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Are major repeater patients addicted to suicidal behavior?

¿Están los grandes repetidores adictos a los comportamientos suicidas?

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Resumen

La escasa literatura existente sugiere que los "grandes repetidores" (individuos con 5 intentos de suicidio a lo largo de la vida) pueden ser considerados "adictos" a los comportamientos suicidas. Este estudio explora si los grandes repetidores sufren una adicción a los comportamientos suicidas usando 7 criterios: tolerancia (Criterio 1), abstinencia (Criterio 2), pérdida de control (Criterio 3), problemas para dejar de tener o disminuir esos comportamientos (Criterio 4), uso de tiempo excesivo (Criterio 5), reducción importante de actividades (Criterio 6), y consecuencias físicas adversas (Criterio 7). La dependencia total a los comportamientos suicidas era diagnosticada si el sujeto cumplía 3 o más de los 7 criterios en los últimos 12 meses. Se trata de un estudio transversal realizado íntegramente en el Hospital Universitario Puerta de Hierro (Madrid, Spain), donde fueron recrutados 118 individuos que se presentaron en los servicios de urgencia por un intento de suicidio, incluyendo 8 grandes repetidores (7%, 8/118), siendo todos ellos mujeres. Se estimó si había asociaciones estadísticamente significativas y el tamaño del efecto con la razón de oportunidades y los intervalos de confianza (95%) entre cada uno de los criterios de adicción a los comportamientos suicidas, la dependencia fisiológica, y la dependencia total. Nuestra hipótesis se verificó, ya que los grandes repetidores presentaron con mayor frecuencia criterios para la dependencia a las conductas suicidas, OR=62.9 (6.4-615). Usamos un modelo de regresión logística para estimar el riesgo de la asociación entre ser un gran repetidor y la dependencia total corregido por diferentes variables. La edad, el trastorno de pánico sin agorafobia, el trastorno de personalidad límite, la historia de ingresos previos en unidad de hospitalización psiquiátrica, y la dependencia total a los comportamientos suicidas fueron introducidos como variables independientes y la categoría de grandes repetidores como variable dependiente. El modelo final seleccionó la dependencia total y la edad como las variables estadísticamente significativas en el último paso. En conclusión, nuestro estudio sugiere que los grandes repetidores podrían ser individuos adictos a los comportamientos suicidas.

Palabras clave: grandes repetidores, comportamiento suicida, adicción, trastorno de personalidad límite.

Abstract

The literature provides support for the hypothesis that some major repeaters (individuals with ≥ 5 lifetime suicide attempts) are addicted to suicidal behavior (SB). This study explores whether major repeaters are addicted to SB or not using 7 criteria: tolerance (Criterion 1), withdrawal (Criterion 2), loss of control (Criterion 3), problems in quitting/cutting down (Criterion 4), much time spent using (Criterion 5), substantial reduction in activities (Criterion 6), and adverse physiological/physical consequences (Criterion 7). Total dependence on SB was indicated by the presence of 3 or more of the 7 criteria in the last 12 months. This cross-sectional study at Puerta de Hierro University Hospital (Madrid, Spain) recruited 118 suicide attempters including 8 major repeaters (7%, 8/118), who were all females. The association between each SB addiction criterion, physiological dependence and total dependence with major repeater status was tested for significance and for effect size with odds ratios (ORs) and their 95% confidence intervals. As hypothesized, major repeaters met significantly higher frequency of criteria for total dependence on SB, OR=62.9 (6.4-615). A backward stepwise logistic regression model was used to provide an OR between major repeater status and total dependence status corrected by confounding variables. Age, panic disorder without agoraphobia, borderline personality disorder, history of psychiatric inpatient admission, and total dependence on SB were introduced as independent variables with major repeater status as the dependent variable. The model selected total dependence and age as the remaining significant variables in the last step. Accordingly, major repeaters appear to be addicted to SB.

Key words: major repeaters, suicidal behavior, addiction, borderline personality disorder.

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Addictions have traditionally been restricted to substance use disorders. However, Goodman adapted and merged the DSM-IV criteria of substance dependence with those of pathological gambling (Goodman, 1990). Thus, in his seminal paper, he expanded the focus of addictions by defining a behavioral addiction “as a process whereby a behavior [...] is employed in a pattern characterized by loss of control and continuation despite significant negative consequences. It is not the type of behaviour, its frequency or its social acceptability that determines whether a behaviour pattern qualifies as an addiction [...]”. His statement preceded a Copernican change that allowed expanding addictions to include behavioral addictions such as internet use, gambling, shopping, sun-tanning, exercise, work, or even love and sex (Cassin and von Ranson, 2007; Favazza, 1989; Goodman, 1992; Kourosh, Harrington, and Adinoff, 2010; Reynaud, Karila, Blecha, and Benyamina, 2010; Sanchez-Carbonell, Beranuy, Castellana, Chamarro, and Oberst, 2008; Tantam and Whittaker, 1992; Tao et al., 2010). Indeed, behavioral addictions are frequent, can be conceptualized as impulse-control disorders, and share many characteristics with substance addictions (i.e., tolerance, withdrawal, and relapse) (Grant, Brewer, and Potenza, 2006). Substance and behavioral addictions share common neurobiological and genetic underpinnings, and psychosocial factors may account for the variability of expressions of addictions within individuals (Ibanez Cuadrado, 2008; Shaffer et al., 2004). In this context, it is surprising to find the paucity of studies testing the hypothesis that some individuals could also be addicted to the repetition of suicidal behavior (SB).

In 1998, Tullis (1998) proposed a theory of suicide addiction that described individuals addicted to SB as having three characteristics: the presence of multiple addictions, mood disorder, and childhood trauma. Until recently, the only study that tested this compelling hypothesis was a report of three cases (Mynatt, 2000). One can review the literature on repeated SB that was collected without the influence of Tullis’s model to explore whether Tullis’s proposed characteristics are related to the repetition of SB or not. Our reading of the literature supports Tullis’s hypothesis for two characteristics; both childhood abuse and addictions are associated with repetition of suicidal behavior (Monnin et al., 2011; Mynatt, 2000; Ystgaard, Hestetun, Loeb, and Mehlum, 2004). The evidence for mood disorders is, however, more controversial. For instance, Kreitman and Casey (Kreitman and Casey, 1988) reported that the presence of mood disorders was negatively associated with repetition of suicidal behavior. Furthermore, one of our studies recently found that both childhood abuse and substance dependence, but not mood disorders, were associated with major repetition of suicide attempts (Blasco-Fontecilla et al., 2014b).

In 2012, we refined Tullis’s theory of suicide addiction by proposing that major repetition of SB could also be con-

sidered as another behavioral addiction within Goodman’s paradigm (Blasco-Fontecilla et al., 2012). Major repeaters (individuals with ≥ 5 lifetime suicide attempts) represent approximately 10% of all suicide attempters (Barnes, 1986; Bille-Brahe et al., 1996; Kreitman and Casey, 1988). These individuals are at higher risk of suicide completion (King et al., 1995; Lewinsohn, Rohde, and Seeley, 1994), are heavy consumers of health resources, and pose a challenge to clinicians (Kreitman and Casey, 1988). We have recently proposed that they are a distinct phenotype sharing some common features with patients presenting addictions (Blasco-Fontecilla et al., 2014b). In this first study comparing with non-major repeaters (< 5 suicide attempts), major repeaters were more likely to be female and more likely diagnosed with anorexia nervosa or substance dependence, and had higher levels of trait anger with lower levels of anger expression-out. In a second study, we demonstrated that major repeaters provided different reasons than non-major repeaters for the more lethal suicide attempts. Major repeaters significantly more frequently endorsed automatic positive reinforcement (“To feel something, because you felt numb or empty”) as an explanation for their SB than the remaining suicide attempters. We found that relieving emptiness may be an important, but not the only, pathway to major repetition of suicide attempts (Blasco-Fontecilla et al., 2014a). The main objective of the present study is to further test our hypothesis that major repeaters can include individuals who appear addicted to SB. To do so, we modified DSM-IV-TR criteria for substance dependence to apply them to SB. We call them “criteria for dependence on SB”. The study hypothesis is that the criteria for dependence on SB will be significantly more frequent in major repeaters than in non-major repeaters.

Method

Sample and procedure

Between June 1, 2013, and March 31, 2014, 118 suicide attempters admitted to the emergency department at Puerta de Hierro University Hospital (Madrid, Spain) were recruited. All participants were assessed using a protocol designed to collect information regarding socio-demographic and clinical variables. A suicide attempt was defined as a self-destructive behavior with intent to end one’s life (O’Carroll et al., 1996; Silverman, Berman, Sanddal, O’Carroll, and Joiner, 2007). To be included patients had to have an age ≥ 18 years, and be Spanish-speaking. All participants signed an informed consent form after the explanation of the study objective and procedures. The local Ethics Committee (Puerta de Hierro University Hospital) approved the study (PI 108-12, *Meeting number 285, date: 25th February, 2013*).

Psychiatric diagnoses using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) were provided by trained psychiatrists and psychiatry residents. Se-

Table 1
Criteria for dependence on suicidal behavior

	DSM-IV-TR criteria for substance use in the last year	Questions modified for SB during the last year*
1	<i>Tolerance, as defined by either of the following:</i> A need for markedly increased amounts of the substance to achieve intoxication or desired effect, or Markedly diminished effect with continued use of the same amount of the substance	(a) Do you feel that you need to spend more and more time on the suicidal behavior in order to feel good, be less anxious, or decrease emotional pain? or (b) Do you feel that the cathartic effect of suicidal behavior decreased in each subsequent suicide attempt?
2	<i>Withdrawal, as manifested by either of the following:</i> The characteristic withdrawal syndrome for the substance, or The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms	(a) Do you feel bad or anxious or any other symptom when you wish to attempt suicide but cannot do so at the time? (b) Do you attempt suicide in order to avoid these symptoms?
3	<i>Loss of control</i> The substance is often taken in larger amounts or over a longer period than was intended	Are suicide attempts more frequent, more severe or longer lasting than initially planned?
4	<i>There is a persistent desire or unsuccessful efforts to cut down or control substance use</i>	Have you tried to stop attempting suicide, but still continue?
5	<i>A great deal of time is spent on activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use of the substance (e.g., chain-smoking), or recovering from its effects</i>	Have you ever missed a social engagement, work, school, or other recreational activities because you were involved in activities related to suicidal behavior (e.g., storing pills, wrist-cutting) or recovering from the suicidal behavior instead?
6	<i>Compulsive use</i> Important social, occupational, or recreational activities are given up or reduced because of substance use	Have you ever gotten into trouble at work, with family, or with friends due to your suicidal behavior?
7	<i>Continued use despite adverse consequences</i> The substance use is continued despite knowledge of having a persistent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)	Do you continue to attempt suicide despite knowing that it is bad – either psychologically or physically – for you?

Note. SB: suicidal behavior.

* These questions were originally written in Spanish [supplementary material provides the questions in Spanish].

verity and lethality of suicide attempts were measured by the Lethality Rating Scale (LRS). The LRS (Beck, Resnik, and Lettieri, 1974) rates the medical consequences of different suicide methods ranging between zero (no consequences) and eight (death). A score > 2 suggests a high lethality attempt, and usually indicates the need for major medical treatment.

Our criteria for dependence on SB are described in Table 1. There are 7 individual criteria (Criterion 1, tolerance; Criterion 2, withdrawal; Criterion 3, loss of control; Criterion 4, problems in quitting/cutting down; Criterion 5, much time spent using; Criterion 6, substantial reduction in activities; Criterion 7, adverse physiological/physical consequences). Then, we also considered the presence of physiological dependence (either Criterion 1 or 2 is present) and total dependence (following our “criteria for dependence on SB”, based on the DSM-IV, the dependence on or addiction to SB was indicated by the presence of three or more of the criteria listed above in the last 12 months). Our criteria are similar to those used to evaluate addiction to sun-tanning (Kourosh, Harrington, and Adinoff, 2010).

Statistical analyses

As in our two prior studies of SB addiction (Blasco-Fontecilla et al., 2014a; Blasco-Fontecilla et al., 2014b), patients were divided into major repeaters (≥5 lifetime suicide at-

tempts) and non-major repeaters (<5 lifetime suicide attempts). The association between the presence or absence of an individual SB addiction criterion, physiological dependence and total dependence on SB with the presence or absence of major repeater status was tested for significance with the Fisher exact test and for effect size with odds ratios (ORs) and their 95% confidence intervals. These are univariate ORs not controlled for confounding variables. Similarly, the Fisher exact test and univariate ORs were used to test for the association between dichotomous sociodemographic variables (Table 3) and clinical variables (Table 4). The association between age and major repeater status was tested with a t Student test. It was planned that any of these confounding variables that reached significance would be entered as independent variables in a logistic regression model with presence or absence of major repeater status as the dependent variable and presence or absence of total dependence on SB as the independent variable. In that way, the logistic regression model would provide an OR between major repeater status and total dependence status corrected by confounding variables. Due to the small sample size a backward stepwise logistic regression model was selected. A $p < 0.05$ was selected as the cut score for introducing variables in the stepwise procedure. All analyses were carried out using SPSS v.20 (Macintosh).

Table 2
Characteristics of major vs non-major repeaters using criteria modified for dependence on SB

	Percentage (%) of major repeaters (n=8)	Percentage (%) of non-major repeaters (n=110)	FET	OR (95% CI)
Criterion 1 (Tolerance)	100	15	<0.001	**
Criterion 2 (Withdrawal*)	43	2	0.002	36.4 (4.7-282.5)
Criterion 3 (Larger, longer)	43	4	0.006	17.8 (2.9-107.8)
Criterion 4 (Quitting/cutting down)	71	9	<0.001	24.2 (4.2-146.2)
Criterion 5 (Much time spent using)	29	4	0.05	9.5 (1.4-64.9)
Criterion 6 (Substantial reduction in activities*)	14	3	0.24	5.2 (0.5-58.7)
Criterion 7 (Physiological/physical adverse consequences)	83	6	<0.001	75.8 (7.6-756.7)
With Physiological Dependence: Evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)	86	8	<0.001	66.7 (7.1-625.2)
Total Dependence	83	7	<0.001	62.9 (6.4-615)

Note. *More than 25% of cells have expected cell counts less than 5.
** OR could not be calculated because one or more cells has a zero value.
Significant results are in **bold**.

Results

Most (92%) suicide attempters tried to kill themselves by drug overdose; lethality, as measured by the LRS, was low (1.76 ± 1). The prevalence of major repeaters was 7% (8/118) and of non-major repeaters was 93% (110/118).

As hypothesized, major repeaters had significantly higher frequency of criteria for dependence on SB (Table 2). Criteria 1 to 5 and 7 were significantly more likely among major repeaters with ORs ranging between 9.5 for Criterion 5 and 36.4 for Criterion 2. Criterion 6 (substantial reduction in activities), was the only criterion with a non-significant OR [5.2 (0.5-58.7)]. Most importantly, all major repeaters displayed tolerance symptoms (Criterion 1), and there were very significant ORs for physiological dependence on SB, 66.7 (CI 7.1-625.2) and total dependence on SB, 62.9 (6.4-615).

Table 3 compares major versus non-major repeaters with regard to socio-demographic characteristics. Major repeaters had significantly younger mean ages than non-major repeaters. All major repeaters were females. This provided an almost-significant p value, but an OR was not calculated because of the presence of null values in the male sex.

Table 4 compares major versus non-major repeaters with regard to clinical characteristics. Major repeaters were more likely to have a diagnosis of panic disorder without agoraphobia, borderline personality disorder (BPD), and a history of psychiatric inpatient hospitalization.

Age, diagnosis of panic disorder without agoraphobia, BPD, and history of psychiatric inpatient admission were introduced with total dependence on SB as independent variables in the backward stepwise logistic regression mo-

Table 3
Comparison of major repeaters versus non-major repeaters: socio-demographic characteristics

	Percentage (%) of major repeaters (n=8)	Percentage (%) of non-major repeaters (n=110)	Significance* (p-value)
Sex			0.057**
Female	100	67	
Male	0	33	
Ethnicity			
Caucasian	88	91	
Other	12	9	
Educational level			
Below university	75	70	
University	25	30	
Living with*			
Partner/spouse with/without children	57	49	
Relatives	43	34	
Other (friends, alone)	0	17	
Socioeconomic level*			
Low	57	74	
Medium	29	22	
High	14	4	
	Mean (SD)	Mean (SD)	t***
Age	30.6 (8.5)	39.2 (14.4)	0.025

Note. SD: standard deviation.
*Only significant or close-to-significant p values are described.
**Fisher exact test was used as more than 20% of cells have expected cell counts less than 5.
***t test with unequal variance was used.

Table 4
Comparison of major repeaters versus non-major repeaters: clinical characteristics

	Percentage (%) of major repeaters (N=8)	Percentage (%) of non-major repeaters (N=110)	Significance* (p-value)	OR (95% CI)
Axis I Diagnosis	88	87		
Generalized Anxiety Disorder	13	48		
Manic Episode (current)	0	0		
Major Depressive Episode (current)	75	64		
Psychotic Disorder (current)	0	3		
Panic Disorder without Agoraphobia	38	7	0.02	9.0 (1.7-49.9)
Panic Disorder with Agoraphobia	0	5		
Alcohol Dependence	14	17		
Alcohol Abuse (current)	14	9		
Substance Dependence	13	6		
Substance Abuse (current)	12	6		
Eating Disorders	0	3		
Borderline Personality Disorder	50	5	<0.001	21.0 (4.0-109.4)
History of psychiatric inpatient admission	63	19	0.013	6.9 (1.5-31.6)
Family history of mental disorders	63	53		
Family history of suicidal behavior	25	16		

Note. CI: confidence interval. OR: odds ratio.

*Only significant p values are described. Fisher exact test was used as more than 20% of cells have expected cell counts less than 5.

Table 5
Backward stepwise logistic regression model for major repeaters*

	Variable	**Wald χ^2	p values	Corrected OR	95% CI
First step	Age	2.31	0.13	0.87	0.73-1.0
	Panic Disorder without Agoraphobia	0.003	0.95	1.14	0.01-109.6
	Antecedents of BPD	0.30	0.58	2.7	0.07-102.2
	History of psychiatric inpatient admission	0.18	0.66	2.0	0.08-45.5
	Total dependence on SB	3.7	0.05	83.1	0.92-7524.7
Fifth step	Total dependence on SB	11.8	0.001	208.1	9.8-4393.4
	Age	4.4	0.036	0.85	0.73-0.98

Note. SB= Suicidal behavior; BPD= Borderline Personality Disorder

*Further statistical proof of the greater importance of dependence on SB in predicting major attempter status was gained with a logistic regression model. Total dependence on SB was significant in the first step but become more significant in the fifth step only after adjusting for age. BPD was not represented in the final model, thus suggesting that the relationship between dependence on SB and major attempter status was not explained by BPD. The logistic regression model included a constant not described in the table. The Hosmer-Lemeshow test was non-significant ($\chi^2=0.727$; $df=8$; $p=0.99$), suggesting that the model fit the data well.

**Degrees of freedom=1.

del with major repeater status as the dependent variable (Table 5). In the first step, total dependence on SB was significant at 83.1 (CI 0.92-7524.7) after correcting for other confounders. The model selected total dependence and age as the remaining significant variables in the last step. The age-adjusted OR for total dependence was 208.07 (9.8-4393.43). This suggested that total dependence on SB was more important than BPD in predicting major repeater status.

Discussion

In the present study, we have further refined the concept of addiction to SB. Our findings are compatible with the hypothesis that major repeaters represent a particular suicidal phenotype characterized by being at risk of developing an addiction to SB (Blasco-Fontecilla et al., 2012, 2014b). Approximately 80% of major repeaters met an SB-modified version of the DSM-IV criteria for substance dependence. Importantly, our findings did not appear to be explained by ei-

ther socio-demographic or clinical variables, thus providing further evidence for our hypothesis that major repeaters may be a distinct clinical phenotype (Blasco-Fontecilla et al., 2012, 2014b).

The prevalence of major repeaters (7%) was fairly consistent with the literature across various countries in Europe (4.5%-16%) (Blasco-Fontecilla et al., 2014b; Haw, Bergen, Casey, and Hawton, 2007; Kreitman and Casey, 1988).

All major repeaters in our sample were women. In our French study with 372 suicide attempters, major repeaters were almost exclusively women (92%) (Blasco-Fontecilla et al., 2014b). But in the other study, the proportion of major repeaters was similar across gender (Blasco-Fontecilla et al., 2014b) which is similar to other studies of major repeaters by other authors (Haw et al., 2007; Kreitman and Casey, 1988). As our three studies of major repeaters were small and in two of them were mostly women, we cannot rule out that our hypothesis of addiction to SB as a possible pathway to explain some cases of major suicide repeaters may apply fundamentally to female major repeaters.

Quite similarly, we found differences between our study and available literature with regard to Axis I disorders. We reported here that major repeaters were more likely diagnosed with panic disorder without agoraphobia. In the French study mentioned above, however, major repeaters were characteristically more likely diagnosed with anorexia nervosa, and substance dependence (Blasco-Fontecilla et al., 2014b). In another study, no Axis I disorder differentiated between major and non-major repeaters (Blasco-Fontecilla et al., 2014a). These differences in Axis I diagnoses might be explained by methodological differences among studies. On the other hand, BPD increased the likelihood of being a major repeater 21-fold. In contrast with socio-demographic factors and Axis I disorders, studies using different methodological strategies have consistently reported an elevated rate of either disturbed personality traits or personality disorders among major repeaters. Thus, in their seminal paper, Kreitman, and Casey (1988) suggested that "personality deviations" were more likely to be core for major repeaters. More recently, we have reported that major repeaters are characterized by elevated trait anger, which is not expressed outwardly (Blasco-Fontecilla et al., 2014b).

But perhaps the most relevant finding of our study is that we confirmed our hypothesis that major repetition of suicide attempts can be conceptualized as a behavioral addiction (Blasco-Fontecilla et al., 2012). We predicted that major repeaters are suicide attempters characterized by developing dependence on SB. Indeed, except for Criterion 6, major repeaters were more likely than non-major repeaters to meet the criterion of dependence on SB. Moreover, most major repeaters presented a physiological dependence on SB. Our results suggest that Goodman's conceptualization of addiction may be correct (Goodman, 1990). Goodman conceptualized addiction as a "process whereby a beha-

avior, that can function both to produce gratification and to provide escape from internal discomfort, is employed in a pattern characterized by loss of control and continuation despite significant negative consequences", and suggested that addictive disorders may include not only substance use disorders, but also impulse control disorders, and some eating disorders, among others. Thus conceptualized, major repetition of SB could be considered a behavioral addiction.

Compared to non-major repeaters, major repeaters were more likely to positively meet the modified DSM-IV-TR Criteria 1 (Tolerance) and 2 (Withdrawal) for dependence on SB. The tolerance for SB can be explained by the progression from non-suicidal self-injury to suicide attempts (Franklin, Hessel, Prinstein, 2011), which is consistent with the theory that suicide attempters gradually lose their fear of suicide (Joiner et al., 2005; Van Orden et al., 2010). Suicide attempters who display a history of non-suicidal self-injury could be particularly at risk of developing tolerance for SB (Stanley, Gameroff, Michalsen, and Mann, 2001). As for withdrawal, in a recent study, we found that around 90% of all suicide attempters endorsed reasons associated with *automatic negative reinforcement* ("To stop bad feelings, psychological pain") to explain why they attempted suicide (Blasco-Fontecilla et al., 2014a). This finding is in keeping with the notion that most people attempt suicide for emotional purposes, such as being relieved of a painful or unbearable state (Maltsberger, 2004; Orbach, Mikulincer, Gilboa-Schechtman, and Sirota, 2003), and places psychological pain at the core of SB (Maltsberger, 2004; Orbach et al., 2003). Shneidman (Shneidman, 1993) and Tossani (Tossani, 2013) have stressed the strong link between psychological pain and SB. Furthermore, our findings are also consistent with the recent suggestion that in any addiction, negative reinforcement is the motivation that ultimately predominates (Wise and Koob, 2014). Given that most suicide attempters improve their affective state in the aftermath of the SB (Gordon et al., 2010), it is plausible that major repeaters are more likely to display withdrawal symptoms, as we reported here. Both tolerance for and withdrawal from SB might be mediated by endogenous opioids. Given that SB reduces mental pain and produces relief from negative emotions, the likely release of endogenous opioids might explain the addiction to SB (Blasco-Fontecilla, 2012, Blasco-Fontecilla, et al., 2014b) (see Figure 1).

The modified DSM-IV-TR Criteria 3 (larger, longer), 4 (quitting/cutting down), and 5 (much time spent using) were also more likely in major repeaters than in non-major repeaters. In other words, major repeaters had SBs more frequent, more severe or lasting longer than initially planned (Criterion 3), unsuccessfully tried to stop attempting suicide (Criterion 4), and had more social and familial consequences (Criterion 5) than non-major repeaters. All three criteria can be explained by the well-known loss of control of substance dependence, but also described among suicide attempters (Schnyder, Valach, Bichsel, and

Michel, 1999). Moreover, the persistent desire or unsuccessful efforts to cut down or control SB (Criterion 4), including suicidal ideation, is in keeping with the literature. In some suicide attempters, suicidal ideation waxes and wanes, but in others, it is persistent. For instance, hopelessness and high levels of life distress have been associated with persistent suicidal ideation (Zhang, Law, and Yip, 2011). Even more convincingly, Suominen et al. (2004) reported that two-thirds (62%) of the suicides occurred at least 15 years after the first suicide attempt. As for Criterion 5 (much time spent using), some authors have previously described suicide attempters as spending a substantial amount of time in suicide-related activities such as browsing how-to websites, imagining the aftermath of death, or storing pills (Van Orden et al., 2010; Van Orden, Witte, Gordon, Bender, and Joiner, 2008).

Finally, major repeaters were more than 70 times as likely to endorse Criterion 7 (continued use despite adverse physiological/physical consequences) compared to non-major repeaters. This is in keeping with the interpersonal theory of SB (Van Orden et al., 2010). This theory posits that SBs are the result of the desire to die paired with the acquired capability for suicide, "which is composed of both increased physical pain tolerance and reduced fear of death, through habituation and activation of opponent processes, in response to repeated exposure to physically painful and/or fear-inducing experiences. In other words, through repeated practice and exposure, an individual can habituate to the physically painful and fearful aspects of self-harm, making it possible for him or her to engage in increasingly painful, physically damaging, and lethal forms of self-harm." This theory fits perfectly well with the notion that endogenous opioids could be involved in the development of an addiction to SB.

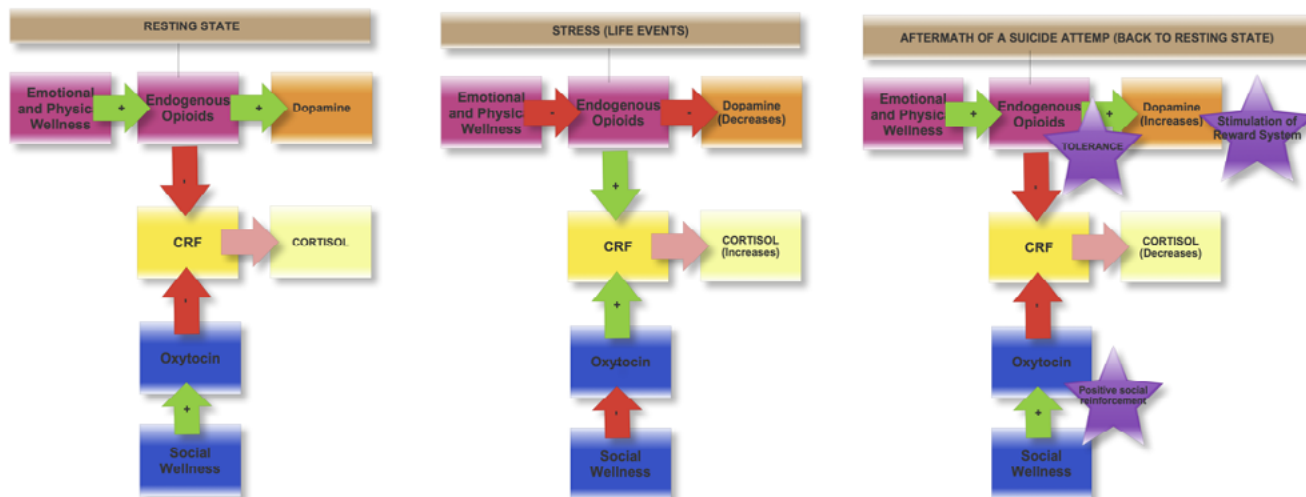
Putative mechanisms involved in the development of addiction to SB

Here, we would like to briefly review some mechanisms that may explain the addiction to SB. Figure 1 displays some of these mechanisms. From a *psychological point of view*, the cathartic effect of SB (Farberow, 1950), defined as a sudden decrease in the symptoms associated with SB following a suicidal crisis (Walker, Joiner, and Rudd, 2001), and Beck's "sensitizing" hypothesis of SB (Beck, 1996) may explain some aspects of the addiction to SB. Beck (1996) suggested that previous SB sensitizes suicidal thoughts and behaviors, such that they become more autonomous and easily precipitated. Self-aggression ameliorates the physical and emotional tension that precedes SB, depressive and anxiety symptoms, and painful emotions (i.e., hopelessness, emptiness) (Davis, 1990; Jallade, Sarfati, and Hardy-Bayle, 2005; Sarfati, Bouchaud, and Hardy-Bayle, 2003; van Praag and Plutchik, 1985; Walker et al., 2001). In a pilot fMRI study with eight female subjects, mental pain triggering SB was associated

with decreased prefrontal activity, whereas "planning and acting out suicidal impulses in response to mental pain" was related to increased activity in the frontal cortex, suggesting that SB reduces mental pain (Reisch et al., 2010). This cathartic effect can be explained by either emotional venting of an unbearable physical and/or emotional state (Jallade et al., 2005; van Praag and Plutchik, 1985), or mobilization of interpersonal support (e.g., caring family, medical attention) (Jallade et al., 2005; Walker et al., 2001). Indeed, SB can be used as a signaling (warning) strategy within the "bargaining model" of depression, which suggests that SB is a way to impose costs to the social group – family, friends, colleagues – where there is a conflict (Hagen, 2003). In this context, some suicide attempters might raise support from their relatives, and therefore, gain a positive reinforcing effect from SB.

In this regard, Stanley et al. (2001) suggested that suicide attempters with a history of self-mutilation are a unique sub-population of suicide attempters who use self-mutilation to deal with mental pain. Esposito, Spirito, Boergers, and Donaldson (2003) suggested that multiple suicide attempters may use self-mutilating behaviors as a way of self-regulating their negative emotions in the short term. In the long term, however, self-mutilating behaviors increase negative affectivity and become another stressor (Linehan, 1993). Esposito et al. (2003) suggested that suicide attempts may then replace self-mutilation as a way of modulating negative emotions in multiple-suicide attempters. In a study comparing 35 suicide ideators and 32 attempters, suicide attempters, relative to suicide ideators, were less likely to display anger after an acute suicidal episode (Negron, Piacentini, Graae, Davies, Shaffer, 1997). Therefore, suicide attempts "may acquire negatively reinforcing properties much in the same way as self-mutilating behavior, thereby increasing the chance that a suicide attempt may be used to modulate negative emotions in the future". In other words, after an initial suicide attempt, suicide repetition may become a coping strategy for dealing with anger, anxiety, and other painful emotions. Beck (1996) suggested that previous SB sensitizes suicidal thoughts and behaviors, such that they become more autonomous and easily precipitated. As suicidal episodes become more easily triggered by stressful life events, they also become more severe and persistent. In other words, repetition of SB may have a sensitization effect. Beck's "sensitizing" hypothesis of SB has gained some empirical support (Bradvik and Berglund, 2011; Joiner and Rudd, 2000; Joiner, Rudd, Rouleau, Wagner, 2000). And even after prolonged suicide-free periods, there is the risk of relapse, often precipitated by the same suicide-associated life events, probably in a similar way to that of drug addiction (Hyman, 2005).

From a *neurobiological (neurotransmitter) point of view*, it is interesting to bear in mind that humans and animals share



1. Graphical representation of the putative mechanism underlying the addiction to SB.

In the resting state (a), some hormones and neurotransmitters – oxytocin, opioids, corticotropin-releasing factor (CRF), and mesocorticolimbic dopamine – are in equilibrium, and the individual feels good. Given the deleterious personal background of most major repeaters, it is probable that they achieve homeostasis via allostatic changes. In a previous study, we reported that major repeaters were characterized by histories of childhood maltreatment and neglect (Grassi-Oliveira et al., 2008). Facing adversities during childhood, an individual is forced to adapt and when allostatic response is inefficient, the individual develops an allostatic load (Grassi-Oliveira et al., 2008). In other words, major repeaters might continue to have altered (allostatic) neurotransmitter equilibrium in the resting state. Facing acute stressful life events (b), the CRF increases and activates the production of cortisol, and decreases the release of opioids and dopamine. These changes are paralleled by emotionally negative symptoms at the clinical level. Vulnerable individuals might attempt suicide when facing these stressful life events. In the aftermath of a suicide attempt, the organism goes back to the resting state and there is a restoration of oxytocin's, opioids', and dopamine's basal levels. Although speculative, it is possible that the addiction to SB is an example of the incapability of returning to homeostasis, driven by allostatic negative-reinforcement processes.

major neurobiological changes in substance use disorders, including a compromised reward system (dopamine and opioid peptides), overactivated brain stress system (corticotropin-releasing factor, CRF), and dysregulation of orbitofrontal/prefrontal cortex function and amygdala (Koob, 2006; Wise and Koob, 2014). In the light of our findings, it is reasonable to hypothesize that the addiction to SB might also involve a compromised functioning of the brain's motivational systems, including the mesocortical dopamine reward system, the endogenous opioid systems (Grigson, 2002; Volkow and Wise, 2005; Wise and Koob, 2014), and an overactivation of the stress system (Lovallo, 2006; Wise and Koob, 2014). Immediate relief of mental pain is probably associated with endogenous opioid release in the central nervous system, as is the case in self-mutilation (Hicks and Hinck, 2008). Several authors have demonstrated elevated endogenous opioid release following stressful events. For instance, Christie and Chesher (1982) showed that chronic stress in mice produces opioid dependence. Coid, Allolio, and Rees (1983) also reported that prolonged mutilating elevates met-enkephalins. This opioid release may ultimately produce tolerance and addiction in vulnerable subjects (Blasco-Fontecilla et al., 2012). In addition, both acute and chronic stress increase the risk of taking drugs (Volkow and Wise, 2005), and CRF is involved in the vulnerability of relapse (Sarnyai, Shaham, and Heinrichs, 2001) and drug withdrawal (Kreek and Koob, 1998). All three systems interact in the forebrain (Lovallo, 2006; Volkow and Wise, 2005) and can be activated either by psychoactive drugs or behaviors (Shaffer et al., 2004).

Strengths and limitations

The major strength of the current study is that all psychiatrists involved in the recruitment of the sample were blind to the addictive hypothesis of SB. Indeed, the study was originally designed to validate the Personality and Life Event Scale, an instrument composed of 27 items created to improve the identification of individuals at risk of SB (Blasco-Fontecilla et al., 2012).

On the other hand, the present study suffers from the typical limitations of cross-sectional and retrospective studies ("What is the cause, and what is the effect of what?". Hjelmeland, 1996). Moreover, we also acknowledge the possibility of alternative explanations to our findings. One might think that our results are explained by the presence of BPD. However, the logistic regression model suggested that total dependence on SB was more important than BPD in predicting and is more strongly associated with major repeater status. Moreover, recent research showed that multiple suicide attempters display greater psychopathology than single suicide attempters even after controlling for BPD diagnosis, thus suggesting that multiple suicide attempter status may not be the same as BPD (Forman, Berk, Henriques, Brown, and Beck, 2004). Recently, we have also reported that emptiness was a stronger predictor of major repetition of SBs than BPD (Blasco-Fontecilla et al., 2014a). Furthermore, we didn't consider the time between episodes in our definition of major repeaters. Interestingly, in a recent study, the authors reported that the proximity in time between episodes of self-harm was a risk factor for repetition of self-harm (Spittal, Pirkis,

Miller, Carter, and Studdert, 2014). Another study limitation is the use of an adaptation of DSM-IV-TR criteria to evaluate the addiction to SB. However, a similar strategy was reported in demonstrating the addiction to sun-tanning (Kourosh et al., 2010). Finally, our study relies on a small sample size of mainly self-poisoners evaluated at the emergency department, thus limiting the generalizability of our results. In any case, we think that the sample size is large enough for a pilot study. Indeed, Hertzog (2008) stated "that a pilot study of more than 40 per group is likely to be unrealistic in terms of time and cost".

Conclusions

Our intuition that major repeaters are a particular subgroup of suicide attempters characterized by meeting the modified DSM-IV-TR criteria for substance dependence was confirmed, thus giving further support to the addiction hypothesis of SB (Blasco-Fontecilla, 2012; Tullis, 1998). This hypothesis is attractive because it provides a plausible explanation regarding individuals exhibiting a repetitive pattern of SB. The validity and reliability of these modified DSM-IV-TR criteria of SB have yet to be demonstrated. As suggested previously (Blasco-Fontecilla et al., 2014b), if our findings are replicated in larger studies, major repeaters may benefit from specific treatment regimens traditionally used for substance dependence. This is of particular relevance if we bear in mind that "addiction changes the brain" (Wise and Koob, 2014). New therapeutic pathways focused on psychological pain and feelings of emptiness might be particularly important in halting the development of addiction to SB. This might prove fundamental for the prevention of suicide, an uncovered clinical need, at least in Spain (Saiz and Bobes, 2014).

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Conflict of interest

In the last three years, Dr. Hilario Blasco-Fontecilla has received lecture fees from Eli Lilly, AB-Biotics, Janssen, Rovi, and Shire. The remaining authors report no conflict of interest.

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Supplementary Material

Table 1. Supplementary Material
Criterios para valorar la DEPENDENCIA al suicidio

El paciente ha presentado **en el último año tres (o más) de los ítems siguientes?**:

1. tolerancia, definida por cualquiera de los siguientes ítems:
 - a. una necesidad de hacer una conducta suicida (intento de suicidio o gesto suicida, especificar) para conseguir el efecto deseado (por ejemplo, aliviar tensión, tranquilizarse, disminuir sufrimiento psíquico)
 - b. el efecto “balsámico” (catártico) de la conducta suicida disminuye claramente con su repetición
2. abstinencia, definida por cualquiera de los siguientes ítems:
 - a. ¿tiene el paciente algún síntoma de abstinencia si no puede realizar la conducta suicida?
 - b. ¿realiza el paciente la conducta suicida para evitar esos síntomas de abstinencia?
3. Realiza más intentos de suicidio, durante más tiempo, o más graves de lo que inicialmente pretendía?
4. Existe un deseo persistente o esfuerzos infructuosos de controlar o interrumpir las conductas suicidas
5. Se emplea mucho tiempo en actividades relacionadas con la realización de la conducta suicida (por ejemplo, ideación, planificación, almacenar las pastillas, etc.), en la realización de la conducta (p. ej., continuamente cortarse) o en la recuperación de los efectos tras la conducta suicida
6. Reducción de importantes actividades sociales, laborales o recreativas debido a la conducta suicida
7. Se continúa realizando la conducta suicida a pesar de tener conciencia de problemas psicológicos o físicos recidivantes o persistentes, que parecen causados o exacerbados por la misma

Especificar si:

Con dependencia fisiológica: signos de tolerancia o abstinencia (p. ej., si se cumplen cualquiera de los puntos 1 o 2)

Sin dependencia fisiológica: no hay signos de tolerancia o abstinencia (p. ej., si no se cumplen los puntos 1 y 2)

Table 2. Supplementary Material
DSM-5 Criteria Adapted for Addiction to Suicidal Behavior (SB)

2 or more of the 11 diagnostic criteria in the past year

Adapted DSM-5 criteria		Questions modified for SB during the last year*
Impaired control		
1	Using in larger amounts or over a longer period of time than was intended	Are suicide attempts more frequent, more severe or longer lasting than initially planned?
2	Persistent desire or unsuccessful efforts to cut down or control substance use	Have you tried to stop attempting suicide, but are unable to stop?
3	A great deal of time is spent in activities necessary to obtain, use, or recover from the effects of the substance	Do you feel that you need to spend more and more time on the suicidal behavior in order to feel good, be less anxious, or decrease emotional pain, or to recover from the effects of suicidal behavior?
4	Cravings, or a strong desire or urge to use the substance	Do you sometimes feel a strong desire to attempt suicide, even without precipitating life events?
Social impairment		
5	Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home	Have you ever gotten into trouble at work, with family, or with friends due to your suicidal behavior?
6	Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	Do you continue to attempt suicide, even if it causes you these problems?
7	Important social, occupational or recreational activities are given up or reduced because of substance use	Have you ever missed a social engagement, work, school, or other recreational activities because you were involved in activities related to suicidal behavior (e.g., storing pills, wrist-cutting) or recovering from the suicidal behavior instead?
Risky use		
8	Recurrent substance use in situations in which it is physically hazardous	Do you attempt suicide in situations in which it is physically hazardous?
9	Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Do you continue to attempt suicide despite knowing that it is bad – either psychologically or physically – for you?
Pharmacological criteria		
10	Tolerance, as defined by either of the following: - A need for markedly increased amounts of the substance to achieve intoxication or desired effect - A markedly diminished effect with continued use of the same amount of the substance	- Do you feel that you need to spend more and more time on the suicidal behavior in order to feel good, be less anxious, or decrease emotional pain? or - Do you feel that the cathartic effect of suicidal behavior decreases with each subsequent suicide attempt?
11	Withdrawal, as manifested by either of the following: - The characteristic withdrawal syndrome for the substance - The substance (or a closely-related substance) is taken to relieve or avoid withdrawal symptoms	- Do you feel bad or anxious or any other symptom when you wish to attempt suicide but cannot do so at the time? - Do you attempt suicide in order to avoid these symptoms?

*The DSM 5 allows clinicians to specify how severe the substance use disorder is, depending on how many symptoms are identified. A mild substance use disorder is suggested by the presence of two to three symptoms, moderate by four to five symptoms and severe by six or more symptoms. Clinicians can also add as course specifiers and descriptive feature specifiers: "in early remission," "in sustained remission," "on maintenance therapy," and "in a controlled environment." The same severity and specifiers definitions can be used for addiction to SB.