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ORIGINAL ARTICLE

Impulsivity and Impulsivity-Related Endophenotypes in Suicidal Patients with Substance Use Disorders: an Exploratory Study

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Abstract
Suicidal behavior (SB) is a major problem in patients with substance use disorders (SUDs). However, little is known about specific SB risk factors in this population, and pathogenetic hypotheses are difficult to disentangle. This study investigated some SB and SUD-related endophenotypes, such as impulsivity, aggression, trait anger, and risk-taking behaviors (RTBs), in forty-eight patients with SUDs in relation to lifetime history of suicide attempts (SAs). Disorders related to alcohol, cannabis, cocaine, opiates, and hallucinogenic drugs were included. Lifetime SAs was significantly associated with both higher impulsivity and higher aggression, but not with trait anger. A higher number of RTBs were associated with lifetime SAs and higher impulsivity, but not with aggression and trait anger. Assessing these endophenotypes could refine clinical SB risk evaluation in SUDs patients by detecting higher-risk subgroups. An important limitation of this study is exiguity of its sample size. Its primary contribution is inclusion of all SUD types.

Keywords Substance use disorder · Suicidal behavior · Impulsivity · Aggression · Anger · Risk-taking behavior

Suicidal behavior (SB) is a significant clinical problem among individuals with substance use disorders (SUDs) (Darvishi et al. 2015; Poorolajal et al. 2016; Rodríguez-Cintas et al. 2018; Rontziokos and Deane 2018). Increased mortality from suicide is found with alcohol, cocaine, and opioid SUDs (Charlson et al. 2015; Ferrari et al. 2014; Pan et al. 2014; Walker et al. 2017). Compared to the general population, individuals with alcohol SUD are almost 10 times more likely to die of suicide, and those who inject drugs are about 14 times more likely (Wilcox et al. 2004). A history of suicide attempts (SAs) is reported in about 40% of patients seeking

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treatment for alcohol (Roy 2003; Roy and Janal 2007), cocaine (Roy 2009), and opioid dependence (Roncero et al. 2016; Roy 2010). In addition, the repercussions of SB involve not only the individual but also survivors, including family members, friends, and communities as a whole, in a profound and lasting way (Pompili et al. 2013). The emotional turmoil in survivors of suicide may end, in some cases, with their own suicide (Pompili et al. 2013).

SB emerges as the by-product of a multifactorial process that integrates at various levels of complexity, including neurobiological, psychiatric, psychological, socio-economic, and cultural factors. This concept has been incorporated into comprehensive models which have the heuristic interest of generalizing and testing hypotheses in the pathogenesis of SB to detect highly vulnerable subjects (Hawton and van Heeringen 2009; Turecki and Brent 2016). In the "stress-diathesis model," the risk for expression of SB is not determined by a unique stressor, nor does it consist in the onset or acute worsening of a psychiatric disorder or of a psychosocial crisis, but rather in a combination of specific vulnerability factors constituting the appropriate terrain (Mann et al. 1999; Mann 2003; Mann and Currier 2010; van Heeringen and Mann 2014). A sequencing of these vulnerability factors into distal and proximal ones, with several socio-demographic variables playing a role of moderators between them, has been conceptualized in the "neurodevelopmental model," which emphasizes the concept of an individual vulnerability life-trajectory, and interacting and managing environmental influences at any moment (Turecki et al. 2012; Turecki and Brent 2016).

Findings on the neurobiological basis of SB have resulted from a number of postmortem and in vivo studies that have investigated neurotransmitter families, the hypothalamic-pituitary-adrenal (HPA) axis, neurotrophic factors, and polyamines at the different biochemical, genetic, and epigenetic levels as well explored neuroanatomical aspects by using correlates of neuropathology and neuroimaging (Hawton and van Heeringen 2009; van Heeringen and Mann 2014, Ernst et al. 2009). Despite the absence of biomarkers that can predict which subjects will develop SB over time (for a review, see Costanza et al. 2014), there has been a wide consensus that a number of neurobiological risk factors are potential indicators. These include 5-HTTLPR, a repeat polymorphic region within the *SLC6A4* gene coding for the serotonin transporter (Bondy et al. 2000), epigenetic changes in genes involved in HPA stress response system among subjects having had early-life aversity (Labonte et al. 2012), and variations in neurotrophic factors (particularly brain-derived neurotrotrophic factor, BDNF) (Costanza et al. 2014). Both prolactin and thyroid hormone (free triiodothyronine, FT3) were studied for association with SAs in psychiatric patients: they may be involved in a complex compensatory mechanism to correct reduced central serotonin activity (Pompili et al. 2012). Both structural and functional neuroimaging data on patients with SB shown deterioration in the prefrontal cortex, in particular in its dorsolateral and ventral portion including the orbitofrontal cortex, the anterior cingulated cortex, and the amygdala (Jollant et al. 2011; van Heeringen et al. 2011). Recent resting-state functional MRI results have showed aberrant neural activity patterns in fronto-lymbic or fronto-parietal-cerebellar pathways among suicide attempters (Serafini et al. 2016).

In this context, the study of endophenotypes has acquired a particular interest. Defined as "measurable components by the unaided eye along the pathway between disease and distal genotype" (Gottesman and Gould 2003) and also named "intermediate phenotypes" or "internal phenotype," they represent a quantifiable biologic or psychological variable (typically, including both biological and behavioral elements) associated with a genetic risk for a disorder (Mann et al. 2009; Griffiths et al. 2012). They must meet certain criteria: (a) association with a candidate gene or gene region, (b) heritability inferred from relative risk

for the disorder in relatives, and (c) disease association parameters (Gottesman and Gould 2003). They emerged as strategic concept in the study of complex psychiatric diseases, constituting "simpler clues to genetic underpinnings than the disease syndrome itself" and promoting "the view that psychiatric diagnoses can be decomposed or deconstructed, which can result in more straightforward–and successful–genetic analysis" (Gottesman and Gould 2003).

A number of clinical and socio-demographic risk factors for SB have been analyzed in individuals with SUDs, most of which are common in the general population (Rodríguez-Cintas et al. 2018; Yuodelis-Flores and Ries 2015). Among them, multiple studies have shown a strong association between SB and psychiatric disorders such as depression, bipolar disorder, posttraumatic stress disorder, conduct and antisocial personality disorder, and, in clinical samples, schizophrenia (Harris and Barraclough 1997; Arsenault-Lapierre et al. 2004).

However, relatively little is known about specific risk factors in individuals with SUDs (Erinoff et al. 2004; Yuodelis-Flores and Ries 2015). Moreover, in many cases, pathogenetic hypotheses are difficult to disentangle (Erinoff et al. 2004; Yuodelis-Flores and Ries 2015). Research suggests that the number of substances used, intravenous use, severity of the SUD, and entry into treatment can be more important in predicting SB than the types of substances used, but arguments for these associations remain heterogeneous (Borges et al. 2000; Voss et al. 2013; Wilcox et al. 2004; Yuodelis-Flores and Ries 2015). Comorbidity with mental disorders is frequent. Nevertheless, the time sequence of mental disorders and the association with SUDs is often unclear, and causal inferences are difficult to determine given the complexity of underlying biological, psychological, and social interactions (Erinoff et al. 2004; Strakowski and DelBello 2000). It is also arduous to determine whether an SUD acts primarily as a distal risk factor (a statistical potential for SB linked to the SUD diagnosis and related psychopathological factors), a proximal risk factor (a condition translating the statistical potential of distal risk factors into action, as with the acute effects of alcohol intoxication), or both (Hufford 2001; Vijayakumar et al. 2011).

For this reason, a growing body of research has addressed various SUDs and SB-related endophenotypes, including impulsivity, aggression, anger, and risk-taking behaviors (RTBs) (Ramirez and Andreu 2006).

Impulsivity, defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others" (Moeller et al. 2001), is a vulnerability marker for SUDs at various key transition phases of those disorders (for reviews, see de Wit 2009; Dougherty et al. 2004; Kozak et al. 2018; Perry and Carroll 2008; Verdejo-García et al. 2008). A positive association between aggression, a "hostile, injurious, or destructive behavior" (Siever 2008), and a SUD diagnosis exists, even at a distance from acute intoxications (Ahmadi et al. 2017; Chermack et al. 2008; Coccaro et al. 2016). Impulsivity and aggression are risk factors for SB (for reviews, see Gvion and Apter 2011; Mann et al. 1999; Mann et al. 2009; Rimkeviciene et al. 2015) and, in conceptual integrations of the literature (Conner and Duberstein 2004), they are specifically suggested as key predisposing factors for SB in patients with alcohol use disorders. However, only a few clinical studies have investigated the association between impulsivity, aggression, and SUDs in patients with SB, and these studies mostly focused on alcohol dependence (Conner et al. 2006; Dick et al. 2010; Haw et al. 2001; Khemiri et al. 2016; Koller et al. 2002; Sher et al. 2005; Wojnar et al. 2009).

Anger, which ranges "from mild irritation to intense fury and rage" (Spielberger and Reheiser 2009; Veenstra et al. 2018), is experienced more often in individuals with SUDs

than in the general population (Coccaro et al. 2016; Cougle et al. 2017; Goldstein et al. 2005; Zarshenas et al. 2017). While it does not always lead to aggression nor is it a necessary cause for aggression, a robust relationship between these two constructs has been noted (Chereji et al. 2012; Henwood et al. 2015; Lee and DiGiuseppe 2018). In particular, anger is identified as a risk factor for aggression in alcohol users (Giancola 2002; Parrot and Zeichner 2002; Walitzer et al. 2015). Additionally, it plays a role in SB (Giegling et al. 2009; Hawkins et al. 2014; Sadeh and McNiel 2013). High scores in anger measures are found in alcohol-dependent patients who have experienced SAs (Haw et al. 2001; Sharma and Salim 2014), but data for those with other SUDs cannot be found.

RTBs, the "propensity to seek out novel, stimulating but potentially harmful experiences" (Dougherty et al. 2015), are often associated with SUDs (Dougherty et al. 2015). Impulsivity, aggression, and anger are considered RTB-related endophenotypes. It is hypothesized that the heterogeneity of RTBs stems from the variability in their possible combinations (Ahmadi et al. 2017; Dougherty et al. 2015). Associations between RTBs and SBs are largely documented in gambling (for more recent works, see Bischof et al. 2016; Cook et al. 2015; Mallorquí-Bagué et al. 2018; Moghaddam et al. 2015), binge drinking (Byeon et al. 2018; Husky et al. 2013), risky sexual behavior (Eaton et al. 2011; Epstein and Spirito 2010; Houck et al. 2008; Husky et al. 2013; Thullen et al. 2016), dangerous driving behavior (Holland et al. 2014; Patel and Luckstead 2000), and extreme sport activities (Tofler et al. 2018). Nevertheless, interplays between RTBs, SB, and SUDs remain unclear.

Investigations of the relationships between impulsivity, aggression, anger, and RTBs in predisposing SBs in patients with SUDs can offer new approaches to refining the clinical assessment of the SB risk in this complex and vulnerable population. The main aim of the present study was to compare SUD patients having a lifetime history of SAs with SUD patients without a lifetime history of SAs, in relation to impulsivity, aggression, trait anger, and RTBs. On the basis of previous data in literature, we hypothesized that lifetime SA would be associated with higher levels of impulsivity, aggression, and trait anger as well with a higher number of RTBs.

Materials and Methods

Sample

This study was performed at the Division for Addiction Psychiatry and the Adult Division of the Psychiatric Emergency Department of the Geneva University Hospitals, Switzerland, between November 30, 2012, and November 30, 2013. Forty-eight patients were recruited. Inclusion criteria were the presence of an SUD (related to alcohol, cannabis, cocaine, opiates, or hallucinogenic drugs) and at least 16 years of age or older (the minimum age for admission to adult healthcare departments in Geneva). Exclusion criteria were acute drug intoxication at baseline examination, intellectual disability, and language barriers. Patients did not receive financial compensation for participation in this study. All the patients signed an informed consent in order to participate. This study was approved by the local Research Ethics Committee.

Assessment and Instruments

Sociodemographic data and history of SAs were collected by the principal investigator. Posner and colleagues' nomenclature was used to define SA: "a potentially self-injurious behavior, associated with at least some intent to die, as a result of the act. Evidence that the individual intended to kill him/herself, at least to some degree, can be explicit or inferred from behavior or circumstance. A suicide attempt may or may not result in actual injury" (Posner et al. 2007). The impulsivity trait was assessed using the *Barratt Impulsiveness Scale*, version 11 (BIS-11) (Patton et al. 1995); anger was measured using the *State and Trait Anger Expression Inventory*, version 2 (STAXI-2) (Borteyrou et al. 2008; Spielberger 1999); and aggression was determined using the *Life History of Aggression* instrument (Coccaro et al. 1997).

We utilized an operational definition of RTB as "any consciously, or non-consciously controlled behavior with a perceived uncertainty about its outcome, and/or about its possible benefits, or costs for the physical, economic or psycho-social well-being of oneself or others" (Trimpop 1994). Presence of RTBs (gambling, binge drinking, risky sexual behavior, dangerous driving behavior, and extreme sport activities) was determined by personal interviews. Participants were administered the Mini-International Neuropsychiatric Interview (MINI; French version 5.0.0) for presence of an SUD and other diagnostic psychiatric screening according to DSM-IV and ICD-10 criteria (Sheehan et al. 1998). Interviews and diagnoses were performed by Dr. A. Costanza.

Statistical Analyses

Bivariate associations were performed using the Wilcoxon test with continuity correction for group comparisons, given the score distributions were skewed. For the same reasons, Spearman correlations were computed for continuous variables. To test the association between a history of lifetime SAs and RTBs, logistic regression was performed using a history of lifetime SAs as the dependent variable and sex, age, and number of RTB types entered as independent variables. Other independent variables were not included due to the small sample and effect sizes. All statistical analyses were conducted using R 3.5.2 (R Core Team 2018).

Results

The sample comprised of 48 patients who ranged in age from 19 to 59 years (mean, 39.8 years; median, 42.5 years; standard deviation, 10.9 years). Of the population, 60.4% were men (Table 1). In this sample, alcohol-related SUDs were present in 66.7% of patients, cannabis-related SUDs in 50%, cocaine-related SUDs in 31.3%, opiates-related SUDs in 20.8%, and hallucinogens-related SUDs in 10.4%. Multiple (≥ 2) SUDs were found in 56.3% of the sample. When evaluating SB, 47.9% of the sample did not have amnestic history of SAs, and 52.1% committed at least one SA. The majority of the patients (83.3%) reported at least one RTBs. Among patients with RTBs, binge drinking was present in 75% of the sample, dangerous driving and risky sexual behaviors were present in 37.5%, gambling in 32.5%, and extreme sport activities in 12.5%. The most prevalent psychiatric diagnoses associated with SUDs were episodes of major depression (58.3%), conduct and antisocial personality disorder (41.7%), and bipolar disorder (24.1%).

Table 1 Characteristics of the sample population

Variable	Categories	Value (*n* (%))
Gender	Female	19 (39.6%)
	Male	29 (60.4%)
Substance use disorder	Alcohol	32 (66.7%)
	Cannabis	24 (50%)
	Cocaine	15 (31.3%)
	Hallucinogens	5 (10.4%)
	Opiates	10 (20.8%)
Suicide attempts	Amnestic history	23 (47.9%)
	Committed at least 1	25 (52.1%)
Risk-taking behavior (RTBs)	Binge drinking	30 (75%)
	Dangerous driving	15 (37.5%)
	Extreme sports	5 (12.5%)
	Gambling	13 (32.5%)
	Risky sexual behavior	15 (37.5%)
Psychiatric diagnosis	Bipolar disorder	13 (24.1%)
	Conduct and antisocial personality disorder	20 (41.7%)
	Major depression	28 (58.3%)

History of lifetime SAs was significantly associated with higher levels of impulsivity (Wilcoxon rank sum test with continuity correction, p value = 0.013). This was confirmed by the positive Spearman's rank correlation between the number of SAs and levels of impulsivity (p value = 0.002). History of lifetime SAs was significantly associated with higher levels of aggression (Wilcoxon test, p value = 0.017). A significant association was not found with levels of anger trait (Wilcoxon test, p value = 0.231). History of lifetime SAs was associated with a higher number of RTBs in the same individual (logistic regression, odds ratio, 2.56, p value = 0.005; Table 2). Other independent variables were tested but not shown due to the small sample and effect sizes. For example, since the bivariate association between the Beck Depression Inventory (BDI) and lifetime SA was not statistically significant (OR = 1.03) and with a very small effect size (OR = 1.03), BDI was not included in the logistic regression in order to keep power to an acceptable level. A higher number of RTBs in the same individual correlated with a higher impulsivity level (Spearman's rank correlation, p value = 0.004), but not with levels of aggression and anger.

Discussion

This study investigated SB and SUD-related endophenotypes, such as impulsivity, aggression, trait anger, and RTBs, in 48 patients with SUDs in relation to lifetime history of SAs. Disorders

Table 2 Logistic regression: association between a history of lifetime suicide attempts (dependent variable) and number of risk-taking behaviors (RTBs)

Independent variables	OR	95% CI	*z* value	*p* value
Gender				
Female	1			
Male	0.82	[0.17;3.74]	−0.26	*0.797*
Age	0.99	[0.92;1.05]	−0.42	*0.672*
Number of RTBs	2.56	[1.42;5.44]	2.79	*0.005*

OR odds ratio, *CI* confidence interval

related to alcohol, cannabis, cocaine, opiates, and hallucinogenic drugs were included in this investigation. Lifetime SAs were found to be significantly associated with both higher impulsivity and higher aggression, but not with trait anger. A higher number of RTBs were associated with lifetime SAs and higher impulsivity, but not with aggression and trait anger.

These results are consistent with data in the literature, which is largely focused on alcohol-related disorders (Conner et al. 2006; Haw et al. 2001; Khemiri et al. 2016; Koller et al. 2002; Sher et al. 2005; Wojnar et al. 2009). Alcohol-dependent patients who commit SAs have shown greater impulsivity (Wojnar et al. 2009), aggression (Sher et al. 2005), or both (Haw et al. 2001; Koller et al. 2002). Impulsivity and aggression were analyzed separately in these studies. However, in a recent cohort of alcohol-dependent patients (Khemiri et al. 2016), these previously coupled traits were found to be associated with elevated SB risks. Aggression was assessed both as an expression of violent behavior and as exposure to violence in childhood and adulthood (Khemiri et al. 2016), and results were consistent with well-documented data that show an association between childhood abuse and SB in SUDs (Darke and Torok 2013; Jakubczyk et al. 2014; Marshall et al. 2013). Aggression tended to be greater in alcohol-dependent patients with a history of violent SAs (Koller et al. 2002). This is of particular interest because, although SUDs are considered predisposing factors to violent and medically serious SAs (Conner et al. 2003; Elliot et al. 1996), specific risk factors associated with this subgroup remain overlooked (Icick et al. 2018). Alcohol-related aggression, intended as an acute state leading to disinhibition, has been shown to characterize impulsive SAs (conceptualized as committed by alcohol-dependent patients without lifetime SI) versus non-impulsive or pre-contemplated SAs (made by alcohol-dependent patients with lifetime history of SI) (Conner et al. 2006). Instead, in the same study (Conner et al. 2006), aggression and co-morbidity between alcohol dependence and illicit drugs did not distinguish impulsive versus pre-contemplated SAs. This agrees with our results related to aggression including patients with SUDs that are not only alcohol-related.

Greater impulsivity, aggression, and SB risk have been found in prisoners who were substance abusers and not in those who were not substance abusers (Cuomo et al. 2008). However, the associations between these traits and SBs were not analyzed, and their excess could be attributed to a number of life history and context-related features peculiar to that cohort. A greater impulsivity has been found in outpatients with SUDs and lifetime SI and SAs, yet only motor impulsivity was associated with SI, although aggression was not studied (Rodríguez-Cintas et al. 2018).

A significant relationship was not found between a history of lifetime SAs and the level of trait anger. This finding contrasts with those found previously, showing greater trait anger in alcohol-dependent patients who committed SAs (Haw et al. 2001; Sharma and Salim 2014). The theoretical premises of the significance of trait anger in SBs (Giegling et al. 2009; Hawkins et al. 2014; Sadeh and McNiel 2013) and in SUDs (Coccaro et al. 2016; Cougle et al. 2017; Goldstein et al. 2005; Zarshenas et al. 2017) and their associations with impulsivity and aggression traits have been documented, particularly with SUDs (Coccaro et al. 2016; Giancola 2002; Parrot and Zeichner 2002; Walitzer et al. 2015). Nevertheless, the role of this endophenotype in predisposing patients with SUDs to SBs has been less investigated than for impulsivity and aggression. Moreover, to our best knowledge, data including any SUD except for alcohol cannot be found.

A history of lifetime SAs was significantly correlated to the number of RTBs in the same individual with an SUD. The literature documents a greater risk of SB among patients with SUDs and RTBs, including gambling (Penfold et al. 2006; Cook et al. 2015), binge drinking

(Byeon et al. 2018; Husky et al. 2013), risky sexual behavior (Bae et al. 2005; Eaton et al. 2011; Epstein and Spirito 2010; Houck et al. 2008; Husky et al. 2013; Thullen et al. 2016), and dangerous driving behavior (Holland et al. 2014; Patel and Luckstead 2000). However, the majority of these studies included adolescents and possibly a small number of adult patients (Penfold et al. 2006; Holland et al. 2014; Husky et al. 2013; James et al. 2014).

A higher number of RTBs in an individual with SUDs correlated with a higher level of impulsivity, but not with levels of aggression or anger. Impulsivity and RTBs commonly co-occur (Blanco et al. 2009; Dantas-Duarte et al. 2016; Dir et al. 2014; Dougherty et al. 2015; Dudek et al. 2016; James et al. 2014; Kahn et al. 2002; Zuckerman and Kuhlman 2000). It has been proposed that impulsivity and RTBs, although overlapping from a psychopathological point of view, are regulated by distinct neuronal mechanisms, and it appears that they develop independently (Harden and Tucker-Drob 2011; Nigg 2017). As seen in those clinical studies, neurobiological correlates of developing RTBs, impulsivity, SUDs, and SB have been more deeply investigated in adolescence, during the "temporal gap" that can occur between the full maturation of impulse control circuitry and the affective system promoting reward-seeking and risk-taking (Dougherty et al. 2015; Geier and Luna 2009; Steinberg 2010). Our findings are not in agreement with the literature which describe the roles of aggression (Zuckerman and Kuhlman 2000) and anger (Schwebel et al. 2006) in predicting RTBs. In our sample of individuals with SUDs, those with a higher number of RTBs and at higher risk of SAs were more impulsive, but they were not the more aggressive or angry ones. Unfortunately, our sample size was small and did not allow us to test the interactions beteween the higher numbers of RTBs and the higher levels of impulsivity in predicting SA risk.

The potential opportunity of detecting higher-risk SUD subgroups of patients rejoins the part of the introduction dedicated to the necessity to refer to some SB euristic comprehensive models, with the intention to transpose into the clinical practice some postulated or acquired data. For example, (1) in the case of SUDs patients with comorbidity for major depression, the presence of high levels of impulsivity and aggression may constitute an important alarm bell, because the latter play a relevant role in triggering SB in depressed patients (Chachamovich et al. 2009). This seems particularly significant in younger patients, in whom impulsivity and aggression were shown underlying both the association and the temporal relationship between suicide and depression (McGirr et al. 2008). The latter argument justified the differences in the SB risk between the subjects who presented impulsivity and aggression compared to those who did not present them (McGirr et al. 2008). Moreover, (2) this approach addressing the association between psychiatric disorders and/or SUDs and SB risk by taking into account specific dimensions possibly underlying SB, as mediation or moderation factors, may enlarge and enriched in a pragmatic way the span of clinical means that a clinician can utilize.

An important limitation of this study is the exiguity of the sample size, which limits the generalizability of our findings and restricts feasible analyses. In particular, it excludes those addressing endophenotype interactions or subgroups by SA type. Moreover, the cross-sectional and retrospective design lacks information that could be inferred from prospective data. Another limitation was that participants were drawn from a treated population, and since treated populations are inherently biased, it follows that findings from such groups are only generalizable to other treated populations who share the same characteristics. Finally, a

psychometrically rigorous tool was not employed to assess RTBs in this study. On the other hand, the strengths of this study are represented by the inclusion of SUDs related to all substances of the concerned population (patients seeking a specialized service in SUD treatment and emergency services). The latter factor can facilitate comparisons between our findings and data from mixed mental health settings.

Conclusions

This study is an exploratory report, which compared a group of SUD patients having a lifetime history of SAs to SUD patients without a lifetime history of SAs, in relation to impulsivity, aggression, trait anger, and RTBs. From a clinical point of view, our work and others indicate that assessing impulsivity and impulsivity-related endophenotypes will contribute to refining SB risk evaluation in patients with SUDs, by detecting higher-risk SUD subgroups of patients. In addition to psychometric evaluation, assessment will be further refined in the future with the identification of bona fide biomarkers which underlie these endophenotypes. To this end, we have collected blood samples from this study population for genetic analyses. Future laboratory work will be focused on further characterizing the endophenotypes, which predispose patients to SAs. Longitudinal and case-control studies including broader cohorts of patients with SUDs are needed. Future directions can address (a) the quantification of interactions between the various endophenotypes in increasing SB risk, and (b) the relevance of SUDs in determining SA subgroups, such as medically serious SAs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Informed Consent Informed consent was obtained from all patients for being included in the study.

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