who used cocaine started before age 18. Inhalation was perceived as more dangerous than using marihuana, but risk perception was significantly lower among those 12 to 17 years old (76%; confidence intervals (CI): 73.7–77.82) than among older people (81.3%; CI: 79.8–83).

2.2. Students

Student surveys also have a tradition in Mexico. The last national survey was conducted in 1991 and data from selected localities have been periodically collected after this date. In the 16 cities where information since 1997 is available, annual prevalence of inhalation ranges from 1.5% to 6%. Rates of ever use and past year use of inhalants among high school students in Mexico City reached 10% and 5.9%, respectively. The annual prevalence in the last year was slightly higher among females (6.2%) than among males (5.5%). The highest rates of use corresponded to students between 14 and 15 years of age. Some experimented once or twice (less than 50%), but 8% of users reported having inhaled 50 times or more. Rates of use in the last year increased from 0.9% in 1976 to 10% in 2012 [55,56].

Inhalation of solvents among students has also been described in other countries. In Europe, school surveys in 15- and 16-year-old students have found high rates (13–17%) in Ireland, the Slovak Republic or Austria, medium rates (8–12%) in Germany, Sweden, Spain, and Finland, among other countries, and low rates (3–7%) in Russia, Poland, Ukraine, and so forth [54]. According to CICAD [27,41], the highest rates among secondary students in the Americas are found in Brazil, Trinidad Tobago, Jamaica, and Mexico. Abuse of these substances has also been reported in Australia, New Zealand, and Greater Pretoria and Bela-Bela in Africa [33].

2.3. Children and adolescents that work in the streets

Rates of inhalation among special groups of the population are available from a study of girls, boys, and adolescents between 6 and 17 years of age that worked in the streets, mainly in the informal economy, undertaken in 100 main cities in Mexico. This study included underage youth who lived at home (95%) and those who had the streets as their daily place of residence (2%). It excluded those that worked in private environments [34]. Mexico City data were analyzed in a separate study. The selected cities were screened to identify meeting places of working children (streets and public places) as well as places where they spent the nights; 11,136 of such places were identified and 114,497 children and adolescents were counted.

Based on this information, 41,876 minors were interviewed: 72% were males and 74% were between 12 and

17 years old (average: 13 years of age). The vast majority lived in households (95%) with one or both parents; 86% gave all or part of their income to their families; 65% were attending school, but 46% enrolled in a level lower than the one expected for their age; 36% had dropped out from school, 27% due to economic problems and 20% because they did not like it; 8% of the girls and 7% of the boys reported that they did not know how to read or write.

Inhalation rates were not high when the whole sample was analyzed: 3.5% and 0.9% for boys and girls, respectively. Rates of use increased slightly in those of 12 to 17 years of age, to 1.1% in females and 4% in males. When only those children living in the streets of any age were considered, inhalation rates were close to 74%. Almost the same proportion that reported inhalant use also reported having used marihuana.

3. Social determinants of inhalation

3.1. Socioeconomic context

In most countries, toluene-based solvents are the inhalants of choice and inhalation is more prevalent among youth coming from low socioeconomic levels. In Mexico, it is almost 4 times higher among males of 12 to 17 years of age and 20 times higher among females that do not work or study (2.3% and 4%, resp.) as compared to those enrolled in school or working (1% and 0.2%). It is also more frequent among students that do not attend school (16.4% in comparison to only 9% of full time students) [12]. Poverty conditions, lack of health attention, having or not a place to live, and being surrounded by parental figures also influence drug use [34]. Some of these variables are analyzed in the following sections.

3.2. Differential vulnerability

Initiation in inhalant misuse occurs at an early age, with most users experimenting before 18 years of age when they are more prone to experimenting new sensations, the brain is still maturing and especially vulnerable to drug effects [10]. There is a high risk that children and adolescents from deprived environments fail to develop their full potential. This is derived both from drug interference with brain development and from hazards intimately linked to opportunities for healthy development.

A reciprocal relation between poverty and illness has been shown in many epidemiological studies [29], but disentangling the multiple factors involved in this relation is not trivial. Different studies have shown that solvent misuse can produce general cognitive impairment and increase the likelihood of neurobiological abnormalities, including cerebellar atrophy correlated with attention dysfunction, impaired motor control, and memory loss [50,66]. Yet, it is also true that inadequate shelter, lack of control of sewage, limited access to potable water, and crowding increase

the likelihood of developmental disabilities. For example, poverty is linked to hunger and malnutrition which lead to iodine deficiency that can cause blindness and low levels of vitamin A that increase the risk of infection; both conditions increase drug-related harmful effects, and lack of health care or access to effective treatments worsens the problem [34].

Poverty is linked to poor education and decreased cognitive potential, circumstances that contribute to poor school performance. It is also documented that abuse and neglect increase the likelihood of substance abuse disorders [3,4]. Accidents threaten brain health and intoxicated youth are prone to get involved in fights, be run over by cars, then fall and hit their heads. Poverty-related factors have a multiplying effect in which one factor exacerbates the impact of the others, increasing the risk of disease and reducing development opportunities.

Environmental risks include *prenatal exposure to psychoactive substances*. Some users continue inhaling while pregnant. Drug users themselves might have had mothers that inhaled or drank alcohol during pregnancy, and both fetal alcohol syndrome and fetal solvent syndrome are characterized by cognitive deficiency [25]. The combination of drug use and poverty creates a vicious cycle of illness and economic deprivation.

3.3. Differential exposure to risks

The Mexican National Household Survey of 2008 included 51,000 households and thus allowed for a more in-depth data analysis, which can be used to illustrate the differential exposure to risks. According to this survey, users of inhalants and methamphetamines perceived their communities as more insecure than marihuana and cocaine users. For instance, occurrence of assaults with arms was 2 times more frequent, rape was 3.5 times more common, fight involvement was twice as common, and selling drugs was 2.7 times more frequent in communities where inhalant users lived compared with communities where marihuana use was common [12].

Similar data were found in an in-depth analysis of the study of underage youth working in the streets of 100 cities [34]. The relation with environmental factors and drug use (any drug, not just inhalants) was analyzed using a model of structural equations [49]. The analysis was based on data from 30,365 minors. The variables included were as follows: (a) *family environment*: living (value = 1) or not (value = 0) with family, and living at home (1) or in the street (0); (b) *schooling development*: school enrollment (1) or not (0), and the presence (0) or absence (1) of schooling deficit measured in terms of two or more years of difference between the current school grade and the grade corresponding to the minor's age; (c) *starting age of work*: assessed as number of working years; (d) *health care*: professional care (1) or not (0) in case of sickness, and number of meals

per day (1 to 3); (e) *degree of environmental risk in which the minor inhabits*: drug use at the workplace (1) or not (0), drugs offered to the minor (1) or not (0); (f) *drug use*, with three indicators: use (1) or not (0), types of drugs, frequency, and quantity; (g) *relationship with the police*: if arrested (1) or not (0); (h) *early sexual intercourse*: if the minor had had sexual intercourse (1) or not (0).

The model is depicted in Figure 1. There was a satisfactory agreement between the theoretical model and the field data (adjustment level of 0.97). As presumed, the availability, amount, and frequency of drug use were largely related to drug presence in the work environment. Minors who worked in less-protected environments and who also used drugs had more health risks because they had less access to medical facilities and ate less. Inadequate schooling development of adolescents was correlated with (a) the number of years at work, (b) working in a safe or unsafe environment, (c) drug use, (d) not having access to an adequate diet, (e) not seeking medical assistance when sick, (e) being arrested by the police, and (f) having early sexual intercourse. As expected, living in adequate family environment was successful in maintaining adolescents in school and was the most important protective factor [34].

3.4. Health outcomes

A combination of exposure to toxic substances and deficient living conditions increases the risk of mortality. Sudden sniffing death is a rare but serious complication that can occur due to poor oxygen supply, direct cardiac effects, and potassium-induced arrhythmias [7]. Suffocation and trauma have been linked to the use of plastic bags over the head to enhance the amount inhaled; this is especially risky if the user loses consciousness. Death by vomit aspiration has also been described, as well as increased risk of accidents when intoxicated [63].

Lifestyles of some inhalant users subgroups raise the burden related to violence and increase the risk of HIV from sexual abuse and prostitution. In the abovementioned study of working youth, it was found that, though uncommon, some children and adolescents declared prostitution as their source of income (less than 1%) [32]. Increased risk of seroconversion among street population has been reported [48]. High rates of psychiatric comorbidity, mood, anxiety, and personality disorders are common among lifetime inhalant users. Higher odds of psychiatric disorders for inhalant users have been reported for poor and less-educated women with early onset of inhalant use, family histories of psychopathology, and personal histories of substance abuse treatment. Risk of suicide has also been described [33].

4. Treatment

Inhalation leads to dependence and there is evidence of withdrawal from inhalant abuse with differences in

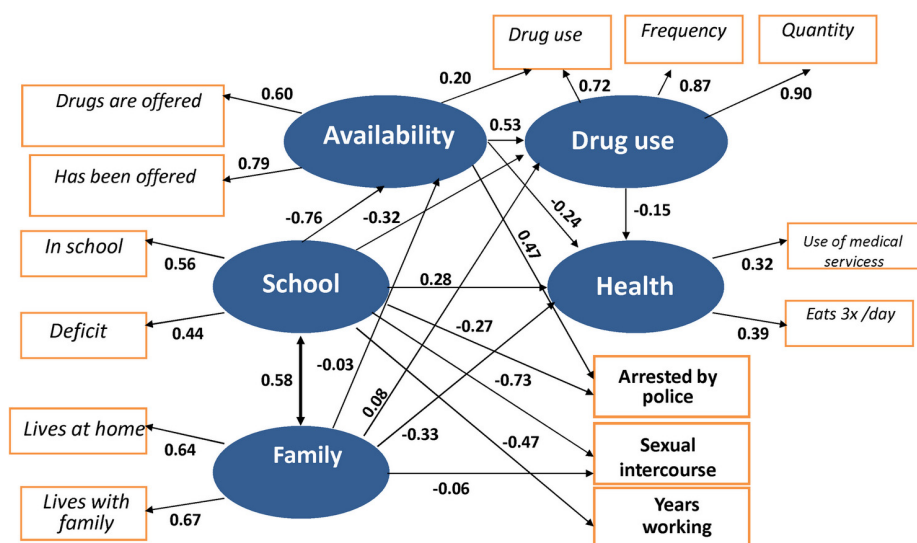


Figure 1: Predictors of drug use among working adolescents. Variables in ovals are latent variables, that is, theoretical constructions indicated by the covariance of two or more indicators (framed in rectangles). For example, the latent variable “Drug use” is constructed from three direct indicators: having used drugs, frequency of intake, and quantities consumed. Similarly, the latent variable “School” is constructed from two indicators that measure whether the adolescent was enrolled in school and deficit, measured as two or more years of difference between the level in which he or she was actually enrolled and the level in which he or she should be enrolled according to their age; a youngster, 12 years of age, studying in fourth or fifth grade of elementary school would qualify for school deficit. The two-pointed arrow indicates correlation; for instance, school is correlated with living at home with family, meaning that it was more likely for adolescents to be enrolled in school if they were living with family and vice versa. One-pointed arrows indicate predictions and trends. Prediction or association strength is shown in the numbers beside the arrows. Negative or positive values indicate how variables connected by the arrows are related to each other. For example, it was less likely for adolescents to work in an environment of high availability of drugs if they were attending school (negative high predictive value of -0.76) but it was more likely to have problems with the police if they worked in an environment where drugs were offered and had been exposed to the opportunity of using (positive prediction value of 0.47).

symptoms across type of substances consumed (aerosols, gases, and solvents) [45,65]. Also, as described in this paper, underage youth that inhale often come from deprived environments where they are exposed to violence, increased availability, and other risks; furthermore, inhalation has important social and health consequences adding challenges to the development of successful treatment approaches.

Despite these adverse situations, there is some evidence of recovery from the severe and persistent neurological disabilities associated with this practice after abstinence; however, this depends on the duration of inhalant misuse [18].

The treatment gap for mental and substance abuse disorders has been estimated to be between 35.5% and 50.3% in developed countries and 76.3% and 85.4% in developing countries [17], with an important delay in first treatment [6]. Perron et al. [42] documented that among a representative sample in USA, 66% of those with inhalant dependence (2.3%) used some sort of service, mainly 12 step programs (68.5%), followed by drug rehabilitation programs (61.2%) and treatment provided by private practitioners (55.6%); 15% reported at least one barrier to

receiving services, with the low-income group reporting more barriers (22.8%).

This evidence calls for the need of prevention, treatment, and policy interventions. A recent review [43] concluded that there is no available specific pharmacological therapy for treating this substance use disorder. Evidence shows a limited success when using risperidone to control paranoid psychosis among solvent abusers [36], carbamazepine or haloperidol to reduce symptoms of inhalant induced psychotic disorders [26], and lamotrigine to reduce craving [52]. A Cochrane review conducted in 2013 found no single published treatment study fulfilling the required criteria for guiding treatment decisions [28]; thus at the moment we need to rely on less-strong evidence for implementing interventions and ultimately aiming at closing the research gap.

Despite this unfortunate gap in knowledge, there are examples of good practices. Promising results have been observed with different approaches. These include (a) residential treatment for indigenous groups that use resiliency and emotional intelligence theories in the context

of indigenous cultural knowledge and healing practices [16]; (b) interventions that fold clients into a functional family structure in Australia [51] and Mexico [31]; (c) cognitive behavioral therapy [40]; (d) social interventions mainly for underage population working, living in the streets or at risk of becoming street kids [24]; (e) harm reduction alternatives within the children meeting places, that included labeling of inhalant containers with warning messages in the groups' own slang, discussion groups aimed at increasing the awareness of the dangers, and strategies for avoiding or minimizing harm [21].

How treatment is provided plays also a major role. Treatment can be divided as that provided within the general health system, in specialized premises, or interventions aimed at solvent abusers and special programs for populations with special needs, such as street children and adolescents.

In Mexico, screening and brief advice or interventions are not provided in primary care and drug treatment is not usually provided at general or specialized hospitals. Since the beginning of the drug problem as we know it today (in the 1970s), prevention and treatment have been provided by specialized (mainly outpatient) clinics, devoted to addiction treatment. Today, the network of specialized centers includes more than 100 outpatient clinics and 12 inpatient facilities for more severe cases. Recently, more than 320 new facilities were added with a more preventing model, mainly aimed at youth initiating the use of drugs, with brief interventions and a prevention model [11]. NGOs and private institutions play a major role in treatment of more severe cases; government and private funding is provided for training, quality control, and payment for the treatment of cases. Yet there is a big room for improvement as the treatment gap is still important.

5. Discussion

5.1. Towards better responses

Several opportunities for intervention have been identified from what is known of inhalant misuse [15]. Immediate actions can be recommended such as (a) redesigning products to make them less toxic, (b) labeling products with clear information concerning composition and risks, (c) regulating availability in formal and informal establishments, (d) raising awareness on inhalant harmful effects among users, parents, and teachers, (e) implementing programs addressed to retailers who may not be aware of the risks of the products they sell, (f) limiting access to commercial products susceptible to be used as inhalants to children and adolescents, (g) promoting community mobilization, and (h) integrating treatment tailored programs to the needs of the different subgroups that use these substances.

Development and quality of life (education and employment skills, opportunities, etc.) should be considered

a therapeutic goal. Populations at risk should have granted access to health systems for different needs (e.g., vaccination, nutrition, acute and chronic disorders, including mental health disorders).

Overall it is evident that the intervention programs require a global base of development aimed at reducing inequities, with emphasis on poor communities, especially those with high levels of insecurity and hidden populations described in this paper. Global programs aimed at reducing violence can reduce the vulnerability of these children and adolescents to get involved in drug misuse.

5.2. Opportunities for research

The information included in this paper calls our attention to the need for better information to support prevention, treatment, and public policies. Some opportunities for research include (a) more basic and mechanistic studies that incorporate different substances and combinations of substances grouped under the name "inhalants," (b) studies specifically addressed to determine reversibility of inhalant-induced damage, (c) preclinical and clinical studies that can derive more promising treatment alternatives, (d) preclinical research to determine cause-effect relationships between exposure to toluene and well-controlled environmental factors (malnourishment, stress, anxiety, etc.), and (e) funding translational research from the laboratory to clinical environments and from controlled scenarios to the community. Studies that compare the acute and long-term effects of individual substances and mixtures are also needed in order to evaluate the influence of drug, patterns, and time of use. There is a need for detection labs to identify the exact composition of what is being used considering the rapid changes of the substances available for inhalation.

In conducting inhalant misuse research it is worth taking into account the invisibility of the problem: the high proportion of hidden populations involved in this practice (see, e.g., [13]), the lack of records that hinder the opportunity to register deaths attributable to inhalation [9], and the paucity of reliable data in terms of age and gender differences [33].

The fact that the gender gap is narrowing and that inhalant misuse is particularly prevalent among children and adolescents should encourage preclinical and clinical studies on the effects of inhalants in females and during development. Considering young brain plasticity, it is relevant to document the extent of recovery that can be expected among children and young adolescents who stop using inhalants, get a proper diet, and receive psychological and health support. It is also relevant to design studies for a better understanding of the disadvantages of early initiation in inhalant misuse in terms of possible alterations in neuronal pruning similar to what occurs with alcohol.

The analysis of the observed gender differences requires more attention to issues such as the relation between the

higher level of stigmatization of female users and the choice of substances, unwanted pregnancies, and exposure during pregnancy and early childhood.

Neuroscientists aim to identify the neural basis of inhalant misuse and dependence, considering that addiction is a brain disease. Social researchers focus on the social, political, and cultural variables involved in the complex phenomena that lead to addiction. Building bridges across these areas can enrich our approach to inhalant misuse and dependence in order to address them as disorders that target the brain, have some defined biological parameters, and are constrained by dynamic sociopolitical and cultural values.

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