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Patterns of Comorbidity of Suicide Attempters: An Update

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Abstract Between 10 and 20 million people attempt suicide every year worldwide, and suicide attempts represent a major economic burden. Suicide attempters suffer from high rates of comorbidity, and comorbidity is the rule in suicide re-attempters. Comorbidity complicates treatment and prognosis and causes a more protracted course. In the present narrative review, we included these patterns of comorbidity: intra-Axis I disorders, intra-Axis II disorders, Axis I with Axis II disorders, and psychiatric with physical illnesses. We also briefly reviewed the patterns of comorbidity in suicide re-attempters. We concluded that comorbidity at different levels appears to be the rule in suicide attempters, particularly in those who re-attempt. However, several issues deserve further research regarding the patterns of comorbidity in suicide attempters.

This article is part of the Topical Collection on *Mood Disorders*

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Introduction

Between 10 and 20 million people attempt suicide every year [1]. Suicide attempts are 10 to 40 times more frequent than suicides [2] and represent a major source of economic burden [3]. Thus, the lifetime prevalence of suicide attempts reported in the US National Comorbidity Survey was 4.6 % [4]. The risk of suicidal behavior (SB) has been associated with schizophrenia [5], bipolar disorder [6], alcohol use disorders (AUD) [7–9], major depressive disorder (MDD), and personality disorders (PD) [10]. Importantly for the present review, most suicide attempts take place in patients diagnosed with comorbid disorders [11–18]. Unfortunately, several issues regarding the impact of various comorbidity patterns of SB remain obscure.

Suicide attempters (SAs) present with significantly more severe psychopathology than psychiatric patients without SA [19]. SAs suffer from high rates of comorbidity, particularly with borderline personality disorder (BPD) and either MDD or substance use disorders (SUD)—including AUD (see [20] for a review). Indeed, patients with PDs often present with at least one Axis I disorder, particularly with either MDD or SUD, or both, thus complicating their treatment and prognosis, causing a more protracted course, and worsening treatment compliance [21]. For instance, in a sample of 68 BPD outpatients, SAs were more likely to display a comorbid SUD [22]. Moreover, the literature suggests putative additive effects between PDs and DSM-IV Axis I disorders, but the particular contribution of each disorder to the risk of SB remains unknown [10]. For instance, although MDD has traditionally been considered to have a stronger association with SB than

AUDs, the relative impact of both disorders when co-occurring in SAs is unknown [20]. Furthermore, high-lethality suicide attempts in patients diagnosed with BPD is usually a byproduct of the interaction of multiple risk factors including older age, poorer socio-economic status, longer history of treatment, and, particularly, the presence of comorbid MDD or antisocial PD [23].

The present article is aimed at reviewing patterns of comorbidity in SB with a focus on how suicide attempts are more likely in those with accompanying comorbid disorders. In our review, we will critically evaluate the literature published in the past 5 years and emphasize controversial discoveries.

Methods

This is a narrative review. Initially, we performed literature searches in PubMed for suicidal behavior (title), suicide attempt* (title), and comorbid* (title) within the last 5 years (from 2012 to 2016). A subset of the studies most closely related to our aim was selected. Studies were selected based on their innovative potential. Furthermore, we performed a manual search of studies that might be considered controversial or innovative, including some of the recent findings from our own studies.

Results and Discussion

Comorbidity Between Axis I Disorders

SAs are usually diagnosed with at least one Axis I disorder. However, psychiatric disorders rarely occur alone, and comorbidity between depression and anxiety is frequent [24]. For instance, in a study published in 1994, the authors reported that depressed patients with comorbid social phobia were more likely to attempt suicide than those without social phobia (19 versus 4 %) [25]. In a more recent study of 73 SAs who attempted suicide by burning charcoal, 40 and 38.4 % had an Axis I disorder plus comorbidity with SUD or AUD, respectively [26]. The alcohol comorbidity was restricted to males.

Among subjects with mood disorders, suicidal acts usually occur during major depressive episodes (MDEs) or mixed episodes concurrent with not only comorbid disorders, particularly BPD, anxiety disorders, and SUD but also some personality traits such as hopelessness, impulsiveness-aggressiveness, and physical illness [17]. In a sample of 157 patients who attempted suicide by paraquat poisoning in Taiwan, mood disorders (54 %), adjustment disorders (40.7 %), and SUD (39.3 %) were the most prevalent diagnoses. The authors stressed that dual diagnoses were frequent. For instance, in the 59 SUD suicide attempters, "except for two having alcohol use disorder as their sole diagnosis, all had another axis 1 psychiatric comorbidities, including 14 concurrent major depressive disorders, 18 dysthymic disorders, 22 adjustment disorders, 2 psychotic disorders, and 1 bipolar disorder" [27]. In a study examining the severity of current suicidal ideation and behaviors in a psychiatric hospital sample diagnosed with MDD alone ($n = 28$) versus MDD plus panic-agoraphobic spectrum disorders ($n = 69$), the latter group was significantly more likely to have had a history of suicide attempt and higher severity of current suicidal behavior compared with the MDD-alone group, after controlling for several clinical factors [28]. In a cross-sectional study of 991 postpartum women, those women with comorbid depression and anxiety disorder diagnosed by the Mini International Neuropsychiatric Interview (MINI) had 17 times more risk of SB using an adjusted Poisson regression model [24]. The authors also reported that women diagnosed with two or more anxiety disorders had also an increased risk of SB.

Furthermore, severe depression and alcoholism are frequently comorbid among suicidal patients, and the risk of suicide is greatest when comorbidity is present [29]. In a study comparing 318 individuals with DSM-IV MDD without a history of any AUD/SUD and 187 individuals with MDD and a history of alcohol abuse/dependence, the latter group had earlier onset, more comorbidity, and a more severe course of illness, including more frequent suicide attempts [30]. In a positron emission tomography study of the same group, the authors reported findings suggesting that the differences between these groups were accounted for by serotonin mechanisms [31]. In a recent study of 22,319 veterans discharged from acute inpatient hospitalization with non-bipolar depression and AUD, the authors concluded, as hypothesized, that when primary depression was severe enough to warrant inpatient hospitalization, a secondary diagnosis of AUD did not increase the risk for non-fatal suicide attempts [20].

Regarding patients with bipolar disorder, alcohol and drugs are often used to help ease painful symptoms or distressed mood [32]. Interestingly, in one study of our group comparing the characteristics of SAs, individuals with suicide gestures, defined as "self-injurious behavior in which there is no intent to die, but to give the appearance of a suicide attempt in order to communicate with others" [33], and individuals with both suicide attempts and gestures, the only variable that remained significant after multivariate analyses in the three groups of patients was comorbid substance abuse [34]. In other words, the only factor that was present in all kinds of patients displaying either suicide gestures or attempts, or both, was substance abuse. We suggest two putative mechanisms explaining the increased risk of suicide attempts/gestures or both: first, by mediating the relationship between impulsivity and these behaviors and, second, that those patients might be using substances as a means of self-medication. Some individuals who self-medicate might be at increased risk for SB [35].

Thus, broadly speaking, it appears that comorbidity among subjects with mood disorders increases the risk of SB, but there are several issues that deserve further research, such as the role played by comorbidity, depending on the severity of the mood disorder.

Similar to other Axis I psychiatric disorders, post-traumatic stress disorder (PTSD) increases the risk of SB [36]. In a study with 1897 Iraq/Afghanistan-era veterans, the authors reported that the comorbidity between PTSD and depression was a significant risk factor for suicide attempts [37]. Indeed, the comorbidity between depression and PTSD appears to be particularly powerful in increasing the risk of SB [38, 39]. In a systematic review of PTSD and SB, the authors concluded that even if PTSD remained an independent risk factor after controlling for depression and other comorbid disorders, depression appeared to mediate the relationship between PTSD and SB [40]. More recently, in a meta-analysis using computed meta-regression analyses to examine the impact of depression on the relationship between PTSD and SB, the authors reported that depression increased the risk of SB—with the exception of completed suicides—among patients with PTSD [36].

Moreover, patients with eating disorders are characterized by presenting frequent comorbidity [41, 42] and SB [41]. For instance, in an inpatient sample of 47 girls diagnosed with eating disorders, 72 % had depressive symptoms, 57 % had disharmonious personality development, and 23 % had substance abuse [43]. Furthermore, in a recent epidemiological study of 364 women with eating disorders, over two thirds of these patients had at least one additional disorder [41]. Contrary to their expectations, the authors did not find a relationship between Axis I comorbidity and an increased risk of SB. However, they acknowledged that they did not consider Axis II disorders in their analyses.

In our opinion, one of the most interesting papers published in the last few years about the influence of comorbidity of MDE and other Axis I disorders on the risk of SB was a case-control study of 336 retrospectively recruited first-time outpatients diagnosed with a current MDE, in which 31 (9.2 %) had attempted suicide. The authors compared SAs to non-attempters. Apart from the usual psychopathological variables included in this type of study, they included the diagnosis of autism spectrum disorders (ASD) including autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD NOS). Logistic regression analysis demonstrated that both agitation during a MDE (OR = 7.15, 95 %, CI = 2.88–17.74) and past SBs (OR = 4.32, 95 % CI = 1.70–10.98) were significantly associated with being a SA. These findings are in keeping with previous literature. However, the most interesting finding of their study was that a comorbid PDD NOS (OR = 4.04, 95 %, CI = 1.20–13.54) also increased the risk of suicide attempts. Furthermore, suicide attempts in those with PDD NOS were more lethal. These findings are particularly important, as the authors stressed that the prevalence of ASD in adults is nearly 1 %, a prevalence much higher than previously recognized [44]. Unfortunately, many patients with high-functioning ASD often stay unrecognized until late in adulthood [45]. In other words, depressed adults with ASD traits were at higher risk for suicide attempts and engaged in more lethal methods.

Another area scarce on literature is the influence of comorbidity on the risk of SB in adolescents [46]. In one of the few exceptions, in a vein similar to adults, Brent [47] reported that comorbid mood disorders and SUDs increased the lethality of suicide attempts among adolescents. More recently, in a sample of 375 adolescent SAs presenting to an urban general hospital, the authors reported, contrary to their expectations, that comorbidity patterns—including anxiety, depression, substance abuse, and disruptive behavior—did not increase medical lethality of suicide attempts [46].

Comorbidity Between Axis I and Axis II Disorders

SAs are frequently diagnosed with at least one PD. In 2001, Söderberg reported a rate of PD of 78 %, particularly BPD (55 %), in a sample of 64 consecutively admitted inpatients after a parasuicide [48]. But PDs are frequently comorbid with either Axis I disorders or another PD, thus complicating prognosis and treatment response. Indeed, comorbidity between Axis I disorders and Axis II disorders is a strong risk factor for SB [49, 50], and a key characteristic of multiple SAs (reattempters) [29, 51, 52]. Quite surprisingly, most research studies have failed to even consider the massive comorbidity of PD diagnoses with either other PDs or Axis I disorders [53]. A notable exception was two recent meta-analytic reviews on the comorbidity of PDs in mood and anxiety disorders, respectively [54, 55]. Personality may be largely mediated by other factors, including comorbid psychopathology and adverse life events [56]. Furthermore, the way PDs influence suicide risk varies depending on the underlying Axis I disorder [56], and the risk of suicide goes beyond the sum of relative risks [56]. For instance, the use of substances in BPD impairs the judgment of the individuals and enhances the risk for impulsive attempts, which may explain why BPD with SUDs shows worse suicide-related outcomes [57].

In the Collaborative Longitudinal Personality Disorders Study, the authors followed 431 participants for 10 years while considering the severity and dimensionality of the PDs. According to their results, paranoid, antisocial, borderline, histrionic, and dependent PDs emerged as independent risk factors for ever-attempting suicide, but only the severity of BPD was retained in the multivariate model [58]. In other words, the common variance underlying multiple PDs that leads to SB may be best reflected by the diagnosis of BPD. Despite these advances, the accurate identification of the more "risky" BPD patients continues to be a challenge in clinical

settings. In any case, comorbid antisocial or schizotypal features may heighten suicide risk in BPD patients [59]. Furthermore, the presence of comorbid mood disorders also increases the risk of SB. In a study of 239 consecutively admitted SAs, the 158 MDD inpatients with comorbid PD had more frequent previous suicide attempts, aggressive behaviors, and alcohol and drug use compared with the 81 patients with MDD but without comorbidity [10]. A study of a large population-based survey in Mexico described multiplicative effects of depressed mood and antisocial behavior regarding suicidal ideation, suicidal plans, and attempts [60].

In the meta-analytic study mentioned above, the authors reviewed 122 empirical papers on mood disorders plus PDs and found that cluster C PDs were more frequent in MDD and dysthymia, while cluster B and C PDs dominated in bipolar disorder [54]. There is a closer link between BPD and affective disorders [61], particularly MDD, but other frequent comorbid disorders of BPD are social phobia, panic disorder, simple phobia, PTSD, SUD, and eating disorders [62]. In one study, the comorbidity of BPD and depression increased the frequency and lethality of suicide attempts [10, 63]. Furthermore, co-occurrence with BPD is frequent in patients with bipolar disorder. In one study, 48 % of bipolar patients also had a comorbid BPD [64]. This is important because suicide attempts are 20 to 30 times more likely in bipolar patients than in the general population [65]. Some risk factors for SB in bipolar patients are a family history of suicide attempts, a history of head trauma, early onset of BD, frequent depressive symptoms, antidepressant-induced mania, social phobia characteristics, and comorbidity with AUD/SUD [66]. Comorbid PD also increases the risk of SB in psychosis, as reported in a sample of 670 patients with psychosis [67].

One of the most interesting studies carried out about the relationship of PDs and MDD published in the last few years was a study comparing 41 patients with MDD plus BPD with 117 patients diagnosed with MDD plus another type of PD, and 81 patients with MDD without any comorbid PD. The first group (MDD + BPD) appeared to be the most severely disturbed group as they were more likely to have a history of mental illness in family members, an early onset of MDD, AUD, and SUD, lifetime aggressive behaviors, or more likely being repeaters. These authors suggested that SAs diagnosed with MDD should be screened for PDs, particularly BPD, because if a BPD is also present, the likelihood for these SAs to display a SUD or AUD is very high, and they will also more likely become suicide re-attempters [10]. Furthermore, the presence of comorbid SUD might halt the symptomatic recovery of SAs with MDD and BPD [10].

Another exciting area of research is the comorbidity between attention-deficit hyperactivity disorder (ADHD) and personality disorders. Recent findings suggest that ADHD, an early neurodevelopmental disorder, shares common etiological mechanisms with PDs [13]. Furthermore, in a recent Spanish sample of 78 adult outpatients, the authors reported high comorbidity between all PD clusters and hyperactive- and combined-type ADHD, and between depressive PD and inattentive ADHD [68]. The comorbidity between ADHD and PDs has been associated with an increased risk of being in a homeless situation both in childhood and adulthood [69].

Finally, in 2013, in a systematic review on the comorbidity between Axis I disorders and PDs, one of the most interesting suggestions was that BPD should be moved to Axis I disorders [70]. However, these authors were reticent to accept the ideas of merging Axis I and Axis II disorders into a single category and of artificially reducing comorbidity by deleting some disorders, as they already had with PDs, whereas the number of Axis I disorders appears to have no limit and is pushing our postmodern societies into a *brave new world*, characterized by the medicalization of life events, a "new" medicine—wish-fulfilling medicine—or even disease mongering [71].

Comorbidity Between Axis II Disorders

Comorbidity between Axis II disorders, particularly if the PD diagnosed is BPD, is very high [72]. Comorbidity between PDs increases the risk of SB. For instance, in a 15-year follow-up of inpatients with BPD, comorbidity with narcissistic PD was associated with a higher risk of death by suicide [73].

Given the high comorbidity among PDs, in 1996, Tyrer and Johnson [74] suggested a new classification system for PDs based on severity. Accordingly, those with a diffuse PD would have at least two PDs from different DSM-IV clusters (A, B, or C). In 2009, we reported that young female SAs diagnosed with a diffuse PD were more likely to repeat suicide attempts, but we found no relationship with the lethality of the suicide attempt [72]. Unfortunately, the use of this classification does not seem to be generalized. In this context, with the advent of DSM-5, the DSM-5 Personality and Personality Disorders Work Group recommended the elimination of schizoid, paranoid, histrionic, narcissistic, and dependent PDs [75]. These authors explored the impact of this decision in a sample of 2150 patients and concluded that their results "do not provide unambiguous support for the DSM-5 proposed elimination of 5 personality disorders" [75]. Indeed, the American Psychiatric Association eventually decided to retain the DSM-IV categorical approach with the same 10 PDs. The Personality Disorders Work Group tried to move from a categorical to a dimensional, personality-trait based approach to PDs, but the initial proposal was rejected due to its high complexity for clinicians. A second proposal, a hybrid model including evaluation of impairments in personality functioning plus five areas of pathological personality traits, was ultimately not accepted for DSM-5's main manual, but was included in Section III for further study (http://www.dsm5.

org/Documents/Personality%20Disorders%20Fact%20Sheet.pdf).

Physical Illness and Psychiatric Comorbidity

Physical illness is very frequent among SAs [76]. Furthermore, physical illness and psychiatric disorders frequently co-occur [32], but little research has explored their combined effect on risk of SB [16]. In a recent nested case-control study of the entire population of Denmark, 27,262 suicides were compared to 468,007 living controls. The authors reported that the interaction of both types of illnesses increased the risk of suicide. Interestingly, when they explored the timing of their interaction, the development of psychiatric disorders after onset of physical illness was what significantly increased the risk of suicide. Furthermore, they suggested that psychiatric comorbidity appears to mediate the relationship between physical illness and suicide [32]. They stressed that not only depression but also SUD, PDs, and schizophrenia spectrum disorders mediated this relationship.

As for the relationship between physical illness and suicide attempts, in 1999, De Leo et al. yet reported in the EPSIS study, with 1269 SAs aged 15 years and over hospitalized within 1 week after a suicide attempt, that physical illness was very frequent among SAs [76]. SAs with a physical illness were significantly more depressed. Moreover, they also reported a previously known finding: that the relevance of physical illness in contributing to SB increases with older age. In a case-control study of 149 SAs compared with healthy and psychiatric controls, the authors reported that major physical illness was one of the most frequent life events significantly associated with the risk of suicide attempt [77]. In another study of 388 self-poisoners, the 57 SAs aged 65 or over, compared to those aged 65 or less, had more lethal suicide attempts, and their attempts were more frequently associated with physical illnesses than psychosocial stressors [78]. More recently, in a study of 101 elderly SAs, the authors divided the sample into "young old" (70–79 years old) and "older old" (aged 80 and above) [79]. The authors found that, in the "young old" group, psychological pain was more likely among SAs with serious physical illness compared with those without physical illness. Given that they did not find the same in the "older old" SAs, the authors suggested that the processes by which physical illness confers risk to old SAs might be age-dependent.

The impact of physical illness on the risk of SB also appears to be dependent on gender. In an exploratory study of our group, we found in a sample of 1183 adults with/without suicide attempts that personal injury or illness was the Holmes-Rahe Social Readjustment Rating Scale's life event more closely related to suicide attempts in men [80]. In women, personal injury or illness was the sixth most relevant life event associated with suicide attempter status.

Repetition of SB and the Concept of Major Repeaters

One of the most interesting topics regarding comorbidity in SAs is the impact of comorbidity on the repetition of SB. Repetition of suicide attempts is frequent. A history of suicide attempts is the strongest predictor of future SB [81]. Indeed, the estimated rate of non-fatal suicide attempt repetition among SAs ranges between 20 and 55 % [82–85] (see Mendez-Bustos et al. [85] for a review). In this systematic review, the authors reported that comorbidity is higher in re-attempters than in single SAs and concluded that psychiatric comorbidity with three or more disorders increased the risk nearly four times (OR = 3.7) for being a suicide re-attempter [85]. Furthermore, repeated SB is related to a more severe personality profile among SAs [86], and the comorbidity between BPD and MDD in suicide re-attempters could be considered classic [87].

Related to this topic of repetition of SB, one of the most interesting ideas in recent years is the addictive hypothesis of self-harming, whether suicidal or not [88]. In a series of studies using various samples from Spain and France, we have postulated a set of different innovative ideas related to this hypothesis: first, in 2012, we suggested that some SAs, those called "major repeaters" (five or more suicide attempts) could be a particular sub-group of SAs characterized by generating a behavioral addiction to SB [89]. The concept of "major" or "grand repeaters" was postulated by Kreitman and Casey in a seminal paper published in 1988 [90]. They arbitrarily divided parasuicide patients into "first-evers," "minor repeaters" (two to four lifetime parasuicides), and "major repeaters". Then, we tested our hypothesis in different samples [91–93]. In a French sample comparing 335 non-major repeaters (<5 suicide attempts) to 35 major repeaters, the latter group was more likely to be female, diagnosed with either substance dependence or anorexia nervosa, and to have higher levels of anger which was not expressed-out [91]. In a second study, we demonstrated that relieving emptiness was an important pathway, even more relevant than BPD diagnosis for explaining the major repetition of suicide attempts in our study [93]. In a third study, we compared eight major repeaters (7 %, all women) to 110 non-major suicide attempters [92]. In this study, we explored whether major repeaters were addicted to SB by using modified DSM-IV criteria for substance dependence. Eighty-three percent of major repeaters met criteria for total dependence on SB. This was similar to the 81 % of patients displaying non-suicidal self-injury (NSSI) who endorsed more than five dependence criteria on NSSI in another study [94]. Furthermore, our study suggested that major repeaters were addicted to SB. Indeed, our findings were not explained by the presence of BPD [92]. Unfortunately, in none of the articles in this series did we explore the role of comorbidity, but we plan to do it in the near future. We synthesized all these findings in a narrative review published in 2016 [88].

Conclusion

Comorbidity at various levels (i.e., intra- or inter-Axis I and II, with personal injury or illness) in SAs appears to be the rule and to play a key role in the repetition of SB. However, to date, there are several issues deserving further research in order to establish the contribution of comorbidity to the risk of SB. For instance, whereas the influence of a PD in the course and prognosis of Axis I disorders is widely studied, the impact of Axis I disorders on the personality of the individual is poorly studied. The major limitation of the present review is the personal selection of some of the articles included within it.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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