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Research article

Explaining the causes and motivations for multiple substance use from the perspectives of users and therapists: A qualitative study

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ABSTRACT

Background: The high prevalence of multiple substance use (MSU) is concerning, given the weak awareness about this issue and the potential impact this unawareness has on the severity of substance use disorder (SUD) and treatment outcomes. The aim of this study is to identify and elucidate the causes and motivations for MSU from the viewpoints of users and therapists in this field.

Methods: In this qualitative study, the conventional content analysis approach and purposive sampling were utilized. Deep semi-structured exploratory interviews were conducted with 17 substance users and 8 addiction therapists (including 4 psychiatrists, 3 general practitioners, and 1 psychologist). Field notes were also taken to identify and explain the motivations and reasons for MSU from the perspectives of users and therapists. The data were analyzed comparatively and simultaneously using the method suggested by Graneheim and Lundman (2004).

Results: Based on the findings of this study, the motivations for MSU are reflected in four main categories: 'Pharmacological factors' with subcategories such as achieving desired states and mitigating the undesirable effects of substances through leveraging the balancing, synergistic, and antagonistic effects of substances, substituting the effects of other substances, self-medication of the undesirable effects of other substances, enhancing the overall consumption experience such as heightened peak experience and enhanced pleasure, moderating the come-down, and seeking euphoria experiences in different substances; 'Biological factors' with subcategories including different neurobehavioral systems, individual differences determining substance dependence and the somatic-neural vulnerability of consumers; 'Psychosocial factors' with the subcategories of undesirable norms like the need for acceptance and social interactions, the context of substance use, consumers' experiences and expectations of substance use, and the maladaptive personality traits of consumers; and 'Addiction's inevitability' with the subcategories of coercion and the need to maintain equilibrium, and the difficulties of substance detoxification.

Conclusion: The motivations behind Multiple Substance Use (MSU) behaviors are multifaceted, including pharmacological, biological, psychosocial, and addiction-related factors. Recognizing

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and comprehending the interplay between these factors and motivations can inform better prevention strategies, assessment of treatment needs, and enhancement of treatment outcomes for individuals dealing with MSU.

1. Introduction

Multiple substance use (MSU) is a significant public health concern and a growing phenomenon causing fatalities and consequences worldwide [1–3], leading to adverse impacts on physical, mental, psychological, and social well-being [2]. This phenomenon is defined as the concurrent or sequential use of multiple substances to achieve specific effects [1,4,5]. While research on substance abuse has predominantly focused on individuals with a substance use disorder, many individuals engage in the misuse of multiple substances [6,7] and fall within a broader pattern of MSU [7]. Studies on the prevalence of this phenomenon indicate that the consumption and misuse of multiple substances are highly common, being more of a rule than an exception [6,8]. Furthermore, the pattern of MSU may vary across different countries, with some findings suggesting that there exist racial/ethnic differences in this regard. Epidemiological research has demonstrated a consistent association between MSU and social and demographic variables [7]. However, studies have yet to examine the distinct characteristics of individuals who use more than one type of substance and how these individuals differ from those who use only a single substance [9].

On the other hand, the extensive consequences of MSU and the worse prognosis of these patients, including poor treatment response [7], treatment non-adherence, and relapse [10], increased medical and psychiatric comorbidities [7,9,11], depression [9], higher lifetime suicide rates [9,10], aggression and violent behavior [10], infection, imprisonment, deviant behaviors, arrest, medical, financial, and legal issues [9], as well as other risky behaviors besides substance use (e.g., risky sexual behavior, gambling) [11], underscore the importance of effective evidence-based interventions [12] and make the understanding of the underlying patterns of substance use and common motivations more vital [12].

Regardless of the consequences, MSU is complex both as a phenomenon and as a term. There is no established theory or unified understanding of MSU, nor is there a standardized method for its measuring. In fact, the existing approaches to measuring MSU are confusing and inconsistent [13]. A qualitative study (2018) highlights four key narratives of patterns and cultural forms of Multiple Substance Use (MSU), including social recreation (seeking pleasure and euphoria and feeling connection to other users), self-discovery (experiencing MSU episodes alone and with the aim of distancing oneself from the outside world to achieve better focus on inner mental perspectives), hustling (a lifestyle characterized by chaos accompanied by regular consumption of multiple substances and various prescription methods within specific social groups), and addiction (compulsive substance use). According to its findings, MSU is a highly diverse and heterogeneous phenomenon with identifiable manifestations and patterns of various risk-taking and control mechanisms that operate within local social and ethical norms and based on similar cultural codes of global drug subcultures [14]. The results of Boeri et al.'s (2008) qualitative study, aimed at examining different patterns of MSU and reasons for combining multiple substances among ecstasy users, indicate the existence of three distinct types of MSU experiences, including separate multiple substance use (the consumption of multiple substances as separate and unrelated experiences depending on social settings, individuals present in the environment, and achieving a specific goal), synergistic use of combined substances (enhancing a high and/or coming down from one), and indiscriminate use of legal and illegal substances due to their availability. While the use of separate multiple substances and synergistic use tended to be intentional, indiscriminate use of multiple substances was often unintentional, involuntary, or unplanned, and associated with greater risk-taking and negative consequences, including excessive consumption [15]. The results of O'Gorman's (2016) qualitative study, which examined differentiated normalisation (recreational substance use as a non-deviant and common practice) from the perspective of young substance users living in a marginalized neighborhood, indicate four categories of intentions for combined substance use with a spectrum of effects, including 'Chillin', 'Buzzin', 'getting mangled', and 'Coming down'. Their routines and substance repertoires reflected primarily rational consumption choices, cost-benefit analyses, and emphasized the pleasure and entertainment of recreational substance users. However, the substance consumption practices of these marginalized youth are due to their experience of social ostracism, deprivation from consumption-centered lifestyles and night time economic, and their involvement in the informal drug economy continue to be considered deviant. Researchers concluded that normalisation depends on the social status of the drug user (and not just differentiated), and despite marginalized youth employing common cultural practices of recreational drug use, they remain outsiders [16].

With a review of the aforementioned studies and considering the diversity of substances consumed, the cultural and social diversity of users, the variety of substance combining practices, the diversity of intentions for combining substances, and given the limitations of quantitative studies in investigating this complex phenomenon, there is a need for further qualitative research on the reasons and motivations for substance use from both the perspectives of consumers and treatment specialists, and from a broader perspective across different cultures, in order to better understand this prevalent social and health phenomenon and to reach a common insight and understanding of it. This will enable the development of preventive, protective, and therapeutic policies tailored to the above-mentioned factors.

Also, since empirical research on multiple substance users is limited [17], especially in developing countries [18], this study, by creating better transparency in understanding the conceptual motivations and reasons behind MSU, can lead to increased awareness among affected individuals and their families, who are in need of assistance and support. It can also enhance the awareness and understanding of healthcare providers regarding the motivations and intentions for MSU, enabling them to fulfill their professional roles more effectively and improve the quality of healthcare services provided to individuals suffering from this condition.

2. Objective

The purpose of this study is to identify and elucidate the intentions and motivations for MSU from the perspectives of both substance users and therapists.

3. Materials and methods

The current qualitative study was conducted from March 2021 to March 2022 using the conventional content analysis approach to identify and illuminate the reasons for MSU, as perceived by both individuals who use substances and treatment experts. A total of 25 participants (including 4 psychiatrists, 3 general physicians, 1 psychologist, and 17 substance users) were purposively selected to maximize diversity and theoretical saturation in the study. Maximum diversity in gender, age, duration and type of substance uses for

Table 1
Semi-structured interview guide.

List for substance users	
Main questions	Probing questions
What is your understanding of MSU and what does it mean to you?	Why do you think users tend towards consuming multiple substances?
What is the first thing that comes to your mind when the term MSU is mentioned?	Please give some examples of what you consider as multiple substance misuse?
	Please tell me more about the example you mentioned.
Do you have any experience of consuming multiple substances simultaneously?	Please give more details.
	Please expand. What happened? What did you do?
	In what situation did you take this action? And why did you do it?
	What feelings did you experience in that situation?
	When was the first time you did so? What was your intention and motivation for doing it?
	When did you feel the need for combining and consuming various substances the most?
Do you have any experience of using multiple substances separately and sequentially?	Please give more details.
	What was your intention and motivation for using these substances?
	In what situations did you use these substances and why?
	What feelings did you experience in these situations?
	Did you feel the need for consuming various substances? In what situations? Which substances? And for what purpose?
Could you describe your experience of the last time you had multiple substance misuse, either simultaneously or separately?	Please describe the situation in details.
	What substances did you use, and what was your main intention and motivation for using them?
	When? Where? What feelings did you experience in that situation?
	What significance and impact has the use of multiple substances had for you so far?
	In what situations do you feel the need or desire to use multiple substances more often?
	What substances are you currently using, and what is your goal for using each substance?
Do you have any experiences of witnessing others engaging in MSU?	Please give more details.
	Why do you think they did that, and what do you think their motivation was for doing so?
Is there anything else you would like to add to this topic?	
List for addiction treatment experts	
General question	Probes
What is your understanding of MSU and what does it mean to you?	In your opinion, why do consumers tend towards the consumption of multiple substances?
What is the first thing that comes to your mind when the term MSU is mentioned?	Can you provide an example of behaviors that, in your view, constitute multiple substance misuse?
	Please tell me more about the example you mentioned.
Can you describe your experiences in treating and interacting with multiple substance users?	Please give more details.
	In your opinion, what might be the primary reasons and motivations for individuals to engage in simultaneous substance use?
	What do you believe could be the primary reasons and motivations for individuals to engage in separate substance use?
	In your view, in what circumstances do individuals tend to lean more towards the consumption of multiple substances?
	What common characteristics, in your opinion, do these multiple substance users share?
	What distinctions do they exhibit compared to single-substance users?
	What particular risk factors do you believe contribute to the emergence of such a phenomenon?
Is there anything else you would like to add to this topic?	

the substance users, and maximum diversity in age, education, and work experience for the treatment experts were considered. Purposive sampling continued until data saturation was achieved, meaning no new categories emerged, and the existing categories reached saturation in terms of characteristics and dimensions. The participants had full control over the selection of the interview location. The interviews with addiction treatment experts and substance misusers were conducted in clinics, neurological and psychiatric hospitals, substance abuse treatment centers, counseling centers, and psychotherapy centers in one of the big cities in the south of Iran.

In this study, participants were substance users diagnosed by a specialist as having a recognized substance use disorder (SUD) based on the DSM-5 criteria. These participants had used at least two or more substances from the 10 drug classes of DSM-5 — namely, alcohol, cannabis, cocaine, heroin, hallucinogens, inhalants, prescription opioids, sedatives or tranquilizers, stimulants, and/or other drugs — either concurrently or simultaneously within the past year. The individuals had been under treatment for at least three months in clinics, neurological and psychiatric hospitals, substance abuse treatment centers, counseling centers, or psychotherapy centers, and had corresponding medical records. It should be noted that our definition of substance use was limited to cases meeting the DSM-5 criteria for SUDs, and did not include subthreshold substance use [19]. Among other inclusion criteria for substance users include being 18 years of age or older, having good verbal communication skills, and the ability to provide rich information about the subject of interest, as well as willingness to participate in the research and respond to the questions.

The inclusion criteria for addiction treatment experts included having a university specialization degree in addiction treatment (psychiatrist, psychologist, or general physician), a minimum of 5 years of work experience in the field of addiction treatment and having rich experience in working with individuals with MSU, which these key informants were selected based on the informed judgment of the first author and interviewer, particularly those with the most knowledge or experience in the field of addiction treatment, both pharmacological and non-pharmacological, and especially in MSU, and who had the ability to articulate their experiences and beliefs in a detailed, coherent, and reflective manner. Moreover, willingness to participate in the research and readiness for interviews were other inclusion criteria.

The exclusion criteria included withdrawal from the study, unwillingness to continue the interviews, and being in a critical situation on the part of the participants.

In this qualitative study, one of the sources of bias was the selection bias, which included the choice of times, locations, and participants. A key strategy for understanding the researchers' biases was reflexivity. This involved the interviewer actively examining, becoming aware of, and taking steps to monitor and control her own biases, values, preferences, and inclinations. Additionally, the researchers addressed biases by having some participants and colleagues review the data and the results. In order to reduce sampling bias, the selection of therapist participants was based on five key criteria: being knowledgeable (having sufficient expertise), being well-recognized (known in the field of MSU treatment), having theoretical knowledge (having a comprehensive understanding of the dimensions of the phenomenon under study), diversity (in various areas of MSU research and treatment), and motivation to participate. The selection of MSU participants was based on the following criteria: being a key MSU user (having sufficient awareness and providing rich information), being recognized (a known MSU case), seeking consultation and treatment for MSU, diversity (diversity in substance use, years of addiction, gender, and age), and motivation to participate.

Another source of bias was the influence of the researcher on the participants and key informants. Given the interviewer's ten years of experience in the field of addiction treatment and personal competencies, efforts were made to focus on the participants' responses with patience and tolerance for ambiguity during the interviews.

3.1. Data collection

In the current study, to gain a better and more comprehensive understanding of the phenomenon under investigation, information was collected through in-depth semi-structured face-to-face individual exploratory interviews and field notes. All interviews were conducted by the first author, who is a lecturer, researcher, and therapist (non-pharmacological interventions) in the field of substance abuse with 10 years of professional experience at the time of conducting the interviews. To focus on the study's concept, interview guides for both participant groups were developed and initially piloted through two pilot interviews (with a poly-substance user and a therapist who were not included in this study) by the first author. Subsequently, these interview guides underwent refinement and polishing through consultation with other authors of the paper. (Table 1).

Written informed consent and permission to record the interview was obtained from the participants before the interview started. The interviews began with general and loosely structured questions, and efforts were made to refine the questions based on the participant's understanding, experiences, and feedback, and in line with the study's objectives. The interviews were transcribed and analyzed as soon as possible upon the completion of each, allowing access to key informants and enabling the incorporation of their insights into subsequent interviews, which led to a richer dataset. The approximate duration of each interview was between 30 and 60 min. The durations varied depending on the situation, participants' cooperation, and environmental conditions. Typically, initial interviews were longer compared to subsequent ones. Additionally, in some cases, especially with specialists, the duration was extended based on the interviewees' willingness. Overall, during the study period, 27 interviews were conducted with 25 participants (2 participants were interviewed twice).

3.2. Data analysis

To analyze the data in the present study, the conventional content analysis approach, based on the method proposed by Graneheim and Lundman (2004), was used [20]. Initially, for the purpose of immersion in the data and gaining an overall sense, the text of each

interview was read multiple times. Words, sentences, or paragraphs containing important points about the reasons and motivations for MSU were then identified as meaning units. Next, these meaning units were labeled and coded with a summary representing the meaning of the selected units. Upon reexamination, the codes were compared for similarities and differences, and similar codes were merged. The codes were then reviewed against the original text. Based on similarity and relevance, themes were categorized and developed, and to ensure the robustness of the codes, the categories were reviewed and re-compared with the data. Through careful deep reflection and comparison among the categories, underlying patterns were identified. It should be noted that the labeling of categories was flexible throughout the analysis; it was subject to changes based on the flow of data until saturation was reached.

The coding and initial data analysis was conducted by the first author and the corresponding author. The process involved the first author identifying and coding units of analysis after multiple readings of the interview transcripts and gaining a deep understanding of the phenomenon under study. Subsequently, the corresponding author, after reading the entire transcript of each interview, reviewed the codes assigned by the first author. Following each interview session, they would convene to reach a consensus on the assigned codes. Afterward, the assigned codes were categorized into sub-subcategories based on conceptual similarity, and then these sub-subcategories, which were conceptually related, were organized within subcategories. Finally, these subcategories were placed within categories. All authors contributed to the development of subcategories and categories, aiming to ensure inter-coder reliability. All codes, along with their sub-subcategories, subcategories, and categories, were reviewed by other authors. In cases of disagreement or different interpretations among researchers, several joint sessions with research team members were held to discuss the organization of codes, sub-subcategories, subcategories, and categories until the final version of the analysis results was achieved. The decision regarding thematic saturation occurred when the authors empirically determined and reached a consensus that no new data would be collected to further enrich and complete the developed categories during the research process.

3.3. Rigor

In the present study, four criteria of credibility, transferability/fittingness, dependability, and confirmability, proposed by Lincoln and Guba for assessing scientific rigor in qualitative research, were utilized [21]. To achieve credibility, continuous and prolonged engagement of researchers with the data was undertaken (spanning 12 months, providing sufficient time for data collection, interviews, field notes, and observations during various sessions and times). Moreover, comparative and concurrent analyses, the integration of perspectives (semi-structured interviews with multiple substance users and addiction treatment experts), and the selection of diverse substance users in terms of gender, age, duration of use, as well as therapists with varying work experiences were employed. Additionally, a mix of settings (clinics, neuro-psychiatric hospitals, treatment centers for substance abuse, and counseling and psychotherapy centers) was included, along with searching for contradictory evidence and negative cases, as well as peer debriefing and review. In order to enhance data transferability, the study sought to delve deeply into the research, paying attention to details and providing thick descriptions of the findings. To guarantee transferability, the search for contrasting cases and purposeful sampling as well as efforts to conduct interviews and gather data from well-informed and diverse participants were also conducted. To

Table 2
Demographic characteristics of the participants.

Participant	Age (years)	Sex	Type of Consumption	Consumption History (years)
P1	42	Male	MSU	18
P2	23	Male	MSU	4
P3	23	Male	MSU	5
P4	35	Male	MSU	9
P5	22	Male	MSU	5
P6	19	Female	MSU	4
P7	31	Male	MSU	7
P8	47	Male	MSU	20
P9	32	Female	MSU	9
P10	36	Male	MSU	9
P11	46	Male	MSU	13
P12	30	Female	MSU	11
P13	45	Male	MSU	14
P14	31	Female	MSU	7
P15	28	Male	MSU	9
P16	24	Female	MSU	7
P17	23	Female	MSU	3
Participant	**Age (years)**	**Sex**	**Education Level**	**Work Experience (year)**
P18	51	Male	Psychiatrist	22
P19	46	Male	Psychiatrist	16
P20	49	Male	Psychiatrist	21
P21	35	Male	Psychologist	10
P22	61	Male	General practitioner	31
P23	46	Male	General practitioner	14
P24	45	Male	General practitioner	15
P25	54	Male	Psychiatrist	24

ensure data dependability, a chain of audit was employed, which included techniques such as proper interview methods, accurate transcription and peer review, revisiting participants to validate the findings, documenting the research processes, and maintaining a meticulous flow of interviews for data collection. For data confirmability, methods like peer review, research documentation, providing detailed and purposeful explanations of the research process, and enabling research auditing by others were employed.

4. Results

The participants consisted of 25 individuals (4 psychiatrists, 3 general physicians, 1 psychologist, and 17 substance users) (Table 2). The initial data analysis yielded 733 raw or open codes. Then, through continuous comparison of codes and raw data based on similarities and differences, similar codes were grouped together, resulting in the initial categorization of codes. The identified exemplars and codes were placed into 32 initial subcategories or sub-subcategories, which were further consolidated into 10 subcategories and 4 main categories. The main categories resulting from data analysis included 'Pharmacological factors', 'Biological factors', 'Psychosocial factors', and 'Addiction's inevitability' (Table 3).

4.1. Pharmacological factors

From the participants' perspective, the primary pharmacological factors can be categorized into two subcategories: 'Achieving the desired state and mitigating undesirable effects of substances' and 'Enhancing the overall consumption experience'. Among the motivations and key drivers behind users' engagement in MSU and combining substances, individuals turn to this behavior due to the balancing effects of MSU, synergistic interactions, reciprocal and contrasting effects of substances, substitution and imitation of the effects of other substances, self-treatment of adverse effects of other substances, as well as experiencing heightened peak effects and amplified pleasure. Moreover, they also engage in MSU to regulate the intensity of the highs associated with the use of different substances and alleviate the effects of coming down. With regard to the subcategory of 'Achieving the desired state and mitigating undesirable effects of substances', one of the addiction treatment experts acknowledged the following:

Table 3
Categories and subcategories emerged in the study.

Category	Subcategory	Sub-subcategory
Pharmacological factors	Achieving a desirable state and moderating the undesirable effects of substances	The balancing effects of substances
		The synergistic effects of substances
		Substituting and mimicking the effects of other substances
		Interactive and contradictory effects of substances
		Self-medication of undesirable side effects of other substances
	Enhancing the overall consumption experience	Experiencing higher peaks and synergistic enhancement of pleasure
		Modification/adjustment of coming down
		Seeking the experience of euphoria in different substances
Biologic factors	Different neurobehavioral systems	Craving for substance use driven by pleasurable motivation
		Craving for substance use due to lack of inhibition
	Individual differences determining substance dependency	Incompatibility of certain substances with the body's organism
		Diverse individual responses to substances
	Physiological-neurological vulnerability	Neurobiological changes
		Illnesses and physical/genetic pains
Psychosocial factors	Undesirable norms	Social acceptance as a gateway to initiation
		The role of peers in substance acceptance
		Diminishing of ugliness and disgust associated with substance use
		The role of substances as social reinforcers
	Substance use context	Type of substance and route of administration
		Early Initiation of Use
		Expectations and Attitudes Towards Substances
		Previous Substance Use Experiences
		Facilitating Environment
	Abnormal psychological personality traits	Distorted self-perception
		Sensation-seeking
		Impulsivity
		Psychiatric disorders
Addiction's inevitability	Compulsion and need to maintaining balance	Loss of control
		Avoidance from pain, hangover, and monotony
	Difficulty of substance detoxification	Efforts to reduce overall consumption
		Using a certain substance to quit the consumption of another substance
		Alleviation of withdrawal symptoms

"The interaction between opioids and stimulants arises from the fact that opioids act as depressants, while stimulants function as accelerants. If people use a stimulant, they become restless and experience palpitations and anxiety, prompting the need for opioids to alleviate these sensations. In turn, the use of opioids has its limitations, and when the individual's drowsiness and lethargy increase, they once again seek stimulation, thus perpetuating this cycle … " (P18)

Continuing with the same topic, one of the individuals engaged in substance misuse expressed her viewpoint as follows:

"When you take the pill alone, you always feel like doing something, you keep sweating, you keep standing up and sitting down, and you become agitated. But when you smoke marijuana, a sense of relaxation comes over you. For instance, in my case, after consuming alcohol, I wouldn't feel like using marijuana, but after taking the pill, I definitely had to smoke marijuana … " (P16)

An expert had the following observation regarding the substitution and imitation of the effects of other substances:

"Sometimes individuals change their consumption patterns simply because their preferred substance has become expensive and they cannot afford it. They shift their consumption patterns toward more affordable substances or combine substances that have similar effects. For instance, an increase in the cost of methamphetamine or heroin may lead to a shift in consumption patterns and individuals' inclination toward stimulants like marijuana, pills, or simultaneous use of these substances … " (P22)

Regarding the experience of heightened peak and synergistic enhancement of pleasure from the subcategory 'Enhancement of overall consumption experience', an individual who consumes substances shared the following experience:

"Every time I used methamphetamine, I experienced a significant pleasure and euphoria, yet I also had inner tension and anxiety. With marijuana consumption, the onset of euphoria and the lasting pleasure was much more intense, and my anxiety decreased. The most prominent aspect for those who take pills and seek marijuana is the immense feeling of pleasure and elation it provides them … " (P5)

Another consumer mentioned the following regarding the moderation of the reduced effects of high:

"When I used substances like 'Mushroom' or 'LSD,' I always had to use marijuana. 'Mushroom' and 'LSD' messed me up in such a way that I needed marijuana, and if I didn't use marijuana, I would go crazy. When you dropped, you couldn't continue without marijuana. It felt like I had introduced poison into my body. You had to smoke marijuana to be okay because you would feel sick." (P7)

On seeking the experience of euphoria with various substances, a consumer stated:

"Since I started using marijuana and cannabis, I would smoke marijuana for a while, and if it didn't give me the desired effect, I would put it aside and try another substance. After a while, when I smoked marijuana again, it would provide the desired effect, and with each substance, after some time, it became repetitive, and I wouldn't get as attached to it. Then I would switch to trying another substance, like alcohol or methamphetamine. Sometimes, I would even try using both together. It's like my mind couldn't stay empty; it had to be filled … It had to be loaded." (P8)

Based on the narratives of the participants, it appears that the primary goal and motivation for users in combining several substances is to achieve a physical and mental equilibrium. Individuals strive to maintain this balance in a back-and-forth or oscillatory movement between the use of soothing substances and stimulants. However, ultimately, the disruption of this temporary equilibrium leads to mental exhaustion, which itself becomes a factor and motivation for the use and combination of other substances as a means of relief from this fatigue and exhaustion.

4.2. Biological factors

Based on the views of the participants, individuals' biology has an impact on MSU, and this idea was described through a few instances like 'Different brain-behavior systems', 'Individual differences determining substance dependence', and 'Physiological-neurological vulnerability'. In this regard, an expert discussed the craving for substance use stemming from the pleasurable motivation under the subcategory of 'Different brain-behavior systems':

"Pleasurable incentives of substances influence neural reactions and processes, causing the brain to become sensitized to substances and the associated pleasure. This heightened sensitivity leads individuals to develop a strong inclination towards substance use, to the point where their thoughts and focus become solely centered around consuming substances. When someone engages in the simultaneous use of multiple substances, these pleasurable incentives become significantly amplified. Essentially, the brain becomes conditioned, even if the pleasure diminishes over time, to constantly seek substance use at any given moment." (P18)

Regarding 'the role of diseases and physical and hereditary pains' in MSU from the subcategory of 'Physiological-neurological vulnerability', one of the experts said:

"Even from a biological perspective, genetic factors may contribute to individuals within a family having a greater predisposition to addiction and MSU. This genetic predisposition likely amplifies individuals' vulnerability to engaging in multiple substance use and experiencing a more intense degree of addiction. On the other hand, many of these individuals turn to the consumption of stimulant and narcotic substances as a means of alleviating the pains and discomforts stemming from hereditary

physical and mental illnesses. Therefore, it can be argued that genetics play a substantial role here. Nevertheless, the specific type of substance also holds importance. For example, cocaine exhibits a higher degree of inheritability compared to other substances … " (P19)

One of the substance users discussed the determinative role of individual differences in substance dependence as follows:

"I never had an interest in marijuana. It didn't appeal to me. It kind of bored me. I've seen many people get energized by it. When my friend and I were driving, he would say he smoked marijuana to get energy for driving, so he could be lively and hyper on the road. I would smoke the same marijuana, and I would be knocked out in his arms; my high would drop, and I wouldn't have any interest in it anymore. I would use methamphetamine to feel awake and hyper. Every time I smoked marijuana after using methamphetamine, I would become locked in, and it was a terrible feeling. It was like I was getting shot, like I was a machine that had its timing belt locked." (P3)

According to the narratives of the participants, biological factors may both increase individuals' vulnerability to MSU and contribute to users' resistance and reluctance to use and combine certain substances. Furthermore, the repetitive rhythm of substance use in the body is not biologically accepted, leading to tolerance and a kind of mental and physical disarray, followed by further engagement in the use and combination of multiple substances in pursuit of physical and mental balance. Thus, individuals become trapped in a vicious cycle. In other words, the role of biology in perpetuating MSU is far more significant than its role in initiating such use.

4.3. Psychosocial factors

Psychosocial factors were categorized into three subcategories: 'Undesirable norms', 'Substance use context', and 'Abnormal psychological personality traits'. As described by participants, these factors were identified as another main dimension of motivations for MSU. The participants highlighted factors such as social acceptance as a gateway to initiation, the role of peers in substance acceptance, desensitization to the ugliness and negativity of substance use, and the reinforcing role of substances in social relationships as undesirable social norms that significantly influence MSU.

An expert acknowledges the concept of 'social acceptance, a gateway to initiate' as in the following:

"Ultimately, substance use starts somewhere. There are various theories about substance use. One of these theories is the 'gateway drug theory'. Addiction often begins with a particular drug. This drug typically holds higher social acceptance and carries fewer social consequences, such as marijuana, cigarettes, and hookah. Addiction initiates with one substance and gradually extends to other substances." (P18)

One of the specialists commented on the significance of gender in MSU, stating:

"In general, MSU is more prevalent among men across all age groups compared to women. This could be attributed to factors such as risk-taking behaviors, impulsive actions based on sudden motivations, engaging in unconventional activities, as well as cultural beliefs and norms. However, in recent years, we have unfortunately observed an increase in the use of various substances among women, indicating cultural shifts and the erosion of gender boundaries in substance use tendencies. Additionally, there are differences between men and women in both biological and sex-specific characteristics—such as dependency, physical problems, and treatment processes—and cultural and social factors related to gender, including social roles, stigmas, and the challenges within the social environment. Women are significantly more vulnerable than men in both respects. The frequency of use, the course of dependency, and relapse patterns differ between genders. For example, the time span from the first experience of substance use to the onset of severe multiple substance dependency is much shorter in women than in men. Furthermore, psychological and behavioral disorders, social factors, Sexual abuse in childhood, and environmental stressors play a more prominent role in the initiation and experience of substance use among women … " (P21)

On the role of peers in substance acceptance, a consumer mentioned the following:

" … I always had a fear of using other substances. During our frequent gatherings and outings, some friends of mine would consume marijuana. After a while, it seemed like I had become more at ease. When the rest of my friends were using marijuana, I eventually allowed myself to partake in its use as well." (P6)

Another substance consumer explains the influence of using methamphetamine as an enhancer on social relationships:

"With regard to sexual relationships, methamphetamine enhanced sexual pleasure and made me engaged in multiple repeated sexual acts. When using methamphetamine, I felt inclined to have multiple instances of sexual activity. This led me to desire engaging in frequent sexual encounters. Despite having a strong affinity for alcohol, the effects of methamphetamine on sexual experiences compelled me to use methamphetamine, specifically for its impact on my sexual experiences." (P4)

According to the opinions of participants in this study, background factors contributing to MSU included the type of substance, route of administration, expectations and attitudes toward substances, early initiation of use, past experiences with substance use, and facilitating environments. In this regard, one of the participants expressed his views on the type and route of substance use:

"The type of substance consumed is also crucial. Using certain substances can predispose an individual to using other substances as well. For example, someone who uses cocaine might be more likely to use heroin, although this could come with a high risk of

overdose. Similarly, individuals who use crystal meth might also consume alcohol or marijuana. Unfortunately, there is a misconception in which some users believe; for instance, they might think that simultaneous use of alcohol and crystal meth can cancel out the negative effects of each of the two substances and enhance feelings of pleasure and euphoria … " (P20)

One of the substance users mentioned their expectations and attitudes toward substances in the following way:

"I myself am willing to live my life the way I want for 60 years, not 90 years without enjoyment! I can't deprive myself of this pleasure. Instead of spending ten hours crying, If I can choose to use a couple of substances to alleviate that emotional pressure, I would do that. It's like skiing; it's risky, but it gives you a certain feeling after all … "(P17)

Abnormal psychological traits such as distorted self-perception, sensation seeking, impulsivity, and psychiatric disorders were identified as further psychological and social causes and motivations for MSU, as described by the participants. In this regard, one of the experts stated:

"Many individuals who use stimulant and psychoactive substances, especially stimulants, suffer from personality disorders, particularly borderline personality disorder. They experience difficulties in understanding and managing emotions and controlling impulses. Their high pathological narcissism, manipulation, and instability in mood and behavior render them vulnerable to substance use and contribute to a weaker prognosis in treatment and a stronger prediction of addiction." (P19)

A substance user regarding 'sensation seeking' stated:

"When I decided to take methamphetamine, I was only thinking about the thrill and high energy it would give me. I would say to myself, let's take it and get energized, then I thought, well, I should be pumped up and become a ball of energy. At that moment, you just think about getting high, becoming that ball of energy. An hour later, a day later, you don't think at all, you tell yourself that everything is worth experiencing at least once … " (P15)

Based on the results obtained from this category, it seems that psychosocial factors play a significant role both in initiating and continuing MSU. Particularly in recreational use and the onset of involvement in MSU, pleasure-seeking, social identity formation, and improvement of social interactions were predominant motivations for multiple substance users. However, during addiction, the role of social factors and identity diminishes, and the primary goal of MSU becomes reducing withdrawal symptoms, maintaining and restoring functioning, and achieving physical and mental balance.

4.4. Addiction's inevitability

The chronic, progressive, and relapsing nature of addiction leads to diversity and variety in substance use, and each substance can have both painful and inevitable outcomes. This category includes two subcategories: 'Compulsion and need to maintaining balance' and 'Substance detoxification difficulties', with concepts such as 'Loss of control', 'Avoidance of pain, hangover, and monotony', 'Attempts to reduce overall use', 'Using one substance to quit another', and 'Relief of withdrawal symptoms'.

A substance consumer described distancing themselves from pain, hangover, and monotony as follows:

"Many times, I would use any substance at hand to escape from discomfort, just to appear normal. In the beginning, when I experimented with various substances, I was mostly curious to see how each substance made me feel. After a while, I felt compelled to use them in order to function and go to work, to lead a regular daily life." (P9)

An expert stated about compulsion and inability to control substance use as follows:

"We cannot tell someone who holds sweet memories of MSU experiences in their mind to erase those memories; it's not possible. This person cannot simply erase them. Often, individuals alter the repetition of these pleasant memories of substance use – changing the number and type of substances, even the method of use – until they reach a point where those memories no longer matter to them. They just want to use substances to alleviate the lingering pains from substance use. It becomes somewhat like the secret to survival for them … "(P25)

Regarding 'The difficulty of detoxification from substances' and 'Using one substance to quit another', a substance user mentioned:

"To quit heroin, I turned to crystal meth. I wanted to quit heroin using crystal meth. After a while, I was using both crystal meth and heroin."(P7)

Another expert also mentioned the following regarding this topic:

"The misuse of multiple substances is common among those attempting detoxification. Patients may use other substances for self-medication of opioid withdrawal symptoms, which are often caused by inadequate doses of medication during withdrawal. Unfortunately, on the other hand, the use of multiple substances can complicate the process of detoxification and require more medical care … " (P23).

Based on participants' accounts, addiction and dependence on substances, along with the Loss of control and repeated, generally unsuccessful, attempts at detoxification and substance withdrawal, are among the main reasons for MSU. In fact, during the addiction phase, the search for and use of substances constitute a significant and vital part of the individual's life, prioritizing over everything else. In other words, the individual's life revolves around substance use, aiming to alleviate withdrawal symptoms and choosing

between lesser pain and greater pain to achieve a temporary physical and mental balance as a means of continuing life and survival. Ultimately, whether it is a combination of sedatives and stimulants or pharmacological interventions and efforts at detoxification, both lead to a common outcome: mental exhaustion and the failure to address the user's addiction.

5. Discussion

According to the findings of this study, the causes and motivations for MSU were generally categorized into four main categories: 'Pharmacological factors', 'Biological factors', 'Psychosocial factors', and 'Addiction's inevitability'. In agreement with these findings, it has increasingly been recognized that biopsychosocial factors such as gender, biological predisposition, emotional seeking, adverse childhood experiences, socio-economic vulnerability, availability, etc. are inherently linked not only to initial use but also to repeated use, maintenance, and its consequences on cognitive dysfunction in the domain of SUD [22]. Other studies also indicate that a complex interplay of factors, including pharmacological factors such as additive effect(s), reinforcement of positive effect(s), contrast of negative effect(s), relief of withdrawal symptoms, and unique substance effects, psychological factors such as alienation, impulsivity, distress, and risk-taking, social and economic factors such as access, price of drugs and alcohol, peer pressure, economic conditions as well as genetic-environmental interaction including genetic makeup (susceptibility to drug and alcohol use), family environment (moral-religious emphasis), and quality of parenting are all involved in MSU [2].

Millar et al. (2021) suggested that environmental, behavioral, and biological factors might partially explain the observed association between patterns and frequencies of cannabis use and the use of other illicit substances, including stimulants [23]. Based on some studies, various mechanisms influence the likelihood of developing substance use disorders: brain changes (biology); learning, social learning, and expectations (psychology); social norms and accessibility (social/environmental context [24]. In a study by Hakkarainen et al. (2019), MSU can be reframed within the concept of 'drug combo, set, and setting'. They posited that, in addition to the immediate physiological effects of substances, interactions between substances can create a specific context for performative pleasures and manageable risks. They suggested that these interactions should be studied in relation to set influences (such as agency, rational choice, expectations) and broader social contexts (such as the contexts and social bonds in consumption sessions, and the environmental and structural influences) [25]. In a mixed-methods study by Kataja et al. (2019) conducted among 512 multiple substance users, the most common reason for MSU was the enhancement of abilities or pleasures (45 %). Some one-third cited treatment or pain reduction (32 %) or getting smashed (31 %) as their reason for MSU, and 29 % mentioned experimentation and experiencing the combined effects of different substances. Thirteen percent reported that their MSU occurred accidently (unplanned and random) without any specific reason. Experimentation with combined effects and enhancing abilities or pleasures were more commonly reported reasons among men, while improvement or pain reduction, getting smashed, or accidental use were more common among women [26].

According to the results of this study, the pharmacological factors with two subcategories of 'Achieving the desired state and mitigating undesirable effects of substances' and 'Enhancing overall consumption experience' holds one of the important dimensions of motivations for MSU, as elucidated by the participants. In line with these findings, Hunt et al. (2009) identified three main types of effects resulting from the combination of different substances: extension (to prolong the effects), enhancement (to intensify the effects of other substances or create a new effect), and mitigation (to reduce undesirable effects) [27]. In the study by Finlinson et al. (2009), certain substances initially used to enhance or mitigate the effects of another substance at a specific time (such as marijuana enhancing cocaine, or crack mitigating heroin) became the primary substances of use. Conversely, some primary substances (like marijuana) were later used to enhance/mitigate the effects of a different primary drug (such as heroin) [28]. The findings of Rigg et al. (2024) indicated that among African Americans, opioids were combined with alcohol, cocaine, and methamphetamine, respectively. Opioids were used with alcohol in an attempt to enhance the desired effect (i.e., intoxication), while stimulants and opioids were combined to counteract the adverse side effects of each other [29].

Studies indicate that the reason for simultaneous substance use often involves balancing or counteracting the effects of one substance using another, increasing consumption, or mimicking the effects of another substance [30], resulting in mutual reinforcement and cross-tolerance [31]. Furthermore, substances may have enhancing effects in a way that a second substance could amplify the positive effects of the first. For instance, alcohol can enhance the stimulant effects of substances like cocaine and amphetamines, as well as the effects of benzodiazepines and sedatives [2]. Opioids can enhance the reward and motivational properties of psychostimulants, particularly when administered simultaneously [32]. Some substances can counteract or mitigate the negative effects or undesirable side effects of other substances [2,24,30]. For example, alcohol can reduce the 'fear' associated with stimulant use and can become a potent conditioned cue for cocaine, often used during cocaine binges to prolong its euphoric effects, reduce cocaine-related negative effects like paranoia and agitation, and decrease post-binge 'crash' [2]. Heroin may be used to avoid negative emotional experiences during stimulant use. Similarly, a stimulant might be employed to prevent feelings of sedation during opioid use or as an antidepressant [30]. Additionally, engaging in the concurrent use of stimulant drugs, such as combining cocaine or methamphetamine with heroin, or combining stimulants with alcohol to attempt delaying the onset of alerting signs resulting from rapid alcohol consumption [24], or using substances with complementary effects simultaneously to counteract undesirable effects of substances have been reported. For instance, medications for erectile dysfunction have been used to counteract the sexual performance-impairing effects of methamphetamine, and cannabis has been reported to increase appetite during stimulant use [30].

Similar to this study, other studies have revealed that one reason for concurrent substance use is the substitution of drugs [2,30]. If a preferred substance is unavailable or is only accessible at a higher cost, substances are mixed to help users achieve the desired effect. For instance, simultaneous use of benzodiazepines and methadone has been reported to mimic the effects of heroin when heroin is not available [30].

According to the study by Leri et al. (2003), some users consume speedball (the simultaneous mixture of heroin and cocaine) to achieve a higher level of euphoria, particularly when they do not have sufficient quantities of either drug [33]. Similarly, the study by Amsterdam et al. (2023) found that the primary motivations for users to concurrently consume opioids and gabapentinoids include seeking a better and lower price and self-medicating for pain/physical symptoms, including withdrawal symptoms. The motivation for combining opioids with methamphetamine or cocaine was to enhance the opioid effects, mitigate heroin withdrawal effects, and have a cheaper alternative to maintain opioid levels [34]. Another study indicated that heroin users often replace heroin with alcohol, cannabis, or benzodiazepines, either individually or in combination, when heroin is unavailable, until heroin becomes accessible again [2].

Moreover, akin to our study, some studies have reported that psychological distress resulting from MSU or the use of a specific drug can lead to increased use of multiple substances as a form of 'self-medication'. For example, individuals using methamphetamine may turn to sedative medications to reduce the anxiety associated with methamphetamine [17], or heavy cocaine users may use heroin to decrease excessive irritability associated with repeated cocaine use [2].

Based on the findings of the current study, 'Enhancement of overall consumption experience' was identified as another subcategory within the pharmacological factors. In line with this, according to the study by Brajević-Gizdić et al. (2009), drug addicts and substance users considered hedonism to be the primary reason for initiating drug use [35].

According to the literature, the pleasures of substance use encompass both immediate physiological effects and more performative pleasures related to the activities and actions facilitated by consuming the substance [25]. Specifically, the enhancement of abilities or pleasures can range from relaxation and recreation to the improvement of physical and mental performance in various contexts, such as work, sports, or leisure environments [26].

Studies suggest that individuals, despite the inherent risk of acute toxicity in MSU, combine substances with the aim of minimizing harm, reducing negative symptoms, enhancing pleasurable feelings, and improving the overall experience [30]. For example, the mixture of heroin and cocaine, allows an individual to experience a 'better' sensation compared to using each substance alone. Benzodiazepines may also be used to amplify the effects of other drugs, such as heroin and/or methadone, to achieve a 'high' [2], or the concurrent use of cocaine and cannabis may create feelings of 'stimulation' and 'elevation' that persist more as compared to the separate use of each alone [32]. According to the study by Boileau-Falardeau et al. (2022), one of the motivations for MSU involves combining drugs to produce synergistic psychotropic effects with the goal of enhancing or intensifying the effects of another substance, usually termed as '*enhancing a high*'. Often, stimulants are combined to prolong euphoria or *increase a high* [30].Similarly, in the study by Boeri et al. (2008), the combination of ecstasy and nicotine was a preferred mix among multiple substance users. For some, ecstasy was perceived as enhancing the smoking experience. In their study, the primary reason for MSU was the achievement of the synergistic effects of combined substances, including those experienced during the comedown. Many participants explained how alcohol enhanced ecstasy and softened its comedown. Marijuana was the most popular substance used while on ecstasy and during the comedown [15]. In O'Gorman's (2016) study, users balanced their focus on pleasure-seeking, getting high, and having a good time with their concern for mitigating the potential severe comedown. In this respect, they perceived quality to be less about the peak high a substance could achieve and more in terms of the level of low experienced after its use [16].

In this study, 'Distinct brain-behavior systems' was identified as one of the subcategories of biological factors. In this regard, it appears that the varying sensitivity of different brain-behavior systems in individuals influences their susceptibility to MSU. It has been suggested that altered reward and punishment processing may be a crucial vulnerability factor leading to substance use disorders [36], and studies indicate that a relatively high sensitivity to rewarding cues across a wide spectrum of externalizing behaviors is associated with substance use disorders [37]. In individuals for whom rewarding cues become potent motivators, these cues elicit tendencies that are difficult to suppress, potentially prompting maladaptive patterns and reward-seeking behavior. As a result, these individuals may be more vulnerable to compulsive behavioral disorders such as addiction [38].According to studies, drug abuse activates the brain's reward circuitry, resulting in a sensation of 'elevation'. This rewarding sensation influences repeated drug use; individuals with a sensitive reward system are more likely to exhibit repeated drug consumption [37]. However, once addiction is established, a reduction in the ability to avoid the craving for drug use and/or control the behavior of seeking drugs typically becomes apparent, despite the diminished pleasurable effects of the drug [39].

According to the findings of this study, the subcategory of 'Physical-neurological vulnerability', with two sub-subcategories of 'Neurobiological changes' and 'Diseases and inherited physical pains', was identified as another biological factor for MSU. Current knowledge about structural brain changes in the users of multiple substances is very limited [40]. However, research in basic neuroscience has demonstrated the key role of biological and genetic factors in an individual's susceptibility to substance use disorders [41]. The findings of Hatoum et al.'s study (2023) indicate a common genetic and highly polygenic architecture underlying MSU [42]. In general, any structural change in the brain (including volume reduction and subcortical enlargement) is either a result of substance uses or may have existed prior to substance use in an at-risk population. Studies indicate that both alcohol and stimulant use are associated with a decrease in gray matter volume [40]. Moreover, there is evidence that neurocognitive changes may prove a link between increased cannabis use and stimulant use. Neuroimaging studies indicate that common neural pathways may increase the risk of subsequent and broader substance abuse [23]. The complex effects of MSU on brain structure and function necessitate further investigation with robust cognitive approaches to inform more effective treatment strategies for users of multiple substances [40].

On the other hand, and in line with our findings, it appears that physical illnesses and damages as well as organ impairments affect the individual's psychological and physical system, leading individuals to turn to substance abuse as a means of escape and relief from pain and suffering. According to literature, chronic pain is a physical problem intricately linked to substance use disorders, particularly opioid misuse and addiction [43–45]. According to a study, poor physical or mental health conditions are among the reasons for using multiple substances [30], as a significant number of young individuals with chronic medical conditions resort to substance use,

including smoking, alcohol, and illicit drugs, and may also engage in non-medical use of prescription drugs [44]. The estimates indicate that over 10 % of patients with chronic pains misuse opioid analgesic drugs, and the number of deaths related to non-medical or inappropriate use of prescription drugs is on the rise [46]. According to Luther et al. (2020), individuals with chronic physical illnesses are more likely to have other substance use disorders compared to healthy individuals. Initial evidence suggests that young individuals with chronic physical illnesses are at a high risk of substance use [45].

In the current study, the subcategory of 'Individual differences determining substance dependency' was identified as one of the dimensions of biological factors involved in MSU. In this regard, based on the literature, it is logical to consider that specific factors (including individual differences in genetic makeup and or environmental exposures) may potentially be established or experienced before exposure to addictive substances or engagement in addictive behaviors early in life, thus contributing to vulnerability or resilience to addiction [47].Several instances of confirmed genetic findings support the notion that specific genetic variants play a role in the susceptibility to particular substance dependencies [43].According to the study by Sherva et al. (2010), there is a shared genetic risk for multiple substance dependencies. In fact, there exit genetic components proving sensitivity to substance abuse and/or addiction to alcohol, nicotine, and illicit drugs. While there are certain factors related to each substance, genetic vulnerability to substance abuse is shared across different substances [48]. According to Dingel et al. (2019), multiple substance users often have a background that includes a genetic predisposition due to a family history of opioid addiction [49].

Furthermore, studies indicate that all substance use disorders do not mean a single phenomenon - sensitivity varies from one substance to another. For example, a predisposition towards alcohol use disorder may or may not coincide with a tendency towards nicotine or cocaine use disorders, and genetic forces linked to certain concurrent issues may also relate to the inclination to develop a specific type of SUD. Overall, there is an interaction between internal (biological and psychological) forces and external environmental forces related to substance abuse [24].

As described by the participants of this study, the psychosocial factors were identified as another major dimension of motivations for MSU. In this context, studies suggest that the interaction of socio-economic background, social environment, and accessibility strategies impact the prevalence and sensitivity to MSU [32]. In other words, the context in which individuals use substances also influences their behavior [50]. Even the choice of substances used in combination depends on the context in which they are employed for specific functional purposes. For example, club drugs are used to enhance feelings of euphoria, sociability, self-insight, and acceptance [30]. Cocaine is primarily favored outside of home settings, while heroin is more prevalent in 'home' environments. Furthermore, the route of administration (e.g., oral consumption, injection, and inhalation) has been found to be particularly important in studies, as it leads to unique patterns of substance use history that may impact the development and severity of addictive behaviors [32].

Similar to our study on the undesirable normative contexts leading to MSU, the literature shows social norms are key social processes that are associated with various behaviors, including substance use and misuse. Groups of individuals may have specific norms regarding the initiation of substance use, acceptable patterns of regular use, excessive or intoxicating use, seeking treatment for substance-related problems or disorders, and supporting recovery [24]. According to the peer cluster theory, certain fundamental conditions such as the environment and the individuals' beliefs and values predispose him or her to engage with or, conversely, resist involvement with drugs [51].Several studies have demonstrated that substance use among adolescents is strongly influenced by peer substance use and peer endorsement of substance use [51,52]. According to the study by Quek et al. (2013), peers' use of alcohol, tobacco, and cannabis showed significant correlations with MSU among young adults [53].Similar to our study, Kataja et al. (2018) have demonstrated that social interaction during the peak experience of MSU is significant, and substance use is something that bonds the group together and defines their togetherness [14].

Furthermore, in line with our findings, research also indicates that there is a relationship between specific attitudes and beliefs about substance use and initiation of substance use. Individuals with a positive attitude toward substance use are more likely to try substances. In fact, attitudes toward substances include cognitive, emotional, and behavioral elements that play a crucial role in initiating substance use, and changing individuals' attitudes toward substances can reduce their inclination to use them [54].

Furthermore, similar to our study, research indicates that the type of substance used is also involved in the development of MSU. Specifically, having a SUD with one substance increases sensitivity to developing dependence on additional substances. It is noteworthy that cocaine and amphetamine users are predominantly multiple substance users. Additionally, cocaine use and cocaine use disorder often co-occur with simultaneous use of heroin, cannabis, tobacco, and alcohol. Similarly, amphetamine users tend to use various other substances, including alcohol, tobacco, cannabis, heroin, and other opioids. Similar to amphetamine users who are 21 times more likely to have a concurrent cannabis use disorder and 7 times more likely to have used cocaine concurrently in the past year, individuals with nicotine use disorder are 3–4 times more likely to develop a second substance use disorder (SUD) [32]. Other epidemiological studies have also shown a significant association between the use of cannabis and the use of harder illicit drugs, such as stimulants like cocaine and ecstasy [23].Moreover, studies have shown that alcohol is often used in combination with another substance. The relationship between alcoholism and multiple substance dependence has been documented. Dependence on marijuana is the most common co-occurring dependence with alcoholism, followed by cocaine dependence [55]. According to Hakkarainen et al. (2019), the consistent presence of alcohol in various forms of MSU confirms its centrality. In fact, alcohol acts as a 'facilitator' of MSU by playing a significant role in the unplanned or unintended consumption of other psychoactive substances [25]. According to the literature, the risk of heroin addiction is doubled for alcohol abusers, tripled for cannabis users, fifteen times higher for cocaine users, and forty times higher for prescription drug abusers [32].

Similar to the findings of our study, other research works also indicate that early initiation of substance use is a significant factor in MSU. There is evidence suggesting that early exposure to alcohol and other substance misuse increases the likelihood of developing substance use disorders in later stages of life [24]. According to Lalwani et al. (2023), perceived risk reduction, early childhood and

adolescent onset, and easy access to marijuana were significantly associated with MSU [56].

According to the literature, early initiation of alcohol, tobacco, and marijuana use is associated with an increased risk of substance misuse and negative consequences related to intoxication. Early initiators are more likely to report MSU, frequent substance use, recurrent periods of intoxication, and the likelihood of developing substance use disorders compared to later initiators. Individuals who initiate substance use at a young age often experience multiple personal, familial, and peer risk factors that are associated with adverse developmental outcomes. Personal characteristics linked to early initiation include externalizing symptoms such as hyperactivity, impulsivity, inattention, and initial aggressive behavior, as well as temperamental traits like novelty-seeking, sociability, and activity, with increased prevalence of negative emotions particularly noted among girls. Early substance users tend to exhibit more problematic attitudes toward substance use, engage in more negative consumption patterns in the first year, and show less attachment to social goals [57].

Consistent with our findings regarding the role of facilitating environment for MSU, other studies also demonstrate that the physical and social contexts in which the use of substance occurs influence substance use behavior. Social and physical environmental factors have significant potential to modify the effects of genetic and psychological influences on health-related outcomes, including substance use initiation, substance misuse, and the development of substance use disorders. In fact, social and physical environmental factors can either compound vulnerabilities or foster resilience against them [24]. Traditionally, economically disadvantaged communities are considered high-risk ecologies for the development of criminality and substance use, often operating through mechanisms such as exposure and social disorder [58].One evident aspect of the physical environment that must be considered is an individual's access to alcohol or other drugs at home, school, workplace, peer groups, or the neighborhood [24]. Therefore, access to highly reinforcing and stimulant drugs, when combined with environmental factors (such as widespread availability of legal and illicit drugs, chronic stress, peer pressure) and individual vulnerabilities (such as pre-existing mental illness, chronic pain, genetic predisposition, gender, youth), influences drug experimentation as well as the risk and prevalence of SUD [59]. Some of the participants in the study by Boeri et al. (2008) asserted that in most cases, they used substances since they were readily accessible [15]. In general, environmental factors appear to have a stronger influence on initiation of use, while genetic factors play a more significant role in the transition from regular use to addiction development [43].

According to the findings of our study, abnormal psychological personality traits are among the other psychological and social reasons and motivations for MSU. In line with these findings, previous studies have shown that personality traits significantly influence substance use disorders and related psychiatric symptoms [60] and are important predictors of substance misuse [61]. It has been demonstrated that certain personality traits may constitute vulnerability factors that interact with other biological, psychological, and social variables in the development of MSU [62]. According to the literature, multiple substance dependence is associated with personality disorders, and individuals who are dependent on multiple substances have higher rates of mood disorders, anxiety disorders, and personality disorders [55]. According to the findings of Novais et al. (2016), in individuals dependent on alcohol, similar to the general population, 'openness to experience' may be a vulnerability factor associated with MSU. Furthermore, the long-term use of multiple substances by an individual dependent on alcohol may also reflect personal needs and preferences related to their personality functioning [62].

Similar to our study, previous research on self-perception disturbances has also shown that greater negative self-perception is associated with increased substance-related problems [63,64]. A longitudinal prospective study by Yan et al. (2020) supports the hypothesis that negative self-perception predicts a relative increase in substance-related problems from late adolescence to early adulthood. A weak self-concept may directly lead to heightened negative emotions and behaviors that diminish self-awareness, or it may indirectly lead to higher stress levels, which then trigger substance use for self-medication purposes [64].

Additionally, consistent with our findings, other studies have shown that high levels of certain personality traits such as sensation seeking and impulsivity [65–67], negative emotionality, emotional dysregulation, and symptoms of personality disorders increase the risk of substance use [66]. Individuals with MSU disorder have reported higher levels of sensation seeking compared to other SUD groups [22]. According to the results of a study, the presence of dispositional traits related to sensation seeking, novelty seeking, or lack of inhibition may indicate key personality vulnerabilities for alcohol-dependent individuals who use multiple substances to enhance their overall psychotropic experience [62]. According to the study by Jensen et al. (2017), sensation-seeking behavior has been associated with higher levels of adolescent experimentation with alcohol, tobacco, marijuana, and other illegal drugs [58].

It is possible that this inclination toward sensation seeking may be due to a combination of the allure of experiencing pleasurable intoxication effects, the thrill of breaking law, and the fact that alcohol and drug use often involve rewarding social interactions with peers, leading to increased experimentation with substance use in adolescents [58]. Studies examining sensation seeking in substance users have shown a positive relationship between the number of substances used and sensation-seeking scores, indicating that users of multiple substances have significantly higher levels of sensation seeking [68]. According to the study by Kataja et al. (2018), three distinct discourses have been identified through which individuals justify their voluntary risk-taking behaviors in MSU. In the discourse of self-development, seeking novelty and unfamiliar experiences outside of personal comfort zones is viewed as a means of personal growth and self-discovery. In the discourse of emotional engagement, risk-taking is perceived as a source of excitement, adventure, and challenge. It is seen as a powerful experience of breaking away from daily routines, often linked to social contexts and sharing. In the discourse of control, the allure of risk-taking lies in an individual's ability to manage and control the experiences and associated risks. This leads to a sense of living a life with personal agency [14].

The current study illustrates that psychiatric disorders are another socio-psychological factor contributing to MSU. Consistent with these findings, studies have shown that many individuals with substance use disorders also have co-occurring psychiatric disorders, and some have MSU disorders [69–71]. Previous research has demonstrated that the likelihood of MSU is higher among individuals with co-occurring psychiatric conditions, including anxiety and mood disorders [31,72] such that the use of multiple psychoactive

substances in mental health settings is more of a rule than an exception [62]. The longitudinal analysis conducted by Booth et al. (2010) indicates a strong association between greater substance use diversity and increased psychological distress [17]. On the other hand, numerous studies have shown that MSU leads to undesirable psychiatric outcomes, including schizophrenia, mood disorders, or multiple psychiatric disorders [71].

Based on the results of this study, the primary category of 'Addiction's inevitability' with two subcategories of 'Compulsion and need to maintaining balance' and 'Difficulty in substance detoxification' was identified as another main dimension of the causes of MSU. According to the literature, addiction is conventionally recognized as a compulsive neurobiological disease, and the concept of compulsion is central to the disease theory of addiction. Compulsivity marks a pivotal point in transition from regular and recreational drug use to addictive substance use. Initially, drug use is a voluntary behavior, but when that switch is thrown, the individual enters a state of addiction characterized by compulsive seeking and drug use. In fact, the essence of addiction is compulsive seeking and drug use, even in the face of negative health and social consequences, leading to fundamental disruptions in health and social functioning [73]. According to a study by Kataja et al. (2018), the compulsory use of multiple substances implies that ensuring the supply of substances takes precedence over all other concerns. Consumers, due to a bleak outlook on life, withdrawal symptoms, or other issues, are unable to function properly. Consequently, the primary goal becomes the need to restore and maintain substance use habits and the ability to function, rather than seeking the pleasurable effects of using multiple substances. This is what users hope to achieve by combining different substances [14]. Given the widespread prevalence of MSU among drug users, it is crucial to determine whether MSU exacerbates the severity of SUD or increased SUD severity leads to MSU [32].

In agreement with our findings regarding avoiding pain and hangover, and alleviation of monotony, considering all the evidence, it appears that while substances serve as a source of pleasure for many consumers, both addicts and non-addicts, they also perform other well-established and documented functions, including pain relief, alleviation of fatigue, stress reduction, boredom mitigation, handling negative emotions and psychological distress, as well as enhancing physical energy, cognitive abilities, social interactions, and even altering experiences, such as spiritual encounters [74], and alleviate withdrawal symptoms [30]. In other studies, it has been indicated that opioid substances provide relief from pain and distress. Amphetamines enhance energy and cognitive abilities, and MDMA increases social connectivity. Psychedelic drugs produce experiences that people describe as some of the most meaningful experiences of their lives [74]. In fact, addiction can function as a means to rapidly induce excitement and can amplify an individual's inclination toward novel experiences. Therefore, these people are more inclined to use drugs as a way to escape monotony [75].

Another motive for MSU described by the participants is 'the difficulty of detoxification from substances. In this regard, studies suggest that relapse is common during the recovery from substance use disorders [76], and alleviating and managing withdrawal symptoms and cravings is one of the motivations for MSU [2,30,31]. Furthermore, it has been shown that MSU increases the overall desire for substances [77], and, compared to those who use only one substance, individuals who use multiple substances are more likely to discontinue treatment programs for substance abuse, experience treatment termination, and relapse [18,77]. According to the study by Boileau-Falardeau et al. (2022), individuals use substances within the same category to mitigate the effects of drugs. The most common combinations of substances for alleviating withdrawal symptoms include using a stimulant with a depressant substance (such as benzodiazepines, alcohol), cannabis, or opioids for relaxation, inducing sleep, reducing anxiety or distress, or avoiding substance cravings induced by a stimulant [30]. Sequential use of psychoactive stimulants and opioids is also prevalent, including the use of cocaine or amphetamines to prevent physical withdrawal symptoms associated with opioids and the use of opioids to reduce excessive stimulation following cocaine use. Cannabis use has been found to lead to shorter periods of abstinence from alcohol and a higher incidence of relapse to cocaine, which has been associated with less efficient treatment. As another example, chronic nicotine treatment also increases alcohol preference, an effect that persists through nicotine withdrawal [32].

In conclusion, we argue that the aforementioned findings regarding the causes and motivations of MSU are worth investigating further and are valuable for providing an operational definition of this phenomenon. Thus, this study can offer worthy insights in this domain to enhance our understanding and, consequently, minimize or overcome the underlying causes and risk factors of this phenomenon at both national and international levels. Additionally, since pharmacological, genetic, and biological factors, personal preferences and choices, as well as psychosocial and environmental contexts play significant roles in the etiology and progression of multiple substance use (MSU) patterns, and since treatment success in all these models is directly related to adherence to the treatment, the best therapeutic outcomes are achieved when patient-centered pharmacological treatments are combined with long-term psychological, social, and environmental interventions. This should be provided by a multidisciplinary team of therapists. Patients dependent on MSU undergo various stages in their treatment, with the characteristics and duration of these stages being unique to each individual. A comprehensive and multi-dimensional assessment—including pharmacological, biological, psychological, and social aspects such as the types of substances used, usage patterns, routes of administration, motivations for use, recent substance use tests, the number of unsuccessful detoxifications, previous attempts at quitting, inpatient and outpatient methods experienced, side effects and symptoms of intoxication, history of physical illnesses and psychiatric disorders, and the individual's socio-economic, occupational, and family status—provides therapists with the necessary information for treatment planning. This information assists in selecting the type of therapeutic intervention, the therapeutic setting, and the necessary supplementary interventions. Additionally, policymakers and planners need to consider the complex and interactive effects of the causes and motivations for MSU over time to better understand behaviors and patterns of MSU. This understanding is crucial for developing laws and implementing potential evidence-based intervention strategies, including prevention, care, treatment, and harm reduction strategies. By doing so, and with the participation of the clients, they can fully address the complex care and treatment needs of this growing population.

5.1. Limitations and strengths

One of the limitations of this work is its qualitative nature, which has restricted the volume and sample size used in the study. Given that the data collection in this research relies on participants' perceptions of the causes of the targeted phenomenon, the results may be subject to significant subjectivity. Additionally, as the context, patterns of substance use, events, conditions, and influential interactions on substance use behavior cannot always be replicated, caution should be exercised when generalizing the findings of this qualitative study to other cultures and societies. Another limitation of this study is that it focuses on exploring the causes and motivations of MSU from the perspectives of substance users and treatment experts. It is suggested that future research should investigate the perceived causes and motivations from the viewpoints of the families of substance users, who are deeply involved in this phenomenon, in order to better understand their strategies for coping with this issue. Furthermore, this study provides a moment-by-moment perspective of the participants' experiences. A longitudinal study could offer insights into how motivations and behaviors change over time, particularly in response to therapeutic interventions.

Future studies can provide an operational definition of MSU by elucidating the lived experiences of individuals with substance use disorder over time. Additionally, more comprehensive and extensive studies are recommended to clarify and comprehend the patterns of MSU associated with high risks of excessive consumption. Despite the limitations of sample size, potential bias, the absence of longitudinal data, and the exclusion of family perspectives, this study offers unique insights into the causes and motivations of MSU and contributes to a better understanding of potential relationships between causes and risk factors for the occurrence and high prevalence of this phenomenon. It can provide valuable and important information for policymakers, treatment experts, and researchers.

6. Conclusion

The findings of this study, presented through organized concepts or themes, can provide a foundation for further insight and a better collective understanding of the causes and motivations of MSU. These findings help depict a richer portrait of the primary drivers behind this behavior. Based on the results, various tangible and subjective factors are prominently evident in individuals' inclination toward MSU. From the perspectives of substance users and addiction therapists, a set of factors has been described as the most important causes and motivations for MSU. Pharmacological factors include achieving an optimal balance and mitigating the adverse effects of substances through leveraging balancing, synergistic, and antagonistic effects, substituting the effects of other substances, self-medication, and enhancing the overall substance use experience with motivations such as seeking a higher peak experience, synergistic pleasure, moderating crashes, and pursuing euphoria from various substances. Biological factors encompass differences in brain-behavior systems, genetic composition, and individual differences that determine substance dependence and physical-neurological vulnerabilities. Psychosocial factors involve abnormal psychological personality traits, unfavorable social norms, the context of substance use, and the inevitability of addiction due to reasons such as the compulsion and need to maintain physical-psychological balance and the difficulty of substance detoxification. In general, the aim of this study was to provide an overview of how and why MSU occurs. Given the high prevalence of this phenomenon, it is recommended that further research in this area be conducted to identify and elucidate risk factors for susceptibility to this issue in various populations.

CRediT authorship contribution statement

Hassan Mokhtarpoor: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Banafsheh Tehranineshat:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Zeinab Naderi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maryam Amirinia:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

Ethical approval statement

All the participants gave written informed consent to participate in the study. The present study was conducted in terms of the principles of the revised Declaration of Helsinki, which is a statement of ethical principles that directs physicians and other participants in medical research involving human subjects. The participants were assured about their anonymity and confidentiality of their information. Moreover, the study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Ethical Code: IR.SUMS.REC.1399.1295, ethics approval date:2021-02-14).

Data availability statement

The data that has been used is confidential.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

MSU Multiple substance use
SUD Substance use disorder
LSD Lysergic acid diethylamide
MDMA 3,4 Methylenedioxymethamphetamine

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