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Anxiety Sensitivity and Intolerance of Uncertainty: Transdiagnostic Risk Factors for Anxiety as Targets to Reduce Risk of Suicide

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Abstract

Purpose of Review Suicide has a profound impact on individuals, families, and society. One prominent, if understudied, risk factor for suicide is anxiety. More than 70% of people with at least one suicide attempt meet diagnostic criteria for an anxiety disorder. There are several limitations to exploring the associations between anxiety and suicide using diagnosis-based classification systems. A better approach would be to consider transdiagnostic risk factors for anxiety.

Recent Findings Through a negative reinforcement model of suicide, anxiety sensitivity (AS) and intolerance of uncertainty (IU) appear to exacerbate the experience of unpleasant anxiety sensations and likely contribute to chronic suicide risk as well as acute suicidal acts.

Summary Although more research is needed to clarify the mechanisms through which AS and IU confer risk, brief interventions may offer an ideal suicide prevention strategy for anxious people.

Keywords Anxiety sensitivity · Intolerance of uncertainty · Suicide · Ideation-to-action · Negative reinforcement

Introduction

Suicide rates in the United States increased more than 32% from 1999 to 2019 [1]. These rates are alarming as suicide has a profound impact on individuals, families, and society, and incurs billion in annual costs due to mortality and disability [2]. Accordingly, researchers have spent decades identifying factors that connote risk for suicidal thoughts and behaviors. One prominent risk factor for suicide is anxiety [3–5]. More than 70% of individuals with at least one suicide attempt meet diagnostic criteria for an anxiety disorder [6]. Paradigm-shifting research is needed to explicate the processes through which anxiety contributes to suicide risk. However, as highlighted by a recent meta-analysis showing that broad categories of risk factors, including categorically defined internalizing psychopathology (anxiety and depressive disorders) are only modestly correlated with suicidal ideation and behavior [7•], the relations between anxiety and suicide are complex. Herein, we examine how the National Institute of Mental Health's (NIMH's) Research Domain Criterion (RDoC) initiative can be used as a framework for exploring important anxiety-related risk factors that appear to extend beyond these discrete diagnoses (i.e., transdiagnostic risk factors).

Anxiety Disorders and Suicide

Anxiety disorders are common in individuals with suicidal ideation and in individuals who have made a suicide attempt. A recent meta-analysis by Moitra and colleagues [8•] demonstrated that people with an anxiety disorder are nearly 5 times more likely to attempt suicide than are people without an anxiety disorder. Notably, the link between anxiety-related disorders and suicide risk is observed across diagnoses including obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), panic

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disorder (PD), and social anxiety disorder (SAD) [9•].[1] For instance, in primary care settings, studies show that 18–33% of patients with SAD or PD have a history of at least one suicide attempt, and 16–32% endorsed recent suicidal ideation [11–14]. In community samples, the likelihood of endorsing suicidal ideation over the past 12 months appears to be even greater [15]. The associations between anxiety disorders and suicide remain when controlling for mood conditions, although data show risk is further elevated in the context of comorbid anxiety and mood disorders [9•]. Findings such as these have led suicide prevention organizations to include anxiety disorders as a key risk factor and intervention target (e.g., American Association of Suicidology, 2018; American Foundation for Suicide Prevention, 2018; National Suicide Prevention Lifeline, 2018).

Negative Reinforcement Models of Suicide

Research and theory have attempted to explain the well-established link between anxiety and suicide. Broadly, this literature converges to suggest that negative reinforcement processes are involved in the emergence and reoccurrence of suicidal thoughts and behaviors. A core example is the functional model of suicide which posits that recurrent suicidal behavior acts as a strategy for regulating strong negative affect [16, 17]. More specifically, negative affect elicits the motivational drive for escape or avoidance, and for some, suicidal behavior is considered a means for affective relief. This theory aligns with an earlier theory by Shneidman [18] positing that suicidal behavior occurs in response to *psychache* or intolerable psychological/emotional distress from which escape is sought. A defining feature of this theory is that individual differences in thresholds for tolerating psychache reflect thresholds for suicidal behavior. Empirical support for these models come from several studies. Emotional relief and situational escape were found to be the most common motives reported among individuals who have attempted suicide [16]. Another study found that suicide attempters who reported experiencing "feeling better" after their first suicide attempt were significantly more likely to have made a second suicide attempt [19•]. Among acutely suicidal individuals with no prior attempts it has been shown that endorsing the perspective that suicide would reduce emotional distress was associated with significantly increased odds of attempting suicide over the next 6 months [20]. People with elevated suicide risk experience significantly larger increases in negative affect and take longer to recover from negative affective states than lower risk people after exposure to a stressful and ambiguous interpersonal situation [21]. Thus, the functional model may best explain the associations between anxiety and suicidal behavior [22, 23].

Anxiety Disorders: Examining Limitations in Risk Factor Research

Although the link between anxiety disorders and suicide is well-established, the validity of internalizing psychopathology as a predictor of suicide is relatively weak [7•]. A recent meta-analysis by Franklin and colleagues compiled studies that examined prospective associations between suicide risk factors and subsequent suicidal ideation and behavior. Internalizing psychopathology (i.e., anxiety and/or depressive disorders) was included in nearly 25% of the effect sizes examined in the meta-analysis [7•]. Although internalizing psychopathology was frequently included in published research, as a discrete category it was one of the weakest predictors of suicidal behavior. Follow-up analyses attempted to address whether specific disorders exhibited more robust predictive validity, but in general, results were modest, and it was concluded that internalizing psychopathology (broadly) and anxiety disorders (specifically) offered limited accuracy in prospectively predicting suicidal ideation and behavior.

There are several reasons for the limited predictive utility of categorically defined anxiety disorders. One reason is that until recently, suicidal ideation and behavior were often collapsed into one variable, ignoring the nuances between outcomes. Markedly, there is growing consensus within the field that suicidal ideation and behavior are not equivocal and an ideation-to-action framework is most valid [24•, 25]. The central tenet of the ideation-to-action framework is that the transition from non-suicidal thoughts to suicidal thoughts and the transition from suicidal thoughts to suicidal acts are distinct processes with distinct underlying mechanisms. As explicitly described in the context of the fluid vulnerability model of suicide [17, 26], variables interact in complex patterns over time to influence the emergence of a *high suicide risk state*, placing individuals at increased risk of suicidal behavior. There is an important distinction between chronic and imminent risk such that many variables can contribute over a wide time range in developing chronic suicide risk, whereas a separate combination of variables and current vulnerability status contributes to suicidal behavior [26]. Thus, it is critical to consider the role of risk factors for developing chronic suicide risk (i.e., transition to ideation stage) and for acute suicidal acts when in a high suicide risk state.

[1] The Diagnostic and Statistical Manual of Mental Disorders [10] no longer considers OCD and PTSD to be anxiety disorders but does reflect the related nature of these disorders through placing these chapters in close proximity to each other.

Another reason to consider the role of risk factors for developing chronic suicide risk is that operationalizing risk using our traditional categorical diagnostic system is notoriously problematic [27–29]. Categorically defined anxiety disorders exhibit significant within-disorder symptom heterogeneity and extensive overlap among symptoms across disorders [30, 31]. It has been noted that our diagnostic system does not 'carve nature at its joints' and, therefore, does not reflect valid disease entities. Many researchers argue that higher-order processes operate on behavior and that transdiagnostic dimensional constructs reflecting core mechanisms of psychopathology are best suited to identify and describe individuals at risk for psychiatric symptoms and maladaptive behavior, including suicide.

A Transdiagnostic Model of Anxiety Risk and Suicide

In 2010, the National Institute of Mental Health (NIMH) proposed the Research Domain Criteria (RDoC) project. The RDoC initiative broadly seeks to re-conceptualize psychopathology and its treatment using a research framework focused on higher-order, transdiagnostic mechanisms of dysfunction [30, 32]. Although suicide is not a psychiatric diagnosis, per se, researchers have suggested that the RDoC framework holds promise for elucidating the mechanisms underlying suicidal ideation-to-action [29, 33•, 34•].

The most current RDoC framework is composed of six domains: negative valence systems, positive valence systems, cognitive systems, systems for social processes, arousal/regulatory systems, and sensorimotor systems. Within these domains are constructs and sometimes subconstructs, which are dimensions considered to be core components of the system. The negative valence system, particularly acute threat (fear) and potential threat (anxiety) constructs, are critical processes in anxiety disorders. It is necessary to highlight that ample evidence indicates that fear and anxiety are distinct aversive responses to different types of stressors or threats [35, 36]. Fear is a short-duration 'fight or flight' response that is time-locked to an identifiable, imminent danger. Meanwhile, anxiety is a long-duration state characterized by generalized apprehension and heightened, sustained vigilance for an uncertain threat [37]. Both fear and anxiety serve adaptive purposes; however, in some, these responses can become excessive and persistent, leading to distress, worry, and maladaptive coping including passive avoidance and substance use.

Glenn and colleagues conducted a recent meta-analytic review of research exploring RDoC domains and risk for suicide [33•]. They found that most risk factors identified were constructs from the negative valence domain and within this set of studies, most explored constructs underlying depression, not anxiety (i.e., loss, frustrative non-reward). Glenn et al. did report on one study by Yaseen et al. that examined the prospective associations between panic attacks and panic symptoms and suicidal ideation and attempts 3 years later in a sample of 2864 participants with a depression diagnosis [38]. In analyses conducted without covariates, past year panic attacks were associated with subsequent suicidal ideation (OR = 1.45, 95% CI [1.01, 2.09]) as well as subsequent suicide attempt in those endorsing suicidal ideation at baseline (OR = 2.12, 95% CI [1.15, 3.43]). Although these findings were not robust to the inclusion of additional risk factors, fear of dying during a panic attack increased the odds of a suicide attempt sevenfold (OR = 7.00, 95% CI [1.53, 32.04]) controlling for additional risk factors. From an RDoC perspective, this suggests that thoughts of death accompanying activation of the system underlying acute threat place an individual at heightened risk for suicide.

Psychobiological Processes of Anxiety Sensitivity and Intolerance of Uncertainty

Keeping in mind the framework for identifying risk factors provided by the RDoC initiative, we argue that key anxiety-focused risk factors that contribute to increased ideation as well as increased likelihood of suicidal behavior are those that stem from individual differences in tolerating and responding to unpredictable contexts (i.e., intolerance of uncertainty [IU]) and resulting anxiety-related sensations (i.e., anxiety sensitivity [AS]). There is emerging evidence that AS and IU are key transdiagnostic mechanisms for anxiety and other forms of psychopathology. At the neural level, the anterior insula cortex (AIC) is the core of the brain's system for monitoring arousal and anxiety and subsequently coordinating appropriate motivational responses. The AIC also generates subjective feelings of distress and the motivational desire for escape and relief. Data indicate the AIC is involved in AS [39, 40] and IU, specifically tolerating and responding to uncertainty [41, 42]. In tandem, numerous studies have demonstrated a link between AIC dysfunction and suicide risk [43, 44, 45•]. These converging findings highlight that AS and IU may be centrally important constructs in explicating the psychobiological connection between anxiety and suicide.

Anxiety Sensitivity

Anxiety sensitivity (AS) refers to the fear of anxiety-related sensations due to the belief that these sensations are harmful [46]. AS is composed of three lower-order dimensions capturing fear of physical sensations, fear of cognitive sensations, and fear of observable anxiety sensations [47, 48].

Two meta-analyses provide robust support for the role of AS in the etiology of anxiety and mood disorders [49, 50]. More recently, studies have found associations between AS and insomnia, eating disorders, substance use, and suicide [51–53, 54•]. Experimental studies have confirmed that AS amplifies the momentary experience of fear. For example, Allan et al. assigned participants to receive either niacin to induce facial flushing or a pill placebo and to then give a brief, recorded speech to a research assistant on a controversial topic [55]. People who received niacin reported elevated panic symptoms when giving their speech and AS social concerns moderated this relation such that people reporting elevated AS social concerns at baseline responded more strongly to the biological challenge agent. In another experimental study, researchers examined whether AS and IU moderated the association between Pavlovian fear generalization (i.e., generalized fear to safe stimuli resembling dangerous stimuli) and maladaptive avoidance (i.e., avoiding safe stimuli unnecessarily) [56•]. The associations between fear generalization, measured via fear-potentiated startle and self-report, and maladaptive avoidance were only significant in the presence of elevated AS. Thus, there is support that AS exacerbates the experience of anxiety and results in maladaptive coping strategies.

AS likely contributes to the transition to ideation and acute suicidal acts when the high suicide risk state has been activated. Stanley and colleagues recently conducted a meta-analysis exploring the concurrent relations between AS and suicide [54•]. AS shared small-to-medium associations with suicidal ideation ($r = 0.24$). A recent cross-sectional study provided further support for the associations between AS and suicidal ideation as well as suicide risk. Across two samples whose data was collected during the COVID-19 pandemic, Allan and colleagues examined associations AS and other risk factors shared with suicide outcomes [57•]. In sample 1, a latent suicide risk variable was modeled as the outcome, and in this model AS was significantly associated with the latent suicide risk variable. In sample 2, the likelihood of endorsing any suicidal ideation was treated as the outcome and AS was associated with this variable. In both models, IU and loneliness were included as covariates. Demirkol et al. examined associations between AS, psychological pain (i.e., psychache), and suicidal ideation in a sample of patients with a GAD diagnosis [58•]. They found that AS was elevated in individuals with a prior suicide attempt. They also found that AS was associated with psychache and suicidal ideation, and in an indirect effects model, psychache fully explained the association between AS cognitive concerns and suicidal ideation. The authors did not test the other AS dimensions or overall AS in this indirect effects model. Although most research exploring the associations between AS and suicide have been conducted using cross-sectional designs, these findings suggest an important future research direction, to determine whether AS is a causal risk factor for the transition to ideation as well as acute risk when a person is in a high suicide risk state.

AS impacts risk for suicide through more indirect paths as well. The association between AS and suicidal ideation is likely at least partially indirect, through the contribution of AS on adopting maladaptive coping strategies that leave a person vulnerable to suicidal ideation. For example, AS may moderate the mechanisms through which substance use contributes to suicide [59]. The association between AS and substance use can also be explained through negative reinforcement processes. Allan et al. examined the relations between AS and alcohol use and found a significant chained indirect path from AS to hazardous alcohol use through anxiety and then through drinking to cope with aversive emotions [60]. These findings provide support for the model proposed in DeMartini and Carey's critical review of the role of anxiety sensitivity in predicting alcohol use [61]. Through experimental studies, DeMartini provided support for negative reinforcement to address negative affect as a key mechanism through which individuals with elevated AS develop substance use difficulties. Researchers have suggested that AS also amplifies anxiety due to uncertain consequences of feared physical sensations [62], indicating that constructs related to an aversion to uncertainty may also be highly relevant to consider in explaining the associations between anxiety and suicide.

Intolerance of Uncertainty

IU is "an individual's dispositional incapacity to endure the aversive response triggered by the perceived absent of salient, key, or sufficient information, and sustained by the associated perception of uncertainty" [p. 31, 62]. As humans, we use information about past experiences and current environments to make inferences about the future. This process affords the opportunity to pursue rewards and avoid dangers. When information is lacking or ambiguous, outcomes become uncertain and the ability to prepare for future events is diminished, resulting in increased anxiety [63, 64]. Uncertainty is universally aversive, and cross-species studies show the less information that is available, the more a situation is appraised as distressing [65, 66]. Importantly, though, individuals differ in how they tolerate and respond to uncertainty with some showing maladaptive cognitive and behavioral responses in the face of many (or all) uncertain contexts [67, 68]. Like AS, IU is also a higher-order risk factor, with lower-order dimensions of prospective IU and inhibitory IU [69]. Recent meta-analyses found strong associations between IU and GAD, depression, OCD, and eating disorders [70, 71]. Other studies have found that IU is elevated in people with SAD, PD, GAD, OCD, and depression, compared to community and undergraduate student samples serving as controls [72]. Recent studies have also found associations between IU and substance use as well as substance use motives [73]. In addition, experimental studies have also demonstrated that IU may serve to increase avoidance in the presence of feared stimuli. In the experimental study that tested AS and IU as moderators of the relations between fear-generalization and maladaptive avoidance, IU moderated the association between self-reported fear-generalization and maladaptive avoidance [56•]. Thus, there is support that IU exacerbates the experience of anxiety and results in maladaptive coping strategies.

Exaggerated sensitivity to uncertainty may contribute to risk for suicide. Individuals who have difficulty tolerating uncertainty tend to experience frequent distress and forecast the worst-case scenario [74•, 75], which increases negative affect and contributes to feelings of hopelessness [76]. Aversion to uncertainty also enhances motivation to pursue known outcomes [77, 78] including suicide, a known reliable escape from affective distress. For sensitive individuals, the concept that situations *might* improve, or distress *may* subside, is likely difficult to grasp. A much more salient thought process is centered on inherent uncertainties of everyday life and resulting sustained arousal. Immediately available escape options likely carry greater perceived value because they preclude the possibility that emotional distress with continue indefinitely. In support of this theory, Lieberman et al. demonstrated that current and lifetime history of suicidal ideation was associated with increased psychophysiological reactivity to unpredictable threat-of-electric shock [79•]. The authors noted sensitivity to uncertainty is one pathway to considering suicide as an escape from unpredictable stressors, particularly in the context of other escalating factors. Ciarrochi et al. found that undergraduates high in IU were also high in suicidal ideation and hopelessness, among other factors [80]. Somewhat inconsistently, Allan et al. found no association between IU and suicide risk and found a negative association between IU and suicidal ideation across their two samples when controlling for AS and loneliness [57•]. Given that IU shared significant, positive bivariate relations with suicide outcomes in this study and in prior studies, it is unclear whether this negative effect was anything more than a spurious finding. Thus, IU likely operates similarly to AS in exacerbating the experience of emotional distress in contributing to suicidal ideation and suicidal behavior, although it should be noted more research is needed, especially to establish IU as an important risk factor for the transition from suicidal ideation to suicidal behavior.

Preventative Interventions Targeting Anxiety Sensitivity and Intolerance of Uncertainty

Herein we briefly highlight two critical anxiety processes involved in the etiology of suicide risk. We also identified several distinct mechanisms through which these risk factors might impact suicide. Fortunately, AS appear to be ideal treatment targets through brief cognitive-behavioral therapy (CBT). There is a large corpus of research indicating that brief CBT-based interventions for AS are efficacious [81–83]. Further, reductions in AS through these interventions reduce anxiety, depression, insomnia, and PTSD symptoms, and even suicidal ideation [81, 84, 85]. For example, Schmidt et al. tested a one-session computerized intervention protocol in a community sample of participants at-risk for suicide [81]. They found that this intervention reduced AS and reduced anxiety, depression, and suicidal ideation through reductions in AS. Schmidt et al. replicated these findings [82]. Norr and colleagues found that reductions in suicidal ideation occurred through a chained mediation model from reductions in AS to reductions in anxiety and finally to reductions in suicidal ideation [86•].

Only recently have researchers begun developing brief CBT-based interventions for IU. In the only published test of a brief CBT-based intervention targeting IU, Shapiro and colleagues assigned participants to receive IU-focused psychoeducation or health-focused psychoeducation. They found significant reductions in IU at 1-month follow-up as well as significant reductions in worry and depression symptoms at 1-month follow-up through reductions in IU. Our team has been following this line of research up with recent efforts to test a brief IU-focused CBT-based intervention that includes a virtual treatment session with a clinician followed by the use of a mobile app to supplement intervention content. We hope to be able to soon determine whether brief CBT for IU is an efficacious intervention strategy for IU, accompanying anxiety, and subsequent suicidal ideation and behavior. Given the relatively low economic cost and low time and effort burden for patient and clinician, brief interventions for AS and IU may be ideal for individuals across the suicide spectrum, from individuals at-risk for developing suicidal ideation to individuals already in the high suicide risk state. Research is needed testing the unique and combination of AS and IU interventions as a suicide prevention tool.

Conclusion

In this review, we determined that the association between anxiety and suicide can be understood through the lens of alternate models of psychopathology, such as the RDoC initiative. We further demonstrated that AS and IU are two highly relevant transdiagnostic risk factors for suicide across the ideation-to-action spectrum by presenting research linking AS and IU to suicidal ideation as well as suicidal behaviors. Finally, we briefly described the potential value of brief CBT-based interventions targeting AS and IU as a way to address suicide across the ideation-to-action spectrum. More work is needed explicating how AS and IU relate to the dynamic system that places people at risk for suicide.

Declarations

Conflict of Interest Dr. Bryan reports grants from the National Institute of Mental Health, grants from the Department of Defense, during the conduct of the study; personal fees and other from Anduril, LLC, outside the submitted work. Drs. Allan, Gorka, and Saulnier declare they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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