

Research Progress on Mechanisms and Interventions for Comorbidity of Adolescent Depression and Non-Suicidal Self-Injury

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Abstract. Adolescent depression and the co-occurrence of adolescent depression and non-suicidal self-injury (NSSI) represents a critical public health problem globally. NSSI detection rates in community samples range from 24.5% to 31.36% and among hospitalized depressed adolescents, the incidence is as high as 32.5% to 80.2%. Comorbidity increases burden of disease and significantly increases the risk of suicide. This review summarizes recent progress in this area with potential mechanisms at the neurobiological, psychological and social ecological levels. Risk factors and protective factors are described for individual, family, social and biological domains, clinical features and prediction models are described, and schemes of intervention are described for psychotherapy, pharmacotherapy and physical therapy. There are indications that comorbidity is genetically determined, is linked to faulty neural circuits, is related to difficulties in emotion regulation and that it is the result of bad environment. A comprehensive intervention system based on psychotherapy, with the addition of family intervention and social support is the mainstream clinical practice. Future research should focus on exploring the pathway for personalized precise intervention, and improve the early identification and warning system.

Keywords: Adolescent depression, Non-suicidal self-injury, Comorbidity mechanism, Intervention strategy, Risk factor

1. Introduction

Depressive disorder is one of the common mental disorders in adolescents, and prevalence estimates for the world range between 2%–5%, showing significant increase in recent years. NSSI refers to the intentional infliction of tissue injury without suicidal intent and with none of the social acceptance, such as cutting, burning, hitting etc. Adolescence is a critical time for both conditions, and there is significant co-occurrence between the conditions.

Epidemiological studies have found prevalence of NSSI in community adolescent samples ranging from 24.5% to 31.36% and in hospitalized depressed adolescents ranging from 32.5% to 80.2%, suggesting that depression is a significant risk factor for NSSI [1]. Depressive symptoms predict future NSSI onset and NSSI increases depressive symptoms, thus forming a vicious cycle.

Comorbidity results in worse psychosocial functioning and is linked to increased risk of suicide attempt, and a history of NSSI increases the risk of suicide attempt 6–10 fold.

Adolescence is an important period of neurodevelopment and psychosocial development. Here, mental health issues that arise tend to be long-term and recurring. Comorbid states exacerbate the severity of symptoms and result in long-term negative consequences for social adaptation, academic achievement and social functioning, representing significant disease burden in the family and society. While plenty of research has been conducted on depression and NSSI pathogenesis individually, only a few studies have explored pathways of internal association, specific risk markers, and effective intervention schemes for comorbidity. The mechanisms of occurrence and development, the risk factors, the clinical features, the methods of intervention and the progress of research are reviewed from five aspects: The existing evidence are integrated, the mechanisms of occurrence and development are explained, the risk factors and clinical features are sorted out, and the research of different intervention methods is summarized, thus a theoretical structure is established for basic research and clinical practice.

2. Possible mechanisms of comorbidity

2.1. Neurobiological mechanisms

The neurobiological mechanisms of depression-NSSI comorbidities are multisystem dysfunctions. In terms of monoamine neurotransmitters, monoamine neurotransmitter hypofunction is a common underlying pathology and CSF 5-HIAA levels are significantly reduced in NSSI patients. The stress response system is over activated and HPA axis dysfunction is manifested as abnormal cortisol circadian rhythm and dexamethasone suppression test disinhibition. Using neuroimaging, a negative correlation was found between the volume of gray matter in the right middle frontal gyrus and the self-harm tendency questionnaire score ($r=-0.512$, $P<0.05$), and gray matter reduction in the prefrontal cortex and cingulate gyrus correlates well with emotion regulation decline [2]. Research of white matter integrity shows abnormalities in voluminous areas of genu of corpus callosum and anterior cingulum fibers that are related to impulse control disorder. There is evidence from functional connectivity studies that abnormal connectivity between default mode network and salience network might represent a neural basis for the comorbidity. However, neuroplasticity research suggests that brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is linked to depression-NSSI susceptibility and that environmental stress interacts with this genotype.

2.2. Psychological mechanisms

The main psychological mechanism that underlies the comorbidity is called emotion dysregulation. 87.6% of depressed adolescents use external emotion regulation as the primary NSSI function, which allows them to quickly escape from negative emotions by engaging in self-injury. As to cognitive impairment, Memory Quotient (MQ) is negatively correlated with Hamilton Depression Rating Scale (HAMD-24) score ($r=-0.456$, $P<0.01$), which means that there is a significant correlation between the degree of depression and memory impairment. But recently, abnormalities in interoception have been of great interest and comorbid patients show reduced accuracy in perceiving their heartbeats and reduced visceral sensation discrimination, which could affect emotion experience and regulation. Experiential avoidance is a mediator between depression and NSSI, in that people feel depressed and avoid painful emotional experiences with NSSI. The total effect of

psychological resilience is 0.457, the moderating effect is -0.15 ($P < 0.05$), indicating that psychological resilience has a mediating effect, and resilience is an important protective factor.

2.3. Social ecological mechanisms

Cumulative effects of risk factors across developmental levels as described by the developmental cascade framework could indirectly increase the risk for NSSI by influencing how adolescents regulate their emotions. In terms of social learning, observing and imitating peers' NSSI behaviors are important pathways for the spread of NSSI, and females are more susceptible to social contagion effects. New potential modes of NSSI contagion are available in the development of online social media, where exposure to online community NSSI content is linked to a higher risk of behavioral imitation. Collectivist cultures make family relationship and academic pressure more salient triggers of NSSI, while identity crisis and peer exclusion are more salient triggers in individualist cultures.

3. Comorbidity risk factors

3.1. Individual and family factors

Individual and Family Factors Female adolescents are 2.75 times riskier of being comorbid as compared to males ($OR=2.75$, 95% CI: 2.14–3.53, $P < 0.001$) [3]. Patients with major depression have a 12.756 times higher risk for NSSI than do patients with mild depression ($OR=12.756$). Those individuals who indicate impulsivity are more likely to engage in self-destructive behavior during negative emotions as they are less inhibited. Comorbidity risk is significantly high if there is low self-esteem and/or poor cognitive emotion regulation strategies such as rumination and catastrophic thinking. It was found that the frequency and severity of NSSI was higher among the chronic or recurrent depression patients than among those with acute depression. Childhood abuse was one of the greatest comorbidity predictors with risk increased by 11.157 times ($OR=11.157$, $P < 0.001$); emotional and sexual abuse resulted in the largest effect sizes. Family dysfunction (low intimacy-high conflict) and insecure parent-child attachment (esp anxious attachment) are highly correlated with comorbidity; parent divorce/separation almost doubles the risk of NSI in adolescence. Maternal CCE is significantly associated with adolescent NSSI ($OR=10.743$) and indicates the inter-generational transference from mothers' emotional response style, parenting style and attachment pattern to adolescents [4].

3.2. Social and biological factors

Important social triggers include school bullying and those who are bullied are 2–3 times more likely to engage in NSSI. Life events such as academic failure, relationship frustration, and loss of significant others have negative effects that contribute to an increased risk of developing comorbidities through cumulative effects. Social support and peer relationship are bi-directional—deficiency is a risk factor and positive peer relationships is a protective factor. HRV studies demonstrate that the vagal tone is lower in comorbid patients, indicating that there is a dysregulation of the ANS. Decreased pressure pain threshold (PPT) reflects abnormal pain perception and reflects peripheral and endogenous opioid system dysfunction. Pro-inflammatory cytokines (IL6, $TNF\alpha$) are associated with depression and NSSI severity and are positively correlated [5].

4. Clinical aspects of comorbidity

4.1. Symptom presentation features

Symptom Manifestation Characteristics Comorbid adolescents have unique symptom patterns. The onset of NSSI is often at ages 12-14, before or at the same time as the full onset of depression symptoms. Gender difference is found in the form of females having the incidence of NSSI about 2.75 times higher than males, and females having a preference for covert methods such as cutting, while males prefer overt methods, such as burning and hitting. As far as the self-injury function is concerned, the most frequent functions were external emotion regulation (87.6%), self-punishment (around 60%) and interpersonal influence (around 40%). Importantly, 78.4% of those with comorbid conditions show addictive behaviors, such as tolerance, withdrawal-like symptoms and an urge to inflict injury on oneself [6].

4.2. Comorbidity patterns and prediction models

Anxiety disorders often co-occur with other disorders, and there is a depression-anxiety-NSSI triad, which worsens functional impairment (4.2 Comorbidity Patterns and Prediction Models). Suicide risk in comorbid patients is much higher than the risk in depression-only or NSSI-only patients; the history of suicide attempts 14.05 times higher the risk of comorbidity ($OR=14.05$, $P<0.001$) [7]. Psychosocial impairment involves decreased functioning in school, withdrawal from peer relations, and increased family conflict, and overall functioning is significantly lower than that of single-diagnosis patients. Recently, new tools for early identification of high risk were provided by machine learning-based prediction models. Liu Qian et al. used depression severity, childhood abuse, impulsivity and social support to develop a logistic regression model, with training set AUC of 0.947, which has an excellent discrimination [8]. The training set AUC of Zhang Yanyan et al.'s model was 0.871 and the validation set AUC was 0.845, which means that the model has a good generalization ability. These models can include evidence-based bases for early clinical screening and resource allocation [7].

5. Interventions methods for comorbidity

5.1. Psychotherapy

As for comorbidity treatment, dialectical behavior therapy (DBT) is currently the best-supported therapy, especially for emotion regulation and repetitive self-injury. Typical DBT protocols involve weekly individual therapy, skills training groups, telephone coaching and therapist consultation teams for 6-12 months. In one randomized controlled trial, 80 adolescent depression-NSSI patients were randomly allocated into observation and control groups with the observation group receiving DBT plus mindfulness-based stress reduction (MBSR) and the control group receiving routine treatment. The 8 week intervention consisted of three sessions per week, 45 minutes each session. Results indicated that there was a significant reduction in the rate of NSSI after the intervention in the observation group (5.62% vs. 16.85%) ($\chi^2=4.507$, $P<0.05$); there was a significant decrease in the HAMA scores (18.65 ± 4.32) at baseline to (9.12 ± 3.15) after the intervention; there was a significant decrease in the HAMD scores (26.38 ± 5.67) at baseline to (11.26 ± 4.08) after the intervention, and there was a significant decrease in the negative emotion scores (56.32 ± 8.46) at baseline to (32.15 ± 6.23) after the intervention; positive emotion scores, NSSI function scores, and

family function scores were all significantly improved after the intervention ($P < 0.05$). The results of the meta-analysis that combined the findings from the multiple RCTs showed that DBT impacted the frequency of NSSI with an effect size $d = 0.82-1.15$, and depression symptoms with an effect size $d = 0.85-1.18$, and reduced NSSI medium and long-term recurrence by more than 40% compared to control groups [9]. Internet-based cognitive behavior therapy (ICBT) is effective in addressing NSSI because of its transcending spatial and temporal boundaries, with effective treatment outcomes in NSSI, suicidal ideation, and problem solving ability, which can be particularly useful for early intervention and long-term follow-up of mild cases [10]. Mindfulness-based stress reduction (MBSR) improves emotion regulation by being mindful and accepting things in the present moment. Family therapy can help strengthen communications between family members, increase family functioning and develop effective crisis coping skills, especially for comorbid adolescents with high level of family conflict.

5.2. Pharmacotherapy and physical therapy

Pharmacotherapy's aim is to control depressive symptoms, which in turn has an indirect effect on reducing the risk of NSSI. Olanzapine-sertraline combination is a relatively well-studied combination. In one randomized controlled trial (RCT) 54 comorbid adolescents showed that after 8 weeks of treatment with olanzapine (2.5–10 mg/d) and sertraline (50–200 mg/d), there was a significantly higher level of recovery (33.3%) than in sertraline alone (10.7%) ($P = 0.042$), and the effective rate of the combination (81.5%) was significantly higher than for sertraline alone (50%) ($P < 0.05$) [11]. The benefit of this combination may result from the synergistic effects of olanzapine's mood stabilizing and impulse controlling effects and sertraline's antidepressant effects. A new physical treatment is called repetitive transcranial magnetic stimulation (rTMS). L-DLPFC 10Hz rTMS 30 minutes, 5 days a week for 4–6 consecutive weeks has been effective in significantly reducing depressive symptoms and NSSI impulses [12]. Low-frequency (1 Hz) stimulation of the right DLPFC also shows improvement in NSSI behaviour and may be more suitable for patients with higher mania risk, while bilateral sequential stimulation (left high-frequency + right low-frequency) is able to regulate the functional imbalance between the hemispheres, further enhancing the efficacy [13, 14]. One systematic review and meta-analysis included 10 RCTs with 562 adolescent depression patients with NSSI, used 10 Hz high-frequency rTMS with stimulation over left DLPFC, 30 minutes per session and 5 sessions per week and 2–6 consecutive weeks; results showed that HAMD-17 score decreased by an average of 14.2 points from baseline in the rTMS group, an effective rate of 78.3% (vs 38.6% in sham stimulation; $RR = 2.03$, 95% CI: 1.56–2.64, $P < 0.001$); NSSI frequency decreased by an average of 76.4% (vs 28.3% in sham stimulation; $P < 0.001$); BIS score (impulsivity scale) decreased by an average of 8.7 points from baseline. Transcranial alternating current stimulation (tACS) works by controlling the oscillatory activity of the cerebral cortex. In one combined rTMS-MBSR therapy, the total score for the NSSI in the combined group at the end of intervention (T3) was 1.26 ± 0.24 , which was significantly lower than the total score of NSSI in the control group as 1.44 ± 0.23 ($P = 0.004$), indicating a synergic effect of physical therapy-psychotherapy therapy [12].

6. Research hotspots and directions

Current work is directed towards four avenues: addictive mechanisms of NSSI and transdiagnostic treatment with substance use disorders; NSSI social contagion mechanisms and prevention in networked environments; multi-omics biomarker discovery (genomics, transcriptomics,

metabolomics); and digital therapeutics development (AI emotion monitoring, online skills training, VR mindfulness). Future studies show three changes: cross-sectional to longitudinal studies on trajectories of comorbidity; from one factor to multiple factor interaction studies (synergistic mechanisms underlying the biological-psychological-social model); and from universal to precision treatment (formulating stratified treatment protocols based on individual risk characteristics and biomarkers). Large-scale longitudinal cohort studies are required for systematic investigation of dynamic development of comorbidity; specific early identification tools based on biomarkers, clinical characteristics and environmental factors should be developed; specific intervention protocols should be tailored to different subgroups in terms of age, gender, and risk features; technologies should be developed in the field of digital therapeutics to make intervention more accessible and effective, and ultimately to reduce the incidence of adolescent comorbidity and improve long-term prognosis.

7. Conclusion

The clinical phenomenon of adolescent depression-NSSI comorbidity is a multi-faceted one involving several neurobiological (e.g., neurotransmitter system dysfunction, HPA axis dysregulation, and structural-functional abnormalities in the prefrontal cortex), psychological (e.g., emotion dysregulation, experiential avoidance, and cognitive impairment), and social ecological (e.g., developmental cascades, social learning, and cultural factors) mechanisms. Primary risk factors are major depression, childhood abuse, female gender and history of suicide attempt. Comprehensive interventions such as DBT-MBSR, olanzapine-sertraline drug combinations and rTMS-psychotherapy combinations have shown favorable clinical efficacy.

The existing studies have the following failings: cross-sectional studies are prevalent and do not allow causal-temporal relationships to be established; sample sizes are generally small and statistical power is limited; the research is limited in both its focus on male adolescents and cross-cultural nature; and the follow-up periods in intervention studies are short, and there is a lack of evidence for long-term efficacy. The future research should focus on strengthening large-scale longitudinal cohort tracking and deeply exploring the interaction between biological, psychological and social factors; building precise risk prediction and intervention system based on biomarker and artificial intelligence; building “four-in-one” intervention system combining biological therapy, psychotherapy, family intervention and social support; and promote the application of digital health technology in early identification, real-time monitoring and remote intervention. It is hoped that a multidisciplinary approach and cross-field integration will clear new routes for prevention and treatment of the comorbidity of adolescent depression and NSSI, with the aim of minimizing the burden of the disease and the risk of adolescent suicide.

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