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EDITORIAL

Mindfulness training in medical education as a means to improve resilience, empathy, and mental health in the medical profession

Edison Iglesias de Oliveira Vidal, Luiz Fernando Alvarenga Ribeiro, Marco Antonio de Carvalho-Filho, Fernanda Bono Fukushima

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Edison Iglesias de Oliveira Vidal, Internal Medicine Department, Botucatu Medical School, Sao Paulo State University (UNESP), Botucatu 18618-687, SP, Brazil

Edison Iglesias de Oliveira Vidal, Marco Antonio de Carvalho-Filho, Fernanda Bono Fukushima, Wenckebach Institute for Education and Training, LEARN - Lifelong Learning, Education and Assessment Research Network, University Medical Center Groningen, Groningen 9713AV, Groningen, Netherlands

Luiz Fernando Alvarenga Ribeiro, Assertiva Mindfulness, Botucatu 18603-970, SP, Brazil

Fernanda Bono Fukushima, Surgical Specialties and Anesthesiology Department, Botucatu Medical School, São Paulo State University (UNESP), Botucatu 18618-687, SP, Brazil

Corresponding author: Edison Iglesias de Oliveira Vidal, MD, PhD, Associate Professor, Internal Medicine Department, Botucatu Medical School, Sao Paulo State University (UNESP), Av. Prof. Mario Rubens Guimaraes Montenegro, S/N, Botucatu 18618-687, SP, Brazil. edison.vidal@unesp.br

Abstract

The high rates of depression, burnout, and increased risk of suicide among medical students, residents, and physicians in comparison with other careers signal a mental health crisis within our profession. We contend that this crisis coupled with the inadequate acquisition of interpersonal skills during medical education results from the interaction between a challenging environment and the mental capital of individuals. Additionally, we posit that mindfulness-based practices are instrumental for the development of major components of mental capital, such as resilience, flexibility of mind, and learning skills, while also serving as a pathway to enhance empathy, compassion, self-awareness, conflict resolution, and relational abilities. Importantly, the evidence base supporting the effectiveness of mindfulness-based interventions has been increasing over the years, and a growing number of medical schools have already integrated mindfulness into their curricula. While we acknowledge that mindfulness is not a panacea for all educational and mental health problems in this field, we argue that there is currently an unprecedented opportunity to gather momentum, spread and study mindfulness-based programs in medical schools around the world as a way to address some longstanding shortcomings of the medical profession and the health and educational systems upon which it is rooted.

Key Words: Mindfulness; Medical education; Mental capital; Mental health; Medical students; Resilience

Core Tip: High rates of depression, burnout, and suicide risk among medical professionals highlight a mental health crisis. We proposed that mindfulness-based practices can enhance mental capital, fostering resilience, flexibility, and learning skills. Mindfulness also promotes empathy, compassion, self-awareness, conflict resolution, and relational abilities. Increasing evidence supports the effectiveness of mindfulness interventions, prompting many medical schools to integrate them into curricula. While not a panacea, mindfulness offers a promising opportunity to address longstanding issues in the medical profession and associated health and educational systems.

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INTRODUCTION

By the end of the 20th century, there was a consensus that medical education should transition its focus from the memorization of factual material to the cultivation of life-long learning skills in students[1-3]. Rather than learning something once and for all, students were expected to acquire the ability to continually update their knowledge. Medical schools were tasked to equip students with the means and skills to foster such attitudes. This shift in perception arose in response to the geometric growth and increased accessibility of information within the field of medicine.

Interestingly, this evolution in medical education did not witness a parallel transformation in the acquisition of relational and conflict-solving skills[4-6]. While medical schools adapted to the changing landscape of information delivery, the emphasis on relational skills did not experience a comparable shift within formal curricula. However, most physicians would probably agree that acquiring proficiency in relational skills with patients, peers, and other healthcare professionals is far more complex than mastering factual information or technical procedures[7]. Compounding this challenge is the consistent evidence showing a decline in empathy among medical students and residents as they progress through their education[8]. This decline not only hampers their ability to understand the patient's perspective but also impacts their competence in working within inter-professional teams, potentially contributing to the development of disruptive behavior, which is an increasingly recognized source of avoidable medical errors and harm to patients[9].

Shapiro *et al*[10] proposed a definition of professionalism as "any intent, action, or words that foster trustworthy relationships." Teaching relational skills that foster such relationships remains at the same time the Achilles' heel and Holy Grail of modern medical education[11,12]. Most experts in this field attribute the challenge of nurturing professionalism in medical students to problems associated with the hidden curriculum of healthcare organizations[13-15]. The hidden curriculum represents the learning derived from the organizational and cultural environment of healthcare institutions[16]. It comprises unspoken, taken-for-granted rules and customs that impart vehement lessons about what is and what is not important, acceptable, or desirable in medicine on a daily basis. Even in the unlikely scenario where medical schools dedicated 1000 h of their formal curricula to teach professionalism to their students, there would still be a significant risk of failure due to the strong influence of unprofessional examples available in every medical school's hidden curriculum.

A few institutions such as Brigham and Women's Hospital, Mount Sinai Medical Center, the University of Pennsylvania Health System, the University of Washington School of Medicine, and Vanderbilt University School of Medicine deserve praise for their efforts in addressing the problem of unprofessional behavior within their hidden curricula. Most of these initiatives involved the establishment of an institutional code of professional conduct and a centralized reporting and management structure for professionalism-related concerns[17].

While such approaches are extremely important, we contend that they are insufficient to change the landscape of declining empathy and other relational abilities within medical education. Our main argument lies in the fact that the inappropriate acquisition and deterioration of interpersonal skills results from the interaction of a challenging environment and the individual mental capital of medical students. By 'environment' we mean not only matters associated with the hidden curriculum but also every experience, positive and negative, students go through during their training. The very nature of medical learning inevitably involves experiencing stress, suffering, pain, loss, and several other challenging situations such as sleep deprivation, heavy study/workload, and responsibility in caring for patients with serious illnesses. By individual 'mental capital,' we refer to both cognitive and emotional resources, encompassing learning abilities, mental flexibility, emotional intelligence, social skills, and resilience in the face of stressful situations, as defined by an influential report from the Foresight Program of the United Kingdom Government Office for Science[18].

Our argument is supported by a recent systematic review of predictors of empathy and compassion among medical students, which included 222 studies[19]. On the one hand, that review revealed that empathy and compassion are negatively associated with factors such as heavy workloads, hierarchical work environments, 'assembly-line' organizational culture, and an educational ethos prioritizing the acquisition of knowledge and academic achievement. On the other hand, that review also found evidence that empathy and compassion were positively correlated with individual characteristics of students, such as emotional intelligence, openness, perspective-taking, and reflexive skills.

If medical schools are indeed committed to changing the picture of declining empathy described above, in addition to addressing their hidden curricula, they should strive to nurture their students' capabilities to cope with adverse and stressful milieus. But what kinds of initiatives have evidence as a means to increase empathy, compassion, self-awareness, stress coping, conflict-solving, and relational abilities?

We posit that mindfulness-based practices offer a way to foster such competencies. Mindfulness has been defined as "the awareness that emerges through paying attention on purpose, in the present moment, and nonjudgmentally to the unfolding of experience moment by moment"[20]. It is an innate ability that can be enhanced by training in several formal and informal mindfulness techniques. These methods originated from ancient contemplative traditions, especially Buddhism, and were systematized by John Kabat-Zinn in 1979 into a program called Mindfulness-Based Stress Reduction. That program did not aim to teach Buddhism or any kind of religious ideology; instead, it intended to instruct patients, who were not responding to usual medical treatments, in meditative methods to cope and relieve physical and psychic suffering.

The program served as a model for a wide range of mindfulness-based initiatives in various fields such as the military, sports, business corporations, education, and healthcare. In the United Kingdom, an all-party parliamentary group conducted an inquiry into the potential of mindfulness-based practices in the domains of health care, education, workplaces, and the criminal system. In its final report, they argued that mindfulness is instrumental for the development of major components of mental capital, such as resilience, flexibility of mind, and learning skills[21]. In addition, they recommended various forms of support for mindfulness-based initiatives in those key areas. Importantly, those recommendations were framed upon the understanding that the United Kingdom is facing a major mental health crisis, with increasing effects of depression, anxiety, and stress on its population, and alternative approaches are urgently needed to address it.

We contend that the high rates of depression, burnout, and increased risk of suicide among medical students, residents, and physicians in comparison with other careers also point to the existence of a mental health crisis within our profession[22-25]. For example, according to the Australian National Mental Health Survey of Doctors and Medical Students, which included over 14000 participants, 24.8% of doctors had thoughts of suicide in comparison to 13.3% of the general population and 12.8% of other professionals[26].

The evidence base around the effectiveness of mindfulness-based interventions has been growing over the years. A review of mindfulness-based programs in medical education concluded that despite the different designs of those programs, their results were uniformly positive among medical students and healthcare professionals and involved increases in empathy, self-compassion, and ability to focus, as well as decreases in stress, anxiety, and depressive symptoms[27].

Another recent systematic review focused exclusively on the effectiveness of mindfulness-based interventions on empathy in healthy populations and included 12 randomized clinical trials and 1 quasi-experimental study[28]. Its meta-analysis found a statistically significant positive standardized mean difference of 0.37 (95% confidence interval: 0.16 to 0.58) favoring the mindfulness-based interventions in improving empathy levels in comparison to controls. Importantly, 7 out of the 13 studies included in that review focused on subjects in medical-related occupations, and 4 studies on medical students.

Similarly, a meta-analysis of the most comprehensive systematic review conducted to date about the effectiveness of mindfulness-based interventions on stress levels in medical students found a pooled standardized mean difference of 0.37 (95% confidence interval: 0.24 to 0.50), favoring the mindfulness arm, in 18 studies[29]. In addition, a recent scoping review of mindfulness training for undergraduate health and social care students highlighted that, besides its positive effects on stress levels, those interventions were associated with improved student self-awareness, ability to attend to patients, peer cohesion, and group support, as well as student insights into the culture of health and social education[30].

Furthermore, it seems relevant to highlight that there is some initial evidence that there may be long-term benefits of mindfulness interventions among students. A randomized controlled trial of a 15-h mindfulness-based stress reduction intervention performed over 7 wk among 288 undergraduate medical and psychology students was associated with improved well-being and coping patterns up to 6 years after the intervention[31]. Lastly, a recent realist review of mindfulness-based interventions in a variety of workplaces, including 75 studies, suggested that the mechanisms behind the positive effects of those interventions involved awareness/self-regulation, acceptance/compassion, a sense of growth, feeling permitted to take care of oneself, and the promise of goal attainment[32]. Importantly, that review also emphasized the paramount role of a supportive environment in realizing the positive effects of mindfulness-based interventions.

As to the pathophysiological mechanisms underlying the effects of mindfulness-based practices, there is some evidence from the neuroscience field indicating that they are associated with neuroplastic changes in the insula, amygdala, anterior cingulate cortex, frontolimbic network, temporoparietal junction, and default mode network. These structures are related to the regulation of attention and emotion and change in perspective on self[33,34].

Finally, it is important to acknowledge that mindfulness-based practices had already made their first steps in medical education decades ago[27]. The University of Massachusetts Medical School has been offering a mindfulness-based stress reduction program for its students as part of its curriculum since 1985. Monash University in Australia integrated a mindfulness program into its core curriculum for all medical students in 2002 and expanded it into other faculties such as

Engineering, Law, and Psychology. Importantly, a 2014 survey found that 43 out of 140 medical schools accredited by the Association of American Medical Colleges in the United States had mindfulness integrated into their curricula[35].

CONCLUSION

The arguments described above do not imply that all questions about mindfulness practices and their role in medical education have been solved, nor that they are a mystic solution for all educational and mental health problems in this field. Instead, they highlight the current unprecedented opportunity to gather momentum, spread, and study mindfulness-based programs in medical schools around the world as a way to address some longstanding shortcomings of the medical profession and the health and educational systems upon which it is rooted.

FOOTNOTES

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ORCID number: Edison Iglesias de Oliveira Vidal 0000-0002-1573-4678; Marco Antonio de Carvalho-Filho 0000-0001-7008-4092; Fernanda Bono Fukushima 0000-0001-8055-5425.

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REVIEW

Adolescent suicide risk factors and the integration of social-emotional skills in school-based prevention programs

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Xin-Qiao Liu, Xin Wang, School of Education, Tianjin University, Tianjin 300350, China

Corresponding author: Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, No. 135 Yaguan Road, Jinnan District, Tianjin 300350, China.
xinqiaoliu@pku.edu.cn

Abstract

Adolescents are considered one of the most vulnerable groups affected by suicide. Rapid changes in adolescents' physical and mental states, as well as in their lives, significantly and undeniably increase the risk of suicide. Psychological, social, family, individual, and environmental factors are important risk factors for suicidal behavior among teenagers and may contribute to suicide risk through various direct, indirect, or combined pathways. Social-emotional learning is considered a powerful intervention measure for addressing the crisis of adolescent suicide. When deliberately cultivated, fostered, and enhanced, self-awareness, self-management, social awareness, interpersonal skills, and responsible decision-making, as the five core competencies of social-emotional learning, can be used to effectively target various risk factors for adolescent suicide and provide necessary mental and interpersonal support. Among numerous suicide intervention methods, school-based interventions based on social-emotional competence have shown great potential in preventing and addressing suicide risk factors in adolescents. The characteristics of school-based interventions based on social-emotional competence, including their appropriateness, necessity, cost-effectiveness, comprehensiveness, and effectiveness, make these interventions an important means of addressing the crisis of adolescent suicide. To further determine the potential of school-based interventions based on social-emotional competence and better address the issue of adolescent suicide, additional financial support should be provided, the combination of social-emotional learning and other suicide prevention programs within schools should be fully leveraged, and cooperation between schools and families, society, and other environments should be maximized. These efforts should be considered future research directions.

Key Words: Adolescent suicide; Risk factors; Social-emotional skills; Social and emotional learning; School; Prevention

Core Tip: Adolescent suicide, as a public health issue with severe consequences and causing significant harm, calls for a more powerful and efficient global response. Adolescents spend the majority of their time in school, making this a natural setting for the implementation of social-emotional learning and the cultivation of social-emotional skills. In the future, efforts to prevent and address adolescent suicide should provide schools with more adequate financial support, further strengthen the combination of social-emotional learning and other suicide prevention programs within schools, and promote higher-quality solutions for the issue of suicide through the combined efforts of schools, families, and society.

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INTRODUCTION

Suicide is defined as a self-directed, harmful, intentional act that results in death[1]. Regardless of age, sex, occupation, or geographical location, individuals are vulnerable to suicide. As a dangerous behavior performed under the influence of multiple factors, suicide poses a significant threat to individuals' physical and mental well-being, life safety, social welfare, and even regional development. Every suicide case is tragic, and suicide has become an urgent global public health issue[2-6]. The World Health Organization's "Preventing Suicide: A Global Imperative" report states that one person dies by suicide every 40 s worldwide, resulting in more than 800000 deaths each year[7]. Suicide has become one of the leading causes of death worldwide, with more than 1 in 100 deaths attributed to suicide, exceeding the number of deaths from malaria, HIV/AIDS, breast cancer, war, and homicide[8]. For example, in the United States, the suicide rate has been increasing continuously for two decades (since 2000). Between 2000 and 2018, the suicide rate in the United States increased by 35%. Although there was a slight decrease in the suicide rate in 2019 due to a slight decline among white individuals, the rates among all other racial/ethnic groups continued to increase or remain stable. The highest suicide rates were observed in the western, midwestern, and southern regions, and the suicide death rate was highest among individuals of specific racial/ethnic groups, such as non-Hispanic American Indian or Alaska Native individuals. The first and second peaks in suicide mortality typically occur among young and older adults[9]. Moreover, the global coronavirus disease 2019 (COVID-19) pandemic has further exacerbated the global risk of suicide. The pandemic has been associated with negative emotions such as distress, anxiety, fear of infection, depression, and insomnia among the general population[10], leading to an increased risk of mental disorders, chronic trauma, and stress, ultimately increasing suicidality and suicidal behaviors[11]. A retrospective study analyzing 24350 cases of suicide deaths in Nepal showed an overall increase in the monthly suicide rate, with an additional 0.28 suicides per 100000 people during the pandemic. Both male and female suicide rates have significantly increased, with rates of 0.26 and 0.3, respectively[12]. A study conducted among college students in the United States during the COVID-19 pandemic showed that 6999 participants reported engaging in non-suicidal self-injury, 3819 reported suicidal ideation, 1531 reported making a suicide plan, and 334 reported a suicide attempt in the past 12 months[13].

Although suicide can impact individuals in all age groups, suicidal thoughts and behaviors (STBs) of adolescents deserve special attention. First, among the various groups at risk of suicide, young people are considered one of the most vulnerable[7], and suicide has become the fourth leading cause of death among the global population aged 15-29 years [14]. In the United States, for every 7 youth, there is 1 who has seriously considered suicide or made a suicide plan, and 1 out of 13 youths had attempted suicide in the previous year[15]. A study on suicidal ideation and behavior among high school students yielded similar conclusions. One study indicated that in 2019, approximately one-fifth of youths had seriously considered attempting suicide, one-sixth had made a suicide plan, one-eleventh had attempted suicide, and one-fortieth had made a suicide attempt requiring medical treatment[16]. Suicide, as a leading cause of death among adolescents, has become a critical global public health priority. Second, the prevention and control of adolescent suicide are crucial for addressing the issue of suicide. Many individuals who have previously considered or attempted suicide did so during their youth; suicide, as a risk event for which intervention can be provided at an early stage, provides a key opportunity for prevention during adolescence[17]. Research has shown that the number of people exhibiting suicidal behaviors dramatically increases during adolescence, with approximately one-third of adolescents with suicidal ideation developing a suicide plan, approximately 60% of adolescents with a suicide plan attempting suicide, and the majority of suicide attempts occurring within the first year after the onset of suicidal ideation[18]. Therefore, if we can fully understand the risk factors for adolescent suicide, promptly assess adolescents' current psychological states, and provide timely warnings and proactive responses when risk factors or negative psychological states arise, we can achieve the goal of suicide prevention. Early intervention during the suicide trajectory can reduce the risk of death and save additional lives. Finally, adolescence is an important turning point in an individual's life[19] and represents a critical period for individual physical and mental development as well as for exploring life experiences, seeking independence, and establishing intimate relationships[20,21]. The rapid development of the mind and body and rapid changes in life not only bring significant opportunities for growth and development for adolescents but also come with certain risks to their mental health[22-26] and lead to conflicts in life[27-31], which cannot be ignored in terms of the risk of suicide. In the future, the physical and mental health of adolescents requires broader public attention, more comprehensive care, and

stronger support from society.

Therefore, adolescent suicide, as a public health issue with detrimental effects and causing significant harm, requires a more powerful and efficient global response. Social and emotional learning (SEL) is considered a powerful measure for addressing the crisis of adolescent suicide and resolving this issue[32]. As an integral part of education and human development, SEL is a process of cultivating social and emotional competencies in which young people acquire and apply knowledge, skills, and attitudes to develop a healthy identity; manage emotions; achieve personal and collective goals; empathize with others; establish and maintain supportive relationships; and make responsible and compassionate decisions[33,34]. The important role of SEL in intervening in adolescent suicide has also been recognized in the World Health Organization's "LIVE LIFE" suicide prevention guidelines, which identify "foster social-emotional life skills in adolescents" as a key effective intervention measure for suicide prevention[35]. Given the severity of the issue of adolescent suicide, the uniqueness of the adolescent population, and the importance of safeguarding adolescents' well-being, it is necessary to systematically examine the risk factors for adolescent suicide and explore more effective solutions. Based on a review and analysis of the risk factors influencing adolescent suicide, this study examined the important role of SEL in the prevention and control of adolescent suicide and explored school-based preventive practices with an emphasis on social and emotional skills as interventions for adolescent suicide. Hopefully, this study will make a substantial contribution to safeguarding the well-being of adolescents and overcoming the crisis of adolescent suicide.

RISK FACTORS FOR ADOLESCENT SUICIDE

Psychological, social, family, individual, and environmental factors are important risk factors for adolescent suicide-related behaviors within the adolescent population (see Figure 1). These factors may contribute to the presence of suicidal vulnerability in adolescents through various direct, indirect, or combined pathways.

Psychological factors

The period from adolescence to early adulthood, ranging from late teens to twenties, is a period of profound change and significance[36]. Individuals at this stage of life experience the joy of growth and maturity, eagerly embracing their new life and gradually embarking on a new phase of their lives with numerous attempts. However, along with the accelerated pace of growth, adolescents also face significant psychological changes, identity and role transitions, and increasingly diverse and complex challenges from their families and institutions[37]. These changes and challenges often accompany immense psychological stress or even distress, which can lead to mental problems, including despair, anxiety, depression, bipolar disorder, and eating disorders; these mental problems are often linked to the risk of suicide-related behaviors and are considered important risk factors by scholars[38-40]. Research has indicated that individuals with psychiatric diseases account for the vast majority of suicide completers and attempters, whose prevalence is at least 10 times greater than that in the general population[41]. Individuals with bipolar disorder, characterized by alternating or mixed manic and depressive episodes, have the highest suicide rate among individuals with all other mental disorders, and suicide is approximately 20 to 30 times more common in the bipolar population than in the general population[42]. In 2019, of the 14 million individuals with eating disorders, nearly 3 million were children and adolescents; anorexia nervosa usually develops during adolescence or early adulthood, and bulimia nervosa is associated with a greater risk of suicide[43]. Although they are experiencing rapid changes in both their physical and mental states, adolescents are still limited by their developmental and age characteristics. Compared to adults, adolescents possess a certain level of immaturity and vulnerability, making them more susceptible to negative emotions or psychological problems in the face of setbacks or adverse events in life. If these issues are not promptly and properly addressed, adolescents may develop suicidal thoughts or even choose to prematurely end their lives under the influence of psychological factors.

Social factors

Race, socioeconomic status, stigma, and bullying are important social risk factors that contribute to adolescent suicide-related behaviors. There are significant racial differences in adolescents' suicidal ideation-related behaviors. On the one hand, adolescents of multiple races are at high risk for suicide-related behaviors[44], with youth from ethnic minority backgrounds having the highest suicide risk during the early stages of life. Black, Asian/Pacific Islander, and American Indian adolescents have the highest suicide risk during adolescence and young adulthood[45]. On the other hand, youth from racial and ethnic minority backgrounds also face barriers in accessing mental health services and encounter issues such as inadequate treatment[46,47]. Many adolescents at risk of suicide often lack or are unable to access necessary mental health interventions and services in a timely manner. Economic factors also influence suicide-related behaviors, with economic recessions appearing to increase overall suicide rates[48]. Economic downturns significantly affect the health, well-being, and living conditions of the population, and economic pressure and unemployment have devastating impacts on families, particularly children[49]. Globally, more than 75% of completed suicides occur in low- and middle-income countries[50], and 88% of adolescent suicide deaths are reported in low- and middle-income countries[8]. Children and adolescents from disadvantaged socioeconomic backgrounds often face multiple life pressures; compared to those from higher socioeconomic backgrounds, children and adolescents from lower socioeconomic backgrounds are more likely to experience mental health problems[51]. After developing psychological issues, these children and adolescents are also more likely to be deterred from seeking treatment due to the high cost and heavy financial burden of these treatments, thus leading to a greater risk of suicide. Stigma is a social process aimed at excluding individuals who are considered potential sources of illness and may pose a threat to effective social life; individuals who are stigmatized experience passive negative emotional reactions from dominant others[52]. Stigmatization has undeniable direct and

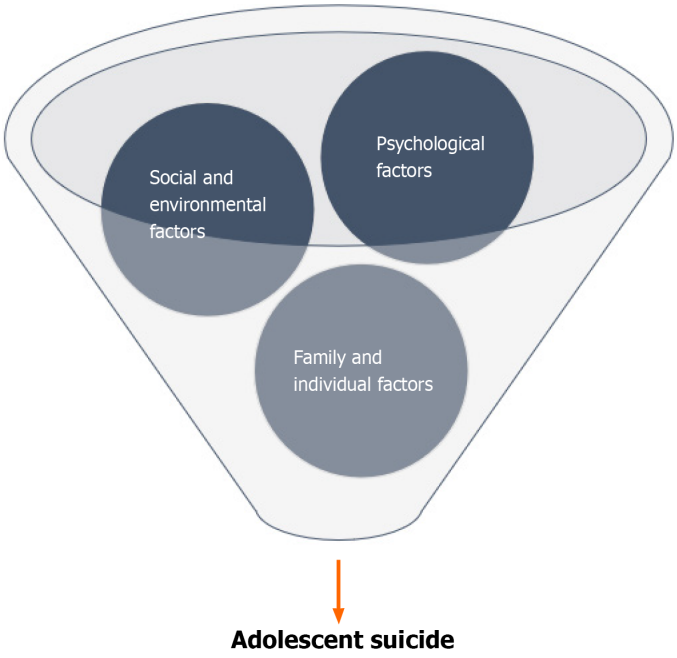

Figure 1 Various risk factors for adolescent suicide.

indirect harmful effects on children and adolescents[53]. The discrimination and shame brought about by stigma can result in worsened mental health conditions or increased mental illness burden among adolescents[54], leading to the emergence of suicidal ideation or suicidal behaviors. Furthermore, due to the fear of stigma-related risks, there may be delays in seeking treatment or poorer medication adherence, consequently resulting in an increase in mortality rates[55]. Moreover, there is a certain association between bullying and the risk of adolescent suicide[56]. Bullying is considered a dynamic risk factor for adolescents, as both victims and perpetrators of bullying are at an increased risk of suicide[57]. Lower levels of social connectedness and higher levels of bullying victimization and perpetration are significantly associated with adolescent suicidal ideation and suicide attempts; the relationship between suicidal ideation and bullying victimization also follows a dose-response pattern, with an increased frequency of victimization associated with an increased risk of suicidal ideation[58]. Results from a cohort study showed that victims of bullying had more suicide ideation, incidences of self-harm, and suicide attempts across all age groups, with being bullied during adolescence being a strong predictor for suicidal behavior and self-harm[59].

Family factors

The family is considered a significant context for adolescent life and development and is closely linked to mental and physical well-being and future prospects. According to ecosystem theory, the family is a microsystem that profoundly influences individual development, with parenting styles, family relationships and atmosphere, and parental educational levels closely associated with child mental health[60]. Adolescents raised in families with parental mental illness, domestic violence, or abuse have a greater risk of developing mental disorders[61]. On the one hand, there is a certain association between a family history of mental disorders and suicide-related behaviors in adolescents. Studies indicate that the suicide rate among families of suicide victims is twice that of the comparison families, and a family history of suicide can predict suicide independent of severe mental disorders[62]. A psychological autopsy study examining 19 cases of adolescent suicide revealed that 84.2% of the adolescents had a history of mental illness in their family, and 47.4% of the families had a history of suicide, with one adolescent's father dying from suicide in the year prior to the adolescent's suicide[63]. On the other hand, a lack of supportive family relationships and environments may act as precipitating risk factors for suicide-related behaviors in adolescents. The extent to which children who are exposed to adversity, including violence, poverty, and disability, can recover depends more on the quality of the environment (rather than on individual characteristics) and the resources available to foster and maintain well-being. Similarly, compared to individual factors, environmental factors have a greater impact on the positive development of individuals exposed to higher levels of stress, such as children who experience abuse[64]. Research suggests that parental support during the relatively psychologically unstable period of adolescence can be crucial in protecting adolescents from the influence of suicidal ideation and promoting the establishment of a positive identity[65]. Therefore, parental and familial support is crucial for adolescent development. If adolescents are already in a relatively psychologically unstable period, face life setbacks or adversities and do not receive material support or emotional care from their families, they are likely to experience severe psychological problems, entertain suicidal thoughts, or even attempt suicide, especially if they experience intense conflicts or severe domestic violence during this critical period.

Individual factors

Sex is considered an important influencing factor in suicide-related behaviors, with males often exhibiting a higher risk of

suicide. Taking the following examples of the United States and Hong Kong: Between 2007 and 2014, the suicide rates for males and females in Hong Kong were 18.3 and 9.7 per 100000 population, respectively, with a male-to-female suicide ratio of 1.9. In the United States, the suicide rates for males and females were 21.3 and 5.6 per 100000 population, respectively, with a male-to-female suicide ratio of 3.8[66]. Within the adolescent population, the absolute number of completed suicides and the suicide rate are greater among male adolescents than among female adolescents[67]. Drug abuse, externalizing disorders, and access to means are identified as sex-specific risk factors for suicide death among males[68]. A multigroup comparison study on adolescent suicide and severe suicide attempts revealed a significant association between suicide risk and male sex; the sex difference in suicide outcomes can be explained by method choices, as male suicide victims often employ more direct and lethal methods, such as hanging, vehicle exhaust gas, firearms, and jumping[69]. Moreover, transgender individuals report higher rates of suicidal ideation and suicide attempts than does the general population[70]. Sexual orientation is also associated with suicide-related behaviors, with sexual minority males and females having an elevated risk of depression, anxiety, suicide attempts or suicide, and substance-related issues[71]. A survey involving 13984 first-year college students from eight countries and 19 institutions revealed that sexual orientation was the factor most strongly correlated with STBs and the transition from ideation to plan; additionally, no heterosexual students had a greater risk of transitioning from ideation to planned and unplanned attempts [72]. Regarding the reasons for suicide-related behaviors, a survey of 876 self-identified lesbian, gay, and bisexual (LGB) youth found that for gay, lesbian, and bisexual girls, the stress of coming out was associated with depression and suicidal ideation, and feeling like a burden to the "people in their lives" was identified as a crucial mechanism explaining higher levels of depression and suicidal ideation among LGB youth[73].

Environmental factors

Adolescents spend the majority of their time in school, which serves as a primary setting for their learning and development. Schools provide opportunities for acquiring knowledge, developing skills, and cultivating relationships with teachers and peers. While schools offer unlimited potential for adolescent growth and achievement, they also lead to certain suicide risks. First, the school environment, which includes teacher support, peer support, the teaching and learning atmosphere, and school safety, has a crucial influence on adolescent suicide; negative perceptions of the school environment are significant risk factors for adolescent suicide, as an unfavorable school atmosphere may hinder the fulfillment of basic psychological needs[74]. Additionally, the school environment may increase the availability of alcohol, tobacco, and illicit drugs[20], leading to the emergence of suicidal ideation or suicide attempts among adolescents. Second, there is a correlation between school material conditions and adolescent suicide risk. Underdeveloped material conditions and relative poverty in schools often indicate greater environmental stress, limited developmental resources, and inadequate psychological support. Students from impoverished schools may face greater risks of mental health problems, including suicidal behaviors[75]. Furthermore, while the school environment offers valuable opportunities for peer interaction, it also entails specific group risks such as bullying. Bullying is considered one of the most common expressions of violence among peers during the school year[76]. Physical contact, verbal harassment, rumor spreading, deliberate exclusion of others from the group and obscene gestures are considered important manifestations of bullying [28]. Young people who are not yet fully mature can easily become perpetrators or passive recipients of bullying behaviors due to the interaction of complex interpersonal interactions and family and social environments. For example, a study noted that victimization is associated with poor parental education, low parental occupation and poverty and that victims of bullying are more likely to come from families with a lower socioeconomic status[77]. This in turn creates challenges for the physical and mental health and overall well-being of adolescents. School bullying, as a stepping stone to poor life outcomes, is harmful and repetitive and is a strong risk marker for negative behavioral, health, social and/or emotional problems and is often associated with suicidal ideation and suicide attempts[78]. For example, during the puberty stage, individuals exposed to verbal bullying, negative rumors and unhealthy interpersonal relationships within schools can present significant self-identity challenges and psychological burdens for adolescents. A survey of 1811 Chinese middle school students revealed a positive correlation between negative rumors in school and suicidal ideation, with the increase in suicidal ideation being mediated by increased academic burnout[79]. Finally, academic performance during the school years is closely associated with adolescent suicide-related behaviors. A systematic study on the relationships between academic stress and adolescent depression, anxiety, self-harm, suicidality, suicide attempts, and suicide demonstrated a positive correlation between academic stress and psychological health issues among adolescents [80]. Suicidal ideation is also significantly associated with depression, test anxiety, academic self-concept, and adolescents' perceptions of parental dissatisfaction with their academic achievements[81]. In addition to the school environment, sudden environmental changes such as earthquakes, accidental fires, typhoons, tornadoes, hurricanes, mudslides, tsunamis, armed conflicts, particulate pollution, extreme temperatures and humidity, and the COVID-19 pandemic can also influence adolescent suicidal tendencies and risks, including suicidal ideation, suicidal behavior, and suicide completion[82,83]. Taking COVID-19 as an example, studies have indicated a 25% increase in suicide attempts among adolescents during the COVID-year, with a particularly significant increase of 195% in suicide attempts among girls during the starting school period[84].

SOCIAL-EMOTIONAL SKILLS AND THEIR IMPORTANT ROLE IN PREVENTING ADOLESCENT SUICIDE

Adolescence is a crucial period of profound physical and psychological change that often leads to certain mental health risks and potential suicidal behaviors; however, this period also has tremendous potential for promoting health and implementing preventive measures that can influence positive health and developmental outcomes[85]. The Collab-

orative for Academic, Social, and Emotional Learning defines SEL as the process through which all young people and adults acquire and apply knowledge, skills, and attitudes to develop self-awareness; manage emotions; achieve personal and collective goals; feel and show empathy; establish and maintain positive relationships; and make responsible and compassionate decisions[34]. Self-awareness, self-management, social awareness, relationship skills, and responsible decision-making are recognized as the five core SEL skills. As a core aspect of comprehensive student development, SEL fosters empathy, resilience, interpersonal skills, and lifelong learning abilities while supporting academic development and psychological growth, contributing to the development of safe, healthy, and equitable communities[86]. Cultivating and promoting social and emotional skills during adolescence contribute to future well-being and positive life outcomes [87].

Self-awareness

Self-awareness is an individual's ability to understand his or her own thoughts, emotions, and values and how they influence his or her behavior[88]. Having a healthy level of self-awareness helps adolescents to have a correct understanding of their strengths and weaknesses, maintain a positive and optimistic attitude toward life, and exhibit sufficient self-esteem, self-confidence, and self-love, thereby effectively avoiding the emergence of suicidal thoughts and suicidal behaviors. Self-esteem is considered an individual's belief about how they perceive themselves and how others perceive them[89]. Self-esteem has a profound impact on adolescents' suicidal tendencies, as low self-esteem is closely associated with depression, hopelessness, and suicidal tendencies[90]. Findings from a cross-sectional study conducted with 1149 Vietnamese secondary school students demonstrated that[91], compared to students with normal self-esteem, students with low self-esteem had twice the likelihood of experiencing anxiety symptoms and nearly six times the likelihood of being at risk of depression; students with low self-esteem also had a significantly higher probability of considering or attempting suicide. Additionally, optimism, as a highly beneficial psychological trait, is closely related to positive emotions, perseverance, achievements, and physical health[92]. Optimism helps individuals actively cope with difficulties, setbacks, and challenges in life. Self-awareness shows tremendous potential in the prevention of youth suicide. Self-awareness not only helps adolescents maintain a healthy level of self-esteem but also enables them to develop a correct understanding of their sex characteristics, physical and mental conditions, and sexual orientations to better cope with mental health challenges. Self-awareness also guides adolescents to maintain a positive and optimistic attitude toward life in the face of challenges such as major disasters and events such as the COVID-19 pandemic, effectively reducing the risk of suicide.

Self-management

Self-management is an individual's ability to effectively regulate his or her thoughts, emotions, and behavior in various situations while working toward achieving goals[88]. Self-management encompasses stress management, goal setting, impulse control, self-motivation, and organizational skills and can be utilized to address issues such as hopelessness, anxiety, substance use, and child sexual abuse[32]. Having strong self-management skills helps adolescents take control of their daily lives through goal setting and effective planning, take timely and effective actions in the face of difficulties and setbacks, seek help and support or release stress in times of psychological crisis, and achieve a sense of accomplishment through self-motivation, effectively mitigating the risk of suicide. For example, in the context of academic problems, the transition to higher education brings about changes in the environment, balancing heavy academic loads, tight schedules, and different learning methods; the loss of the comfort zone from childhood; and the fear of not achieving good grades, which often leads to increased stress among adolescents[93]. Under the pressure of such severe stressors, academic problems are often accompanied by negative emotions such as anxiety, depression, hopelessness, and breakdown and are correlated with risky behaviors such as self-harm and suicide[94]. In this context, if adolescents can develop and possess strong self-management skills, they can effectively manage themselves in scientific goal setting, implement effective study plans, adjust their study pace flexibly, and employ appropriate learning motivation. By improving learning efficiency and experiencing academic achievements, adolescents can reduce their psychological issues and lower their risk of suicide.

Social awareness

Social awareness is the ability to understand social perspectives and empathize with individuals from different backgrounds[88]. Having a good level of social awareness enhances adolescents' empathy, enabling them to consider the viewpoints of other individuals from diverse backgrounds and cultures on the basis of the mastery of social and ethical norms and understanding of social perspectives while also utilizing the resources available in their families, schools, and communities to seek support for their own development. Empathy is associated with positive outcomes such as increased emotional well-being, enhanced social connections, improved health conditions, helping behaviors, cooperation, and altruism[95]. Empathy is negatively correlated with bullying behavior, as understanding and experiencing others' emotions help children avoid engaging in antisocial behaviors, including bullying; defenders of children who experience bullying also demonstrate a high level of empathy[96]. Families, schools, and communities serve as the primary environments for adolescents' growth and life experiences; these environments are naturally connected to adolescents and provide diverse material and spiritual resources. These are commonly considered the main settings for implementing interventions related to adolescent suicide prevention[97-99]. For example, a study on racial discrimination and suicidal behaviors among Black adolescents revealed that school safety can reduce suicidal behaviors and moderate the relationship between discrimination and suicide plans and attempts[100]. In light of this, the development of social awareness helps adolescents effectively cope with social risks and impacts. Cultivating empathy reduces bullying and stigmatizing behaviors and guides adolescents to seek help and support from their families, schools, and communities when facing difficulties, effectively reducing the risk of suicide.

Relationship skills

Relationship skills refer to the ability of an individual to develop and maintain healthy and supportive relationships with people from different backgrounds as well as to navigate social situations[88]. Having good interpersonal skills helps adolescents develop various types of relationships by actively listening, communicating in a friendly manner, and collaborating effectively while also resolving conflicts and disagreements with others in a productive manner. Interpersonal interactions are a significant aspect of adolescent life, as adolescents engage and interact with a diverse range of people, including teachers, peers, and parents[101-103]. However, these interactions inevitably bring about interpersonal conflicts and tensions, which may pose a risk of suicidal behavior. A cross-sectional case-control study of 381 Danish adolescents aged 10 to 17 years revealed that having an estranged relationship with parents, siblings, or friends was an early risk factor for suicide, while having problems with parents, boyfriends/girlfriends, or friends accounted for 66%, 17%, and 14.5%, respectively, of all suicide attempts[104]. In this context, fostering relationship skills in adolescents plays a crucial role in the prevention and management of suicide-related behaviors. On the one hand, having good interpersonal skills helps adolescents expand their social networks, with increased interpersonal and emotional support provided by close relationships and interactions. On the other hand, having good interpersonal skills allows adolescents to navigate relationships with their parents, peers, and teachers more effectively, enabling them to resolve interpersonal conflicts constructively and reducing the risk of suicide.

Responsible decision-making

Responsible decision-making refers to the ability of an individual to make caring and constructive social and behavioral choices[88]. Responsible decision-making involves adolescents considering the real-life consequences of their actions based on factors such as personal well-being, others' feelings, moral standards, and social norms. Suicide, as a highly harmful event, often does not occur abruptly but rather occurs through a certain process. It typically includes crucial points such as suicidal ideation, suicide attempts, and suicide completion. While there may be connections between these markers, they do not always show continuous progression over time. For instance, research indicates that the majority of individuals with suicidal ideation do not proceed to make suicide attempts[105]. In other words, suicidal thoughts may not always develop into attempted or completed suicide. In this context, responsible decision-making plays a crucial role in adolescent suicide intervention. On the one hand, compared to adults, adolescents often have less mature and comprehensive thinking when considering issues, and they are more prone to impulsivity[104]. "Hot-headed" situations can easily arise, and responsible decision-making can guide adolescents to assess the potential consequences of suicidal behavior based on various real-life considerations, thereby reducing impulsive suicidal acts. On the other hand, responsible decision-making requires adolescents to consider the potential impact on others, social norms, and relevant laws and regulations before engaging in actions. To some extent, responsible decision-making can help curb the occurrence of acts such as school violence, bullying, and stigmatization, ultimately leading to effective intervention by addressing the root causes of suicide risk.

SCHOOL-BASED INTERVENTIONS FOR ADOLESCENT SUICIDE BASED ON SOCIAL-EMOTIONAL SKILLS

The severity of adolescent suicide and the importance of safeguarding adolescent well-being call for more powerful and effective solutions to mitigate this issue. Various interventions, including school-based interventions, community interventions, family interventions, clinical interventions, and digital interventions, have been widely utilized in suicide prevention practices[98,106-108]. School-based interventions based on the school environment are considered robust approaches for implementing health education and addressing suicide risk. Positive school environments, good facilities, friendly social atmospheres, harmonious interpersonal relationships, and professional training programs provide strong support for resolving adolescent suicide issues and have been widely applied in practice. A realist review on the effectiveness of school-based suicide prevention measures highlighted that such interventions can help identify and treat potential mental illnesses, address potential risk factors related to alcohol use, enhance problem-solving abilities, provide support and coping skills, and eliminate cultural barriers and taboos associated with suicide[109]. The integration of social-emotional skills training with school education provides motivation for the resolution of adolescent suicide problems. School-based interventions for adolescent suicide based on social-emotional competence demonstrate significant potential in the prevention and treatment of adolescent suicide.

First, school-based interventions for adolescent suicide based on social-emotional skills are appropriate for addressing the crisis of adolescent suicide. As one of the microsystems where adolescents are situated, school has the most direct influence on adolescent development[110]. Adolescents spend a significant portion of their adolescence in the school environment, where they learn, socialize, and grow, acquiring various interpersonal skills. Therefore, the cultivation and improvement of social-emotional competence are crucial and inevitable outcomes of school life. The development of social-emotional competence and the resulting improvements in interpersonal relationships and psychological support within the school environment can enhance adolescents' sense of well-being to a certain extent, thereby preventing the emergence of psychological problems and reducing the risk of suicide. On the other hand, educators, school support staff, and peers are well positioned to identify and address risk factors and emerging mental health issues in adolescents, linking them to resources[85], including social-emotional learning programs. This allows real-time monitoring of adolescent suicide risk factors and enables timely intervention and guidance based on appropriate social-emotional competence when suicide risk is detected or when suicidal behaviors occur.

Furthermore, the necessity of school-based interventions for adolescent suicide based on social-emotional skills in addressing the crisis of adolescent suicide should be emphasized. Given the high severity of adolescent suicide status and the significant harm caused by suicidal outcomes, school-based interventions for adolescent suicide based on social-emotional competence require a high level of professionalism and precision. Haphazardly or superficially implemented interventions may not only fail to enhance adolescents' social-emotional competence and dispel suicidal thoughts but also might even have adverse effects, further exacerbating their mental conditions or increasing their risk of suicidal behaviors. Against this backdrop, schools have become crucial settings for implementing school-based interventions for adolescent suicide based on social-emotional competence. Professional staff[111,112] can develop relatively comprehensive suicide prevention plans, provide systematic courses on social-emotional learning, and conduct scientific, reasonable, and targeted social-emotional learning for adolescents. Moreover, they can provide suitable platforms for social-emotional competence training and practice. By implementing scientifically designed curricula and providing professional training, schools can effectively promote the practical enhancement of adolescents' social-emotional competence and improve their mental well-being, thus facilitating efficient interventions for adolescent suicide.

Additionally, school-based interventions for adolescent suicide based on social-emotional skills are cost effective and comprehensive for addressing the crisis of adolescent suicide. From an economic perspective, school-based suicide prevention and mental health education programs are considered efficient and cost-effective approaches to youth education[113]. As representatives of educational institutions, schools naturally possess professional teams, program curricula, and physical facilities for conducting adolescent suicide interventions. They also provide a platform for learning and communication to cultivate adolescents' social-emotional competence. Therefore, implementing school-based interventions for adolescent suicide based on social-emotional competence does not require the construction of new platforms or organizational development. Concentrated and efficient suicide interventions can be provided for adolescents while minimizing manpower, material, and time costs. From a comprehensive perspective, schools play a crucial intermediary role in connecting families and society. On the one hand, societal demands are conveyed to students through schools, and it is through schools that the plans and programmes for adolescent suicide intervention can truly materialize. On the other hand, families and schools are cooperative partners, and schools can, to some extent, regulate pressure from families, providing potential opportunities for adolescents to escape from negative parenting[114].

Finally, school-based interventions for adolescent suicide based on social-emotional skills are effective at addressing the crisis of adolescent suicide. Social-emotional skills are associated with important social, behavioral, and academic outcomes for healthy development. Social-emotional skills not only predict significant life outcomes in adulthood but can also be improved through feasible and cost-effective intervention measures[33]. School-based SEL programmes have been shown to enhance students' abilities. The effective implementation of evidence-based SEL programs can lead to measurable and potentially long-lasting improvements in various aspects of children's lives[115], including improvements in mental well-being and a reduction in suicide risk, which has been acknowledged by the academic community. For example, in response to a series of suicide tragedies in 2015, Tooele County Public Schools in Utah implemented evidence-based SEL curricula in all elementary and junior high schools. Two years later, while youth suicidality rates continued to rise in other counties in the state, the youth suicidality rate in Tooele County actually declined[32]. A meta-analysis involving 213 school-based universal SEL programs and 270034 kindergarten-to-high school students showed that, compared to control groups, the SEL program group demonstrated significant improvements in social and emotional skills, attitudes, behavior, and academic performance, with an 11 percentage point increase in achievement [116]. Similarly, a meta-analysis of 82 school-based universal SEL interventions involving 97406 kindergarten-to-high school students showed that SEL interventions can promote positive development in adolescents. Participants in the intervention group had significantly better social-emotional skills, attitudes, and indicators of well-being than did those in the control group. Additionally, SEL interventions had consistent positive effects on students from different racial and socioeconomic backgrounds, as well as domestic and international student populations[117]. In this context, school-based interventions for adolescent suicide based on social-emotional competence are considered realistic and effective approaches for addressing the crisis of adolescent suicide. These interventions led to enhanced social and emotional skills, improved academic performance, an increased sense of happiness, increased prosocial behaviors, reduced behavioral and internalizing problems, and alleviated mental health conditions, providing new opportunities for reducing adolescent suicidal behavior and ultimately resolving the issue of adolescent suicide.

CONCLUSION

Suicide poses a significant threat to individuals' physical and mental health, life safety, social well-being and even regional development. Adolescents are considered one of the groups most affected by suicide. Given the severity of the current situation and the urgency of addressing adolescent suicide, this article systematically reviewed the risk factors for adolescent suicide and analyzed the important role of social-emotional learning in suicide prevention and intervention. It also explored school-based interventions for adolescent suicide based on social-emotional skills. Psychological, social, family, individual, and environmental factors are important risk factors for adolescent suicidal behaviors. Social-emotional learning is regarded as a powerful intervention measure for addressing and preventing adolescent suicide. The five core competencies of social-emotional learning, namely, self-awareness, self-management, social awareness, relationship skills, and responsible decision-making, have been shown to effectively address various suicide risks among adolescents and provide necessary protection against suicidal behaviors. Among the various suicide intervention methods, school-based interventions for adolescent suicide based on social-emotional skills have shown immense potential in preventing and addressing adolescent suicide. These methods are appropriate, necessary, cost effective,

comprehensive, and effective at tackling the crisis of adolescent suicide. These interventions, which promote enhanced social and emotional skills, improved academic performance, increased happiness, increased prosocial behaviors, reduced behavioral and internalizing problems, and the alleviation of mental health conditions, provide new hope for reducing adolescent suicidal behaviors and ultimately resolving the issue of adolescent suicide.

To further unleash the potential of school-based interventions for adolescent suicide based on social-emotional competence and better address the issue of adolescent suicide, further promotion measures are recommended in the following areas. First, adequate funding support should be provided. While school-based interventions for adolescent suicide based on social-emotional skills are cost effective and can minimize manpower, resources, and time costs, continuous improvement in adolescent suicide effectiveness requires ongoing project adjustments, curriculum reforms, facility development, platform building, and gatekeeper training within schools. These activities require sufficient funding support to ensure steady operation. Second, the combination of social-emotional learning and other suicide prevention programs within schools should be fostered to avoid fragmentation in suicide intervention efforts. While school-based interventions for adolescent suicide based on social-emotional skills are effective at addressing the crisis of adolescent suicide, the importance of other suicide prevention approaches should not be overlooked. Only through mutual collaboration and cooperation can the effectiveness and comprehensiveness of adolescent suicide interventions be fully promoted. Finally, synergies among schools, families, society, and other environments should be fully leveraged. In addition to the school environment, families and society are important places for the development of social-emotional skills in adolescents. Therefore, schools should strengthen cooperation with other parties, expand the scope of social-emotional learning spaces, jointly develop social-emotional learning curricula, and build social-emotional learning platforms to promote collective effort in adolescent suicide prevention. This collaboration will enable better resolution of suicide issues on the "last mile" based on resource sharing and personnel cooperation.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Xin-Qiao Liu 0000-0001-6620-4119; Xin Wang 0009-0001-1098-0589.

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ORIGINAL ARTICLE

Case Control Study

Psychiatric outcomes in outpatients affected by long COVID: A link between mental health and persistence of olfactory complaint

Victoria Metelkina-Fernandez, Louise-Emilie Dumas, Clair Vandersteen, David Chirio, Auriane Gros, Arnaud Fernandez, Florence Askenazy, Valeria Manera

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Victoria Metelkina-Fernandez, Department of Psychiatry, Nice University Hospital, Nice 06000, France

Louise-Emilie Dumas, Arnaud Fernandez, Florence Askenazy, Department of Child and Adolescent Psychiatry, Université Côte d'Azur, Nice 06200, France

Clair Vandersteen, ENT, Head and Neck Institute, Nice 06100, France

David Chirio, Department of Infectiology, Nice University Hospital, Nice 06200, France

Auriane Gros, Department of Orthophony, Université Côte d'Azur, Nice 06100, France

Arnaud Fernandez, Valeria Manera, Cobtek, Université Côte d'Azur, Nice 06100, France

Corresponding author: Arnaud Fernandez, MD, PhD, Assistant Professor, Department of Child and Adolescent Psychiatry, Université Côte d'Azur, 57 avenue de la Californie, Nice 06200, France. arnaud.fernandez@hpu.lenval.com

Abstract

BACKGROUND

Anosmia was one of the main symptoms of coronavirus disease 2019 (COVID-19). A psychiatric history (*i.e.*, depression) may be an independent contributor to the risk of COVID-19 diagnosis, and COVID-19 survivors appear to have an increased risk of neuropsychiatric sequelae (bidirectional association).

AIM

To compare the rate of psychiatric disorder among post-COVID patients without anosmia *vs* patients with persistent olfactory complaints.

METHODS

We conducted a prospective case control study from March 2020 to May 2021. Patients recruited at the ENT department of Nice University Hospital had a subjective olfactory complaint (visual analogue scale) for over 6 wk and a molecular or CT-proven severe acute respiratory syndrome coronavirus 2 diagnosis confirmed by serology. Post-COVID patients without persistent olfactory disorders were recruited at the university hospital infectiology department. Psychiatric medical histories were collected by a psychiatrist during the

assessments.

RESULTS

Thirty-four patients with post-COVID-19 olfactory complaints were included in the first group of the study. Fifty percent of the patients were female (n = 17). The group's mean age was 40.5 ± 12.9 years. The control group included 32 participants, of which 34.4% were female (n = 11), and had a mean age of 61.2 ± 12.2 years. The rate of psychiatric disorder among post-COVID patients with olfactory complaints was significatively higher (41.7%) than among patients without (18.8%) (χ^2 = 5.9, P = 0.015).

CONCLUSION

The presence of a psychiatric history may constitute a potential risk factor for the development of long COVID due to persistent anosmia. It therefore seems important to establish reinforced health monitoring after a COVID 19 infection in at-risk patients. Further prospective, translational, and collaborative studies are needed to extrapolate these results to the general population.

Key Words: COVID-19; Anosmia; Psychiatry; Stress; Neuroplasticity; Psychiatric history

Core Tip: Our study reveals a significant association between a psychiatric history and persistent anosmia in post-coronavirus disease 2019 (COVID-19) patients. With a higher rate of psychiatric disorder observed in individuals experiencing long-COVID symptoms, our findings underscore the need for reinforced health monitoring of at-risk patients. This emphasizes the importance of considering psychiatric factors in the assessment and management of post-COVID-19 sequelae. This study will thus contribute to a broader understanding of the multifaceted impact of the virus on mental health.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic originated in China. It was first identified in Wuhan (Hubei province) in December 2019 before spreading to other continents[1]. It resulted in a still active global pandemic.

Olfactory loss was one of the main symptoms among European patients with mild-to-moderate COVID-19 (70.2%)[2]. Even if several pathogenic mechanisms of olfactory dysfunction in patients with COVID-19 were postulated, the precise mechanisms remain unclear. Neuroplasticity is known to play a major role in recovery after loss of smell[3]. However, it has been observed that the plasticity of the human brain can be affected by (certain) stressful events, by a psychiatric history (*e.g.*, depression) and by lifetime sensory experiences[4]. Thus, Taquet *et al*[5] (2021) have suggested bidirectional associations between COVID-19 and psychiatric disorders.

Interestingly, in their study, a psychiatric diagnosis in the previous year was shown to be an independent risk factor of COVID-19 diagnosis[5]. In a further study, Taquet *et al*[6] (2021) suggested that a COVID-19 diagnosis was associated with psychiatric and neurological outcomes at 6 months in one third of patients.

Based on these results, we can hypothesize that the persistence of an olfactory complaint could also be affected by the patient's psychiatric history.

The main objective of our study was to compare the psychiatric history within the previous year of post-COVID patients without olfactory complaints (with a total recovery < 1 month) *vs* patients with persistent post-viral olfactory complaints.

The secondary objectives were: (1) To assess the rate of post-traumatic stress disorder (PTSD) among patients with post-viral olfactory complaints (COVID-19) and to compare it with the rate of PTSD among patients without olfactory complaints (with a total recovery < 1 month); and (2) for patients with persistent olfactory complaints, to correlate the intensity of post-traumatic symptoms with self-reported olfactory recovery.

MATERIALS AND METHODS

Study registration

The study was approved by the institutional review board of Nice University Hospital (CNIL number: 412). This study is

part of a large prospective work registered under a ClinicalTrials.gov number (ID: NCT04799977). For this large trial, we prospectively recruited patients of the ENT department of Nice University Hospital, starting in March 2020. All had been contaminated by COVID-19 and had persistent olfactory disorders lasting more than 6 wk (3 to 15 months).

We retrospectively extracted the patients' demographic data and clinical features, including subjective taste impairment, subjective olfactory impairment (qualitative and quantitative dysosmia), weight (measured at home in the previous week on a personal scale), nasofibroscopy (assessing nasal cavity patency and differential diagnosis), and olfactory loss using Sniffin' Sticks Test® (SST; Medisense, Groningen, The Netherlands).

Population

In this study, patients with persistent olfactory disorders were recruited at the ENT department of Nice University Hospital during the period from March 2020 to February 2021. Patients were self-referred or referred by colleagues, general practitioners or recommended by the infectiology department that recorded all COVID-19 declared patients (city guidelines). Patients had an olfactory complaint for over 6 weeks and a molecular-proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis or a CT-proven SARS-CoV-2 diagnosis secondarily confirmed by serology. Patients with other pathologies that could affect the olfactory system were excluded, as confirmed by their medical history and nasofibroscopy results: olfaction disorders, ENT cancer, head radiotherapy history, and post viral (before the pandemic) olfactive history.

Post-COVID patients without persistent olfactory disorders were recruited at the university infectiology department during the same period.

Measures and trial design

For patients with persistent olfactory complaints, olfactory function was evaluated by an otorhinolaryngologist using a visual analogue scale (VAS) assessing the subjective perceived olfactory recovery.

A psychiatric interview performed by an experienced psychiatrist explored the psychiatric history, the diagnostic categories (according to the DSM 5), the presence of stress factors, and exposure to recent or past psychotrauma. Psychiatric assessments included validated self-report questionnaires for PTSD (PCL-5).

Patients without olfactory complaints were interviewed by a psychiatrist who conducted a medical and psychological evaluation. Special attention was paid to their psychiatric history. They also completed the PCL-5 questionnaire at home using Google Forms.

Statistical analysis

Data are presented as mean (SD) for quantitative variables and as frequency and percentage for qualitative variables. To compare age between groups (patients with persistent olfactory complaints *vs* patients without olfactory complaints), we used independent-sample *T* tests for normally distributed variables (age), and Mann-Whitney *U* tests for non-normally distributed variables (PCL-5). To investigate gender differences across groups, we performed Chi2 analyses. We also ran an exploratory logistic regression analysis to verify whether the presence of previous mental disorders could have had an impact on the presence of olfactory disorders lasting more than one month.

To investigate correlations between subjective reports (VAS) and PCL-5 scores, we performed bivariate correlation analyses. As data were not normally distributed (as suggested by the Kolmogorov-Smirnov test), non-parametric Spearman's correlations were made.

RESULTS

Demographic features

The patients' demographic and clinical features are presented in Table 1. Thirty-four patients with post-COVID-19 olfactory complaints were included in the first group of the study. Fifty percent of the patients were female (n = 17). The patients' mean age was 40.5 ± 12.9 years. They were interviewed 5.3 ± 2.8 mo after COVID-19 infection. The day of the interview, patients reported having recovered only 37.7% ± 27.5% of their olfaction (ranging from 0% to 90%). The control group included 32 participants, of which 34.4% were female (n = 11), and had a mean age of 61.2 ± 12.2 years. The two groups differed in terms of mean age ($t_{(64)} = 6.7$, $P < 0.001$), while gender did not differ between groups ($Chi2_{(1)} = 1.6$, $P = 0.199$).

Psychiatric history

In the group with olfactory complaints, 47.1% of the subjects (n = 16) reported a psychiatric history prior to SARS-CoV-2 infection. Only 18.8% of subjects in the control group (n = 6) reported a psychiatric history prior to SARS-CoV-2 infection (Figure 1). Chi2 analysis confirmed that the proportion of people with a previous psychiatric history was significantly higher in the patients with persistent olfactory complaints compared to the control group ($\chi^2_{(1)} = 5.9$, $P = 0.015$). Logistic regression analysis suggested that the presence of a previous psychiatric history had a significant impact on the probability of having post-COVID-19 olfactory complaints (B = 1.35, $P = 0.018$).

Presence of post-traumatic stress symptoms

Subjects with olfactory complaints had a mean PCL-5 score of 17.8 (SD = 22.4), while control subjects had a mean score of 18.1 (SD = 20.0). The difference was not statistically significant (U = 461.5, P =0.285). In the olfactory complaint group, no

Table 1 Demographic and clinical characteristics of the patients in the two groups

	Olfactory complaints, *n* = 34	No olfactory complaints, *n* = 32	*P* value
Age, mean (SD)	40.5 (12.9)	61.2 (12.2)	< 0.001[1]
PCL-5, mean (SD)	17.8 (22.4)	18.8 (20.0)	0.285[2]
Sex, *n* (%)			0.199[3]
Female	17 (50.0)	11 (34.4)	
Male	17 (50.0)	21 (65.6)	
Psychiatric history, *n* (%)			0.015[3]
Yes	16 (47.1)	6 (18.8)	
No	18 (52.9)	26 (81.3)	

[1]*t*-test.
[2]Mann-Whithney test.
[3]χ^2 test.

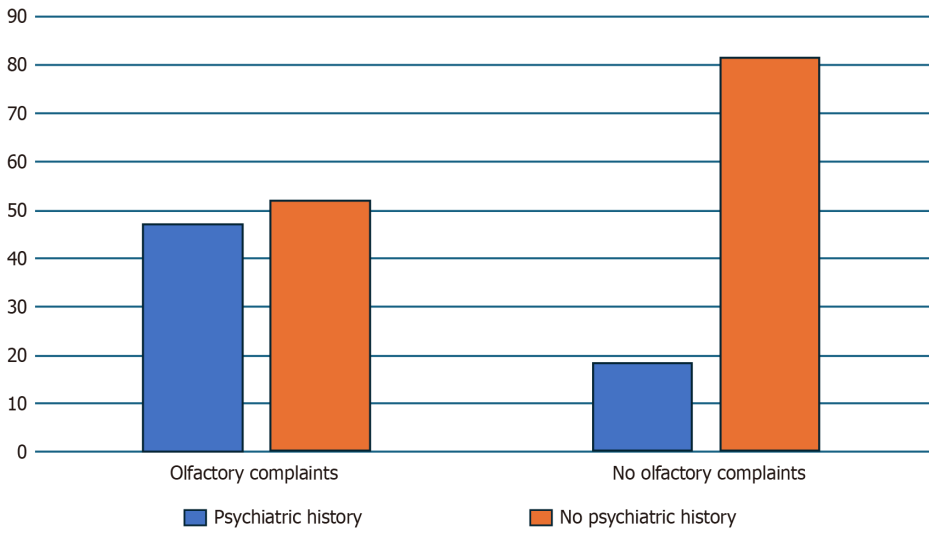

Figure 1 Link between psychiatric history and olfactory complaints.

significant correlation was found between the percentage of subjective olfactory recovery (VAS) and PCL-5 (rho $_{(32)}$ = 0.02, P = 0.925).

DISCUSSION

Several factors have been shown to influence the likelihood of developing persistent olfactory disorders after COVID-19 infection, such as belonging to an ethnic minority, socioeconomic deprivation, smoking, and obesity[7]. Here we investigated whether a psychiatric history before SARS-CoV-2 infection was more frequent in patients with and without olfactory complaints. Our results suggest that psychiatric history and certain psychological conditions such as stressful events were more common in patients with persistent olfactory complaints.

Olfactory complaint was one of the main symptoms among European patients with mild-to-moderate COVID-19 (70.2%); in a seminal study that included 1420 patients, Lechien *et al*[2] (2020) found that olfactory complaints persisted at least 7 d in 37.5% of these cases. Since the beginning of the COVID-19 pandemic, several pathogenic mechanisms of olfactory dysfunction have been postulated. However, the precise mechanisms still remain unclear. Reichert *et al*. (2018) conducted research on the role of neuroplasticity in recovery after loss of smell, focusing on the decrease in white and grey matter[3]. They also highlighted the efficacy of olfactory training programs. In a large review, McEwen[4] (2007) suggested that the plasticity of the human brain could be affected by stressful life events, a psychiatric history (*e.g.*, depression), lifetime sensory experiences, and stress-related social problems. Taquet *et al*[5] (2021) suggested bidirectional associations between COVID-19 and psychiatric disorders. They observed that a psychiatric diagnosis in the previous year was an independent risk factor of COVID-19 diagnosis. In a further study, they showed that COVID-19 diagnosis was associated with psychiatric and neurological outcomes in one third of patients 6 months after the infection[6]. These

results are supported by evidence that COVID-19 can have an impact on the brain. As mentioned above, McEwen has shown that stress can have a damaging effect on the brain, and that the brain can also respond to stress by manifesting behavioral and physiological symptoms[8]. More broadly, life experiences modify brain function *via* synaptic transmission[8].

The data presented in this study suggests that a psychiatric history and certain psychological conditions, such as stressful events, may have a negative impact on the persistence of an olfactory complaint. These results are consistent with several hypothesized mechanisms of brain involvement in SARS-CoV-2 infection. Indeed, it has been shown that SARS-CoV-2 can infect the Central Nervous System by crossing the neural-mucosal interface and more specifically by crossing the olfactory mucosa and following neuroanatomical structures due to its neurotropism[9]. Moreover, in a large systematic review, Rogers *et al*[10] (2020) have pointed out that depression, anxiety, PTSD, and other neuropsychiatric syndromes can appear after COVID-19. Once infected, people with pre-existing mental disorders are at high risk of experiencing persistent symptoms of COVID[11]. In our study, we failed to demonstrate that PTSD was a risk factor for developing persistent anosmia, but we did not explore the risk of developing PTSD after COVID infection.

Limitations

The main limitation of this study is the small sample size, which is not representative of the whole population. Furthermore, the two samples of participants with and without persistent anosmia were recruited in different facilities, making it impossible to exclude a recruitment bias. Patients in both groups also differed in age, which limits comparability between them. These results should be interpreted with caution and should be replicated in bigger samples.

CONCLUSION

In conclusion, the human brain might be affected by a psychiatric history (including stressful events). This brain damage could partially be an explanation for olfactory complaint persistence months after a SARS CoV-2 infection, showing the key importance of post COVID-19 psychiatric follow-up and of preventive mental health care.

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FOOTNOTES

Author contributions: Askenazy F, Dumas LE, Vandersteen C and Metelkina-Fernandez V initiated the project and designed the experiment; Dumas LE, Chirio D, Gros A, Fernandez A and Metelkina-Fernandez V conducted clinical data collection; Manera V conducted several collation and statistical analyses; Metelkina-Fernandez V wrote the original manuscript; Chirio D, Gros A, Manera V, Metelkina-Fernandez V and Fernandez A revised the paper; and all authors reviewed and approved the paper and approved the final manuscript.

Institutional review board statement: The study was approved by the institutional review board of Nice University Hospital (CNIL number: 412).

Informed consent statement: This study was carried out as part of routine care. Patients were informed of their inclusion in this study and gave their informed consent to participate. Patients' non-objection to study participation was requested orally and recorded in the patient's medical record. Patients were informed that they could refuse to participate or withdraw their consent at any time during the study. Data were anonymized before the analyses.

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ORCID number: Arnaud Fernandez 0000-0002-6326-9096.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clarifying the relationship and analyzing the influential factors of bronchial asthma in children with attention-deficit hyperactivity disorder

Gui-Xia Wang, Xiao-Ying Xu, Xi-Qing Wu

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Gui-Xia Wang, Department of Infectious Diseases, Dongying People's Hospital, Dongying 257000, Shandong Province, China

Xiao-Ying Xu, Department of Children's Health, Dongying People's Hospital, Dongying 257000, Shandong Province, China

Xi-Qing Wu, Department of Children's Health, Shengli Oilfield Central Hospital, Dongying 257000, Shandong Province, China

Corresponding author: Gui-Xia Wang, Associate Chief Physician, Department of Infectious Diseases, Dongying People's Hospital, No. 317 Dongcheng South 1st Road, Dongying 257000, Shandong Province, China. wangguixia710525@163.com

Abstract

BACKGROUND

Bronchial asthma is closely related to the occurrence of attention-deficit hyperactivity disorder (ADHD) in children, which can easily have adverse effects on children's learning and social interactions. Studies have shown that childhood asthma can increase the risk of ADHD and the core symptoms of ADHD. Compared with children with ADHD alone, children with asthma and ADHD are more likely to show high levels of hyperactivity, hyperactive-impulsive and other externalizing behaviors and anxiety in clinical practice and have more symptoms of somatization and emotional internalization.

AIM

To explore the relationship between ADHD in children and bronchial asthma and to analyze its influencing factors.

METHODS

This retrospective cohort study was conducted at Dongying People's Hospital from September 2018 to August 2023. Children diagnosed with ADHD at this hospital were selected as the ADHD group, while healthy children without ADHD who underwent physical examinations during the same period served as the control group. Clinical and parental data were collected for all participating children, and multivariate logistic regression analysis was employed to identify risk factors for comorbid asthma in children with ADHD.

RESULTS

Significant differences were detected between the ADHD group and the control group in terms of family history of asthma and allergic diseases, maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status ($P < 0.05$). Out of the 183 children in the ADHD group, 25 had comorbid asthma, resulting in a comorbidity rate of 13.66% (25/183), compared to the comorbidity rate of 2.91% (16/549) among the 549 children in the control group. The difference in the asthma comorbidity rate between the two groups was statistically significant ($P < 0.05$). The results of the multivariate logistic regression analysis indicated that family history of asthma and allergic diseases, maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status are independent risk factors increasing the risk of comorbid asthma in children with ADHD ($P < 0.05$).

CONCLUSION

Children with ADHD were more likely to have comorbid asthma than healthy control children were. A family history of asthma, adverse maternal factors during pregnancy, and parental relationship status were identified as risk factors influencing the comorbidity of asthma in children with ADHD. Clinically, targeted interventions based on these factors can be implemented to reduce the risk of comorbid asthma. This information is relevant for results sections of abstracts in scientific articles.

Key Words: Attention-deficit hyperactivity disorder; Children; Bronchial asthma; Risk factors; Anxiety; Depression

Core Tip: Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children. The incidence of ADHD has been increasing in recent years, which seriously affects children 's physical and mental health. Bronchial asthma is the most common chronic respiratory disease in children. Previous studies have shown that childhood asthma can increase the risk of ADHD and the core symptoms of ADHD. By exploring and analyzing the correlation between these two diseases and their influencing factors, this study will help to better understand the etiology of ADHD and provide reference for early prevention of ADHD.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in children that is primarily characterized by persistent inattention, hyperactivity, and impulsivity[1] and significantly impacts children's physical and mental health. The incidence of childhood ADHD has been on the rise in recent years. Incomplete statistics[2] show that the global prevalence of ADHD among children and adolescents has reached 7.2%, but the etiology and pathogenesis of ADHD have not yet been fully elucidated. Previous studies considered genetics to be the most crucial factor in ADHD, but recent research[3,4] has indicated that ADHD results from the interaction of multiple factors. Studies have shown[5] a close association between chronic childhood diseases and the development of ADHD. Bronchial asthma, characterized by recurrent coughing, wheezing, shortness of breath, and chest tightness, is a heterogeneous disease and the most common chronic respiratory disorder in children[6], adversely affecting their learning and social interactions. Previous research has suggested that asthma can increase children's risk of developing ADHD and its core symptoms. Compared to children with ADHD alone, those with comorbid asthma tend to exhibit greater hyperactivity, hyperactive-impulsive behaviors, and anxiety, as well as more somatization and emotional internalization symptoms[7]. Therefore, exploring and analyzing the associations and influencing factors between these two diseases can enhance our understanding of the etiology of ADHD and provide new approaches for its early prevention and treatment. Currently, there is limited literature on the relationship between ADHD and asthma in children in China. This study aimed to analyze the occurrence of asthma in children with ADHD and its influencing factors, providing a reference for clinical prevention and treatment.

MATERIALS AND METHODS

Study participants

This retrospective cohort study was conducted at Dongying People's Hospital from September 2018 to August 2023. As the study did not involve mandatory therapeutic interventions, all the data were anonymized prior to analysis and processing, in accordance with the Declaration of Helsinki. Children who were diagnosed with ADHD at our hospital between September 2018 and August 2023 were selected as the ADHD group, while children without ADHD who underwent physical examinations during the same period composed the healthy control group. The inclusion criteria for the ADHD group were as follows: (1) Children aged 4-14 years who met at least six of the nine ADHD symptom criteria as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[8]; (2) children with a score ≥ 85 points on the Wechsler Intelligence Scale for Children; and (3) children with complete clinical records. The exclusion criteria included: (1) Comorbid psychiatric disorders; (2) the use of ADHD medication for more than one year; and (3) concurrent neurological abnormalities. The inclusion criteria for the healthy control group were children aged 4-14 years and children with complete clinical records, excluding those with developmental disorders, mental retardation, or neurological abnormalities.

The sample size calculation was based on previous studies reporting that the prevalence of ADHD and asthma in children was 9%[9] and 3.02%[10], respectively, with a comorbidity rate of 10.9%[11]. A 1:3 matching ratio was used [m = control group sample size (m_0)/ADHD group sample size (n_1) = 3]. With a significance level (α) of 0.05 and a power (β) of 0.2, the calculated sample size for the ADHD group was 183, and that for the control group was 549.

Methods

The data collected for both groups of children included sex, age, ethnicity, feeding method at birth, gestational age at delivery, history of brain injury, and family history of asthma and allergic diseases. Parental data, including highest educational level, average monthly household income, maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal smoking during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status, were also collected.

Statistical analysis

Methods data were analyzed using SPSS version 25.0 and graphically represented using GraphPad Prism 8. Normally distributed quantitative data are expressed as the mean ± SD and were compared using *t* tests. Categorical data are expressed as the number of patients and were compared using chi-square tests. Multivariate logistic regression analysis was utilized to identify risk factors for comorbid asthma in children with ADHD. The statistical significance threshold was set at $P < 0.05$.

RESULTS

Comparison of clinical data between the ADHD and control groups

There was a statistically significant difference in the proportion of children with a family history of asthma and allergic diseases between the ADHD and control groups ($P < 0.05$). No significant differences in the remaining clinical data were found between the two groups ($P > 0.05$), as shown in Table 1.

Comparison of parental data between the ADHD and control groups

Significant differences were observed between the ADHD and control groups concerning maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status ($P < 0.05$). There were no significant differences in the other parental data between the two groups ($P > 0.05$), as detailed in Table 2.

Comparison of asthma comorbidity rates between the ADHD and control groups

Among the 183 children in the ADHD group, 25 had comorbid asthma, resulting in a comorbidity rate of 13.66% (25/183). Among the 549 children in the control group, 16 had comorbid asthma, resulting in a comorbidity rate of 2.91% (16/549). The difference in the asthma comorbidity rate between the two groups was statistically significant ($\chi^2 = 29.981$, $P < 0.001$), as illustrated in Figure 1.

Univariate analysis of factors influencing the asthma comorbidity rate in children with ADHD

Significant differences were observed between children with ADHD with and without comorbid asthma in terms of family history of asthma and allergic diseases, maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status ($P < 0.05$). No significant differences were found in the other clinical data between the two groups ($P > 0.05$), as shown in Table 3.

Table 1 Comparison of clinical data between the attention-deficit hyperactivity disorder and control groups

Parameter	ADHD group (n = 183)	Control group (n = 549)	χ^2/t	P value
Sex (cases)				
Male	96	283	0.046	0.831
Female	87	266		
Age (yr, mean ± SD)	9.41 ± 1.68	9.62 ± 1.77	1.407	0.160
Ethnicity (cases)				
Han	171	517	0.129	0.720
Non-Han	12	32		
Feeding method (cases)				
Breastfed	121	383	0.985	0.611
Formula-fed	26	74		
Mixed feeding	36	92		
Gestational Age at Birth (wk)				
Full-term	155	469	0.315	0.855
Preterm	16	50		
Postterm	12	30		
Brain Injury (cases)				
Yes	3	6	0.338	0.561
No	180	543		
Family history of asthma/allergic diseases (cases)				
Yes	41	65	12.371	< 0.001
No	142	484		

ADHD: Attention-deficit hyperactivity disorder.

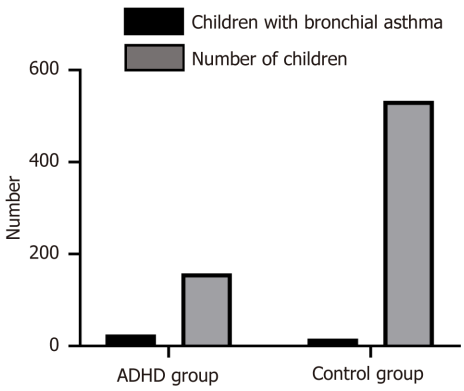

Figure 1 Comparison of the asthma comorbidity rate between the attention-deficit hyperactivity disorder and control groups. ADHD: Attention-deficit hyperactivity disorder.

Multivariate logistic regression analysis of factors influencing the asthma comorbidity rate in children with ADHD

Using comorbid asthma in children with ADHD as the dependent variable and the statistically significant items from the univariate analysis as independent variables (variable assignment details are shown in Table 4), a multivariate logistic regression analysis was conducted using stepwise regression, with an inclusion criterion of 0.10 and an exclusion criterion of 0.05. The results of the multivariate logistic regression analysis showed that a family history of asthma and allergic diseases, maternal complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status were independent risk factors for comorbid asthma in children with ADHD (P < 0.05), as presented in Table 5.

Table 2 Comparison of parental data between the attention-deficit hyperactivity disorder and control groups

Parameter	ADHD group (*n* = 183)	Control group (*n* = 549)	χ^2/t	*P* value
Parental highest educational level (cases)				
Junior high school or below	41	125	0.160	0.923
High school or vocational school	54	169		
College degree or above	88	255		
Average monthly household income (cases)				
< 5000 RMB	95	290	0.046	0.831
≥ 5000 RMB	88	259		
Maternal pregnancy complications (cases)				
Present	31	42	13.191	< 0.001
Absent	152	507		
Use of asthma/allergy medications during pregnancy (cases)				
Yes	38	59	11.981	0.001
No	145	490		
Maternal smoking during pregnancy (cases)				
Yes	26	75	0.034	0.853
No	157	474		
Maternal anxiety and depression during pregnancy (cases)				
Yes	28	39	11.091	0.001
No	155	510		
Parental relationship status (cases)				
Good	141	424	20.052	< 0.001
Average	23	109		
Poor	19	16		

ADHD: Attention-deficit hyperactivity disorder.

DISCUSSION

In recent years, there has been an increase in both national and international reports on children with ADHD with comorbid asthma. Studies[12] have indicated that approximately 35 out of every 100 children with ADHD have allergic diseases, with 25 having comorbid asthma. Our retrospective study analyzing the clinical data of 183 children with ADHD showed that 25 out of the 183 children in the ADHD group had comorbid asthma, resulting in a comorbidity rate of 13.66%, which is significantly lower than the rates reported in foreign literature[13]. This discrepancy might be attributed to the smaller sample size of our study compared to larger-scale population studies, which offer greater representativeness and can more accurately reflect the overall situation of comorbid asthma in children with ADHD. Previous research[14] has suggested that asthma control levels are lower in children with ADHD who also have oppositional defiant disorder, possibly due to lower medication adherence in these children. Asthma also impacts ADHD, with studies reporting[15] that asthma increases the risk of developing ADHD, and children with multiple airway hyperreactivity diseases have a greater risk of ADHD than those with a singular airway hyperreactivity disease. Moreover, asthma increases the severity of core ADHD symptoms; children diagnosed with asthma are more likely to exhibit symptoms of inattention and hyperactivity-impulsivity and have comorbid ADHD and oppositional defiant disorder. Studies[16] have shown that children with both asthma and ADHD are more likely to exhibit higher levels of hyperactivity, hyperactivity-impulsivity, externalized behavior, anxiety, somatization, and emotional internalization symptoms than are children with ADHD alone. Therefore, exploring the factors influencing comorbid asthma in children with ADHD is crucial.

The correlation between asthma and ADHD has been confirmed in multiple studies. Cortese *et al*[17], through meta-analyses and population studies, found a significant correlation between asthma and ADHD. This correlation remained significant even after adjusting for variables such as sex, birth year, birth weight, maternal age during pregnancy, gestational age at birth, and family income. This study revealed a weak to moderate correlation between asthma and ADHD, as well as between other allergic diseases, such as eczema, allergic rhinitis, and allergic conjunctivitis, and ADHD. Our univariate and multivariate analyses indicated that a family history of asthma and allergic diseases, maternal

Table 3 Univariate analysis of factors influencing the asthma comorbidity rate in children with attention-deficit hyperactivity disorder

Parameter	Comorbid group (n = 25)	Non-comorbid group (n = 158)	χ^2/t	P value
Sex (cases)				
Male	13	83	0.002	0.961
Female	12	75		
Age (yr, mean ± SD)	9.35 ± 1.72	9.49 ± 1.63	0.396	0.693
Ethnicity (cases)				
Han	23	148	0.098	0.754
Non-Han	2	10		
Feeding method (cases)				
Breastfed	16	105	0.395	0.821
Formula-fed	3	23		
Mixed feeding	6	30		
Gestational age at birth (wk, cases)				
Full-term	21	134	0.642	0.726
Preterm	3	13		
Postterm	1	11		
Brain injury (cases)				
Yes	1	2	1.007	0.317
No	24	156		
Family history of asthma/allergic diseases (cases)				
Yes	9	32	32.821	< 0.001
No	16	517		
Maternal pregnancy complications (cases)				
Present	16	15	45.581	< 0.001
Absent	9	143		
Maternal use of asthma/allergy medications during pregnancy (cases)				
Yes	18	20	46.201	< 0.001
No	7	138		
Maternal smoking history during pregnancy (cases)				
Yes	4	22	0.076	0.782
No	21	136		
Maternal anxiety and depression during pregnancy (cases)				
Yes	15	13	44.641	< 0.001
No	10	145		
Parental relationship status (cases)				
Good	10	131	36.952	< 0.001
Average	4	19		
Poor	11	8		

complications during pregnancy, maternal use of asthma and allergy medications during pregnancy, maternal anxiety and depression during pregnancy, and parental relationship status are independent risk factors influencing comorbid asthma in children with ADHD (P < 0.05). The reason may be that family history may play an important genetic role in the development of asthma, allergic diseases and ADHD. Some genes may increase the risk of asthma and allergic diseases in individuals and may also be related to ADHD. Maternal complications during pregnancy may have a negative

Table 4 Variable assignment details

Variable	Assignment method
Family history of asthma/allergic diseases	No = 0, Yes = 1
Maternal pregnancy complications	No = 0, Yes = 1
Maternal use of asthma/allergy medications during pregnancy	No = 0, Yes = 1
Maternal anxiety and depression during pregnancy	No = 0, Yes = 1
Parental relationship	Poor = 1, Average = 2, Good = 3

Table 5 Multivariate logistic regression analysis of factors influencing the asthma comorbidity rate in children with attention-deficit hyperactivity disorder

Factors	β	SE	Ward χ^2	*P* value	OR	95%CI
Family history of asthma/allergic diseases	0.992	0.339	7.944	< 0.001	2.697	1.353-5.377
Maternal pregnancy complications	0.813	0.367	5.747	< 0.001	2.254	1.160-4.380
Maternal use of asthma/allergy medications during pregnancy	1.098	0.341	8.950	< 0.001	2.998	1.460-6.155
Maternal anxiety and depression during pregnancy	0.933	0.388	7.485	< 0.001	2.542	1.303-4.960
Parental relationship status	0.686	0.339	3.122	0.029	1.985	0.928-4.247

impact on fetal development and health. The fetuses of mothers who experience complications are adversely affected in the womb, and the key organs, such as the brain and immune system, may be affected, increasing the risk of various diseases in the future, including ADHD and asthma. The use of some drugs, such as steroids and antihistamines, during pregnancy to treat asthma and allergic diseases may affect the neurodevelopment of the fetus. These drugs may penetrate the placenta and affect the development of the fetal brain, thereby increasing the risk of neurodevelopmental problems (such as ADHD) in children. Maternal anxiety and depression during pregnancy can increase the secretion of cortisol, which reaches the fetus through the blood, affecting the development of the nervous system and increasing the risk of comorbid asthma in offspring who develop ADHD. Family conflict and poor parental relationships may lead to immune system disorders and increase the risk of asthma in children.

Both asthma and ADHD are diseases influenced by a combination of genetic and environmental factors. The perinatal period is a particularly sensitive time when exposure to adverse factors may predispose children or adults to various diseases. Studies have shown[18] that the occurrence of childhood asthma is closely related to perinatal intrauterine and extrauterine environmental exposures. Maternal allergies during pregnancy involving the presence of certain allergens may alter the microenvironment and immune balance of the body, thus increasing the risk of asthma in offspring. Research by Wenderlich *et al*[19] revealed an increased incidence of ADHD in children whose parents had asthma, especially when the mother had asthma, with this association being more significant when both parents had asthma, suggesting that intrauterine exposure may also play a role. A study on a large and representative population[20] showed that parental use of asthma and allergic rhinitis medications increased the risk of offspring needing to use ADHD medication. Furthermore, studies have shown[21] that adverse maternal factors during pregnancy, including negative emotional states and exposure to toxic substances, can influence the development of comorbid asthma in children with ADHD. Maternal exposure to toxic substances during pregnancy can affect the normal growth and development of the fetus, especially central nervous system development, leading to abnormalities in brain function and an increased likelihood of ADHD in children. Maternal anxiety and depression during pregnancy can affect cortisol secretion, leading to increased levels. Cortisol reaches the fetus through the bloodstream, affecting the development of the nervous system and increasing the risk of comorbid asthma in children with ADHD. Additional research[22] has shown that the quality of the parental relationship and the home environment impact children's psychological health and immune system function. Family conflicts and poor parental relationships may lead to immune system dysregulation in children, increasing the risk of asthma.

CONCLUSION

In summary, children with ADHD are more prone to comorbid asthma than healthy controls are, with a family history of asthma, adverse maternal factors during pregnancy, and parental relationship status all being risk factors. Clinical interventions targeting these factors can reduce the risk of comorbid asthma. The retrospective nature and smaller sample size of our study may have introduced bias into the results. Future studies with larger sample sizes are planned to analyze the specific pathogenesis of comorbid asthma in children with ADHD. The limitation of this study is that the psychological mechanism of the children was not considered, and the relevant variables were mostly variables related to

heredity, family history and parents. The main reason is that the children included in the study were 4 to 14 years old. The psychological differences of children in this age group are relatively large. Multivariate logistic regression analysis cannot specifically explain the impact of children's psychological development on comorbid ADHD and asthma. In the future, the sample size will be increased, and qualitative analysis, time series analysis and other methods will be combined to analyze the mechanism of children's psychological development.

ARTICLE HIGHLIGHTS

Research background

The relationship between bronchial asthma and attention-deficit hyperactivity disorder (ADHD) in children and its pathogenesis have become a hot and difficult issue in the field of pediatrics. The latest large sample report based on the population confirmed that ADHD can be associated with a variety of allergic diseases, including bronchial asthma, but the specific relationship between the two and the related risk factors are unknown. Therefore, this study intends to preliminarily analyze the relationship between ADHD and asthma, and analyze the related risk factors, in order to further understand the relationship between them, avoid the exposure of related risk factors of bronchial asthma and ADHD children to reduce the risk of disease. In order to better clinical management of children with asthma and ADHD.

Research motivation

This study mainly analyzes the association between childhood asthma and ADHD and related risk factors, which is of great significance for the individualized clinical comprehensive management of these two diseases, and is helpful for clinical prevention and treatment according to the exposure of related risk factors.

Research objectives

This study mainly expounds the relationship between childhood asthma and ADHD. Individualized intervention measures for risk factors can effectively reduce the risk of asthma, and provide reference for the prevention and treatment of the pathogenesis of the two in the future.

Research methods

In this study, a retrospective study was conducted to collect the clinical data and parental data of all selected children. Multivariate logistic regression analysis was used to analyze the risk factors of comorbid asthma in children with ADHD. Multivariate logistic regression analysis has the advantages of controllable covariate effect, model flexibility, and consideration of interaction, which can better and more comprehensively understand and explain the changes of dependent variables.

Research results

The results of this study found that ADHD children are more likely to suffer from asthma than healthy control children. Family history of asthma, adverse factors of mother during pregnancy, and parental relationship are all factors affecting the risk of comorbidity of asthma in ADHD children. Targeted interventions can be taken to reduce the risk of comorbidity of asthma. However, this study is a retrospective study, and the sample size is small, which may cause some bias to the research results. In the future, the sample size will be expanded to analyze the specific pathogenesis of ADHD children with asthma.

Research conclusions

Through retrospective cohort study, this study further confirmed that ADHD children are more likely to suffer from asthma than healthy control children, and ADHD children are more likely to suffer from asthma than healthy control children, which is an important factor affecting the comorbidity of the two diseases.

Research perspectives

In the follow-up study, the sample size will be further increased, and the specific pathogenesis of bronchial asthma will be analyzed according to the different clinical subtypes of ADHD.

FOOTNOTES

Author contributions: Wang GX and Xu XY initiated the project, designed the experiment and conducted clinical data collection; Wu XQ performed postoperative follow-up and recorded data; Wang GX and Xu XY conducted a number of collation and statistical analysis, and wrote the original manuscript.; all authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Dongying People's Hospital, and the ethics committee agreed to waive informed consent.

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ORIGINAL ARTICLE

Retrospective Study

Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China

Jing-Wen Xu, Xiao-Bo Guan, Xue-Ying Wang, Yang Feng, Qi Zhang, Jun-Juan Zhu, Jian-Hua Chen

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Jing-Wen Xu, Qi Zhang, Department of Medicine, Shanghai No. 3 Mental Health Center of Civil Administration, Shanghai 200435, China

Xiao-Bo Guan, The Fourth Sick Ward, Shanghai No. 3 Mental Health Center of Civil Administration, Shanghai 200435, China

Xue-Ying Wang, Jun-Juan Zhu, Jian-Hua Chen, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Psychotic Disorders, Shanghai 200030, China

Yang Feng, The First Sick Ward, Shanghai No. 3 Mental Health Center of Civil Administration, Shanghai 200435, China

Corresponding author: Jian-Hua Chen, MD, PhD, Chief Physician, Professor, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai Key Laboratory of Psychotic Disorders, No. 600 Wanping Nan Road, Shanghai 200030, China.
jianhua.chen@smhc.org.cn

Abstract

BACKGROUND

Prior studies have noted great variability in the plasma levels of risperidone (RIS). Plasma concentrations of RIS and its active moiety are highly variable and depend on absorption, metabolism, and other predictors of metabolic dysregulation; however, these factors are poorly understood and the association between metabolic change and change in psychopathology is uncertain.

AIM

To ascertain the characteristics of chronic schizophrenic patients treated with RIS, and to assess their relationship with plasma RIS levels.

METHODS

This was a descriptive cross-sectional study of 50 patients with a diagnosis of schizophrenic psychosis treated with RIS in a psychiatric service. The plasma concentrations of RIS and its metabolite 9-hydroxyrisperidone were determined by high performance liquid chromatography. The patients' demographic and clinical characteristics, and psychopathologies were assessed, and the associations between clinical variables and plasma levels of RIS were explored.

RESULTS
Male patients received higher doses of RIS than female ones, but plasma concentrations of RIS and risperidone + 9-hydroxyrisperidone (active moiety) were higher in female patients. Age and the mean scores of the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS) were significantly positively correlated with plasma concentrations of risperidone + 9-hydroxyrisperidone adjusted for weight and dose in all 50 subjects. In male subjects, we found a statistically significant positive correlation between the concentrations of risperidone + 9-hydroxyrisperidone in plasma/(dose × kg) and age, mean PANSS negative subscale scores, mean PANSS general psychopathology subscale scores, and mean PANSS total scores.

CONCLUSION
Long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects.

Key Words: Antipsychotics; Risperidone; 9-hydroxyrisperidone; Plasma drug concentration monitoring; Chronic schizophrenia

Core Tip: Prior studies have noted great variability in the plasma levels of risperidone (RIS). Fifty patients confirmed to have schizophrenia were selected for this study. We assessed the patients' demographic and clinical characteristic, and psychopathologies, and explored the associations and correlations between clinical variables and plasma levels of RIS. The results of this study indicate that the long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects.

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INTRODUCTION

Schizophrenia is a severe disabling psychiatric disorder which is found in all regions of the world; however, the etiopathology of schizophrenia remains unknown[1]. Antipsychotic medication is a key component of treatment for schizophrenia patients, which acts by stabilizing acute psychotic episodes and preventing recurrences and relapses[2]. Risperidone (RIS) is a second-generation antipsychotic (SGA) with selective antagonistic properties, acting against the serotonin 5-HT2A and dopamine D2 receptors[3]. Currently, RIS is widely applied in the clinical treatment of schizophrenia and a broad spectrum of other psychiatric disorders in China.

RIS is fundamentally metabolized by the hepatic microsomal enzyme cytochrome P450 (CYP)2D6, and, to a lesser extent, by CYP3A4[2]. Its main metabolite, 9-hydroxyrisperidone, is pharmacologically active. Preclinical studies have indicated that 9-hydroxyrisperidone has approximately 70% of the pharmacological activity of RIS[3]. Since the pharmacological activity of 9-hydroxyrisperidone is claimed to be similar to that of the parent compound, the sum of the plasma concentrations of RIS and 9-hydroxyrisperidone is referred to as the clinically relevant "active moiety"[4].

Large intra- and inter-individual variations in plasma concentrations of both RIS and 9-hydroxyrisperidone have been identified in prior studies[2]. Therapeutic drug monitoring (TDM) in the clinic uses the quantification of drug concentrations in plasma or serum to assist physicians in making treatment decisions related to an individual patient. The determination of plasma concentrations of RIS as well as 9-hydroxyrisperidone is used to evaluate patient compliance with the therapy, to optimize treatment, and to minimize the risk of adverse drug reactions (ADRs). By adjusting the dose, a drug concentration associated with the highest probability of response and the lowest risk of ADRs and toxic effects can be achieved. The TDM thus provides a valid method for individual dose titration and careful monitoring, and is strongly recommended in the guidelines for adults treated with RIS[5].

Plasma concentrations of RIS and active moiety are highly variable and depend on absorption, and metabolism, as well as other predictors (for example, age, sex, body mass index, and smoke) of metabolic dysregulation; however, these factors are poorly understood and the association between metabolic change and change in psychopathology is uncertain [6]. Therefore, these factors should be considered in studies.

The primary aim of the present study was to assess the plasma concentrations obtained at different daily doses for the commonly used drug RIS in a natural setting, to examine the clinical situation of patients with chronic schizophrenia treated with RIS, and the possible relations between patient characteristics and plasma concentrations of RIS.

MATERIALS AND METHODS

Study design, sample, and procedures

This was a descriptive transversal study of all the patients treated with RIS in a Psychiatric Hospital with the diagnosis of schizophrenic psychosis. Fifty patients confirmed to have schizophrenia by a group of psychiatrists according to the ICD-10 were selected for this study. None of the patients had serious illness, or current alcohol and/or drug abuse. Patients were treated with oral RIS at doses ranging from 2 to 6 mg/d. The RIS dose was adjusted individually according to the clinical response. The plasma concentrations of RIS and its metabolite 9-hydroxyrisperidone were determined by high performance liquid chromatography (HPLC). Sociodemographic and clinical variables were studied, together with anthropometric measurements, life signs, hemogram, metabolic parameters, and ADRs, between February and March 2021.

HPLC uses a high-pressure infusion pump to pump the specified mobile phase into a chromatographic column containing fillers; the injected sample is brought into the chromatographic column by the mobile phase, and each component is subjected to intermolecular forces in the column. The adsorption-desorption process is carried out between the mobile phase and the stationary phase, so that each component is separated and enters the detector for detecting. A chromatographic signal is recorded and processed by the integrating instrument or the data processing system. In the daily routine testing, the samples are tested in parallel with quality controls, and three quality control concentration levels are used to observe the passing of quality controls. The standard curve graph is prepared, and the data in this study are all between the detectable range of each drug concentration. Chromatographic conditions were as follows: One-dimensional column: AstonSX1 (3.5 mm × 25 mm, 5 μm); intermediate column: Aston SCB (3.5 mm × 10 mm, 5 μm); two-dimensional column: Aston SCB (4.6 mm × 125 mm, 5 μm). The steps of RIS and paliperidone (major metabolite of RIS) detection were: Processing method: ORG-1 1000 μL + blood sample 400 μL, high-speed centrifugation to take the supernatant; detection wavelength: CH1: 276 nm, CH2: 286 nm; flow rate: Pump A: 1.20 mL/min, pump B: 0.01 mL/min, pump C: 0.80 mL/min; temperature: 40 °C; injection volume: 500 μL.

Study variables and scales

The clinical and research staff and participants were not blinded to any of the study conditions, as there was no comparison control group. Clinical interviews were conducted and blood was taken and sent for laboratory analysis. The following parameters were evaluated: An electrocardiogram was performed to evaluate patients' heart rate and QT interval (QTc). Data on patient age, weight, body mass index, blood pressure, and cigarettes smoked per day were also acquired. The discrete evaluated parameters included sex, smoker or not, and taking trihexyphenidyl/laxatives or not (according to the doctor's advice in the medical record) as ADRs occurred. Plasma concentrations of RIS and 9-hydroxyrisperidone were determined while fasting in the morning, without having eaten during the night or taken the breakfast dose of RIS. Using this value, the plasma concentrations of "active moiety" (RIS + 9-hydroxyrisperidone) and concentrations of RIS + 9-hydroxyrisperidone in plasma/(dose × kg) were calculated.

Psychopathological examination, which was completed within 3 d of blood testing, covered the following areas: Psychotic symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS)[7]; depressive symptoms were scored on the Patient Health Questionnaire Depression Scale (PHQ-9)[8], with the results classified as follows: 0-4 points, normal; 5-9 points, mild depression; 10-14 points, moderate depression; and 15-27 points, severe depression.

Statistical methods

All statistical analyses were carried out using IBM SPSS statistics, version 22.0 and GraphPad PRISM, version 7.0. The categorical variables are described as frequencies and percentages, while continuous variables are reported as the mean ± SD or range. Parameters were tested for normal distribution by the one-sample Kolmogorov-Smirnoff test. In the case of continuous variables, the Student's *t*-test was used to compare differences between the averages among groups for two independent samples of normally distributed data, or the Mann-Whitney *U*-test was used to compare data which was not normally distributed. The Pearson correlation coefficient was computed for normally distributed data, and the Spearman rank correlation coefficient was computed for non-normally distributed data. A P value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

A total of 52 patients diagnosed with schizophrenia and treated with RIS were initially enrolled. Of these 52 patients at the time of the study, 2 were excluded for the following reasons: One id not speak and was unable to complete the scales measurement, and the other because of the absence of plasma concentration of RIS. In the end, 50 subjects were included in the study.

The patients were aged from 38 to 69 years old (mean age, 58.4 years, SD = 8.3); 36% (n = 18) were women. All patients had been diagnosed with schizophrenia. Of these, 90% had been in treatment with RIS for more than 5 years, and none had undergone dose changes during the 2 mo prior to the study. Seven (14%) were obese [body mass index (BMI) ≥ 30], while 70% had normal weight (BMI < 25). All smokers (n = 23; 46%) were male, with an average consumption of 16.1 cigarettes/d (SD = 8.8). In the depressive symptom evaluation, three patients (6.0%) showed mild depression, while the

others scored within the normal range according to the PHQ-9 criteria. Details are displayed in Table 1.

Comparisons by sex

The doses of RIS prescribed varied from 2 mg/d to a maximum dose of 6 mg/d, and plasma concentrations of RIS varied from 0 to 43.68 ng/mL, while plasma concentrations of 9-hydroxyrisperidone varied from 10.57 to 98.87 ng/mL. Table 2 shows the dose of RIS and plasma concentrations of RIS and 9-hydroxyrisperidone divided according to gender. Male subjects received higher doses of RIS than female ones, in terms of absolute dose and dose/kg. However, plasma concentrations of RIS and risperidon + 9-hydroxyrisperidone (active moiety) were higher in women, while plasm concentrations of 9-hydroxyrisperidone were higher in men, although these differences were not statistically significant. Statistically significant values in comparison of average plasma concentrations of risperidon + 9-hydroxyrisperidone/dose (Figure 1A) and (dose × kg) according to sex were found (Figure 1B).

Correlation analysis

Regarding the clinical and psychopathological variables, we did not find significant associations between the concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) and any of the variables studied, except for age (P = 0.015, Figure 2) and mean PANSS general psychopathology subscale scores (P = 0.027), which were significantly positively correlated with plasma concentrations of active moiety adjusted for weight and dose in the 50 subjects.

In male subjects (n = 32), a statistically significant positive correlation was found between the concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) and age (P < 0.05), mean PANSS negative subscale scores (P < 0.05), mean PANSS general psychopathology subscale scores (P < 0.05), and mean PANSS total scores (P < 0.05). Regarding female subjects (n = 18), no correlation was found between the average values of plasmatic risperidon + 9-hydroxyrisperidone/(dose × kg) and the clinical and psychopathological variables (P > 0.05, Table 3).

Comparisons of ADRs

Regarding ADRs, anticholinergic or laxative medications were taken according to the doctor's recommendations; such a prescription was indicative of an ADR. Ten of the 50 patients were taking trihexyphenidyl (anticholinergic drug), and there was no statistical difference in each plasma drug concentration variable when compared between the ADR and non-ADR groups (P < 0.05). Among the 50 patients, 10 were taking laxative drugs, and no statistical difference was found in all variables in group comparison (P < 0.05) (Table 4).

DISCUSSION

This study investigated the sociodemographic and clinical characteristics of 55 patients diagnosed with chronic schizophrenia disorder and treated with RIS, in order to clarify any possible associations between these variables and the dosage and plasma concentrations of RIS. Many patients in this study were using RIS for a long time to guarantee blood collections occurring after achieving steady plasma concentrations of RIS and 9-hydroxyrisperidone.

Based on previous studies of groups of patients with chronic schizophrenia, the characteristics of this cohort can be expected: Mostly male, with high rates of smoking, and mainly negative symptoms. However, the small sample size and male predominance could be considered as limitations of this work.

Our study findings show that age was positive correlated with concentrations of RIS + 9-hydroxyrisperidone in plasma/(dose × kg). Some smaller studies have reported slower elimination and/or higher levels of 9-hydroxyrisperidone in the elderly[9-11]. Elimination of 9-hydroxyrisperidone is mainly renal[12], and the most plausible explanation for the accumulation of 9-hydroxyrisperidone in older patients is an age-dependent decline in kidney function. In conclusion, ageing results in a significantly increased dose and weight adjusted plasma concentration of RIS active moiety. This factor must therefore be taken into account when deciding on the dosage in the elderly. The TDM is a good option for dose decisions in this population. If the patient's conditions permit, we recommend measuring plasma RIS and its metabolites in routine clinical practice.

We found that plasma concentrations were significantly higher in women than in men for RIS + 9-hydroxyrisperidone adjusted for dose, as well as for active moiety adjusted for weight and dose, although the men received higher doses of RIS than the women. The same result has been observed in previous studies using SGA[13]. Several factors may explain these sex-related differences, including differences in hepatic clearance of drugs, caused by a lower liver volume in women, while the possible variations in compliance for antipsychotics between males and females should be taken into account[14], although the study was conducted in a hospital setting while all patients are hospitalized. As this was a monocentric study, men received higher doses than women; however, this could be a function of the predominance of men in the relatively small sample; as such, these results may not be generalizable to other settings.

Smoking prevalence in schizophrenic patients is higher than that in the general population[15]. In this study, smoking habits did not appear to influence the plasma concentrations of RIS and 9-hydroxyrisperidone. Berecz *et al*[16] reported that no influence of smoking on RIS metabolism could be found among 40 patients (Berecz *et al*[16] unpublished results). It should be noted that nicotine induces CYP1A2 and CYP2B6 activity, while RIS is extensively metabolized in the liver by CYP3A4 as well as CYP2D6 into the major active metabolite, 9-hydroxyrisperidone[17-19]. This metabolite is the predominant circulating molecule and appears to be of approximately equal efficacy as the parent compound[20]. This may explains why smoking has no influence on RIS metabolism.

Table 1 Characteristics of sociodemographic and clinical variables

Characteristic (*n* = 50)	Minimum value	Maximum value	Mean value	SD
Age (yr)	38	69	58.38	8.31
BMI	16.02	36.05	23.95	4.82
Course of illness (yr)	15	51	33.32	9.18
Systolic blood pressure (mmHg)	90	180	130.08	18.21
Diastolic blood pressure (mmHg)	60	105	78.60	10.32
Heart rate (per min)	60	103	79.86	9.79
QTc	0.38	0.52	0.45	0.03
Mean PANSS positive subscale score	7	20	10.92	3.17
Mean PANSS negative subscale score	9	31	22.32	4.20
Mean PANSS general psychopathology subscale score	22	51	31.04	5.07
Mean PANSS total score	48	101	64.28	8.89
PHQ-9	0	9	1.82	1.64

BMI: Body mass index; QTc: QT interval; PANSS: Positive and Negative Syndrome Scale; PHQ-9: Patient Health Questionnaire Depression Scale.

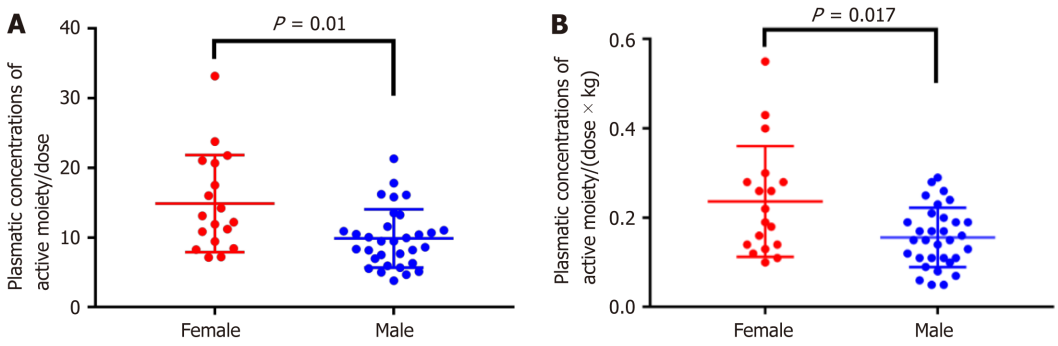

Figure 1 Comparison of concentrations of plasma risperidone + 9-hydroxyrisperidone/dose and plasma risperidone + 9-hydroxyrisperidone/(dose × kg) between males and females. A: Concentrations of plasma risperidone + 9-hydroxyrisperidone/dose (Student's *t*-test); B: Concentrations of plasma risperidone + 9-hydroxyrisperidone/(dose × kg) (Mann-Whitney *U*-test).

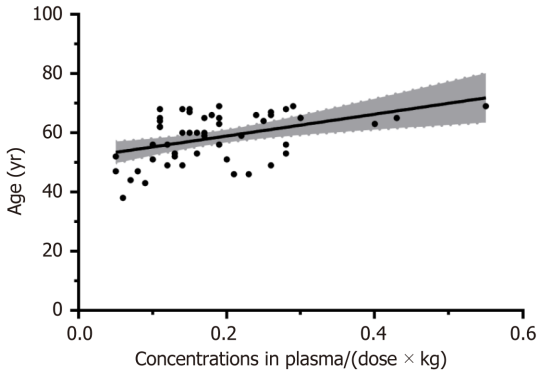

Figure 2 Correlation of sum of steady-state trough risperidon + 9-hydroxyrisperidone concentrations in plasma/(dose × kg) with age for 50 patients (Pearson's correlation coefficient = 0.436, *P* < 0.01).

Table 2 Risperidone dose and plasma concentrations of risperidone and 9 hydroxyrisperidone according to sex

	Sex	*n*	Average	SD	*P* value
Risperidone dose (mg)[1]	Male	32	4.09	1.12	0.003
	Female	18	3.11	0.90	
	Total	50	3.74	1.14	
Risperidone dose per kg weight[2]	Male	32	0.06	0.02	0.010
	Female	18	0.05	0.02	
	Total	50	0.06	0.02	
Concentration of risperidone in plasma (ng/mL)[1]	Male	32	8.61	10.80	0.134
	Female	18	15.13	15.27	
	Total	50	10.96	12.83	
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[1]	Male	32	32.37	18.63	0.887
	Female	18	29.24	10.25	
	Total	50	31.24	16.07	
Concentration of risperidone + 9-hydroxyrisperidone in plasma (ng/mL)[1]	Male	32	40.98	23.98	0.293
	Female	18	44.37	18.79	
	Total	50	42.20	22.11	
Concentration of risperidone + 9-hydroxyrisperidone in plasma/dose[2]	Male	32	9.87	4.18	0.010
	Female	18	14.89	6.96	
	Total	50	11.68	5.81	
Concentration of risperidone + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	Male	32	0.16	0.07	0.017
	Female	18	0.24	0.12	
	Total	50	0.18	0.10	

[1]Mann-Whitney *U*-test.
[2]Student's *t*-test.

The risk of cardiac side-effects by antipsychotic drugs has become a matter of public concern which can result in a prolongation of the QTc on the electrocardiogram[16]. RIS can increase the corrected QTc, although clinically relevant QTc prolongation is rare[21]. In this study, no correlation was found between weight and dose-adjusted concentrations of RIS active metabolite and QTc. This may indicate that RIS at a therapeutically effective plasma concentration does not seem to predispose patients to QTc interval lengthening. Nevertheless, this result has to be interpreted carefully due to the small sample size. One previous study reported that in patients treated with RIS, the QTc was related to CYP2D6 genotypes[22]; however, none of the patients were at risk of arrhythmia.

In our small sample, concentrations of active metabolite adjusted for weight and dose in the steady state were positively correlated with clinical scales, including mean PANSS negative subscale scores, mean PANSS general psychopathology subscale scores, and mean PANSS total scores only in males. We speculated that patients with a higher PANSS score may have more obvious psychiatric symptoms and thus may be prescribed a higher dose of RIS, leading to the higher plasma concentrations of RIS. One prior prospective study found no correlation between serum concentrations of RIS (including sum and ratio of RIS and 9-hydroxyrisperidone) and any other clinical values (*e.g.*, PANSS score)[23]. This prior study involved younger patients without any prior exposure to RIS as a prerequisite. Conversely, the present study was only a cross-sectional study with older subjects who had been taking RIS for a long time and had stable psychiatric symptoms. Therefore, the relationship between RIS concentrations (concentrations of active metabolite adjusted for weight and dose) and psychiatric symptoms in patients (especially among men) with chronic psychosis may need to be clarified with further follow-up.

We chose the use of anticholinergic drugs and laxatives as criteria for ADR, and found no difference between the ADR group and non-ADR group. Our findings are partly consistent with previous data supporting a prominent role of 9-hydroxyrisperidone, but not of RIS, in the development of ADRs[3]. RIS has a high 5-HT2A/D2 ratio, which should protect against extrapyramidal symptoms. However, at higher doses, RIS produces significant EPS, indicating that 5-HT2A antagonism alone cannot eliminate the EPS associated with substantial D2 receptor blockade[24]. In this study, we found that the concentration of 9-hydroxyrisperidone in the ADR group was higher than that of the non-ADR group, although this difference did not reach significance. The metabolite 9-hydroxyrisperidone seems to be the major circulating active moiety, with plasma concentrations 22-fold higher than those of RIS[25]. Clinicians may be advised to

Table 3 Correlation of average concentrations of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg) according to sex with clinical and psychopathological variables

Correlation of average concentration in plasma/(dose × kg) with	Correlation coefficient	*P* value
Male (n = 32)		
Age (yr)	0.457[2]	0.008
Number of cigarettes (smokers)	-0.359[1]	0.092
Systolic blood pressure	0.096[2]	0.600
Diastolic blood pressure	0.126[2]	0.492
BMI	-0.271[1]	0.134
Heart rate	-0.173[1]	0.344
QTc	0.060[2]	0.743
Mean PANSS positive scale score	0.179[2]	0.328
Mean PANSS negative scale score	0.373[1]	0.035
Mean PANSS general psychopathology subscale score	0.389[1]	0.028
Mean PANSS total score	0.481[2]	0.005
Female (n = 18)		
Age	0.436[1]	0.071
Systolic blood pressure	-0.173[2]	0.492
Diastolic blood pressure	0.024[2]	0.925
BMI	-0.446[2]	0.064
Heart rate	0.132[2]	0.600
QTc	0.059[2]	0.816
Mean PANSS positive subscale score	-0.254[1]	0.310
Mean PANSS negative subscale score	-0.130[2]	0.607
Mean PANSS general psychopathology subscale score	0.375[2]	0.125
Mean PANSS total score	0.064[2]	0.801

[1]Spearman's correlation coefficient.
[2]Pearson's correlation coefficient.
BMI: Body mass index; QTc: QT interval; PANSS: Positive and Negative Syndrome Scale; PHQ-9: Patient Health Questionnaire Depression Scale.

reduce the daily dosage in patients based upon the concentration of 9-hydroxyrisperidone rather than RIS. A further limitation of this study is the lack of an association between EPS and RIS levels. Similarly, we did not find a relationship in this sample between either BMI or blood glucose and plasma concentrations of RIS, which may be attributed to the smaller sample size and long-term RIS administration. As such, further studies with larger samples are needed to draw definite conclusions.

CONCLUSION

To conclude, the results of this study indicate that the long-term use of RIS should be closely monitored in older patients and females to minimize the risk of high concentrations which could induce side effects. The variability of the dose of RIS, as well as the physical and psychopathological situation of patients underlines the importance of therapeutic monitoring of plasma RIS and 9-hydroxyrisperidone concentrations to adjust the dose of RIS used in patients with chronic schizophrenia. These study findings provide useful insight to understand and address how TDM is necessary in schizophrenic patients receiving RIS while undergoing long-term hospitalization.

Table 4 Comparison between adverse drug reaction groups and non-adverse drug reaction group

	Trihexyphenidyl group (n = 10)	No trihexyphenidyl group (n = 40)	P/Z value
Risperidone dose per kg weight[2]	0.07 ± 0.03	0.06 ± 0.02	0.129
Concentration of risperidone in plasma (ng/mL)[1]	11.18 ± 11.98	10.90 ± 13.18	0.899
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[2]	42.94 ± 26.33	28.32 ± 10.98	0.117
Concentration of risperidon + 9-hydroxyrisperidone in plasma (ng/mL)[2]	54.12 ± 33.68	39.22 ± 17.52	0.205
Concentration of risperidon + 9-hydroxyrisperidone in plasma/dose[1]	11.77 ± 5.67	11.65 ± 5.92	0.923
Concentration of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	0.17 ± 0.08	0.19 ± 0.10	0.577
	Laxative drug group (n = 10)	**No laxative drug group (n = 40)**	***P/Z* value**
Risperidone dose per kg weight[2]	0.06 ± 0.02	0.06 ± 0.02	0.667
Concentration of risperidone in plasma (ng/mL)[1]	11.87 ± 14.22	10.71 ± 12.65	0.971
Concentration of 9-hydroxyrisperidone in plasma (ng/mL)[1]	37.77 ± 28.34	29.61 ± 11.20	0.914
Concentration of risperidon + 9-hydroxyrisperidone in plasma (ng/mL)[1]	49.64 ± 36.20	40.35 ± 17.15	0.877
Concentration of risperidon + 9-hydroxyrisperidone in plasma/dose[1]	12.81 ± 6.25	11.39 ± 5.75	0.465
Concentration of risperidon + 9-hydroxyrisperidone in plasma/(dose × kg)[1]	0.19 ± 0.07	0.18 ± 0.11	0.607

[1]Mann-Whitney *U*-test.
[2]Student's *t*-test.

FOOTNOTES

Co-first authors: Jing-Wen Xu and Xiao-Bo Guan.

Co-corresponding authors: Jian-Hua Chen and Xue-Ying Wang.

Author contributions: Xu JW, Guan XB, Wang XY, and Chen JY conceived, designed, and refined the study protocol, analyzed the data, and drafted the manuscript; Xu JW, Guan XB, and Feng Y were involved in the data collection; Zhang Q contributed to laboratory analysis and electrocardiogram test; Wang XY and Zhu JJ revised and translated the manuscript. All authors were involved in the critical review of the results and have contributed to, read, and approved the final manuscript. The reasons for designating Xu JW and Guan XB as co-first authors are twofold: First, they made equal contributions to the writing and revision of the manuscript. Second, this study was conducted collaboratively, and the designation of co-first authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. The rationale behind selecting Chen JY and Wang XY as co-corresponding authors lies in their equal contributions to formulating, conceptualizing, and executing the study. In summary, the co-first and co-corresponding authors in this study not only reflect our team's collaborative spirit and equal contributions, but also enhanced the rationality and depth of the research topic.

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Country/Territory of origin: China

ORCID number: Jing-Wen Xu 0009-0003-0154-0359; Jian-Hua Chen 0000-0003-0326-3124.

Corresponding Author's Membership in Professional Societies: Chinese Association of Psychiatry; Basic and Clinical Branch of Psychiatry, Chinese Neuroscience Society; Mental Illness Professional Committee of Chinese Association of Integrated Traditional and Western Medicine; Professional Committee of Psychology and Psychiatry, Chinese Society of Research Hospitals.

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ORIGINAL ARTICLE

Observational Study

Analysis of acupoint massage combined with touch on relieving anxiety and pain in patients with oral implant surgery

Jin-Hong Qu, Cheng-Cheng Shou, Xin He, Qin Wang, Yue-Xia Fang

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Jin-Hong Qu, Department of Stomatology, Hangzhou Lin'an Traditional Chinese Medicine Hospital, Hangzhou 311300, Zhejiang Province, China

Cheng-Cheng Shou, Department of Software R&D, Hangzhou Broadlink Technology Co, Ltd., Hangzhou 311300, Zhejiang Province, China

Xin He, Department of Stomatology, Hangzhou Red Cross Hospital, Hangzhou 310003, Zhejiang Province, China

Qin Wang, Department of Cardiovascular, Hangzhou Lin'an Traditional Chinese Medicine Hospital, Hangzhou 311300, Zhejiang Province, China

Yue-Xia Fang, Department of Traditional Chinese Medicine Development, Hangzhou Lin'an Traditional Chinese Medicine Hospital, Hangzhou 311300, Zhejiang Province, China

Corresponding author: Yue-Xia Fang, RN, Associate Chief Nurse, Department of Traditional Chinese Medicine Development, Hangzhou Lin'an Traditional Chinese Medicine Hospital, No. 288 Xishui North Road, Jinbei Street, Lin'an District, Hangzhou 311300, Zhejiang Province, China. 710125030@qq.com

Abstract

BACKGROUND

Oral implant surgery is an effective procedure for artificial implants in missing tooth areas under local anesthesia. Because patients under local anesthesia are conscious during this procedure, compared with general anesthesia-related operations, they are more likely to experience negative emotions, such as anxiety and tension. These emotional reactions result in shivering and chills in the limbs, leading to poor doctor-patient cooperation and even avoidance of treatment. In traditional Chinese medicine, it is believed that acupoint massage regulates blood and Qi, dredge menstruation, and relieve pain, which is beneficial for patients' emotional adjustment; however, there are few related clinical studies.

AIM

To observe the changes in anxiety and pain in patients with oral implant after acupoint massage combined with touch therapy.

METHODS

One hundred patients undergoing oral implantation in our hospital between May

2020 and May 2023 were randomly divided into control and study groups, according to a random number table, with 50 patients in each group. The control group received routine intervention, and the study group received acupoint massage combined with touch on the basis of the control group. Anxiety [assessed using the Modified Dental Anxiety Scale (MDAS)], pain severity, blood pressure, heart rate, and satisfaction were compared between the two groups.

RESULTS

Before intervention, the difference in MDAS score between the two groups was not significant ($P > 0.05$), while after the intervention, the MDAS scores decreased in both groups compared with those before the intervention ($P < 0.05$); the MDAS score of the study group was lower than that of the control group, with a statistically significant difference ($P < 0.05$). The degree of pain in the intervention group was significantly lower than that in the control group ($P < 0.05$). Before the intervention, there were no significant differences in systolic and diastolic blood pressures or heart rate between the two groups ($P > 0.05$). The systolic and diastolic blood pressures and heart rate in the intervention group, during and after the intervention, were significantly lower than those in the control group ($P < 0.05$). The total degree of satisfaction in the study group was significantly higher than that in the control group ($P < 0.05$).

CONCLUSION

Acupoint massage combined with touch better relieves anxiety and pain in patients undergoing dental implant surgery, improving the perioperative comfort of these patients and ensuring safety and a smooth operation.

Key Words: Oral implant; Acupoint massage; Touch; Anxiety; Degree of pain

Core Tip: Traditional Chinese medicine believes that acupoint massage can regulate blood and Qi, dredge menstruation, and relieve pain, all of which are beneficial for patients' emotional adjustment. However, patients undergoing oral implant surgery are in a state of local anesthesia and consciousness, and can feel tension and pain, which may lead to the interruption of treatment. Therefore, acupoint massage combined with touch may improve treatment efficacy.

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INTRODUCTION

Oral implants are a new technology developed jointly by bionics and tissue engineering, which integrates materials science, oral surgery, medical cosmetology, prosthodontics, and other multidisciplinary technologies, and have gradually become the primary treatment for oral diseases, such as missing anterior teeth and severe alveolar bone absorption[1-4]. Compared with traditional restorative approaches, oral implant technology has received favorable reviews from clinical doctors and patients in terms of aesthetics and oral function restoration[5-7]. Oral implants are effective in edentulous areas under local anesthesia. However, it should be noted that patients under local anesthesia are conscious. Compared to general anesthesia-related surgery, patients are more likely to experience negative emotions, such as anxiety and progression. These emotional reactions often lead to limb tremors and colds. Additionally, they are relatively sensitive to the operating environment and equipment, and many patients experience aggravated pain. To a certain extent, these phenomena affect doctor-patient cooperation and even prevent treatment, which is not conducive to smooth operation[8-12]. To relieve adverse psychological emotions and pain levels in patients undergoing oral implant therapy, in traditional Chinese medicine, it is believed that acupoint massage is beneficial to the emotional management of patients by regulating blood and Qi, dredging channels, and relieving pain[13,14]. Studies have shown that[15] acupoint massage has certain antidepressant and anxiety effects in patients with diabetic retinopathy, and the operation is simple and easy to use; Another study[16] confirmed that touch therapy combined with acupoint massage has a significant effect in reducing the pain of patients during percutaneous laser disc decompression and improving the medical experience of patients. Therefore, it is presumed that acupoint massage combined with touch can relieve anxiety and pain of patients undergoing oral implant surgery. Therefore, in this study, acupoint massage combined with touch therapy was performed on patients with oral implants to observe changes in the degree of anxiety and pain, with the aim of helping patients benefit from it.

MATERIALS AND METHODS

General data

Study participants were selected from 100 patients with oral implants admitted to our hospital between May 2020 and May 2023. The participants were divided into two groups, according to the random number table: 50 cases in the control group, including 15 males and 35 females (age was between 22–50 years, with an average of 35.25 ± 5.08 years). There were 50 cases in the study group, including 18 males and 32 females (age was between 20–58 years, with an average of 36.15 ± 5.15 years). There was no significant difference in age or sex between the two groups ($P > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria: (1) All participants who received oral implant-related treatment for the first time; and (2) all the participants signed the consent form voluntarily.

Exclusion criteria: (1) Patients with abnormal coagulation function or those who took anticoagulant drugs recently; (2) patients with periodontal tissue lesions; (3) systemic diseases, such as liver and kidney dysfunction and osteoporosis; (4) medication history, including anti-inflammatory drugs, glucocorticoids, and immunomodulatory agents within one month before enrollment; (5) complications of infectious diseases and ineffective treatment; and (6) combined cachexia.

Method

Control group: The patients received conventional intervention: They were informed of the operating procedures, possible problems in the treatment, and corresponding solutions, and specific explanations were given for the questions raised by the patients. The patients communicated with each other during the operation interval, and anxiety and progressive emotions were relieved by verbal reassurance.

Study group: Acupoint massage combined with touch was performed in the study group on the basis of the control group, preparation work: Environment: The indoor temperature was controlled at 24-26 ℃, and the humidity was controlled at about 70% (heating or air conditioning is required in winter and summer); Light songs or soft music can be played in the room to relax the patients and make them in a relaxed and quiet state. Before operation, the operator should wash his hands with warm water to ensure that the palm temperature is appropriate. Patients were placed in a comfortably in the supine position, as far as possible. One arm of the patient was held alternately and gently with both hands from top to bottom, and the upper arm to the wrist was massaged. During this process, the middle finger and thumb of one hand were placed at the Neiguan and Waiguan points, and the Hegu and Shenmen points were gently pressed by rotating the two fingers for approximately 3 min. We can also press the feet, massage the Sanyinjiao point on the ankle with emphasis, and adopt the manipulation of twisting, rotating, tamping and moving, 20 times per method. The opposite hand was massaged using the same technique for approximately 20 min. The patient's reaction, expression and pulse changes was observed during the massage, and a pressing force was adjusted if the patient experienced it, or hold patient's hand in time or tap the patient's left front upper limb shoulder, or press the patient's forehead outward from the center of the eyebrow, and ask patient to breathe deeply at the same time. During this process, the massage and touch areas should be far from the operation area so as not to affect the procedure of the operator.

Outcome indicators

Anxiety: The Modified Dental Anxiety Scale (MDAS)[17] was used to evaluate and compare the anxiety of the patients in the two groups before and after the intervention. The MDAS contains four items; each item is assigned according to a 1–5 grading system, with a score range is 4–20 points. The higher the score, the more serious the dental anxiety. When the total score is ≥ 13 points, the patient is assessed to also have dental anxiety.

Pain severity: Pain was assessed using the World Health Organization pain classification[18], and pain during dental implant surgery was compared between the two groups. The assessment was mainly based on the subjective feelings of the patients: No pain was rated as grade 0; mild pain: Slight pain sensation, but bearable; moderate pain: The pain sensation was slightly aggravated, but all of them were within the tolerance range of the patient; and severe pain: the pain was severe and beyond the patient's tolerance, and the patient started shouting.

Blood pressure and heart rate: Blood pressure and heart rate were measured and compared between the two groups using an upright sphygmomanometer before, during, and after the intervention. Radial arterial pulse was also recorded.

Satisfaction: A self-made scale was used to assess satisfaction of the patients (Cronbach's α coefficient was 0.89, and re-test validity was 0.88). The assessment content of the scale mainly included the development of clinical work, work suggestions, and work attitudes. The full score on both sides was 100 points, with a score of ≥ 90 points was very satisfactory, 70–89 points was generally satisfactory, and < 70 points was unsatisfactory.

Statistical analysis

Statistical analysis was performed using SPSS version 24.0. All measurement data were subjected to Shapiro–Wilk normality test, and the measurement data was represented by mean ± SD in line with a normal distribution. An independent sample *t* test was used for intergroup comparisons, and analysis of variance was used for multi-time point comparisons. Count data were expressed as percentage using χ^2 test, and rank data were tested using rank-sum test, with the test level of $\alpha = 0.05$.

RESULTS

Comparison of anxiety (MDAS score)

Before the intervention, the difference in the MDAS anxiety scores between the two groups was not significant ($P > 0.05$). After the intervention, the MDAS scores of the two groups were lower than those before the intervention ($P < 0.05$). Moreover, the MDAS score of the intervention group was significantly lower than that of the control group ($P < 0.05$) (Table 1).

Comparison of the degree of pain

The degree of pain in the intervention group was significantly lower than that in the control group ($P < 0.05$) (Table 2).

Comparison of blood pressure and heart rate

Before the intervention, there were no significant differences in systolic blood pressure, diastolic blood pressure, or heart rate between the two groups ($P > 0.05$). Compared with the control group, the systolic blood pressure, diastolic blood pressure, and heart rate of patients in the study group, during and after the intervention, were significantly lower ($P < 0.05$) (Table 3).

Comparison of degree of satisfaction

The total degree of satisfaction in the intervention group was significantly higher than that in the control group ($P < 0.05$) (Table 4).

DISCUSSION

Anxiety, tension, and other emotions of patients undergoing oral implantations are triggered by many factors. For example, many patients undergoing oral implantations face unfamiliar medical specialties and treatment experiences due to lack of adequate cognition of dental treatment and understanding of related medical interventions. This triggers a series of negative emotions, such as tension and anxiety, leading to increased secretion of endogenous epinephrine and sympathetic nerve excitability. The final manifestations in these patients include increased blood pressure, heart rate, sweating, chest congestion, and palpitations. The patients were skeptical about the treatment or even evaded it, which affected the smooth development of oral treatment and oral health. Deteriorating oral health could adversely cause anxiety in patients, thereby forming a vicious circle[19-21]. Therefore, it is particularly important to implement effective measures to alleviate anxiety in patients undergoing oral implant surgery.

Touch is a non-drug intervention method. Regular, scientific, and orderly mild touch is performed on a patient's body with both hands. Combined with energy technology, touch is an auxiliary method for adjusting and balancing a patient's energy field, thereby affecting patient's physical, psychological, and emotional aspects through intentional guidance[22-24]. In traditional Chinese medicine, it is believed that the body and mind are integrated, internal organs correspond to five aspirations and five emotions of the body, and the running channels of Qi and blood are fundamentally meridians and collaterals. Acupoint massage, as an external therapy in traditional Chinese medicine, can achieve the purpose of harmonize Qi, blood, and the body and mind by stimulating specific acupoints to follow the meridians. Modern pharmacology indicates that acupoint massage can increase nervous system excitability, accelerate metabolism, and improve the immune system[25,26]. The results of this study showed that the degree of pain was lower in the experimental group than that in the control group. The systolic blood pressure, diastolic blood pressure, and heart rate of patients in the study group were lower during and after the intervention, and the overall satisfaction was high, suggesting that acupoint massage combined with touch was beneficial in relieving the degree of pain, improving anxiety, and improving satisfaction. The reasons for this findings may be as follows: (1) Touch can increase the production of natural morphine-like substances, such as dynorphin and enkephalin in the brain, which are transported to the whole body through the body conduction system, to help the body relieve pain and promote emotional excitement[27,28]; (2) touch can reduce the expression of norepinephrine and cortisol, which in turn, improves the stress levels of the body and relieves tension and anxiety[29,30]; and (3) Shenmen and Neiguan points are acupoints in the heart and pericardium meridians, which have the effects of tranquilizing and relieving anxiety. The large intestine meridian runs from the upper arm to the head, and the Hegu point is the source point of the large intestine meridian, and is of great significance in stimulating the healthy Qi of the body for resist stasis[31]. Touch and acupoint massages exhibit strong operability, good randomness, and repeatability. Additionally, acupoint massage uses hand-to-point instead of a needle, which can integrate the respective advantages of the two methods to achieve the effects of moving Qi and activating blood, dredging meridians and collaterals, relieving local pain in patients, and tranquilizing the mind[32,33]. The frontal lobe is the emotion generating center of the human brain, the left frontal lobe is mainly responsible for regulating and generating positive emotions, while the right frontal lobe is responsible for regulating and generating negative emotions. Changes in frontal lobe function are important factors for anxiety. Fan *et al*[34]'s study found that transcutaneous electrical acupoint stimulation of Neiguan can effectively relieve anxiety, with the most obvious changes in the left and right frontal lobes, suggesting that transcutaneous electrical acupoint stimulation of Neiguan can alleviate anxiety through promoting the brain functional activities of the frontal lobe, but it is different from the acupoint massage stimulation in this study. Whether the mechanism of improving anxiety and depression is consistent still needs further study. He *et al*[35] compared the anxiety and pain levels of 36 cases of oral implant patients receiving conventional nursing care, and 36 cases of oral implant patients receiving acupoint massage in combination with touch. Their results showed that the anxiety and pain

Table 1 Comparison of anxiety (Modified Dental Anxiety Scale score) between the two groups (mean ± SD, point)

Group	Pre-intervention	Post-intervention	*t* value	*P* value
Control group (*n* = 50)	17.12 ± 1.05	11.85 ± 0.58	31.066	< 0.001
Study group (*n* = 50)	17.15 ± 1.07	8.25 ± 0.45	54.216	< 0.001
t value	0.142	34.676		
P value	0.888	< 0.001		

MDAS: Modified Dental Anxiety Scale.

Table 2 Comparison of pain severity between the two groups, *n* (%)

Group	Painless	Mild pain	Moderate pain	Severe pain
Control group (*n* = 50)	3 (6.00)	25 (50.00)	20 (40.00)	2 (4.00)
Study group (*n* = 50)	42 (84.00)	8 (16.00)	0	0
Z value	7.890			
P value	< 0.001			

Table 3 Comparison of blood pressure and heart rate between the two groups (mean ± SD)

Group	Pre-intervention	Under intervention	Post-intervention	*F* value	*P* value
Systolic blood pressure (mmHg)					
Control group (*n* = 50)	130.12 ± 10.20	138.25 ± 15.52	128.25 ± 10.75	9.208	< 0.001
Study group (*n* = 50)	130.25 ± 10.22	120.12 ± 8.25	115.25 ± 6.85	40.027	< 0.001
t value	0.064	7.294	7.211		
P value	0.949	< 0.001	< 0.001		
Diastolic blood pressure (mmHg)					
Control group (*n* = 50)	85.25 ± 5.15	90.25 ± 8.15	88.25 ± 8.25	5.900	< 0.001
Study group (*n* = 50)	85.23 ± 5.12	75.12 ± 5.50	72.12 ± 4.50	92.253	< 0.001
t value	0.020	10.881	12.137		
P value	0.985	< 0.001	< 0.001		
Heart rate (beats/min)					
Control group (*n* = 50)	115.25 ± 8.10	120.25 ± 5.25	95.25 ± 10.12	134.211	< 0.001
Study group (*n* = 50)	115.20 ± 8.05	92.25 ± 5.85	82.25 ± 5.80	322.693	< 0.001
t value	0.031	25.189	7.881		
P value	0.975	< 0.001	< 0.001		

Table 4 Comparison of satisfaction between the two groups, *n* (%)

Group	Very satisfied	General satisfaction	Dissatisfied	Total satisfaction
Control group (*n* = 50)	12 (24.00)	32 (64.00)	6 (12.00)	44 (88.00)
Study group (*n* = 50)	48 (96.00)	2 (4.00)	0	50 (100.00)
χ^2 value				4.433
P value				0.035

levels of patients with oral implants receiving acupoint massage in combination with touch were significantly lower than those of patients receiving conventional nursing care. Additionally, their findings suggest that a combination of acupoint massage and touch could alleviate pain and anxiety of patients, which were consistent with the conclusions of this study. Liang *et al*[36] compared the efficacy of 50 cases of adult dental anxiety patients receiving conventional nursing care, and 50 cases of adult dental anxiety patients receiving psychological intervention combined with traditional Chinese medicine acupoint massage. Their results showed that the total effective rate of the treatment group (64.00%) was higher than that of the control group (22.00%), suggesting that psychological intervention combined with acupoint massage can alleviate the anxiety and depression of dental anxiety patients, which is also consistent with the conclusion of this study.

CONCLUSION

Acupoint massage combined with touch is conducive for alleviating anxiety and pain severity of patients undergoing oral implant surgery, thereby improving the perioperative comfort of these patients and ensuring a safe and smooth operation. However, it should still be noted that due to the small sample size and single center research, the credibility of the research conclusion needs to be verified by increasing the sample size and carrying out multi center research in the future.

ARTICLE HIGHLIGHTS

Research background

Oral implant surgery generally involves local anesthesia, and patients are in a conscious state. Under normal circumstances, patients are prone to negative emotions, such as nervousness, and may resist treatment and other uncooperative situations, which are not conducive for a smooth operation. In traditional Chinese medicine, it is believed that acupoint massage can regulate blood and Qi, dredge menstruation, and relieve pain, and its application in oral implant surgery may have certain effects in relieving pain.

Research motivation

At present, there are few clinical studies on the application of acupoint massage combined with touch in patients undergoing oral implant surgery; therefore, this study applied acupoint massage combined with touch in patients undergoing oral implant surgery to observe its influence on anxiety and pain.

Research objectives

This study aimed to observe the changes in anxiety and pain in patients with oral implants using acupoint massage combined with touch.

Research methods

One hundred patients undergoing oral implantation were randomly divided into control and study groups, according to a random number table, with 50 patients in each group. Anxiety [assessed using the Modified Dental Anxiety Scale (MDAS)], pain severity, blood pressure, heart rate, and satisfaction were compared between the two groups.

Research results

The MDAS score and degree of pain were lower in the study group than those in the control group. The systolic blood pressure, diastolic blood pressure, and heart rate of patients in the study group were lower during and after the intervention, and the overall satisfaction was high.

Research conclusions

Acupoint massage combined with touch is better in relieving anxiety of patients undergoing dental implant surgery, thereby relieving their pain and improving perioperative comfort.

Research perspectives

It should be noted that due to the small sample size and single center research, the credibility of the research conclusion needs to be verified by increasing the sample size and carrying out multi center research in the future.

FOOTNOTES

Co-first authors: Jin-Hong Qu and Qin Wang.

Author contributions: Qu JH and Wang Q contributed equally to this work as co-first authors; Qu JH, Shou CC, He X, Wang Q, and Fang YX designed the research study; Qu JH, Shou CC, He X, Wang Q, and Fang YX performed the research; Qu JH and Wang Q contributed new reagents and analytic tools; Qu JH and Wang Q analyzed the data and wrote the manuscript; and all authors have read and approve

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ORCID number: Jin-Hong Qu 0009-0003-1931-4923; Cheng-Cheng Shou 0009-0006-9299-4488; Xin He 0009-0006-5306-3082; Qin Wang 0009-0007-5008-4176; Yue-Xia Fang 0009-0009-3734-4943.

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ORIGINAL ARTICLE

Observational Study

Resilience provides mediating effect of resilience between fear of progression and sleep quality in patients with hematological malignancies

Yuan Tian, Ying-Li Wang

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Yuan Tian, Department of Hematology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou 121000, Liaoning Province, China

Ying-Li Wang, Department of Cardiology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou 121000, Liaoning Province, China

Corresponding author: Ying-Li Wang, MBBS, Nurse, Department of Cardiology, The First Affiliated Hospital of Jinzhou Medical University, No. 2 Section 5, People Street, Guta District, Jinzhou 121000, Liaoning Province, China. 13897850411@163.com

Abstract

BACKGROUND

Hematological tumors are common malignant tumors, with high morbidity and mortality rates. Most patients with hematological malignancies develop sleep disorders that seriously affect their life and health because of acute onset of disease, rapid progression, high recurrence rates, complex treatment methods, and treatment costs.

AIM

To explore the mediating effect of resilience on fear of disease progression and sleep quality in patients with hematological malignancies.

METHODS

A cross-sectional analysis of 100 patients with hematological malignancies, treated in the First Affiliated Hospital of Jinzhou Medical University between August 2022 and August 2023, was conducted. Patients were assessed using a general data survey, a simplified scale for the fear of progression (FoP) of disease, a resilience scale, and the Pittsburgh Sleep Quality Index. Statistical analysis was conducted to determine the relationship between various patient characteristics and FoP, resilience, and sleep quality. Spearman's correlation analysis was used to examine the correlations between mental resilience, FoP, and sleep quality.

RESULTS

The total FoP score mean value in patients with hematological malignancies was 38.09 ± 5.16; the total resilience score mean value was 40.73 ± 7.04; and the Pittsburgh Sleep Quality Index score mean value was 10.72 ± 1.90. FoP, resilience,

and sleep quality of the patients were associated with family per capita monthly income and patient education level ($P < 0.05$). Spearman correlation analysis revealed that FoP was negatively correlated with resilience and sleep quality scores (r = -0.560, -0.537, $P < 0.01$), respectively, and resilience was significantly associated with sleep quality scores (r = 0.688, $P < 0.01$). Mediation analysis showed that the mediating effect of resilience between FoP and sleep quality in patients with hematological malignancies was -0.100 and accounted for 50.51% of the total effect. This indicated that FoP directly and indirectly affected sleep quality through the mesomeric effect of resilience.

CONCLUSION

Resilience is an intermediary variable between FoP and sleep quality in patients with hematological malignancies. Medical staff should evaluate and follow-up FoP and resilience to implement measures to improve sleep quality.

Key Words: Resilience; Blood tumor; Fear of progression; Sleep quality; Mediating effect

Core Tip: Hematological tumors are common malignant tumors. Most patients with hematological malignancies develop sleep disorders that seriously affect their quality of life and health, owing to the acute onset, rapid progression, and high recurrence rate of these tumors. In this study, we conducted a cross-sectional analysis of 100 patients with hematological malignancies in the oncology department of our hospital. A general data survey, simplified fear of disease progression scale, resilience scale, and the Pittsburgh Sleep Quality Index were used to investigate the mediating effect of resilience between fear of disease progression and sleep quality in patients with hematological malignancies.

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INTRODUCTION

In recent years, the incidence and mortality of hematological tumors in China have increased[1]. Owing to the characteristics of hematological malignancies, such as acute onset, rapid progression, easy recurrence, complex treatment methods, and high treatment costs[2], concern about the progression or recurrence of the disease may seriously affect physical and mental health as well as sleep quality in patients. The term fear of progression (FoP) denotes a psychological condition marked by apprehension, fear, or worry regarding the potential advancement or recurrence of a medical condition[3]. Studies have shown that FoP is one of the most common pain symptoms in patients with carcinomas and other chronic diseases. An increase in these levels may lead to patient dysfunction and affect happiness, quality of life, and social function[4]. It is difficult to provide an effective relief of symptoms in cancer patients who have an obvious fear of disease progression. FoP is an urgent problem that must be addressed in patients with hematological tumors.

Elevated FoP levels in patients with cancer and other chronic diseases may lead to health dysfunction, including sleep problems. Sleep is an important marker of related functions in the human body and is crucial for maintaining individual physical and mental health[5]. Saletin *et al*[6] proposed a simple definition of sleep: A reversible behavioral state that is detached and unresponsive to the environment. The typical characteristics of sleep include closed eyes, lying supine, behavioral immobility, and reduced reactivity[6]. However, abnormal conditions may also occur during sleep, such as individuals exhibiting certain behaviors (sleepwalking, somniloquy, grinding teeth) or sleep problems (insomnia, dreaminess, wakefulness)[6]. In view of this, researchers have proposed the concept of sleep quality to better probe the sleep status in individuals. Sleep quality refers to a person's subjective evaluation of sleep quality, including the evaluation of sleep duration, sleep continuity, and wake-up feelings[7]. However, there is currently no standardized definition of sleep quality. Subjective and objective indicators are used to measure sleep quality, and some instruments convert sleep-related physiological indicators into sleep quality indicators[8,9]. Several studies have shown that patients with cancer have difficulties in initiating or maintaining sleep, wake up earlier than expected, and are unable to fall back to sleep; furthermore, they experience excessive daytime sleepiness and other sleep disorders, which remain as well during the recovery period[10]. Studies have shown that the stronger the fear of recurrence in patients with cancer, the worse their sleep quality[11].

Research has confirmed that the occurrence of sleep disorders is associated with individual negative emotions and mental disorders[12]. Bad mood can lead to decreased sleep quality, and approximately 80% of patients with depression have sleep disorders such as insomnia, early waking, and excessive sleep[13]. Resilience has attracted the attention of many researchers in the field of positive psychology. Resilience refers to an individual's positive internal coping abilities and good adaptation processes in the face of adversity and trauma. It is a complex internal psychological potential that has a significant impact on the development and growth of an individual[14]. Studies have found that the degree of

mental resilience in patients after cancer surgery is inversely proportional to the degree of FoP[15]. Furthermore, resilience has been demonstrated to improve sleep quality[16]. Overall, hematologic malignancies, such as leukemia, lymphoma, and myeloma, usually involve long-term and complex treatment processes, posing significant psychological and emotional burdens on patients and their families. Therefore, psychological resilience plays a crucial role in the study of patients with hematologic malignancies, affecting not only their mental health but also significantly impacting their treatment outcomes and quality of life.

Based on previous studies, in this study, we aimed to investigate the relationship between FoP and quality of sleep in patients with hematological malignancies. To the best of our knowledge, this is the first attempt to explore the mediating effect of resilience on FoP and sleep quality in this group of patients, providing a theoretical basis and practical reference for promoting quality of sleep in these patients from the perspective of FoP.

MATERIALS AND METHODS

Research participants

A cross-sectional design was used in this study. The research process is illustrated in Figure 1. One hundred patients with hematologic malignancies treated at the First Affiliated Hospital of Jinzhou Medical University between August 2022 and August 2023 were included in this study. The inclusion criteria were as follows: (1) Patients with hematological malignancies; (2) Age ≥18 years old; (3) Primary school or above education level, able to correctly communicate and answer the questions included in the tests; and (4) Awareness of their illness and willingness to cooperate with the study. The following exclusion criteria were applied: (1) Impairment of cognitive function or other psychiatric diseases; (2) Serious damage to vital organs such as the heart, brain, and kidneys; (3) Malignant tumors at other sites; and (4) Other primary sleep disorders such as sleep apnea syndrome.

Research methods

Patient data collection: Data regarding sex, age, marital status, education level, average monthly family income, medical payment method, place of residence, occupation type, illness course, religious beliefs, and family history were collected.

FoP Questionnaire-short Form: This instrument was developed by Mehnert *et al*[17] and translated into Chinese by Cheng *et al*[18]. The questionnaire includes 12 items and two dimensions: Physical health (six items) and social family (six items) assessed on a 5-point Likert scale (1 = never and 5 = always). Cronbach's α coefficient was 0.820. On a scale of 12-60 points, the score was correlated to the severity of fear.

Connor-Davidson Resilience scale: The scale was translated and revised into Chinese by Xie *et al*[19] and included three dimensions: Toughness respectively (13 items), optimism (4 items), and self-strengthening (8 items), with a total of 25 items assessed on a 5-point Likert scale (0 = "never" and 4 = "almost"). Cronbach's α coefficient was 0.897 and Cronbach's α coefficient for each table was 0.66-0.88. On a scale of 0-100 points, the higher the sum of the scores in each dimension, the stronger the mental resilience in patients.

Pittsburgh Sleep Quality Index: Buysse *et al*[8] evaluated sleep quality in hospitalized patients. Cronbach's α coefficient for the table was 0.750. The scale comprises 18 items, categorized into seven dimensions including sleep efficiency, sleep disorders, sleep time, sleep quality, daytime dysfunction, and use of hypnotic drugs. Each table is scored on a 0-3 scale, with a total score of 0-21. Scores ≥ 8 indicate a sleep disorders. Cronbach's α coefficient was 0.850.

Statistical methods

IBM SPSS (version 26.0) was used to analyze the data. Measurement data are described as mean ± SD, and counting data are described as component ratio (%). Spearman's rank correlation analysis was used to test the correlations between fear of disease progression, mental resilience, and sleep quality. The macro program Process in IBM SPSS 26.0 was applied to inspect the mediating effect between fear of disease progression, resilience, and sleep quality, and the bootstrap method was applied to verify the mediating effect between mental resilience and fear of disease progression and sleep quality. The test level was $\alpha = 0.05$, and a P value < 0.05 was considered statistically significant.

RESULTS

Resilience, FoP, and sleep quality scores of patients

The total FoP score mean value in patients with hematologic malignancies was 38.09 ± 5.16. The total resilience score mean value was 40.73 ± 7.04. The total sleep quality score mean value was 10.72 ± 1.90. The scores for each scale are presented in Table 1.

Relationship between general data and FoP, resilience, and sleep quality

Statistical analysis showed that the FoP, resilience, and sleep quality in patients with hematological malignancies were associated with per capita monthly household income and education level ($P < 0.05$). The per capita monthly income of households and education level were inversely proportional to the FoP score and directly proportional to the resilience

Table 1 Patient fear of progression, resilience, and sleep quality scores

Project	Number of items	Rating range	Score
Fear of disease progression	12	12-60	38.09 ± 5.16
Physical health	6	6-30	19.56 ± 3.01
Social family	6	6-30	18.53 ± 4.06
Resilience	25	0-100	40.73 ± 7.04
Toughness	13	0-52	19.69 ± 5.45
Optimistic	4	0-16	6.33 ± 2.92
Self-strengthening	8	0-32	14.70 ± 3.60
Sleep quality	18	0-21	10.72 ± 1.90
Sleep efficiency	1	0-3	1.30 ± 0.90
Sleep disorders	9	0-3	2.36 ± 0.62
Sleeping time	2	0-3	2.52 ± 0.64
Sleep time	1	0-3	0.56 ± 0.37
Sleep quality	1	0-3	2.04 ± 0.77
Daytime dysfunction	3	0-3	1.26 ± 0.83
Use of hypnotic drugs	1	0-3	0.67 ± 0.56

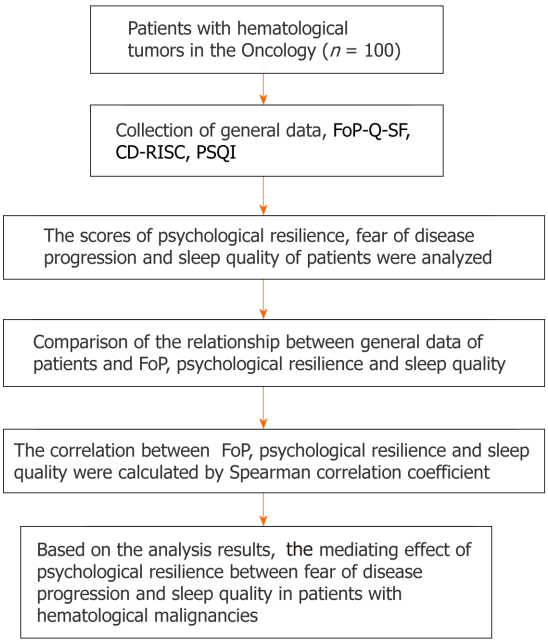

Figure 1 Flowchart of the research study process. CD-RISC: Connor-Davidson Resilience scale; FoP: Fear of progression; FoP-Q-SF: Fear of Progression Questionnaire-short Form; PSQI: Pittsburgh Sleep Quality Index.

and sleep quality scores (Tables 2-4).

Correlation analysis of patient FoP, resilience, and sleep quality

Spearman's correlation analysis was performed on the FoP, resilience, and sleep quality in patients with hematological malignancies, and the results revealed that FoP was negatively correlated with resilience and sleep quality scores (r = -0.560, -0.537, P < 0.01). Resilience was significantly associated with sleep quality scores (r = 0.688, P < 0.01) (Table 5 and Figure 2).

Table 2 Relationship between general patient data and fear of progression

Projects	Number, *n* (%)	Score	*t*/*F*	*P* value
Sex				
Male	49 (49)	36.46 ± 4.30	3.232	0.002
Female	51 (51)	39.65 ± 5.47		
Age (yr)				
≤ 35	34 (34)	38.69 ± 5.37	0.426	0.654
35-60	36 (36)	37.55 ± 3.83		
≥ 60	30 (30)	38.04 ± 6.30		
Marital status				
Married	27 (27)	37.09 ± 4.55	0.190	0.827
Unmarried	48 (48)	39.19 ± 5.55		
Divorce/widowhood	25 (25)	37.04 ± 4.74		
Family per capita monthly income (RMB)				
< 3000	32 (32)	41.71 ± 4.65	32.112	0.000
3000-5000	38 (38)	38.62 ± 3.27		
> 5000	30 (30)	33.54 ± 4.23		
Medical expenses payment method				
Medical insurance	46 (46)	37.54 ± 5.09	0.896	0.412
Agricultural insurance	51 (51)	38.39 ± 5.14		
Other	3 (3)	41.21 ± 7.24		
Educational level				
Junior high school and below	40 (40)	38.65 ± 4.75	3.189	0.046
High school/technical secondary school	41 (41)	38.76 ± 4.88		
College degree or above	19 (19)	35.45 ± 5.98		
Type of occupation				
Employment	46 (46)	37.10 ± 4.39	1.782	0.078
Unemployment	54 (54)	38.93 ± 5.65		
Type of residence				
Rural	34 (34)	39.08 ± 4.09	1.396	0.166
Town	66 (66)	37.57 ± 5.60		
Disease course				
Less than 2 yr	50 (50)	37.64 ± 5.08	-0.859	0.393
2 yr and above	50 (50)	38.53 ± 5.26		
Religious beliefs				
Yes	5 (5)	37.99 ± 5.60	-0.806	0.422
No	95 (95)	39.90 ± 5.15		
Family history				
Yes	16 (16)	38.79 ± 4.41	-0.594	0.554
No	84 (84)	37.95 ± 5.30		
Tumor type				
Leukemia	29 (29)	39.15 ± 6.07	1.068	0.366
Lymphoma	30 (30)	37.95 ± 3.79		

Multiple myeloma	21 (21)	36.54 ± 5.21
Myelodysplastic syndrome	20 (20)	38.38 ± 5.43

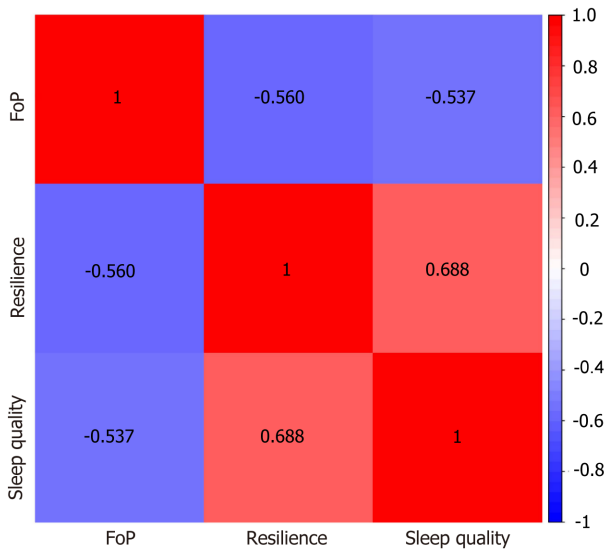

Figure 2 Spearman correlation heat map. Darker colors indicate stronger correlations between the two indicators. FoP: Fear of progression.

The mediating effect of resilience on FoP and sleep quality in patients with hematologic malignancies

Using the FoP in patients with hematological malignancies as an independent variable (X), resilience as a mediating variable (M), and sleep quality (Y) as a dependent variable, SPSS 26.0, Macro Process Model 4 was applied to analyze the mediating effect of resilience. Regression analysis indicated that the total effect value "*c*" of FoP on sleep quality was -0.539 ($P < 0.05$). The regression coefficient "*a*" of FoP on resilience was -0.566 ($P < 0.05$). The regression coefficient "*b*" of resilience on sleep quality was 0.481 ($P < 0.05$). When resilience was added, the direct effect value "*c*'" of FoP on resilience was -0.267, which was still significant ($P < 0.05$). These results suggest that resilience mediates the relationship between FoP and sleep quality in patients with hematological malignancies. The bootstrap method was used to further examine the mediating effects of resilience. The results showed that the mediating effect value was -0.100 (95% confidence interval: -0.139 to -0.068), indicating that the mediating effect of resilience was established and accounted for 50.51% of the total effect (Tables 6 and 7, Figure 3).

DISCUSSION

Hematological malignancies are common; owing to characteristics such as acute onset, long treatment cycle, and high risk of recurrence, these tumors have a considerable physical and mental impact on patients. Optimizing the sleep quality in patients has recently attracted significant research attention. In this study, a cross-sectional analysis of 100 patients with hematologic malignancies in our hospital showed that FoP could affect patient sleep quality directly as well as indirectly through the mediating effect of resilience.

The purpose of this study was to improve our understanding of the mediating effect of resilience between FoP and sleep quality in patients with hematologic malignancies. This study utilized a cross-sectional design to ascertain the prevalence of blood cancers in certain populations, along with associated risk or protective factors. Cross-sectional designs are advantageous owing to their cost-efficiency and ease of implementation, enabling concurrent investigation into the progression of blood cancers, psychological resilience, and sleep quality. Nevertheless, the simultaneous data collection precludes direct demonstration of causality between variables or the observation of how these variables change over time. Consequently, in this study, we have advanced to using mediation effect analysis to assess the causal links among variables. Additionally, future studies should incorporate longitudinal research to better understand the dynamic interrelations among the variables.

First, using general data and FoP Questionnaire-short Form, Connor-Davidson Resilience scale and Pittsburgh Sleep Quality Index surveys, we found that the total FoP score mean value in patients with hematological malignancies was 38.09 ± 5.16, which was slightly higher than that described by Zhang *et al*[20]. The total resilience score of 40.73 ± 7.04 was consistent with the results reported by Greup *et al*[21] in a study on young patients with cancer. The total sleep quality score of 10.72 ± 1.90 was similar to that reported by Fox *et al*[10] in a study on sleep quality in patients with cancer during chemotherapy[22]. Furthermore, the FoP, resilience, and sleep quality in patients were associated with per capita monthly family income and educational level, which was consistent with results of both domestic and international research[23-25]. Family per capita monthly income and education level are among the problems faced by patients with hematologic

Table 3 Relationship between general patient data and patient resilience

Projects	Number, *n* (%)	Score	*t*/*F*	*P* value
Sex				
Male	49 (49)	41.87 ± 7.08	-1.615	0.110
Female	51 (51)	39.62 ± 6.88		
Age (yr)				
≤ 35	34 (34)	41.94 ± 5.81	1.386	0.255
35-60	36 (36)	40.98 ± 6.73		
≥ 60	30 (30)	39.05 ± 8.44		
Marital status				
Married	27 (27)	40.82 ± 6.23	0.877	0.419
Unmarried	48 (48)	41.48 ± 7.28		
Divorce/widowhood	25 (25)	39.18 ± 7.40		
Family per capita monthly income (RMB)				
< 3000	32 (32)	33.56 ± 4.29	121.749	0.000
3000-5000	38 (38)	40.54 ± 2.96		
> 5000	30 (30)	48.60 ± 4.16		
Medical expenses payment method				
Medical insurance	46 (46)	43.30 ± 6.68	2.231	0.113
Agricultural insurance	51 (51)	39.45 ± 7.21		
Other	3 (3)	38.23 ± 5.98		
Educational level				
Junior high school and below	40 (40)	38.32 ± 7.23	7.744	0.001
High school/technical secondary school	41 (41)	40.84 ± 5.96		
College degree or above	19 (19)	45.55 ± 6.52		
Type of occupation				
Employment	46 (46)	41.68 ± 6.96	-1.25	0.214
Unemployment	54 (54)	39.92 ± 7.07		
Type of residence				
Rural	34 (34)	40.58 ± 7.31	-0.147	0.883
Towns	66 (66)	40.80 ± 6.95		
Disease course				
Less than 2 yr	50 (50)	40.92 ± 7.11	0.277	0.782
2 yr and above	50 (50)	40.53 ± 7.03		
Religious beliefs				
Yes	5 (5)	40.50 ± 3.59	0.073	0.942
No	95 (95)	40.74 ± 7.18		
Family history				
Yes	16 (16)	40.79 ± 7.21	0.192	0.848
No	84 (84)	40.42 ± 6.23		
Tumor type				
Leukemia	29 (29)	39.67 ± 6.71	0.841	0.475
Lymphoma	30 (30)	39.92 ± 7.50		

Multiple myeloma	21 (21)	41.90 ± 7.82
Myelodysplastic syndrome	20 (20)	42.23 ± 5.90

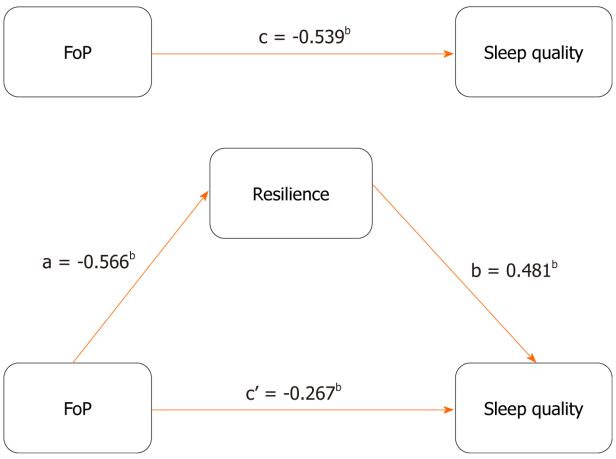

Figure 3 Mediating effect of resilience between fear of progression and sleep quality. [b]*P* < 0.01. FoP: Fear of progression.

tumors. Enhancing sleep quality necessitates a heightened focus on individual patient factors during the disease management process, encompassing aspects such as family income, educational attainment, and occupational stress levels.

Second, Spearman's correlation analysis demonstrated that the progression of fear of disease was negatively correlated with resilience and sleep quality scores (r = -0.560, -0.537, P < 0.01), and resilience was significantly associated with sleep quality scores (r = 0.688, P < 0.01). The reasons for these results may be as follows: The factors of FoP in patients with hematological malignancies mainly include persistent pain, fatigue, anxiety, and depression related to the disease itself and its treatment[26], which also affect sleep quality to varying degrees[27]. However, external factors played an important role in the degree of pressure affecting the patients in this study. These included concerns over practical problems caused by the disease, such as poor mental state and decreased physical function, family economic difficulties, lower career competitiveness after returning to work, and the possibility of cancer recurrence or metastasis. Decreased ability to regulate negative emotions[28,29]. Patients with poor mental resilience often immerse themselves in their own thoughts, which aggravates the production of negative emotions and affects their sleep quality. Therefore, fear of recurrence, resilience, and sleep quality in patients with cancer are correlated.

Finally, in the results of mediation analysis, we found that resilience played a mediating role between the FoP of disease and sleep quality. That is, FoP (c = -0.539, P < 0.05) and resilience (b = 0.481, P < 0.05) had predictive effects on quality of sleep in patients with hematological malignancies. In addition, the FoP of disease could indirectly predict sleep quality in patients with hematologic malignancies through resilience (c' = -0.267, P < 0.05), with a mediating effect size of 50.51%. There are several explanations for these results. First, FoP has an important impact on sleep quality. Cancer is a major stressor and negative event in individuals. Patients are prone to negative emotions such as loneliness, meaninglessness, worthlessness, and guilt due to decreased physical function, changes in social roles, increased leisure time, and high treatment costs, leading to sleep disorders[30-32]. Moderate fear can be the driving force of self-health management among patients; however, excessive fear can further aggravate negative emotions and sleep disorders. Second, poor mental resilience aggravates sleep disorders. Patients with fear of the disease experience significant psychological pressure and are more prone to anxiety and depression. It is necessary to show positive emotions such as optimism, tenacity, and self-improvement, and take actions such as actively seeking external support to promote physical and mental health and alleviate negative emotions[33]. In contrast, patients with hematological malignancies with low psychological resilience are prone to social withdrawal, avoidance of social activities, and other escape behaviors when facing stressful events. Thus, these patients receive less social support and are more likely to breed negative emotions, such as pessimism and despair, which further aggravates the FoP and affects their sleep quality[34]. Among them, cognitive-behavioral therapy, meditation, stress management training, relaxation techniques, and adjustments in daily routines are effective to enhance patients' psychological resilience. Notably, family and social support for blood cancer patients are of utmost importance. A supportive social environment and peaceful, joyful family life often significantly boost patients' psychological resilience, which in turn improves their sleep quality and prognosis. Therefore, it is important that medical intervention targeting sleep disorders in patients with hematological malignancies strengthens their resilience. In clinical practice, clinicians should pay attention to the psychological status in patients, help them establish a strong, optimistic, and self-strengthening mentality, and reduce negative psychological problems. Furthermore, personalized intervention plans tailored to the specific needs of patients can more effectively enhance psychological resilience.

Table 4 Relationship between general patient data and sleep quality

Projects	Number, *n* (%)	Score	*t*/*F*	*P* value
Sex				
Male	49 (49)	10.87 ± 1.90	-0.762	0.448
Female	51 (51)	10.58 ± 1.99		
Age (yr)				
≤ 35	34 (34)	10.80 ± 1.68	0.248	0.781
35-60	36 (36)	10.82 ± 1.70		
≥ 60	30 (30)	1.52 ± 2.35		
Marital status				
Married	27 (27)	10.62 ± 1.74	0.599	0.551
Unmarried	48 (48)	10.93 ± 2.10		
Divorce/widowhood	25 (25)	10.44 ± 1.65		
Family per capita monthly income (RMB)				
< 3000	32 (32)	8.98 ± 1.23	58.580	0.000
3000-5000	38 (38)	10.76 ± 1.21		
> 5000	30 (30)	12.53 ± 1.44		
Medical expenses payment method				
Medical insurance	46 (46)	10.93 ± 1.83	0.558	0.574
Agricultural insurance	51 (51)	10.56 ± 1.91		
Other	3 (3)	10.24 ± 3.11		
Educational level				
Junior high school and below	40 (40)	10.13 ± 1.75	8.12	0.001
High school/technical secondary school	41 (41)	10.67 ± 1.70		
College degree or above	19 (19)	12.11 ± 1.98		
Type of occupation				
Employment	46 (46)	10.82 ± 1.64	-0.48	0.632
Unemployment	54 (54)	10.64 ± 2.10		
Type of residence				
Rural	34 (34)	10.36 ± 1.55	-1.388	0.168
Towns	66 (66)	10.91 ± 2.04		
Disease course				
Less than 2 yr	50 (50)	10.78 ± 1.79	0.292	0.771
2 yr and above	50 (50)	10.67 ± 2.01		
Religious beliefs				
Yes	5 (5)	11.21 ± 2.13	-0.586	0.559
No	95 (95)	10.70 ± 1.89		
Family history				
Yes	16 (16)	10.76 ± 1.91	0.509	0.612
No	84 (84)	10.50 ± 1.84		
Tumor type				
Leukemia	29 (29)	10.38 ± 1.98	0.890	0.449
Lymphoma	30 (30)	10.75 ± 1.80		

Multiple myeloma	21 (21)	11.26 ± 2.12
Myelodysplastic syndrome	20 (20)	10.63 ± 1.66

Table 5 Correlation analysis of fear of progression, resilience and sleep quality

Variables	FoP	Resilience	Sleep quality
Fear of progression	1		
Resilience	-0.560[a]	1	
Sleep quality	-0.537[a]	0.688[a]	1

[a]$P < 0.01$.

Table 6 Regression analysis of the relationship between variables in the mediation model

Regression equation		Overall fitting index		Significance of regression coefficient	
Outcome variable	Predictor variable	R^2	F	b	t
Sleep quality	FoP	0.284	40.208	-0.539	-6.341[a]
Resilience	FoP	0.314	46.226	-0.566	-6.799[a]
Sleep quality	FoP	0.437	39.361	-0.267	-2.920[a]
	Resilience			0.481	5.254[a]

[a]$P < 0.01$.
FoP: Fear of progression.

Table 7 Mediating effect of resilience between fear of progression and sleep quality

Effect relationship	Effect value	Standard error	95%CI		Proportion of effect (%)
			Lower limit	Upper limit	
Total effect	-0.198	0.031	-0.260	-0.136	100.00
Direct effect	-0.098	0.034	-0.165	-0.031	49.49
Indirect effect	-0.100	0.018	-0.139	-0.068	50.51

CI: Confidence interval.

This study has some limitations. First, owing to the limitations of manpower and material resources, this study only selected patients with hematological malignancies from one hospital; therefore, the sampling was not sufficiently comprehensive. Second, a questionnaire survey was used to measure the studied variables, and patient attitudes when completing these questionnaires may have affected the validity of the research results. Therefore, in future research, qualitative interviews should be conducted.

CONCLUSION

This cross-sectional investigation explored the mediating role of resilience on FoP and sleep quality in patients with hematological malignancies. Our results showed that sleep quality in patients was suboptimal. Further, FoP can directly affect sleep quality and play an indirect role through resilience, which may furnish treatment decisions for the intervention in patients with blood tumors who have FoP. Medical staff should focus on the progression of fear of disease and the level of resilience in patients with hematological malignancies, to implement effective measures to reduce excessive fear in patients, improve the effectiveness of disease management, and promote sleep quality.

FOOTNOTES

Author contributions: Tian Y designed the questionnaire, conducted the statistical analysis of the data, and drafted the initial manuscript; Wang YL supervised and guided the study and revised the manuscript.

Institutional review board statement: This study was reviewed and approved by the First Affiliated Hospital of Jinzhou Medical University.

Informed consent statement: All study participants or their legal guardians provided written informed consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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Country/Territory of origin: China

ORCID number: Yuan Tian 0009-0002-0457-2762; Ying-Li Wang 0009-0001-5563-599X.

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ORIGINAL ARTICLE

Observational Study

Nurse anesthetists' perceptions and experiences of managing emergence delirium: A qualitative study

Yi Xin, Fu-Cai Lin, Chen Huang, Bin He, Ya-Ling Yan, Shuo Wang, Guang-Ming Zhang, Rui Li

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Yi Xin, Fu-Cai Lin, Bin He, Ya-Ling Yan, Wuxi Medical College, Jiangnan University, Wuxi 214122, Jiangsu Province, China

Chen Huang, Shuo Wang, Guang-Ming Zhang, Department of Anesthesiology, Tongren Hospital Shanghai Jiao Tong University School of Medicine, Shanghai 200335, China

Rui Li, Department of Nursing, Tongren Hospital Shanghai Jiao Tong University School of Medicine, Shanghai 200335, China

Corresponding author: Rui Li, MSc, Chief Nurse, Department of Nursing, Tongren Hospital Shanghai Jiao Tong University School of Medicine, No. 1111 Xianxia Road, Changning District, Shanghai 200335, China. 18616365160@163.com

Abstract

BACKGROUND

This study employs a descriptive phenomenological approach to investigate the challenges anesthesia nurses face in managing emergence delirium (ED), a common and complex postoperative complication in the post-anesthesia care unit. The role of nurses in managing ED is critical, yet research on their understanding and management strategies for ED is lacking.

AIM

To investigate anesthetic nurses' cognition and management experiences of ED in hopes of developing a standardized management protocol.

METHODS

This study employed a descriptive phenomenological approach from qualitative research methodologies. Purposeful sampling was utilized to select 12 anesthetic nurses from a tertiary hospital in Shanghai as research subjects. Semi-structured interviews were conducted, and the data were organized and analyzed using Colaizzi's seven-step analysis method, from which the final themes were extracted.

RESULTS

After analyzing the interview content, four main themes and eight subthemes were distilled: Inefficient cognition hinders the identification of ED (conceptual ambiguity, empirical identification), managing diversity and challenges (patient-centered safe care, low level of medical-nursing collaboration), work responsib-

ilities and pressure coexist (heavy work responsibilities, occupational risks and stress), demand for high-quality management (expecting the construction of predictive assessment tools and prevention strategies, and pursuing standardized management processes to enhance management effectiveness).

CONCLUSION
Nursing managers should prioritize the needs and suggestions of nurses in order to enhance their nursing capabilities and provide guidance for standardized management processes.

Key Words: Anesthetic nurse; Emergence delirium; Postoperative complications; Cognition; Disease management; Qualitative research

Core Tip: This study employs a descriptive phenomenological approach to investigate the challenges anesthesia nurses face in managing emergence delirium (ED), a common and complex postoperative complication in the post-anesthesia care unit. The role of nurses in managing delirium is critical, yet research on their understanding and management strategies for ED is lacking. The findings indicate that anesthesia nurses have insufficient knowledge about ED but acknowledge the necessity for further education and have proposed numerous proactive management strategies. The study also underscores the need for management to prioritize nurse welfare to foster the growth of a high-quality care team.

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INTRODUCTION

Delirium is a neuropsychiatric-behavioral syndrome characterized by altered levels of consciousness, inattention, and disturbances in sleep-wake cycles[1,2]. Delirium occurring from the end of general anesthesia to the post-anesthesia care unit (PACU) period is defined as emergence delirium (ED) with an incidence rate ranging from 3.7% to 45.0%[3]. ED not only tends to lead to a series of adverse consequences, such as surgical incision splitting, self-removal of tubes, falling out of bed, violent behavior, *etc*., but also increases the burden of supervision of the medical staff in the resuscitation room, and in the long term may even lead to the development of postoperative delirium, postoperative cognitive impairment and other complications[4,5]. Guidelines clearly state that nurses play a vital role in the management of delirium[6]. Nurses are capable of early identification of delirium predisposing and precipitating factors, effectively implementing handover, prevention, and management strategies for delirium by providing supportive or restorative treatments, thereby reducing the harm of delirium to patients. In intensive care units (ICUs), nurse-led delirium management has achieved significant results[7]. However, current studies mainly focus on the role of ICU nurses in delirium management within the ICU setting[8-10], with relatively limited research on the management of ED by anesthesia nurses caring for patients with rapidly changing conditions during the peri-anesthesia period. Therefore, this study employs qualitative research methods to delve into the cognitive status and management experiences of anesthesia nurses when dealing with ED patients. By understanding the issues, difficulties, and feelings they face in ED management, the aim is to provide references for the development of standardized ED training and management systems, ultimately enhancing the capabilities of anesthesia nurses in the management of ED.

MATERIALS AND METHODS

Design

This study employs the descriptive phenomenological method within qualitative research. Following a review of relevant literature domestically and abroad, as well as consultations with experts to align with the research objectives, a preliminary interview outline was developed. Two anesthetic nurses were pre-interviewed, and after discussion by the research team, the outline was revised, and the interview guide was as follows: (1) Could you please describe a memorable patient with ED? (2) How do you observe or assess the symptoms of ED in a patient? (3) In your opinion, what risk factors are likely to contribute to a patient developing ED? (4) What preventive or management measures do you take when dealing with ED? What challenges do you face? (5) How do you feel internally when dealing with a patient who has ED? and (6) How did you acquire knowledge about ED? What are your views or suggestions on this topic?

Data collection and ethical considerations

Purposeful sampling was utilized to select anesthesia nurses from a certain tertiary hospital in Shanghai as research participants from July to August 2023.

The inclusion criteria were as follows: (1) Active-duty nurses who have worked in the PACU for three years or longer; (2) Nurses who have previously provided care for ED patients; (3) Nurses who have obtained and registered their nursing practice license; (4) Nurses who are able to adequately express their inner feelings and who have given informed consent to participate in the study.

The exclusion criteria were as follows: Nurses who are on further study or rotation from other departments. Engage in advance communication with the interviewees to determine the interview schedule and location. Opt for a quiet office or lounge for a face-to-face interview and obtain consent for audio recording. Begin the interview with a self-introduction, stating the purpose and establishing a relaxed atmosphere. Utilize the interview outline for questioning while also paying attention to non-verbal cues and encouraging nurses to share their experiences. Limit the interview duration to 30 minutes, concluding when no new themes are generated from the information. The study was reviewed and approved by the Jiangnan University Medical Ethics Committee (Approval No. JNU20230301IRB16). All research participants provided informed written consent prior to registering for the study. Interviewees have the right to refuse participation or withdraw from the interview at any time, and all interviewees' data will be kept confidential.

Data analysis

Within 24 h after the interview concluded, one researcher transcribed the audio data into text and documented non-verbal information in the corresponding sections of the file. Two researchers independently analyzed, coded, and extracted themes from the data using Colaizzi's 7-step analysis method[11]. The specific analysis steps included: (1) Thoroughly read the material to fully understand the content; (2) Identify meaningful statements or descriptive sentences; (3) Organize meaningful statements into units of meaning; (4) Categorize and induct units of meaning to identify common themes; (5) Provide detailed descriptions of each theme, summarizing its characteristics and essence; (6) Derive a fundamental structure from the detailed descriptions, clarifying core content; and (7) Validate the accuracy and completeness of the fundamental structure through feedback. Following the completion of the data analysis, the researchers presented the findings back to the interviewees for verification to ensure the accuracy of the information. The general data of the interviewees were analyzed using SPSS 26.0 and are presented as mean ± SD.

RESULTS

In total, 12 anesthesia nurses agreed to participate in this study, comprising 11 females and one male, with an average age of 36.750 years ± 6.864 years, an average nursing tenure of 15.920 years ± 7.833 years, and an average duration of specialty-specific work experience of 6.750 years ± 4.245 years. Table 1 depicts the primary sociodemographic data of the inter-viewees. Following data collection and analysis, four main themes and eight subthemes were identified, revealing the cognitive perceptions and management experiences of anesthesia nurses regarding the incidence of ED in postoperative patients. Table 2 depicts the four main themes and eight subthemes of this article.

Theme 1: Inefficient cognition hinders the identification of emergence delirium

Subtheme 1 conceptual ambiguity: Anesthesia nurses exhibit some ambiguity regarding the concept of ED, and some even attribute ED to what they consider a "normal" consequence of residual anesthetic drugs during surgery.

After the patient woke up, they were non-compliant, restless, agitated, and unable to control themselves; I'm not sure if this is ED or not (No. 8).

I speculate that the most likely cause of ED is the inhalation anesthesia, as the patient has not completely metabolized the ether. Once the inhaled anesthetic agents are fully metabolized, the patient will naturally regain consciousness, and the symptoms of ED will improve (No. 6).

Subtheme 2 empirical identification: Research[12] indicates that only 1.6% of delirium cases are classified as the hyperactive subtype, while 43.5% are hypoactive, and 54.1% are present with mixed features. However, in everyday practice, anesthesia nurses tend to recognize ED primarily by its overt, hyperactive symptoms, with a noticeable deficiency in identifying hypoactive delirium. They often underestimate its incidence and lack systematic assessment awareness.

The most common type encountered involves patients twisting and turning in bed, constantly moving in an agitated manner (No. 6).

The instances of ED we usually encountered were infrequent, and hypoactive delirium was even less commonly identified. There might have been cases that went unnoticed. We typically lacked the awareness to assess whether a patient was experiencing ED (No. 4).

Furthermore, anesthesia nurses reported that they typically rely on previous empirical recognitions of specific presentations in patients with ED to make an assessment.

The manifestations of ED include being particularly agitated and uncooperative after awakening, attempting to free themselves from restraints such as intravenous lines and electrocardiogram leads, or unconsciously repeating phrases like "I need to go to the bathroom." The judgment is mainly based on the clinical presentation observed after the patient experiences ED (No. 3).

Table 1 Sociodemographic data of respondents

Number	Sex	Age	Educational background	Position	Title	Years of nursing experience (yr)	Years of specialized work (yr)
No. 1	Female	38	Undergraduate	Nurse	Senior nurse	16	6
No. 2	Female	39	Undergraduate	Nurse	Senior nurse	20	6
No. 3	Female	35	Undergraduate	Head nurse	Nurse supervisor	15	5
No. 4	Male	27	Undergraduate	Nurse	Nurse	4	4
No. 5	Female	41	Undergraduate	Nurse	Senior nurse	20	17
No. 6	Female	35	Undergraduate	Assistant head nurse	Nurse supervisor	15	5
No. 7	Female	30	Undergraduate	Nurse	Senior nurse	8	6
No. 8	Female	43	Junior college	Nurse	Senior nurse	24	14
No. 9	Female	49	Vocational school	Nurse	Senior nurse	30	6
No. 10	Female	26	Undergraduate	Nurse	Senior nurse	4	4
No. 11	Female	43	Undergraduate	Nurse	Nurse supervisor	21	3
No. 12	Female	35	Undergraduate	Nurse	Senior nurse	14	5

Table 2 Themes and subthemes of the study

Themes	Subthemes
Inefficient cognition hinders the identification of emergence delirium	Conceptual ambiguity
	Empirical identification
Managing diversity and challenges	Patient-Centered safe care
	Low level of medical-nursing collaboration
Work responsibilities and pressure coexist	Heavy work responsibilities
	Occupational risks and stress
Demand for high-quality Management	Expecting the construction of predictive assessment tools and prevention strategies
	Pursuing standardized management processes to enhance management effectiveness

Theme 2: Managing diversity and challenges

Subtheme 1 patient-centered safe care: During the interview, the anesthesia nurse stated that they always adhere to the principle of "safety first" when addressing unconscious patients' agitated behaviors. To ensure patient safety and prevent adverse incidents such as falls from the bed or accidental decannulation, the anesthesia nurse employed a series of restraints and monitoring measures.

Firstly, immobilization is required, securing the restraint straps and closely monitoring whether the tubes might become dislodged (No. 5).

Protective measures were provided to prevent the patient's arms or legs from hitting the bed rails (No. 6).

However, anesthesia nurses also emphasized that individual differences in patients had to be taken into account when safety measures were implemented to avoid potential negative effects, maintaining concern and sensitivity towards the patients.

The application of restraints must be situation-specific, as sometimes securing them too tightly can increase the risk of ED (No. 1).

For elderly and critically ill patients, their condition can change rapidly. Prolonged restraint can easily lead to agitation as they dislike the feeling of being confined and may even develop feelings of persecution or delusional paranoia (No. 7).

Furthermore, the enclosed and unfamiliar environment of the PACU tends to predispose patients to delirium[13]. Anesthesia nurses expressed that when dealing with patients experiencing ED, it is crucial to prioritize compassionate care. By engaging in communication, providing companionship, and offering physical touch, they actively alleviate the discomfort of the patient and facilitate a quicker emergence from the state of ED.

We soothe him through verbal communication, telling him, "Where you are today, and what you are here for (No. 2)".

I once had a conversation with a patient without the use of medication or physical restraints. I held his hand and engaged with him in his dream, diverting his attention and resulting in a quieting effect. His attention was absorbed in the narrative of his own mind, which meant his body stopped moving erratically. After patiently accompanying him for twenty minutes, he regained clarity (No. 11).

Subtheme 2 low level of medical-nursing collaboration: Anesthetic nurses have expressed that when encountering patients experiencing ED, anesthesiologists often rely on their personal clinical experience and preferences when managing the condition. If nurses are unable to quickly adapt, this can lead to a decrease in collaboration between the medical and nursing staff.

As anesthetic nurses, we mostly follow the instructions of the anesthesiologist, but each doctor has a different style, and their approach to managing ED can vary, which sometimes may not align seamlessly with the nurses' practices (No. 3).

Some physicians are reluctant to administer drugs and may prefer to allow a patient who remains unresponsive to spend more time in the PACU; others are more proactive and may prophylactically use medications; while some may decide on drug interventions based on the intraoperative medication situation (No. 2).

Meanwhile, there's some discrepancy among anesthetic nurses regarding the use of sedatives.

If a patient exhibits mild symptoms of ED, we may reassure them and observe for a while; if symptoms are more severe, we might administer a sedative, but this can lead to delayed recovery, which is undesirable. However, without medication, patients can become very agitated and behave excessively, risking injury from falling out of bed (No. 7).

Theme 3: Work responsibilities and pressure coexist

Subtheme 1 heavy work responsibilities: During the interviews, anesthesia nurses emphasized the responsibility of managing concurrent care requirements for different patients. Anesthesia nurses must not only handle the complexities of ED patients but also balance multiple tasks and needs, ensuring both the safety of patients with ED and the provision of care for others.

What we, as nurses, can do is ensure patient safety; firstly, we prevent the patient from falling out of bed or inflicting self-harm. Secondly, we try to keep the patient's mind as calm as possible because agitation can lead to unintended incidents like tube removal (No. 11).

At times like this, it's not just one person restraining or caring for them at the bedside, ensuring their safety. In the PACU, there are also other patients; while caring for him, I need to keep an eye on everyone else (No. 6).

When faced with complex scenarios and multitasking demands, anesthetic nurses indicate they prioritize the management of ED lower to ensure the important needs of other patients are met promptly and to maintain the overall synergy of the healthcare team.

During busy times in the PACU, if we focus too much energy on the patient with ED, we might not be able to fully take care of other patients (No. 6).

When patients recovering from anesthesia first wake up, we must immediately determine whether they require interventions such as extubation and suctioning. These tasks are essential and something we must address. However, ED is not an emergency situation and can be dealt with later (No. 10).

Subtheme 2 occupational risks and stress: Anesthesia nurses expressed that high levels of agitation pose a dual challenge, both endangering patient safety and requiring nurses to remain vigilant in order to prevent unforeseen incidents. This can easily lead to psychological burdens and mental fatigue for the nurses.

There is considerable pressure when dealing with the elderly in PACU at night. We fear their agitation, as it is our responsibility to prevent them from removing any medical lines. Hence, this one-hour period is constantly filled with heightened tension (No. 7).

Additionally, patients with delayed recovery disrupt subsequent surgical plans and work schedules to some degree, increasing the workload and pressure on healthcare providers.

If a patient experiences delayed recovery, our bed remains occupied, preventing the admission of subsequent patients or causing surgical delays. Consequently, we have to work overtime as well (No. 7).

Theme 4: Demand for high-quality management

Subtheme 1 expecting the construction of predictive assessment tools and prevention strategies: In this study, anesthesia nurses expressed that work in the PACU is stressful and human resources are scarce; therefore, anticipating and intervening in the early stages of ED is crucial to reducing the risk of its occurrence in patients and alleviating the workload of nurses.

If we could predict the likelihood of ED before the removal of the endotracheal tube, we wouldn't need as many staff to handle the aftermath. We could intervene early and not prolong recovery time. For instance, similar to a scale, we could assess if they are at high risk and what preventive measures should be administered to them in advance, then develop corresponding prevention strategies (No. 3).

Anesthesia nurses also believe that such tools and strategies could be integrated into the routine processes of the PACU to provide scientific and systematic guidance to healthcare professionals.

We could have a system where we take no action below a certain score, take specific measures between certain scores, and implement pharmacological treatment above a certain threshold. I think this could be incorporated as a standard procedure within the PACU (No. 12).

Due to the rapid turnover of patients in the PACU, anesthesia nurses believe that a streamlined and efficient digital assessment tool should be designed. This tool would be capable of quickly and accurately identifying patients with specific susceptibility factors, thereby enabling targeted management of those at high risk of ED.

There are two main issues with PACU patients: One is the high volume of turnover, and the other is the relatively short duration of time patients spend in recovery. For instance, young patients without any underlying health issues may not require routine screening and assessment. It's essential to screen certain populations, such as elderly patients above a certain age or according to specific thresholds (No. 6).

The scale must not be too burdensome for nurses, yet it must accurately identify patients with ED (No. 3).

The assessment tool should be as convenient as possible with the integration of information technology (No. 10).

Subtheme 2 pursuing standardized management processes to enhance management effectiveness: The development of standardized procedures plays a significant role in ensuring patient safety and improving the quality of medical services, yet there is currently a lack of standardized management protocols for ED. Anesthesia nurses believe that establishing standardized procedures will help medical staff reach a consensus, increase the efficiency of ED management, and provide patients with more standardized nursing care.

There is a lack of a standard for ED management in the PACU. Sometimes, there is a small section in the consensus among anesthesia experts, but it is not expanded upon in detail. If there is a guideline that could unify the understanding of medical staff, then the management would be more convenient and smoother in the future (No. 3).

Having such a standardized process would enable clinical medical staff to handle ED more systematically, which would greatly benefit patients. If some people do not follow the standard and instead rely on their own experience, outcomes for patients could vary greatly. If their experience exceeds the standard, it is highly beneficial for patients; however, if their experience falls below the standard, it could lead to poor outcomes for patients (No. 11).

Furthermore, the anesthesia nurses involved in this study expressed the desire for diverse and systematic training methods for ED, highlighting the urgent need for training that integrates theoretical knowledge with practical skills. The recommendations covered various educational formats, including simulation training, the establishment of delirium teams, and multidisciplinary collaboration models.

Anesthesia nurses, being specialists, require dedicated theoretical study, which is essential, and repeated clinical training is needed (No. 6).

This could be medical simulation or virtual reality. Cases could be set up in a mock operating room for nurses to experience and allow for trial and error, something not often feasible in clinical practice (No. 3).

If senior nursing management could establish systematic delirium training that then cascades to the clinical level, it would likely be better in terms of implementation and standardization. Similar to wound care groups or intravenous therapy groups, these smaller collectives can drive transformation throughout the entire hospital with their capabilities (No. 11).

Preoperative, intraoperative, and postoperative departments could collaborate to provide comprehensive and systematic management for ED patients (No. 8).

DISCUSSION

Although nurse anesthetists have received relevant learning and training, there are still deficiencies in the identification and care of ED patients. Due to the ill-defined concept of ED, the use of inaccurate terms such as "agitation" and "restlessness", as well as bedside interactions and empirical judgments of ED, nurse anesthetists' knowledge of its occurrence is relatively low. Studies[14] have shown that nurses relying only on their personal experience of observation can only accurately identify 19% of patients with delirium, and this empirical judgment substantially increases the rate of missed diagnoses. Other studies[15] have also noted that nurses' familiarity with delirium knowledge may affect early recognition and nursing intervention and that delirium recognition rates can be significantly improved by implementing educational intervention programs. Therefore, it is recommended that administrators should reinforce the training of nurse anesthetists in ED expertise. Targeted tests should be administered first to assess nurses' current level of knowledge and nursing burden, and then individualized educational curricula should be developed based on the results of the tests in the form of videos, examples of clinical practice, and interactive discussions. In addition, delirium knowledge learning channels were provided, and relevant posters were created and posted in office areas to increase knowledge dissemination[16]. Workshop model, training competition activities and clinical simulation teaching are all effective training methods to help nurse anesthetists keep up-to-date with the latest research knowledge related to ED and improve their ability and self-confidence in handling ED patients in practice. Finally, the training effects are then consolidated through continuous quality improvement programs to ensure that nurse anesthetists are able to cope with the challenges of the ED in a more professional and confident manner.

Nurse anesthetists face complex nursing issues and challenges in ED management, especially in the high-pressure environment of the PACU, where the importance of nurse anesthetists in ED management has been marginalized due to the tight staff, high workload, and low level of awareness of the ED. In addition, the prevention and treatment strategies for ED have not yet been clearly defined, the level of healthcare cooperation is low, and doctors and nurses take pharmacological or non-pharmacological management measures mainly based on their personal clinical experience when dealing with it. A mature ED management system has not yet been established in China, so there is an urgent need to establish a standardized process. The establishment of this standardized process requires the support of the organizational system. Relevant administrators should build ED assessment and management norms based on evidence-based practices and hospital characteristics. To ensure the implementation of the norms, hospitals need to appropriate medical manpower

and resources are needed, and the norms should be included in the quality control management indicators. At the same time, it is recommended that an electronic ED processing board be constructed and integrated into the medical order processing system for monitoring, evaluating, and recording symptoms, as well as to supervise the full implementation of ED assessment and management by nurse anesthetists. To improve teamwork and the quality of ED management, ED management teams can be established. In a study by Morandi *et al*[17], an interdisciplinary delirium management prevention program effectively reduced nurses' workload by developing individualized treatment and follow-up plans through comprehensive assessment. In addition, nonpharmacological treatment is the primary measure of ED treatment [18], so nurse anesthetists should take a leading role in ED nonpharmacological management. Through the construction of nursing norms, the establishment of organizational systems and standardized steering groups, nursing managers can promote the practical application of these changes in the clinical setting. This is important for improving patient prognosis and enhancing the quality of care.

This study found that anesthetic nurses have limited attention to ED, focusing mainly on the diagnosis and treatment stages while neglecting effective prevention of ED. Related research[14] indicates that up to 40% of delirium cases are potentially preventable. Risk prediction models, as a scientific, statistical assessment method, play a significant role in evaluating and identifying early high-risk populations[19]. Xing *et al*[20] constructed a postoperative delirium risk prediction model with an accuracy rate of up to 92%, which exhibits excellent performance in the early identification of high-risk groups, providing a basis for medical staff to take timely preventive treatments and care. Cao *et al*[21] built an early risk stratification model through the E-PRE-DELIRIC theory, successfully reducing the incidence of delirium in ICU patients, reducing the rate of adverse drug reactions, and shortening the ICU stay of patients. Hence, it is recommended that researchers should formulate ED risk warning models based on perioperative anesthesia and surgery-related risk factors, combined with the specific risk factors of PACU, and conduct risk stratification. The risk warning model for ED should be used during the perioperative period to assess the risk of ED, identify high-risk patients, and develop personalized prevention strategies based on corresponding risk factors. This includes actively taking supportive or restorative treatment measures, ensuring prevention, handover, and management of ED, securing patient safety and recovery, and improving the quality of ED management. In the context of limited medical resources, the ED risk warning model can also help medical staff identify high-risk patients who may need more attention and resource allocation, enhancing the efficiency of medical resource utilization and alleviating the burden of subsequent treatment. This systematic prevention strategy is expected to effectively reduce the incidence of ED and improve the overall quality of patient care.

The nursing care for patients with ED is complex, and the simultaneous needs of other patients, combined with limited human resources, impose dual physical and psychological pressures on anesthetic nurses. Domestically, anesthetic nurses face issues of ambiguous job responsibilities, unclear business scopes, and uneven distribution of human resources[22], leading to excessive workload, which in turn lowers job satisfaction and increases turnover rate. Therefore, administrators need to focus on optimizing the management and resource allocation of the anesthesia operation rooms to ensure reasonable work arrangements and nurse-to-patient ratios. Researchers[15] suggest that, in critical care units, the nurse-to-patient ratio should fluctuate between 1:1 and 1:3. Especially in the presence of patients with delirium, a nurse should be specifically assigned to care for the delirious patients to ensure individualized and close monitoring, alleviate the workload of other nurses, and enhance the quality of care as well as the utilization of medical resources. Furthermore, managers should also focus on incentive mechanisms, as low job control and high job demands can reduce job satisfaction among nurses[23]. Granting anesthetic nurses a certain degree of autonomy, rewards, and opportunities for professional development and clarifying their responsibilities and authority while encouraging the standard procedure for ED treatment can elevate the level of motivation among anesthetic nurses, thereby enhancing patient satisfaction and the quality of nursing services. Nursing managers should actively listen to the concerns and issues of anesthetic nurses, providing constructive feedback and suggestions. Implementing stress management strategies such as psychological health counseling, health promotion activities, and flexible work arrangements can help alleviate work pressure. Lastly, nursing managers may introduce effective stress relief strategies such as mindfulness-based stress reduction and the formation of Balint groups[24]. The former relieves stress by focusing on present sensations and emotions, while the latter is a form of social support that provides understanding and backing to nurses by sharing workplace challenges and pressures among colleagues. These methods have been demonstrated to positively reduce nurse stress and improve job satisfaction. Therefore, anesthetic nurses should pay attention to personal stress management and proactively adopt these strategies to promote their physical and emotional wellbeing.

The innovative aspect of this research lies in the application of qualitative methods to explore the perceptions and management experiences of anesthesia nurses in handling patients with ED from their own perspective. By engaging in face-to-face communication, the study delves deeply into the challenges, difficulties, and emotions anesthesia nurses encounter during the management of ED, thereby enriching the body of research in the field of ED. The limitations of this study are attributed to the low proportion of male nurses in the clinical setting which resulted in the inclusion of only one male nurse in this research. Consequently, the perspectives and viewpoints of male nurses are underrepresented. Future research should consider increasing the number of interviews with male nurses. In addition, subsequent studies could reference the findings of this research to develop standardized, information-driven tools and procedures for the assessment and management of ED, which can be implemented in clinical practice for the benefit of patients.

CONCLUSION

This study employed semi-structured interviews to deeply explore the experiences of anesthetic nurses in the cognition and management of ED. The findings revealed that inefficient cognitive patterns impede the timely detection and

management of ED, highlighting the challenges anesthetic nurses face in managing the complexity and variability of conditions, the trade-offs and coping strategies between work responsibilities and load, and the anesthetic nurses' anticipation for more diversified management approaches. Addressing these issues, researchers believe it is crucial to prioritize the physical and mental health of nurses and suggest improvements in the following areas: first, strengthening professional knowledge training to enhance nurses' cognition of ED and providing them with more effective tools and strategies. Secondly, standardizing the ED management processes will establish a systematic and scientific management model to deal with the variability of ED and enhance management efficiency. Additionally, building early warning models and developing corresponding prevention strategies can help to identify high-risk patients in advance, effectively reducing the incidence of ED. Lastly, hospital management should pay attention to nurses' work environment and psychological state, meeting their expectations for management approaches in more humanized and diversified ways, thereby improving their work experience. Therefore, through comprehensive improvement measures, we can expect to manage ED patients more effectively, raise the quality of care, and promote the sustainable development of healthcare services.

ARTICLE HIGHLIGHTS

Research background

The emergence delirium (ED) is a common postoperative complication in the post-anesthesia care unit, representing a significant management challenge. Given the vital role of nurses in the management of delirium, it is crucial to explore the experiences and challenges of anesthesia nurses in managing ED.

Research motivation

Currently, the issues and perspectives of anesthesia nurses in the management of ED are not well understood. Therefore, this study adopts a qualitative research approach to thoroughly explore the cognition and experiences of anesthesia nurses in managing ED patients.

Research objectives

To understand the issues, challenges, and experiences faced by anesthesia nurses in managing ED, with the aim of providing a reference for the development of standardized ED training and management systems and enhancing the abilities of anesthesia nurses in ED management.

Research methods

A descriptive phenomenological research method was employed in this study, using purposive sampling to select anesthesia nurses for face-to-face semi-structured interviews. The collected data were then analyzed and thematic findings were derived using the Colaizzi's seven-step analysis approach.

Research results

Anesthesia nurses are currently lacking theoretical knowledge in addressing ED, and their practical handling of such patients has not reached a proficient level, leading to significant physical and mental stress. However, they have shown great enthusiasm for learning about and managing ED and have put forward multiple constructive opinions and suggestions, which are worth drawing inspiration from and learning.

Research conclusions

Nursing managers should pay full attention to the cognitive and management experiences of anesthesia nurses in managing patients with ED, by strengthening knowledge learning, establishing standardized management systems, developing early warning strategies, and promoting physical and mental well-being. This will enhance the abilities of anesthesia nurses in ED care and provide helpful guidance in formulating standardized management protocols for ED.

Research perspectives

Future research can develop detailed and standardized protocols for managing ED based on the recommendations of this study and apply them in clinical practice.

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FOOTNOTES

Co-first authors: Yi Xin and Fu-Cai Lin.

Co-corresponding authors: Rui Li and Guang-Ming Zhang.

Author contributions: Xin Y, Lin FC, Zhang GM, and Li R contributed to the research design and thesis writing; Xin Y, Lin FC, and Huang C collected and analyzed the data; Xin Y, He B, Wang S, and Yan YL contributed to the data collection; Zhang GM and Li R overall supervise the study; and all authors contributed to the article and approved the submitted version. The reasons for designating Xin Y and Lin FC as co-first authors are twofold: Firstly, both co-first authors jointly contributed to experimental design, data collection, and analysis, playing a crucial role in ensuring the reliability and validity of the research. Secondly, both co-first authors collaborated in writing and revising the research paper, thereby enhancing the overall quality of the manuscript. The reasons for designating Li R and Zhang GM as co-corresponding authors are threefold: Firstly, they possess expertise in the fields of anesthesiology and nursing, providing crucial professional support and advice for the research. Secondly, they serve as leaders and mentors within the research team, playing significant organizational and guidance roles throughout the entire research project. Lastly, their contributions to the review and revision of this manuscript are equal. In summary, the co-first authors and co-corresponding authors of this study, by analyzing and presenting the research content from multiple professional perspectives, ensured the breadth and depth of the research findings.

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ORCID number: Yi Xin 0009-0008-7155-5093; Fu-Cai Lin 0009-0004-5448-4319; Chen Huang 0009-0003-4942-3688; Bin He 0009-0009-5079-7912; Ya-Ling Yan 0009-0000-0403-509X; Shuo Wang 0009-0000-4857-7683; Guang-Ming Zhang 0000-0003-0423-7497; Rui Li 0009-0000-5214-3132.

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ORIGINAL ARTICLE

Basic Study

Tanshinone IIA improves Alzheimer's disease *via* RNA nuclear-enriched abundant transcript 1/microRNA-291a-3p/member RAS oncogene family Rab22a axis

Long-Xiu Yang, Man Luo, Sheng-Yu Li

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Long-Xiu Yang, Man Luo, Sheng-Yu Li, Department of Neurology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530000, Guangxi Zhuang Autonomous Region, China

Sheng-Yu Li, Department of Neurology, Wuming Hospital of Guangxi Medical University, Nanning 530199, Guangxi Zhuang Autonomous Region, China

Corresponding author: Sheng-Yu Li, MD, Doctor, Teacher, Department of Neurology, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Qingxiu District, Nanning 530000, Guangxi Zhuang Autonomous Region, China. 15177821212@163.com

Abstract

BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative condition characterized by oxidative stress and neuroinflammation. Tanshinone IIA (Tan-IIA), a bioactive compound isolated from *Salvia miltiorrhiza* plants, has shown potential neuroprotective effects; however, the mechanisms underlying such a function remain unclear.

AIM

To investigate potential Tan-IIA neuroprotective effects in AD and to elucidate their underlying mechanisms.

METHODS

Hematoxylin and eosin staining was utilized to analyze structural brain tissue morphology. To assess changes in oxidative stress and neuroinflammation, we performed enzyme-linked immunosorbent assay and western blotting. Additionally, the effect of Tan-IIA on AD cell models was evaluated *in vitro* using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Genetic changes related to the long non-coding RNA (lncRNA) nuclear-enriched abundant transcript 1 (NEAT1)/microRNA (miRNA, miR)-291a-3p/member RAS oncogene family Rab22a axis were assessed through reverse transcription quantitative polymerase chain reaction.

RESULTS

In vivo, Tan-IIA treatment improved neuronal morphology and attenuated oxidative stress and neuroinflammation in the brain tissue of AD mice. *In vitro*

experiments showed that Tan-IIA dose-dependently ameliorated the amyloid-beta 1-42-induced reduction of neural stem cell viability, apoptosis, oxidative stress, and neuroinflammation. In this process, the lncRNA NEAT1 - a potential therapeutic target - is highly expressed in AD mice and downregulated *via* Tan-IIA treatment. Mechanistically, NEAT1 promotes the transcription and translation of Rab22a *via* miR-291a-3p, which activates nuclear factor kappa-B (NF-κB) signaling, leading to activation of the pro-apoptotic B-cell lymphoma 2-associated X protein and inhibition of the anti-apoptotic B-cell lymphoma 2 protein, which exacerbates AD. Tan-IIA intervention effectively blocked this process by inhibiting the NEAT1/miR-291a-3p/Rab22a axis and NF-κB signaling.

CONCLUSION

This study demonstrates that Tan-IIA exerts neuroprotective effects in AD by modulating the NEAT1/miR-291a-3p/Rab22a/NF-κB signaling pathway, serving as a foundation for the development of innovative approaches for AD therapy.

Key Words: Tanshinone IIA; Alzheimer's disease; Nuclear-enriched abundant transcript 1; Member of RAS oncogene family Rab22a; Reactive oxygen species

Core Tip: Tanshinone IIA (Tan-IIA), a compound isolated from *Salvia miltiorrhiza*, demonstrates neuroprotective effects against Alzheimer's disease (AD). This study reveals that Tan-IIA improves neuronal health, reduces oxidative stress and neuroinflammation, and promotes neural stem cell viability. Importantly, it targets the nuclear-enriched abundant transcript 1/microRNA-291a-3p/member RAS oncogene family Rab22a/nuclear factor kappa-B pathway, offering a potential therapeutic avenue for AD.

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INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia worldwide, is a progressive neurological condition that affects millions of individuals and presents a serious public health issue[1,2]. The amyloid-beta 1-42 (Aβ1-42) peptide is a primary component of the amyloid plaques found in the brains of individuals with AD. It is believed to play a critical role in the neuropathology of AD by initiating a cascade of events that leads to neuronal dysfunction and death[3]. Memory loss and cognitive decline are caused by the buildup of Aβ plaques, neurofibrillary tangles, and synaptic and neuronal loss in individuals with AD[4-6]. Despite extensive research on AD, current treatment options only focus on symptomatic relief rather than disease remission, and the development of new therapeutic agents and targets is required to improve the disease prognosis.

Growing evidence points to neuroinflammation and oxidative stress being key factors in the etiology of AD[7,8]. Nitric oxide (NO) gas is produced in greater amounts when there is an excessive buildup of reactive oxygen species (ROS) in the body. An increased production of NO causes oxidative stress, which damages neurons and exacerbates AD[9]. This process lowers the levels of the antioxidants superoxide dismutase (SOD) and glutathione (GSH), making them less effective at scavenging ROS[10,11]. In addition, the release of neuroinflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6, exacerbates neuronal damage and contributes to the progression of AD[12,13]. Long non-coding RNA (lncRNA) furthermore acts as a molecular sponge for microRNA (miR, miRNA) adsorption to regulate miRNA expression[14], and such changes in miRNA expression critically affect the transcription and translation of downstream targets[15]. For example, a study by Zhao *et al*[16] showed that the lncRNA nuclear-enriched abundant transcript 1 (NEAT1) promotes the development of AD through the miR-124/beta-site amyloid precursor protein-cleaving enzyme axis. In addition, miR-291a-3p, which is associated with inflammation, oxidative stress, and apoptosis, may be downregulated in neural injury[17,18]; however, its role and mechanism of function in AD remain unclear.

RAB22A, member RAS oncogene family (Rab22a) is another important tumor regulator[19,20], but its mechanism of action in AD is unclear. Its role in promoting neuroinflammation and oxidative stress[21] warrants the inclusion of Rab22a in the present study to explore its role in AD, especially since it affects Aβ accumulation[22]. Additionally, the nuclear factor kappa-B (NF-κB) pathway is triggered by the neuroinflammatory response in AD, which can aggravate the disease progression. The role of the B-cell lymphoma 2 (Bcl-2) protein in this process is significantly inhibited in contrast to that of pro-apoptotic proteins; the greater the ratio of Bcl-2/Bcl-2-associated X protein (Bax), the greater the anti-apoptotic ability. However, the role of Rab22a on NF-κB and the regulation of downstream pro- and anti-apoptotic proteins require elucidation.

Salvia miltiorrhiza, also known as danshen or red sage, produces a bioactive molecule called tanshinone IIA (Tan-IIA; chemical structure depicted in Figure 1A) with reportedly anti-inflammatory, antioxidant, and anti-apoptotic activities [23,24]. Previous studies demonstrated that Tan-IIA reduces oxidative stress and neuroinflammation, two factors known to worsen AD[25,26]. Although Tan-IIA has been shown to improve AD, the mechanism underlying this improvement is not well understood.

In this study, we investigate processes involving the NEAT1/miR-291a-3p/Rab22a/NF-κB signaling pathway that may underlie the neuroprotective benefits of Tan-IIA, using both *in vivo* and *in vitro* models of AD. Our results help to clarify the intricate regulatory network that controls oxidative stress and neuroinflammation connected to AD and may serve as a foundation for the creation of new treatment options for the disease.

MATERIALS AND METHODS

Animal models and neural stem cell isolation

The Guangdong Medical Experimental Animal Center (Guangzhou, China) provided all mice; AD was induced in some mice *via* a bilateral injection of Aβ1-42 oligomers into the CA1 region of the hippocampus, as previously described[27]. All animal treatments were approved by the Guangxi Medical University's Animal Care and Use Committee [approval no. 2021(KY-E-292); Nanning, China] and were carried out in accordance with the Guide for the Care and Use of Laboratory Animals.

The mice were maintained under a 12-h light/dark cycle and provided with unlimited access to food and water. Mice were randomly placed in one of four treatment groups (n = 6 each): A control group, comprising healthy mice; an AD group, in which AD was induced without further treatment; and two Tan-IIA groups, with AD mice receiving either 5 or 20 mg/kg of Tan-IIA (HY-N0135; MedChemExpress LLC, NJ, United States). Tan-IIA was dissolved in dimethyl sulfoxide (DMSO; Solarbio, Beijing, China) and administered intraperitoneally once daily for 4 wk in mice of the relevant treatment groups. Subsequently, the mice were anesthetized and sacrificed, and their brain tissues were removed and placed in Hank's balanced salt solution (Gibco, Thermo Fisher Scientific, MA, United States) with 1% penicillin-streptomycin (Gibco) to isolate the neural stem cells (NSCs). Tissues from the hippocampus and subventricular zone were carefully removed, chopped, and subjected to enzymatic digestion with trypsin-EDTA (Gibco) for 15 min at 37 °C. Fetal bovine serum (Gibco) was used to terminate digestion, after which the cell solution was filtered through a 40 m mesh cell strainer (BD Biosciences, CA, United States) to remove debris. The cells were centrifuged at 300 rpm for 5 min, and the resulting cell pellet was resuspended and cultured in NSC culture medium (Procell, Wuhan, China) at 37 °C and in 5% CO_2. The medium was replaced every 2 d, and the NSCs were passaged until 80%-90% confluence was reached before being used for subsequent experiments.

Immunofluorescence analysis

The obtained NSCs were incubated with bovine serum albumin for 30 min and incubated further (overnight, at 4 °C and in the dark) with microtubule-associated protein 2 (MAP2; 1:500, ab254264; Abcam, Cambridge, United Kingdom), β III tubulin (3 μg/mL, ab18207; Abcam), and nuclear factor erythroid 2-related factor 2 (Nrf2; 1:100, ab62352; Abcam) antibodies. Thereafter, the cells were incubated at 37 °C for 1 h with either goat anti-rabbit Alexa Fluor® 488 (1:250, ab150077; Abcam) or 647-conjugated secondary antibodies. Finally, the NSCs were mounted on microscope slides using a gold antifade medium containing DAPI stain (ProLong™, Thermo Fisher Scientific). MAP2 and βIII tubulin were used to confirm the isolation of NSCs, and Nrf2 was used to analyze their subcellular localization.

NSC transfection and treatment

NSCs at 1, 2, 5, and 10 μM were treated for 24 h with Aβ1-42 (Sigma-Aldrich, St Louis, MO, United States) dissolved in DMSO; DMSO alone was used as treatment for a control group. Before Aβ1-42 treatment, the NSCs were pretreated with Tan-IIA at doses of 1, 5, 10, 20, and 40 μM for 1 h. The NEAT1 overexpression plasmid (ov-NEAT1), Rab22a small interfering RNAs (siRNAs) (si-Rab22a-1, si-Rab22a-2, and si-Rab22a-3), and miR-291a-3p mimic/inhibitor were purchased from Sangon Biotech Co., Ltd. (Shanghai, China) and transfected into the NSCs (following their Aβ1-42 treatment) using Lipofectamine 3000 Reagent (Invitrogen, Waltham, MA, United States); all the relevant sequences are listed in Table 1.

Hematoxylin and eosin staining

Mouse brains were sectioned into 5 μm thick slices, which were immersed in paraffin and preserved in 4% paraformaldehyde. The sections were deparaffinized, rehydrated, and submitted to hematoxylin and eosin (HE) staining. Histological images were captured at a 400 × magnification using an Olympus light microscope (IX73, Olympus, Shinjuku, Tokyo, Japan).

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) kits (Solarbio) were used in accordance with the manufacturer's instructions to determine the levels of malondialdehyde (MDA), NO, SOD, GSH, TNF-α, IL-1, and IL-6 in brain tissue homogenates and NSC supernatants. Absorbance was determined at 450 nm using a microplate reader (Thermo Fisher Scientific).

Table 1 Sequences of the three small interfering RNAs targeting *Rab22a* and a microRNA-291a-3p mimic or inhibitor

	Sequences of si-Rab22a 5′-3′
si-Rab22a-1	GGAAATGATCACAAGTAGAGG
si-Rab22a-2	GGAAATGGTAATAAAGACATA
si-Rab22a-3	CGATCTTACTGATGTCAGAGA
si-NC	TTCTCCGAACGTGTCACGTTT
	Sequences of the miR-291a-3p mimic and inhibitor 5′-3′
Mimic NC	ATTGATTTGTTCCGAAGGCCCT
miR-291a-3p mimic	AAAGTGCTTCCACTTTGTGTGC
Inhibitor NC	TCGCTCTATCCTGATCGAATGAA
miR-291a-3p inhibitor	GCACACAAAGTGGAAGCACTTT

Microarray raw dataset analysis

The GSE150696 dataset was analyzed using the DataSet analysis tool (GEO2R, Gene Expression Omnibus 2). The differential expression of lncRNA between the prefrontal cortex of patients with AD and that of elderly individuals without neurological or psychiatric diseases was normalized for log2 |fold change| > 1.5 and $P < 0.05$.

Flow cytometry analysis

Cells were collected, rinsed with phosphate buffered saline, and then resuspended in binding buffer in order to analyze apoptosis. Following the manufacturer's instructions, they were stained with propidium iodide (PI) and Annexin V-fluorescein isothiocyanate (FITC) using an Apoptosis Detection Kit (BD Biosciences, California, United States). Cells were subjected to a 15-min at dark incubation period with Annexin V-FITC and PI at 21 °C, followed by analysis using a BD Biosciences flow cytometry.

ROS measurement

First, 10 M of 2′,7′-dichlorofluorescin (DCF) diacetate (Sigma-Aldrich) was added to the brain tissue homogenates and NSCs lysates, which were then allowed to incubate in the dark for 30 min at 37 °C. The quick oxidation of DCF in the presence of ROS produces extreme fluorescence, of which the intensity was measured with a fluorescence microplate reader (Thermo Fisher Scientific) at excitation and emission wavelengths of 485 and 530 nm, respectively.

Cell viability assay

Following treatment of the NSCs with Aβ1-42 and Tan-IIA, their cell viability was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, the treated NSCs were seeded into 96-well plates at a density of 3×10^4 cells per well. Each well was supplemented with 20 μL of MTT solution (5 mg/mL), and the plates underwent a 4 h incubation period at 37 °C. After carefully removing the media, DMSO (150 μL) was used to dissolve the formazan crystals that the living cells had generated. Cell viability was then determined (and compared to that of the untreated control group) using a microplate reader to detect absorbance at 570 nm.

Reverse transcription quantitative polymerase chain reaction assay

Total RNA was extracted using TRIzol reagent (Invitrogen). A PrimeScript RT Reagent Kit (Takara Bio, Shiga, Japan) was used to construct complementary DNA from 1 μg of total RNA. Polymerase chain reaction (PCR) was conducted using a QuantStudio 6 Flex Real-Time PCR System (Thermo Fisher Scientific) with SYBR Green PCR Master Mix (Applied Biosystems, CA, United States). Thermal cycling conditions were as follows: 40 cycles of denaturation at 95 °C for 15 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s. A preliminary denaturation was then performed at 95 °C for 10 min. The expression levels of NEAT1, Rab22a, and miR-291a-3p were assessed using the $2^{-\Delta\Delta Ct}$ method, with GAPDH or U6 as internal controls for standardization. Primer sequences for all RNAs are shown in Table 2.

Nucleocytoplasmic separation

Nuclear and cytoplasmic fractions were separated according to the manufacturer's instructions using an NE-PER Nuclear and Cytoplasmic Extraction Kit (Thermo Fisher Scientific). The cell pellet was briefly resuspended in CER I buffer obtained from the kit, followed by the addition of CER II buffer. The mixture was vortexed and then rested on ice for an additional 5 min. The cytoplasmic fraction (supernatant) and nuclear pellet were separated from the homogenate *via* centrifugation at 16000 rpm for 5 min at 4° C. The purified nuclear and cytoplasmic fractions were then subjected to reverse transcription quantitative PCR (RT-qPCR).

RNA pull-down assay

Biotin-labeled NEAT1 RNA (bio-NEAT1) and mutant NEAT1 RNA (bio-mut) were synthesized by Sangon Biotech. The NSCs lysates were incubated overnight with bio-NEAT1, bio-mut, or bio-NC at 4 °C. Streptavidin-coated magnetic beads

Table 2 Primer sequences used for reverse transcription quantitative polymerase chain reaction analysis

Primers	Forward primer 5'-3'	Reverse primer 5'-3'
NEAT1	TGGAGATTGAAGGCGCAAGT	AAGCACGGAACCTAGGCAAA
miR-291a-3p	ACACTCCAGCTGGGAAAGTGCTTCCACTTT	CTCAACTGGTGTCGTGGA
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT
Rab22a	ATCAATCCAACCATAGGGGCAT	TTGGTGCCAATGCACGAAATC
GAPDH	GTGGCAAAGTGGAGATTGTTGCC	GATGATGACCCGTTTGGCTCC

U6 was used to normalize miR-291a-3p expression, and GAPDH was used to normalize nuclear-enriched abundant transcript 1 mRNA expression. NEAT1: Nuclear-enriched abundant transcript 1.

were added to and incubated with the reaction mixture for 1 h at 4° C to allow the formation of RNA-protein complexes. The beads were then washed, and bound RNA was eluted from them for RT-qPCR analysis to assess enrichment.

Dual-luciferase reporter assay

The miR-291a-3p binding sites from the 3' untranslated regions of NEAT1 and Rab22a were cloned into a psiCHECK-2 dual-luciferase reporter vector (Promega, WI, United States). Using Lipofectamine 3000 reagent (Invitrogen), NSCs were then co-transfected with the reporter plasmids with miR-291a-3p mimic or mimic NC. Luciferase activity was assessed after 48 h using the Dual-Luciferase Reporter Assay System (Promega), in accordance with the manufacturer's instructions. Activity of the *Renilla* luciferase gene was used to normalize firefly luciferase activity.

Western blotting analysis

Total protein was extracted from the mouse brain tissues and NSCs using RIPA lysis buffer (Abcam) along with protease and phosphatase inhibitors (Thermo Fisher Scientific). The protein content was determined using a BCA Protein Assay Kit (Thermo Fisher Scientific). Similar quantities of proteins were separated *via* sodium-dodecyl sulfate gel electrophoresis (Millipore, MA, United States) and then transferred to polyvinylidene fluoride membranes. The membranes were incubated overnight and at 4 °C with primary antibodies (all from Abcam, Cambridge, United Kingdom) against Rab22a (1:1000, ab137093), p65 (1:1000, ab32536), phospho (p)-p65 (1:1000, ab76302), Bax (1:1000, ab32503), Bcl-2 (1:2000, ab182858), and GAPDH (1:2000, ab181602). Next, the membranes were treated with HRP-conjugated secondary antibodies (1:3000, Abcam) for 1 h at 22 °C. Electrochemiluminescence Western Blotting Substrate (NIH, Bethesda, MD, United States) was used to visualize the protein bands, which were quantified using ImageJ software.

Statistical analyses

Data are presented as the mean and standard deviation. GraphPad Prism 8.0 (GraphPad Software, CA, United States) was used for all statistical analyses. One-way analysis of variance was used to evaluate group differences, followed by Tukey's *post-hoc* test. Statistical significance was set at $P < 0.05$.

RESULTS

Tan-IIA ameliorates oxidative stress and inflammatory responses in AD mice

In the healthy control group, neurons were neatly arranged in brain tissues, displaying intact cell structures and clearly visible cell membranes and nuclei. In contrast, the neurons in AD mouse brain tissues showed extreme disarray and irregularities in size and shape, with a drastic reduction in cell number and blurred cell structures. These problems were significantly improved in the treatment group that received 20 mg/kg of Tan-IIA, which proved to be more effective than the 5 mg/kg treatment (Figure 1B). Furthermore, the ELISA showed that Tan-IIA effectively alleviated the elevated oxidative stress (*via* reduced ROS, MDA, and NO and increased SOD and GSH levels) and neuroinflammation (*via* reduced TNF-α, IL-1β, and IL-6 levels) in the AD mouse brain tissue (Figure 1C-J), confirming that 20 mg/kg of Tan-IIA was more effective than 5 mg/kg. A total of 32 associated lncRNAs were identified in the GSE150696 dataset (Table 3), with NEAT1 displaying the highest fold-change to confirm it as a potential therapeutic target (Figure 1K). This lncRNA was both highly expressed in mouse brain tissues and reduced by Tan-IIA treatment (Figure 1L).

Tan-IIA ameliorates Aβ1-42-induced oxidative stress and inflammatory responses in NSCs

To investigate the protective mechanism of Tan-IIA, we isolated mouse NSCs and used Aβ1-42 induction to establish an *in vitro* cellular model of AD. Immunofluorescence results showed substantial positivity for MAP2 and β-III tubulin expression in isolated and cultured NSCs (Figure 2A), indicating successful isolation. Aβ1-42 dose-dependently inhibited NSC viability (Figure 2B), with a subsequent dose of 10 μM Aβ1-42 used for validation. After Tan-IIA pretreatment, doses of 20 and 40 μM reduced NSC viability (Figure 2C); therefore, safe doses of 1, 5, and 10 μM were chosen for subsequent experiments to exclude factors intrinsic to Tan-IIA. The validation results confirmed that Tan-IIA dose-dependently

Table 3 Differentially expressed long non-coding RNAs in the GSE150696 dataset

Gene symbol	Fold change	*P* value
NEAT1	2.19	0.0170
LINC01377	1.98	0.0248
EYA transcriptional coactivator and phosphatase 3- intronic transcript 1	1.95	0.0027
LINC01354	1.68	0.0119
LINC00537	1.64	0.0498
LINC01441	1.63	0.0082
LINC01094	1.63	0.0328
Cancer susceptibility 16	1.6	0.0376
LINC01101	1.55	0.0342
LINC00327	1.54	0.0028
LINC00323	1.54	0.0459
LINC00644	1.53	0.0119
LINC00358	1.53	0.0411
LINC00347	1.51	0.0409
LINC00641	-1.53	0.0332
LINC00294	-1.55	0.0471
Maternally expressed 8	-1.56	0.0073
Prader-Willi region non-protein coding RNA 1	-1.59	0.0005
LINC00672	-1.66	0.0010
LINC00969	-1.72	0.0302
Prostate androgen-regulated transcript 1	-1.8	0.0049
LINC00622	-1.8	0.0175
LINC00507	-1.81	0.0000625
LINC00403	-1.84	0.0043
LINC01128	-1.87	0.0179
LINC00889	-1.92	0.0113
LINC00473	-2.43	0.0323
LINC00622	-2.5	0.0037

LINC: Long intergenic long non-coding RNA; NEAT1: Nuclear-enriched abundant transcript 1.

ameliorated Aβ1-42-induced reductions in cell viability (Figure 2D), apoptosis (Figure 2E), oxidative stress (increased ROS, MDA, and NO; decreased SOD and GSH) and increases in neuroinflammatory markers (TNF-α, IL-1β, and IL-6) (Figure 2F-N). In the process, the Aβ1-42-induced expression of NEAT1 lncRNA was suppressed (Figure 2O). For subsequent mechanistic studies, a safe dose of 10 μM Tan-IIA was selected, as it ameliorated Aβ1-42-induced effects most efficiently.

LncRNA NEAT1 reverses the improvements of Tan-IIA treated Aβ1-42-induced NSCs via miR-291a-3p

Nucleocytoplasmic separation experiments revealed that the lncRNA NEAT1 was abundantly expressed in the cytoplasm, a result similar to that observed in the positive control GAPDH and opposite to that of U6 (Figure 3A). In verifying the efficacy of the constructed ov-NEAT1 (Figure 3B), it was observed that it partially counteracted the protective effect of Tan-IIA preconditioning on NSCs, partially reversing the Tan-IIA improvement of Aβ1-42-inhibited cell viability (Figure 3C), promoted apoptosis (Figure 3D), oxidative stress (increased ROS, MDA, and NO levels; decreased SOD and GSH levels) and neuroinflammation (increased TNF-α, IL-1β, and IL-6) (Figure 3E-L). A joint analysis using Starbase and Lncbase identified miR-291a-3p as a potential target of NEAT1 (Figure 3M), which was confirmed to be one of the key miRNAs in ameliorating AD[28]. Indeed, miR-291a-3p was downregulated in both the *in vivo* and *in vitro* models of AD and upregulated upon Tan-IIA treatment (Figure 3N and O), further supporting this hypothesis. After

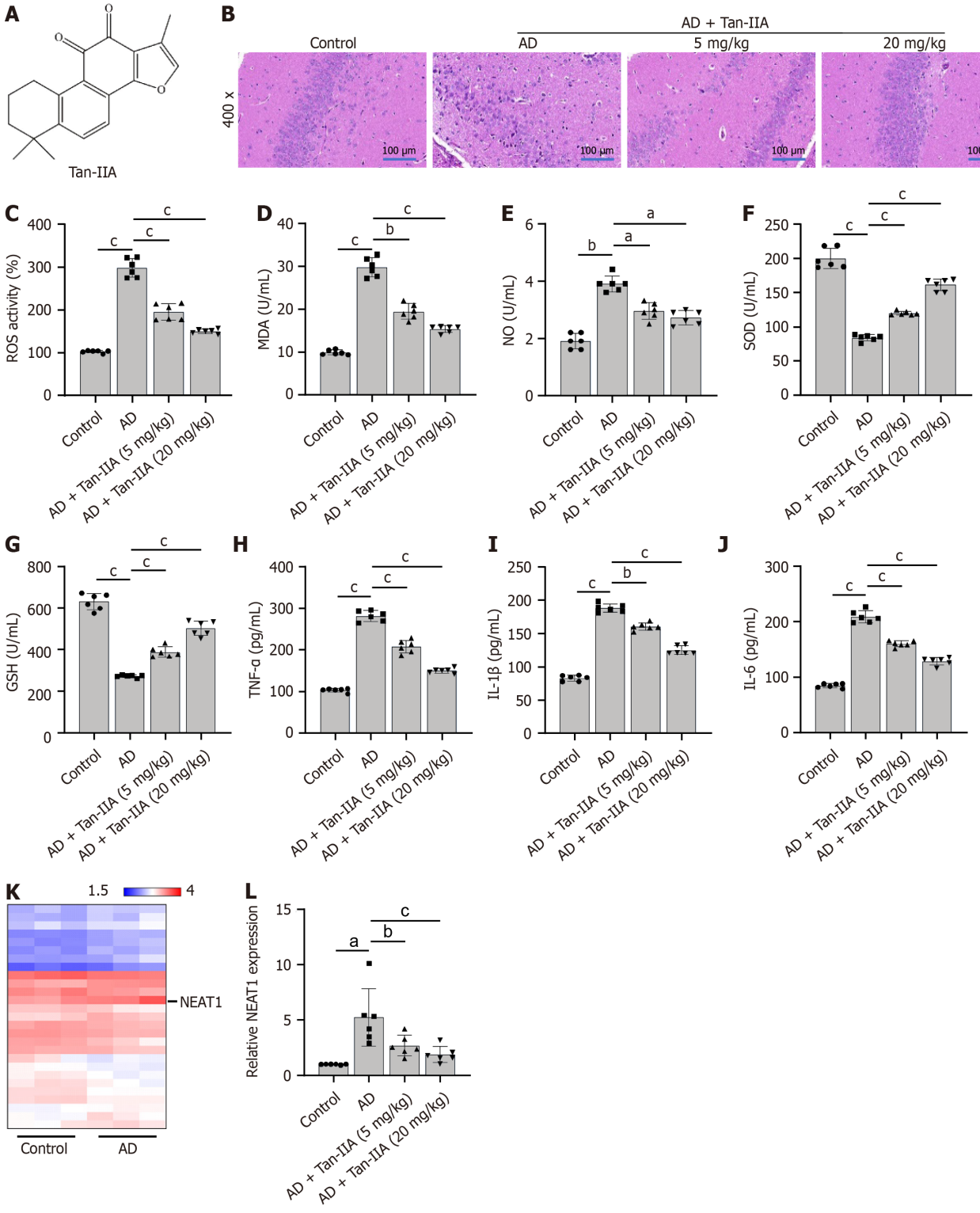
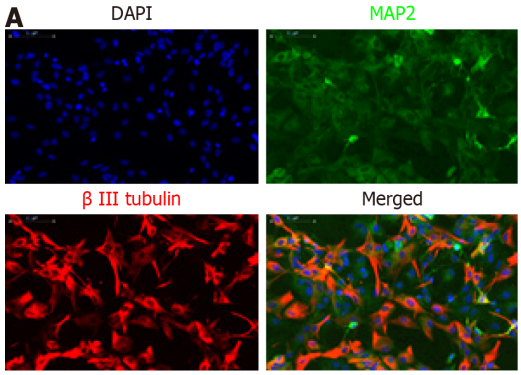
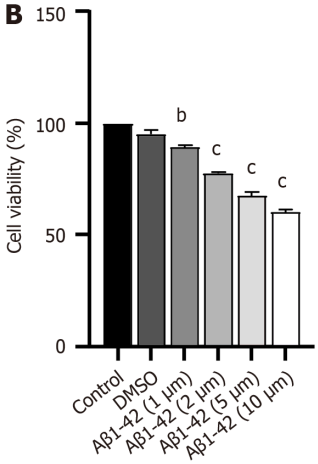
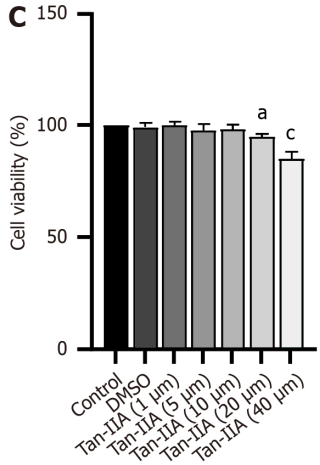
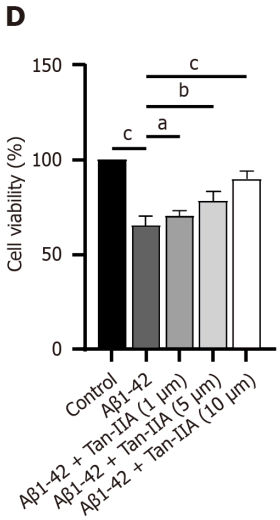


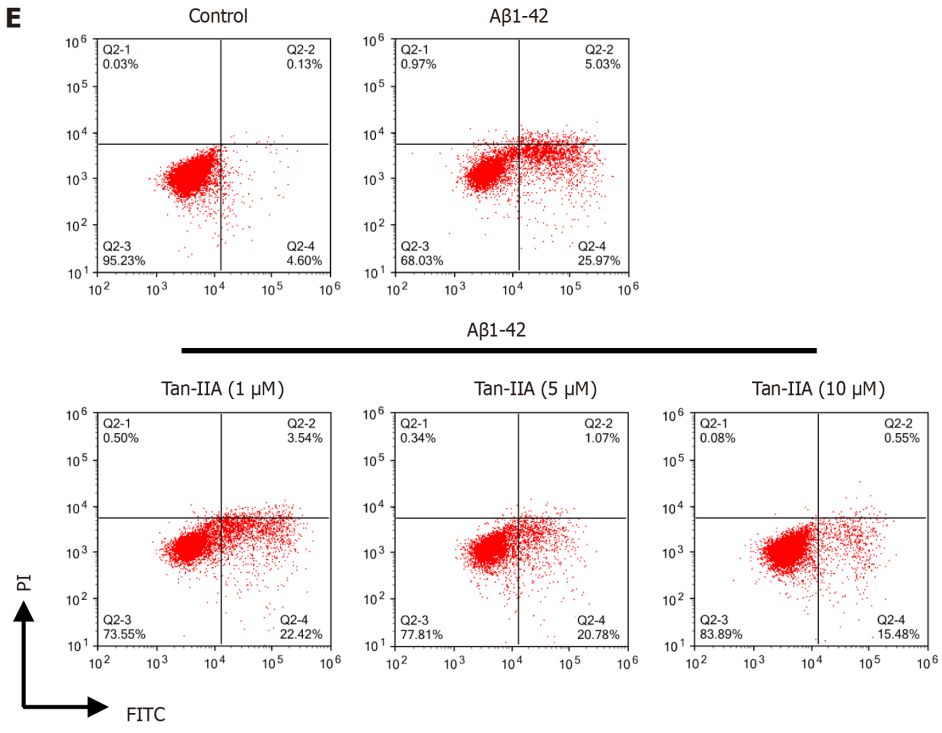
Figure 1 The impact of tanshinone IIA in a murine model of Alzheimer's disease, with the long non-coding RNA nuclear-enriched abundant transcript 1 as a potential target. A: Chemical structure of tanshinone IIA (Tan-IIA); B: Hematoxylin and eosin staining of brain tissues from control, Alzheimer's disease, and Tan-IIA-treated mice (400 × magnification); C: Results of the 2',7'-dichlorofluorescin diacetate analysis of the reactive oxygen species ratio in mouse brain tissues, either with or without prior Tan-IIA treatment; D-J: Enzyme-linked immunosorbent assay analysis of oxidative stress factors (malondialdehyde; nitric oxide; superoxide dismutase; glutathione) and neuroinflammation markers (tumor necrosis factor-alpha; interleukin 1β; interleukin 6) in mouse brain tissues; K: GEO2R web tool analysis of the GSE150696 data set for long non-coding RNA screening; L: Analysis the expression of nuclear-enriched abundant transcript 1 in Tan-IIA-treated mouse brain tissues. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. AD: Alzheimer's disease; Tan-IIA: Tanshinone IIA; ROS: Reactive oxygen species; MDA: Malondialdehyde; NO: Nitric oxide; SOD: Superoxide dismutase; GSH: Glutathione; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin 1β; IL-6: Interleukin 6.

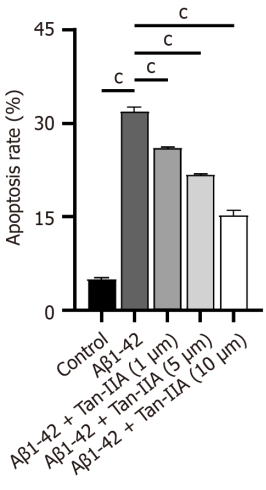

A
DAPI
MAP2
β III tubulin
Merged


B
Cell viability (%)
150
100
50
0
b
c
c
c
Control
DMSO
Aβ1-42 (1 μm)
Aβ1-42 (2 μm)
Aβ1-42 (5 μm)
Aβ1-42 (10 μm)


C
Cell viability (%)
150
100
50
0
a
c
Control
DMSO
Tan-IIA (1 μm)
Tan-IIA (5 μm)
Tan-IIA (10 μm)
Tan-IIA (20 μm)
Tan-IIA (40 μm)


D
Cell viability (%)
150
100
50
0
c
b
a
c
Control
Aβ1-42
Aβ1-42 + Tan-IIA (1 μm)
Aβ1-42 + Tan-IIA (5 μm)
Aβ1-42 + Tan-IIA (10 μm)


E
Control
Aβ1-42
Q2-1 0.03%
Q2-2 0.13%
Q2-3 95.23%
Q2-4 4.60%
Q2-1 0.97%
Q2-2 5.03%
Q2-3 68.03%
Q2-4 25.97%
Aβ1-42
Tan-IIA (1 μM)
Tan-IIA (5 μM)
Tan-IIA (10 μM)
Q2-1 0.50%
Q2-2 3.54%
Q2-3 73.55%
Q2-4 22.42%
Q2-1 0.34%
Q2-2 1.07%
Q2-3 77.81%
Q2-4 20.78%
Q2-1 0.08%
Q2-2 0.55%
Q2-3 83.89%
Q2-4 15.48%
PI
FITC


Apoptosis rate (%)
45
30
15
0
c
c
c
c
Control
Aβ1-42
Aβ1-42 + Tan-IIA (1 μm)
Aβ1-42 + Tan-IIA (5 μm)
Aβ1-42 + Tan-IIA (10 μm)

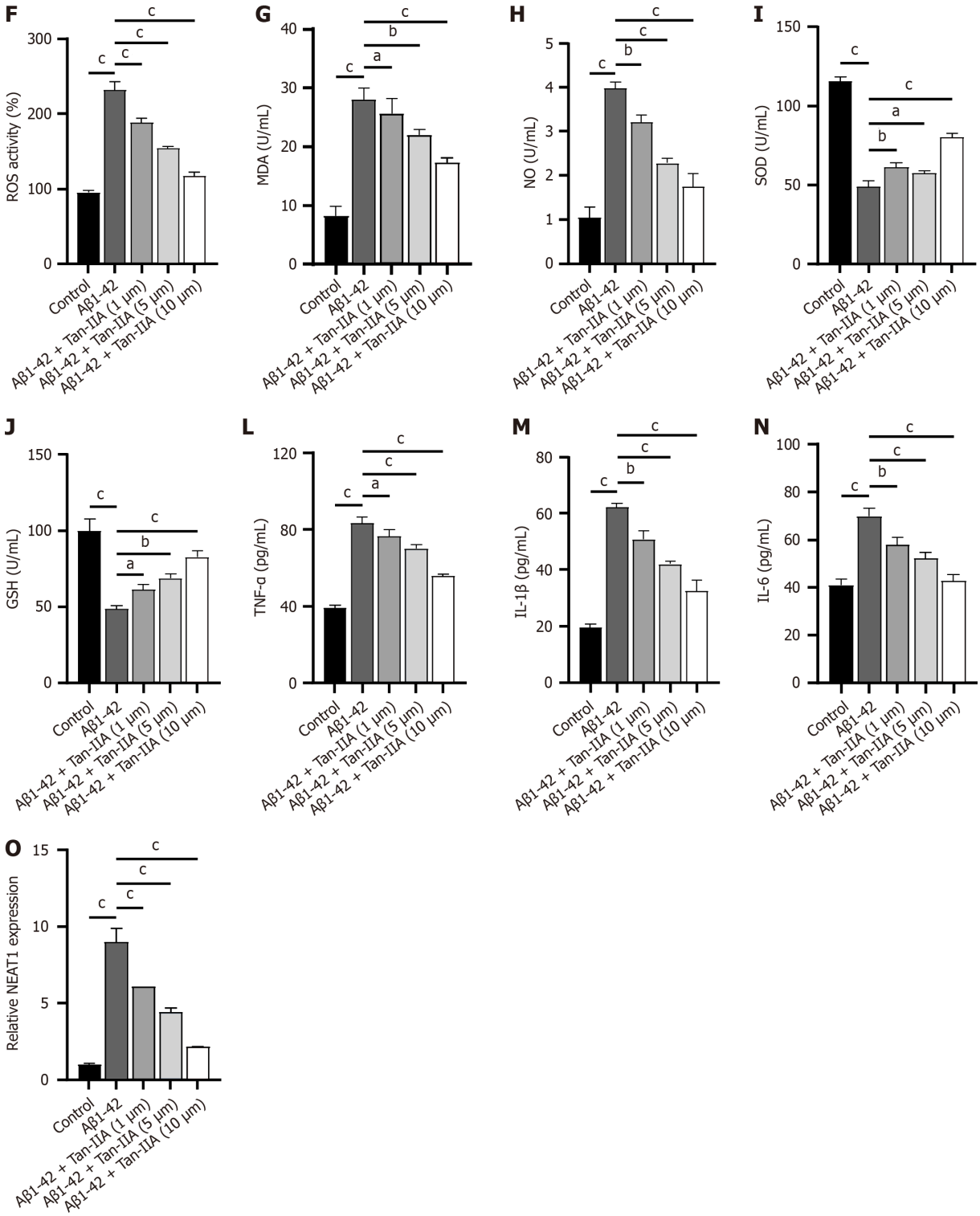
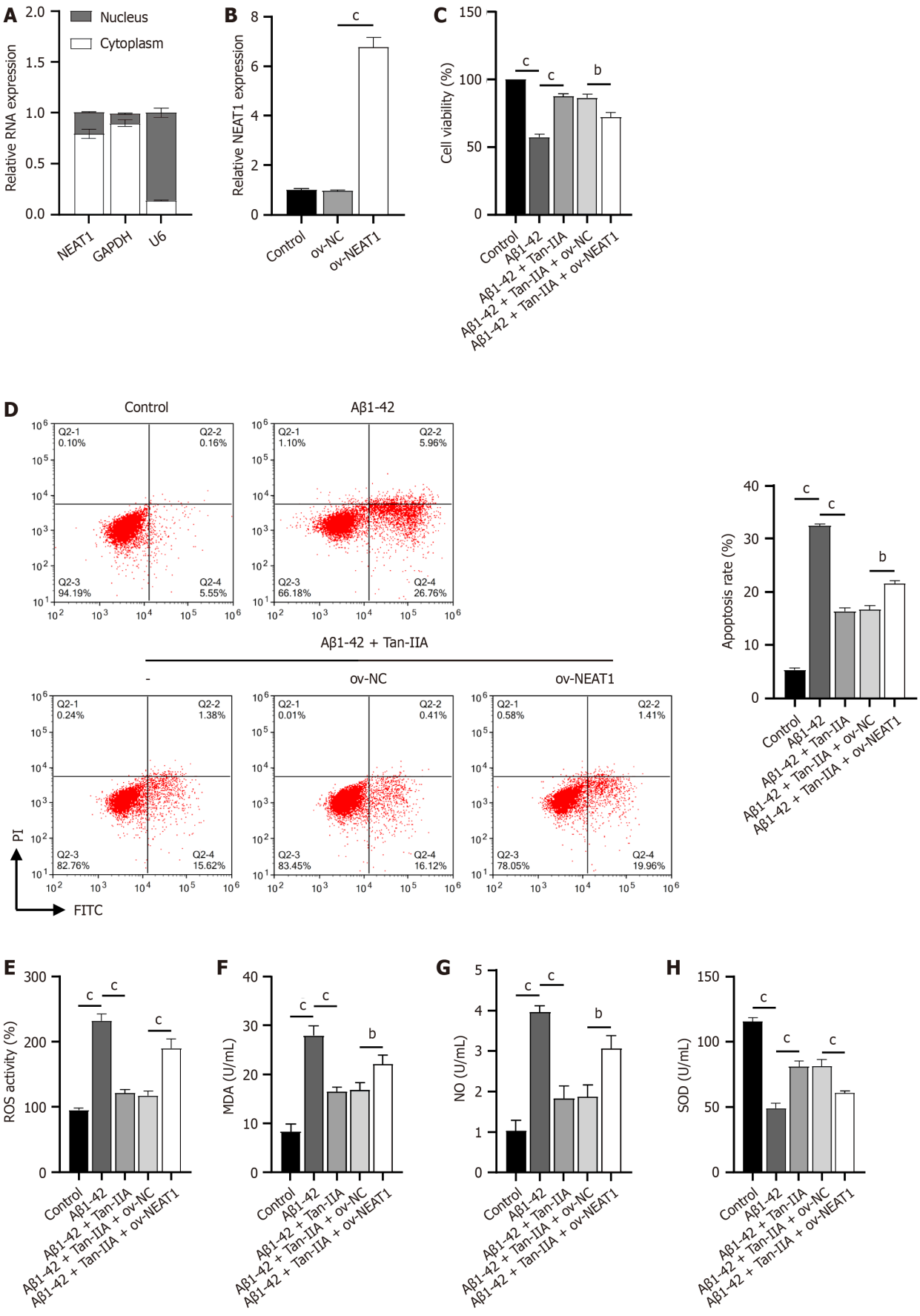


Figure 2 Protective effects of tanshinone IIA in murine neural stem cells induced with amyloid-beta 1-42 peptides. A: Immunofluorescent identification of neural stem cells (NSCs) for isolation, using DAPI stain (blue), microtubule-associated protein 2 (green), and β III tubulin (red); B-D: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay of the effect of different amyloid-beta 1-42 (Aβ1-42) and tanshinone IIA (Tan-IIA) doses on NSC viability; E: Flow cytometry results indicating that different Tan-IIA doses improve the effect of Aβ1-42 on the apoptosis of NSCs; F: 2',7'-dichlorofluorescin diacetate analysis of the reactive oxygen species ratio in NSCs, either with or without prior Tan-IIA treatment; G-N: Enzyme-linked immunosorbent assay results of different Tan-IIA doses in enhancing the effect of Aβ1-42 in improving levels of oxidative stress factors (malondialdehyde; nitric oxide; superoxide dismutase; glutathione) and neuroinflammation markers (tumor necrosis factor-alpha; interleukin 1β; interleukin 6) in NSCs; O: Reverse transcription quantitative polymerase chain reaction analysis of different Tan-IIA doses used to improve the effect of Aβ1-42 on nuclear-enriched abundant transcript 1 expression in NSCs. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. MAP2: Microtubule-associated protein 2; DMSO: Dimethyl sulfoxide; PI: Propidium iodide; FITC: Fluorescein isothiocyanate; Aβ1-42: Amyloid-beta 1-42; Tan-IIA: Tanshinone IIA; ROS: Reactive oxygen species; MDA: Malondialdehyde; NO: Nitric oxide; SOD: Superoxide dismutase; GSH: Glutathione; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin 1β; IL-6: Interleukin 6; NEAT1: Nuclear-enriched abundant transcript 1.


A
Nucleus
Cytoplasm
Relative RNA expression
NEAT1
GAPDH
U6
B
Relative NEAT1 expression
Control
ov-NC
ov-NEAT1
C
Cell viability (%)
Control
Aβ1-42
Aβ1-42 + Tan-IIA
Aβ1-42 + Tan-IIA + ov-NC
Aβ1-42 + Tan-IIA + ov-NEAT1
D
Control
Aβ1-42
Aβ1-42 + Tan-IIA
-
ov-NC
ov-NEAT1
Q2-1 0.10%
Q2-2 0.16%
Q2-3 94.19%
Q2-4 5.55%
Q2-1 1.10%
Q2-2 5.96%
Q2-3 66.18%
Q2-4 26.76%
Q2-1 0.24%
Q2-2 1.38%
Q2-3 82.76%
Q2-4 15.62%
Q2-1 0.01%
Q2-2 0.41%
Q2-3 83.45%
Q2-4 16.12%
Q2-1 0.58%
Q2-2 1.41%
Q2-3 78.05%
Q2-4 19.96%
PI
FITC
Apoptosis rate (%)
E
ROS activity (%)
F
MDA (U/mL)
G
NO (U/mL)
H
SOD (U/mL)

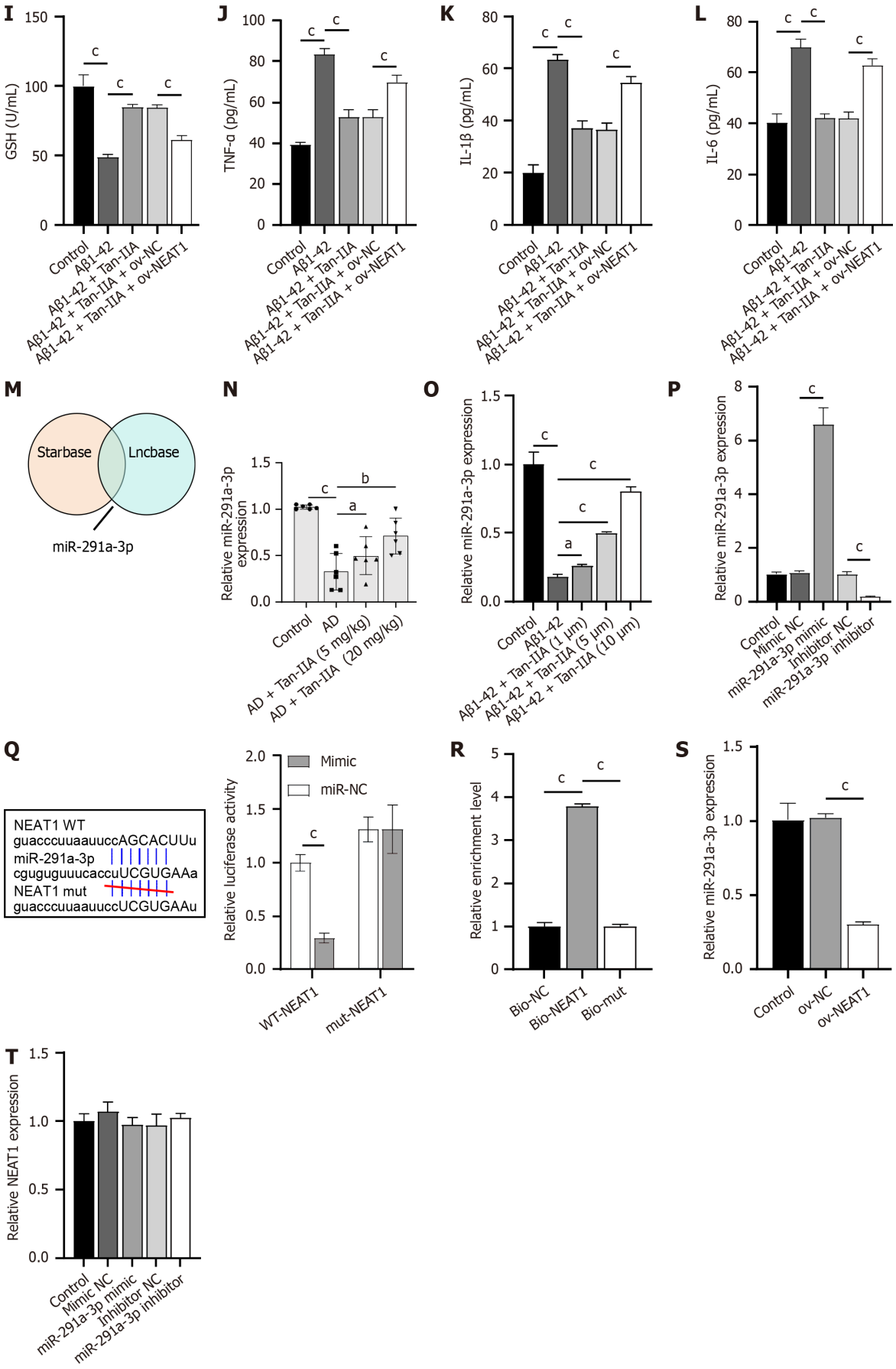


Figure 3 Localization of the long non-coding RNA nuclear-enriched abundant transcript 1 in the cytoplasm, and its interaction with the microRNA miR-291a-3p. A: Nucleocytoplasmic separation was performed to detect the localization of the long non-coding RNA nuclear-enriched abundant

transcript 1 (NEAT1) in neural stem cells (NSCs); B: Reverse transcription quantitative polymerase chain reaction validation of the NEAT1 overexpression vector; C: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide results of the effect of NEAT1 overexpression on the cell viability of amyloid-beta 1-42 (Aβ1-42)-induced NSCs that received tanshinone IIA (Tan-IIA) pretreatment; D: Flow cytometry results of the effect of NEAT1 overexpression on the apoptosis of Aβ1-42-induced NSCs that received Tan-IIA pretreatment; E: 2',7'-dichlorofluorescin diacetate analysis of the effect of NEAT1 overexpression on the reactive oxygen species ratio of Aβ1-42-induced NSCs that received Tan-IIA pretreatment; F–L: Enzyme-linked immunosorbent assay results for the effect of NEAT1 overexpression on oxidative stress factors (malondialdehyde; nitric oxide; superoxide dismutase; glutathione) and neuroinflammation markers (tumor necrosis factor-alpha; interleukin 1β; interleukin 6) in Aβ1-42-induced NSCs that received Tan-IIA pretreatment; M: Starbase and Lncbase analysis, confirming miR-291a-3p as a potential target of NEAT1; N and O: Reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis of miR-291a-3p expression in the Alzheimer's disease mouse model and Aβ1-42-induced NSCs; P: RT-qPCR analysis of the expression of synthesized miR-291a-3p mimic/inhibitor; Q: Dual-luciferase assay confirming binding between NEAT1 and miR-291a-3p; R: RNA pull-down assay showing miR-291a-3p enrichment in bio-NEAT1; S and T: RT-qPCR analysis of the expression levels of miR-291a-3p (S) and NEAT1 (T) in NSCs. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. PI: Propidium iodide; FITC: Fluorescein isothiocyanate; Aβ1-42: Amyloid-beta 1-42; Tan-IIA: Tanshinone IIA; ROS: Reactive oxygen species; MDA: Malondialdehyde; NO: Nitric oxide; SOD: Superoxide dismutase; GSH: Glutathione; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin 1β; IL-6: Interleukin 6; NEAT1: Nuclear-enriched abundant transcript 1.

confirming the efficacy of the synthesized miR-291a-3p mimic and inhibitor (Figure 3P), a dual-luciferase assay was performed. The fluorescence activity in the WT-NEAT1 and miR-291a-3p mimic co-transfected group was significantly lower than that in the WT-NEAT1 and mimic NC co-transfected group, whereas there was no significant difference in fluorescence activity between the mut-NEAT1 and miR-291a-3p mimic or mimic NC co-transfected groups (Figure 3Q). RNA pull-down results showed significant enrichment of miR-291a-3p in bio-NEAT1, with no discernible differences in its expression between the bio-mut and bio-NC groups (Figure 3R). Overexpression of NEAT1 significantly suppressed miR-291a-3p expression (Figure 3S). However, changes in miR-291a-3p expression had no apparent effect on NEAT1 expression (Figure 3T). These results confirm that NEAT1 directly targets and binds to miR-291a-3p.

Rab22a is a direct target of miR-291a-3p

Joint analysis using miRDB and TargetScan databases identified Rab22a, an inhibitor of the AKT pathway, as a potential target of miR-291a-3p (Figure 4A). Rab22a expression increased in both the *in vivo* and *in vitro* models and decreased upon Tan-IIA treatment (Figure 4B-D). Dual-luciferase assay results showed that luminescence activity was significantly lower in the WT-NEAT1 and miR-291a-3p mimic co-transfection group than in the WT-Rab22a and NC mimic co-transfection groups, and no significant effects on luminescence activity were found between the mut-Rab22a and miR-291a-3p mimic or NC mimic co-transfection groups (Figure 4E). In addition, Rab22a expression was negatively regulated by miR-291a-3p (Figure 4F) and increased upon NEAT1 overexpression (Figure 4G). Therefore, Rab22a may be a potential target of miR-291a-3p. Among the constructed siRNAs, si-Rab22a-1 was selected for further study because of its high Rab22a silencing efficiency in NSCs (Figure 4H) and because the expression of si-Rab22a did not significantly affect miR-291a-3p (Figure 4I).

Tan-IIA inhibits oxidative stress and neuroinflammation by activating AKT/Nrf2 signaling through the NEAT1/miR-291a-3p/Rab22a axis

To investigate the protective mechanism of Tan-IIA against Aβ1-42-induced damage, the miR-291a-3p mimic, ov-NEAT1, and si-Rab22a were co-transfected into NSCs. As expected, Tan-IIA ameliorated the Aβ1-42-induced reduction in cell viability, promoted apoptosis, oxidative stress (increased ROS, MDA, and NO levels; decreased SOD and GSH levels), and neuroinflammation (increased TNF-α, IL-1β, and IL-6) (Figure 5A-J). The miR-291a-3p mimic enhanced the effects of Tan-IIA, whereas ov-NEAT1 counteracted or partially counteracted the effects of the miR-291a-3p mimic. However, these effects were reversed by si-Rab22a treatment (Figure 5A-J). Notably, the total p65 protein level was unchanged, and p65 phosphorylation and Bax protein levels were opposite to those of RAB22A and Bcl-2. Tan-IIA reduced Aβ1-42-induced p65 phosphorylation and Bax activation, and the miR-291a-3p mimic further enhanced these effects. In addition, the counteracting effects of ov-NEAT1 on that of miR-291a-3p were inhibited by si-RAB22A (Figure 5K), and the Bcl-2/Bax ratio was consistent with that of Bcl-2. Similar to the *in vitro* results, Tan-IIA reduced p65 phosphorylation and Bax activation and increased Bcl-2 levels in AD mice *in vivo*. The enhancing effects of the miR-291a-3p mimic on Tan-IIA were counteracted by NEAT1, but inhibited by si-RAB22A (Figure 5L), and the ratio of Bcl-2/Bax was consistent with that of Bcl-2.

DISCUSSION

Studies have shown that the dysregulation of lncRNAs - such as lung adenocarcinoma transcripts 1 and NEAT1, which are associated with metastasis - can be critical in the pathogenesis of many degenerative diseases[29-31], including AD. In this study, we investigated the neuroprotective effects of Tan-IIA using both *in vivo* and *in vitro* (Aβ1-42-induced NSCs) models of AD to elucidate the underlying mechanisms involving the lncRNA NEAT1/miR-291a-3p/Rab22a signaling axis.

Consistent with previous reports, our results showed that Tan-IIA treatment significantly ameliorated AD-induced histopathological changes, reduced oxidative stress, and attenuated neuroinflammation in the brain tissue of AD mice[26, 32]. In particular, the dose-dependent improvements observed in Aβ1-42-induced NSCs *in vitro* supported the potential of Tan-IIA as a promising AD therapeutic agent. During this process, the expression of NEAT1 - a promising key

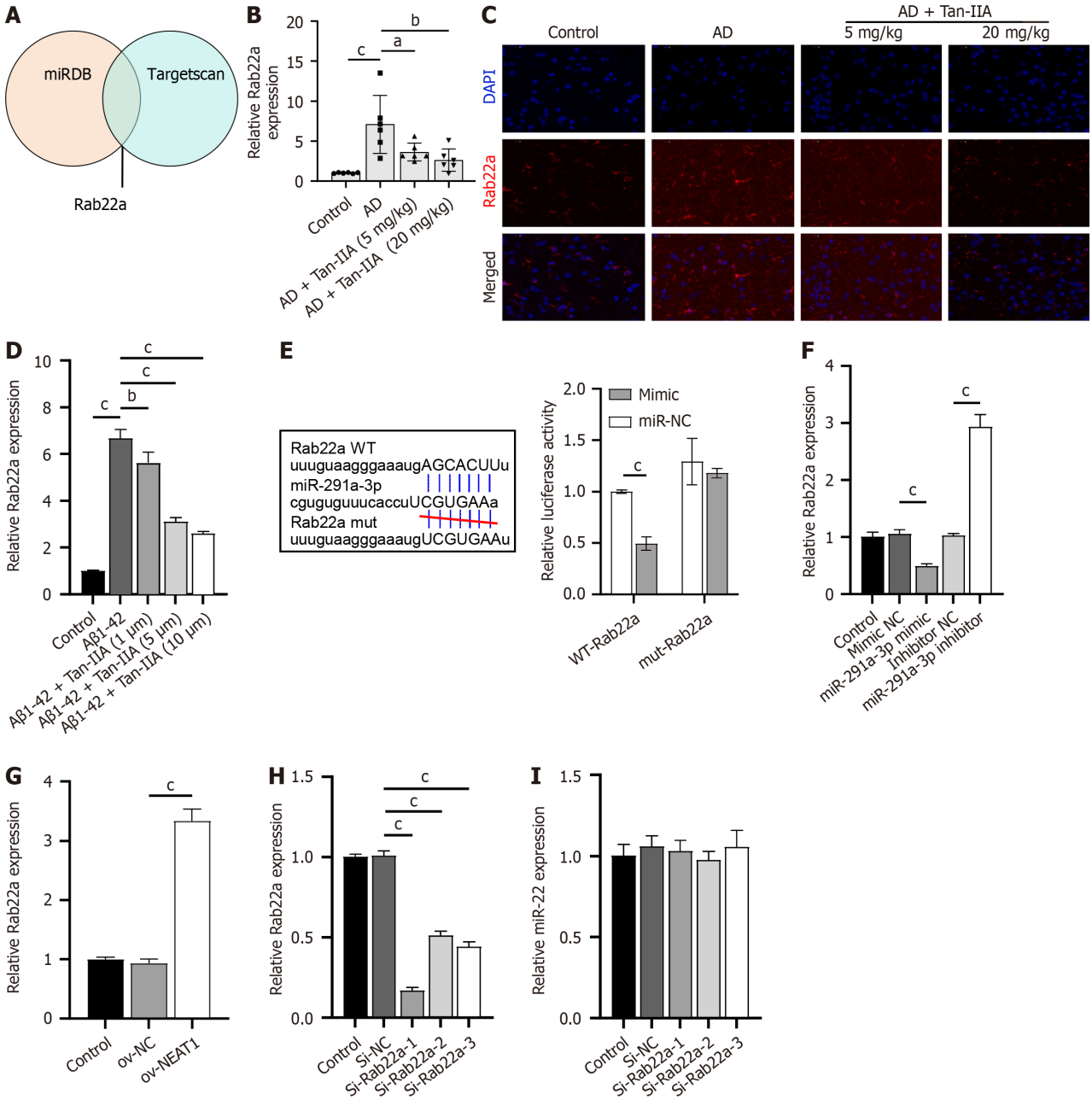
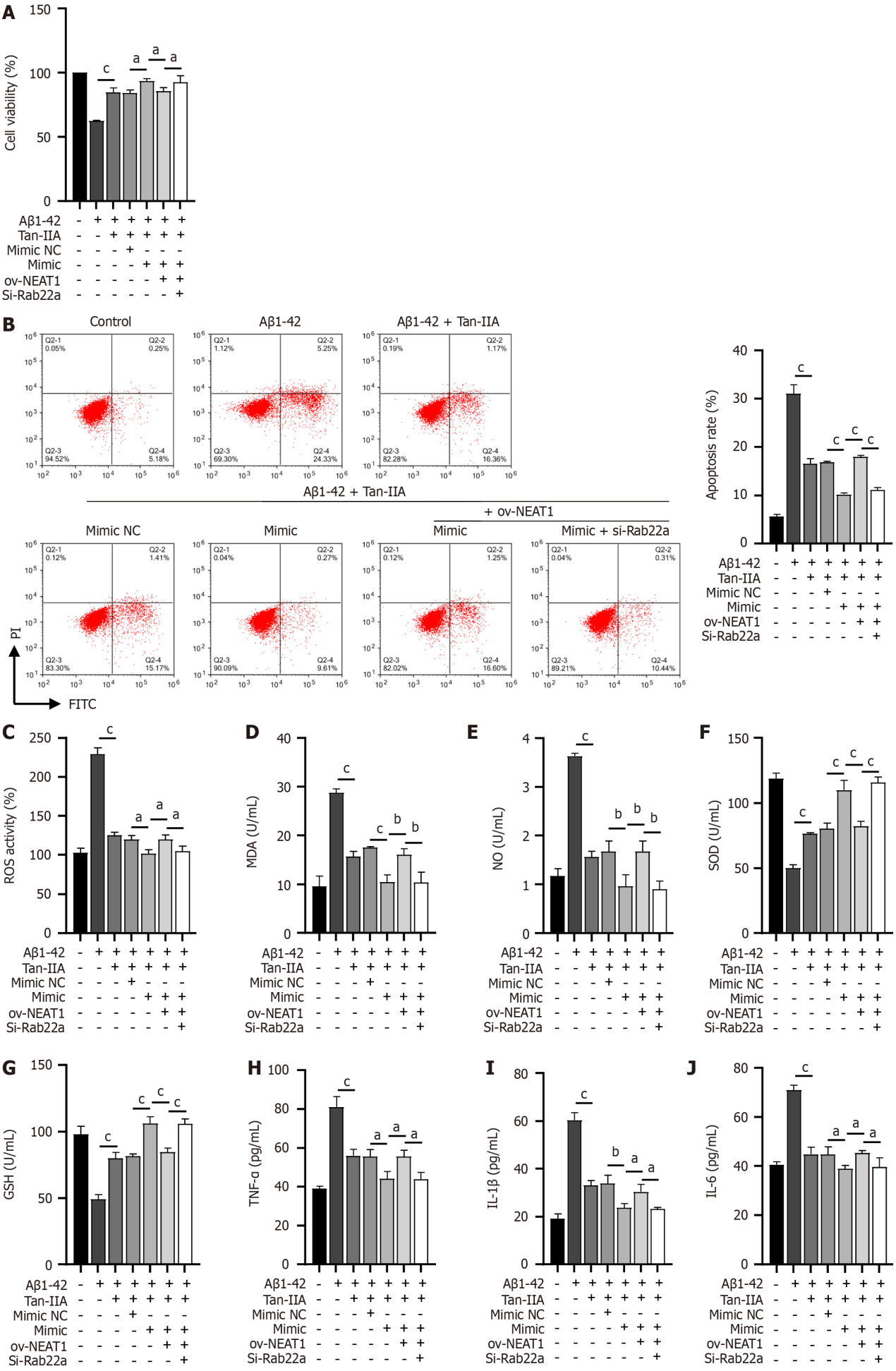


Figure 4 Rab22a as a target of miR-291a-3p, and its role in the nuclear-enriched abundant transcript 1/miR-291a-3p axis. A: MiRDB and Targetscan database joint analysis identified Rab22a as a potential target of miR-291a-3p; B: Reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis of Rab22a expression in the Alzheimer's disease (AD) mouse model; C: Immunofluorescence analysis of Rab22a expression in the AD mouse model; D: RT-qPCR analysis of Rab22a expression in amyloid-beta 1-42 (Aβ1-42)-induced neural stem cells (NSCs); E: Dual-luciferase assay confirming binding between Rab22a and miR-291a-3p; F and G: RT-qPCR analysis of the effect of miR-291a-3p (F) and nuclear-enriched abundant transcript 1 (G) overexpression on Rab22a expression; H: RT-qPCR validation of the inhibitory efficiency of 3 si-Rab22a on Rab22a expression in NSCs; I: RT-qPCR analysis of the effect of 3 si-Rab22a on miR-291a-3p expression. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. AD: Alzheimer's disease; Aβ1-42: Amyloid-beta 1-42; Tan-IIA: Tanshinone IIA.

therapeutic target lncRNA obtained from the GSE150696 dataset analysis - was suppressed in a Tan-IIA dose-dependent manner, suggesting its possible involvement in the protective mechanism of Tan-IIA. Indeed, NEAT1 has been shown to be one of the major lncRNAs that exacerbate AD[33]. This hypothesis was confirmed in our observation that an overexpression of NEAT1 counteracted the ameliorative effect of Tan-IIA on Aβ1-42 induction. This is the first time that the ameliorative effect of Tan-IIA in alleviating AD symptoms has been linked to NEAT1, suggesting the possibility of a new regulatory axis for subsequent lncRNAs, which is important for the development of new therapeutic strategies against AD.

We further revealed a direct interaction between NEAT1 and miR-291a-3p, an important player in nerve injury[34]. Our results show that NEAT1 acts as a sponge for miR-291a-3p, thereby regulating miR-291a-3p availability and function, which is the first confirmation that miR-291a-3p contributes to the regulation of AD mitigation. We also confirmed that Rab22a, a regulator of activated NF-κB signaling, is a direct target of miR-291a-3p. This finding is notable because it is the first time that Tan-IIA regulation of Rab22a *via* the NEAT1/miR-291a-3p axis has been shown to reduce the activation of


A
Cell viability (%)
Aβ1-42
Tan-IIA
Mimic NC
Mimic
ov-NEAT1
Si-Rab22a
B
Control
Aβ1-42
Aβ1-42 + Tan-IIA
Mimic NC
Mimic
+ ov-NEAT1
Mimic + si-Rab22a
PI
FITC
Apoptosis rate (%)
C
ROS activity (%)
D
MDA (U/mL)
E
NO (U/mL)
F
SOD (U/mL)
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GSH (U/mL)
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TNF-α (pg/mL)
I
IL-1β (pg/mL)
J
IL-6 (pg/mL)

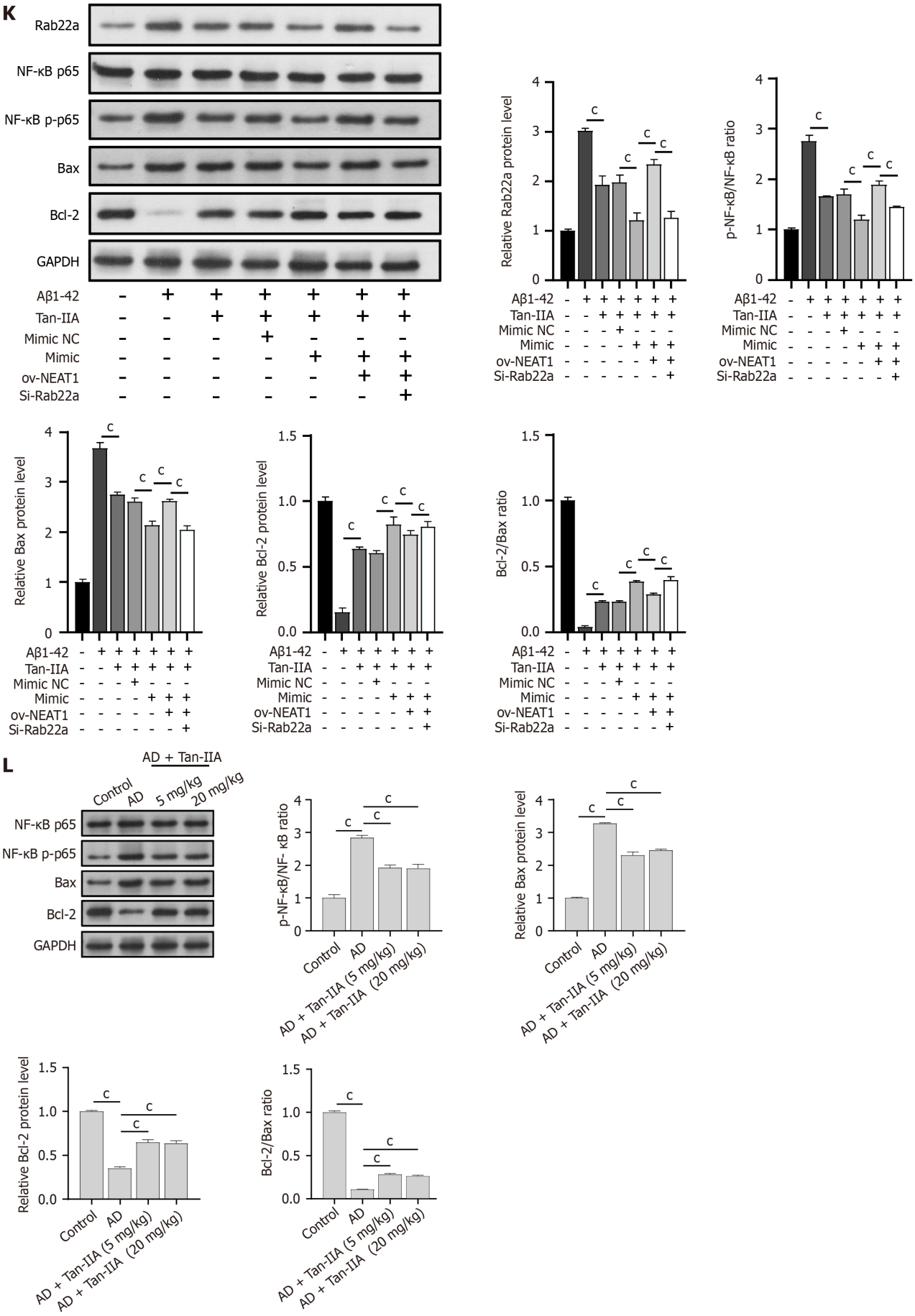

Figure 5 Neuroprotective effects of tanshinone IIA as mediated through the nuclear-enriched abundant transcript 1/miR-291a-3p/Rab22a

axis. A: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide analysis of the role of nuclear-enriched abundant transcript 1 (NEAT1)/miR-291a-3p/Rab22a axis in the improvement of cell viability in amyloid-beta 1-42 (Aβ1-42)-induced neural stem cells (NSCs) following tanshinone IIA (Tan-IIA) treatment; B: Flow cytometry analysis of the role of the NEAT1/miR-291a-3p/Rab22a axis in Tan-IIA ameliorating Aβ1-42-induced apoptosis in NSCs; C: 2',7'-dichlorofluorescin diacetate analysis of the role of the NEAT1/miR-291a-3p/Rab22a axis in Tan-IIA ameliorating Aβ1-42-induced reactive oxygen species levels in NSCs; D-J: Enzyme-linked immunosorbent assay analysis of the role of NEAT1/miR-291a-3p/Rab22a axis in Tan-IIA to ameliorate oxidative stress factors (malondialdehyde; nitric oxide; superoxide dismutase; and glutathione) and neuroinflammation (tumor necrosis factor-alpha; interleukin 1β; and interleukin 6) in Aβ1-42-induced NSCs; K: Western blots indicating the role of the NEAT1/miR-291a-3p/Rab22a axis in the mechanism of Tan-IIA improving the role of Rab22a, p65, p-p65, Bax, and Bcl-2 protein levels in NSCs induced by Aβ1-42; L: Western blots showing the effect of Tan-IIA treatment on the protein levels of p65, p-p65, B-cell lymphoma 2-associated X protein, and B-cell lymphoma 2 in AD mice. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$. PI: Propidium iodide; FITC: Fluorescein isothiocyanate; Aβ1-42: Amyloid-beta 1-42; Tan-IIA: Tanshinone IIA; ROS: Reactive oxygen species; MDA: Malondialdehyde; NO: Nitric oxide; SOD: Superoxide dismutase; GSH: Glutathione; TNF-α: Tumor necrosis factor-alpha; IL-1β: Interleukin 1β; IL-6: Interleukin 6; NEAT1: Nuclear-enriched abundant transcript 1; NF-κB: Nuclear factor kappa-B; Bcl-2: B-cell lymphoma 2; Bax: B-cell lymphoma 2-associated X protein; AD: Alzheimer's disease.

NF-κB signaling, a key pathway involved in oxidative stress, neuroinflammation and cell survival in AD. This was confirmed by changes in the levels of factors related to oxidative stress and neuroinflammation. Therefore, we identified the NEAT1/miR-291a-3p/Rab22a axis as an important signaling axis for the Tan-IIA-mediated amelioration of oxidative stress and neuroinflammation levels in both *in vivo* and *in vitro* models of AD.

The activation of NF-κB signaling is known to lead to altered activation of the downstream pro- and anti-apoptotic proteins, Bax and Bcl-2[35,36]. In the present study, we observed that Tan-IIA inhibited NF-κB signaling, leading to reduced levels of the pro-apoptotic Bax and activation of the anti-apoptotic Bcl-2 proteins in both our *in vivo* and *in vitro* models of AD. The ratio of Bcl-2/Bax was consistent with that of Bcl-2, and these results corresponded to its amelioration of Aβ1-42- induced apoptosis in NSCs, which increases our understanding of the role of Tan-IIA in the mechanism of AD. This study has several limitations. First, it presents no clinical data to confirm the roles of Tan-IIA and NEAT1 in patients with AD. Second, many lncRNAs have not yet been analyzed and verified through GEO data mining. Third, this study was the first to propose miR-291a-3p and Rab22a as novel therapeutic targets for AD, which requires further validation. Finally, our focusing on the NEAT1/miR-291a-3p/Rab22a axis may have overlooked alternative molecular pathways that contribute to the neuroprotective effects of Tan-IIA. The directions and goals of future research should aim to bridge these research gaps.

CONCLUSION

This study revealed the potential therapeutic role of Tan-IIA in AD by demonstrating its ability to attenuate oxidative stress and neuroinflammation in a mouse model and in Aβ1-42-induced murine NSCs. By elucidating the involvement of the NEAT1/miR-291a-3p/Rab22a signaling axis in the neuroprotective effects of Tan-IIA, this research not only deepens our understanding of the molecular mechanisms underlying AD but also highlights a promising target for the development of new therapeutic strategies.

ARTICLE HIGHLIGHTS

Research background

Alzheimer's disease (AD) is a prevalent neurodegenerative disorder characterized by cognitive decline and neuronal loss. Oxidative stress and neuroinflammation play pivotal roles in the pathogenesis of this disease. Tanshinone IIA (Tan-IIA), which is derived from *Salvia miltiorrhiza*, shows potential neuroprotective effects. Understanding the molecular mechanisms underlying these effects is crucial for the development of novel therapeutic strategies.

Research motivation

The motivation for this study was to elucidate the mechanisms by which Tan-IIA exerts neuroprotective effects in AD, focusing on the potential modulation of the long non-coding RNA (lncRNA) nuclear enriched abundant transcript 1 (NEAT1), microRNA (miR)-291a-3p, and RAB22A, member of the RAS oncogene family (Rab22a) signaling pathways. This has important implications for the development of new AD therapies.

Research objectives

The objective of this study was to investigate the neuroprotective effects of Tan-IIA in AD models and elucidate the underlying molecular mechanisms. Specifically, we aimed to determine how Tan-IIA affects oxidative stress, neuroinflammation, and neuronal viability through the NEAT1/miR-291a-3p/Rab22a signaling axis.

Research methods

The study employed both *in vivo* and *in vitro* models of AD using mice and neural stem cells, respectively. Methods included histopathological examinations, enzyme-linked immunosorbent assays, western blotting, 3-(4,5-dimethylthiazol-

2-yl)-2,5-diphenyltetrazolium bromide assays, reverse transcription quantitative polymerase chain reaction assays, and various molecular biology techniques to elucidate the role of the NEAT1/miR-291 a-3p/Rab22a pathway in mediating the effects of Tan-IIA.

Research results

Tan-IIA ameliorated AD-related pathological changes, reduced oxidative stress, and attenuated neuroinflammation in the mouse models. It modulated the expression of NEAT1, miR-291a-3p, and Rab22a, indicating the involvement of this signaling axis in its neuroprotective effects. This is the first study to link the amelioration of AD symptoms by Tan-IIA with the downregulation of NEAT1.

Research conclusions

Tan-IIA has potential therapeutic roles in AD by attenuating oxidative stress and neuroinflammation, primarily through the NEAT1/miR-291a-3p/Rab22a signaling axis. This highlights the intricate molecular interplay involved in AD and identifies lncRNAs and miRNAs as potential therapeutic targets.

Research perspectives

Future research should focus on validating the identified therapeutic targets, namely miR-291a-3p and Rab22a, in clinical AD models. It is also crucial to explore other potential molecular pathways affected by Tan-IIA to fully understand its neuroprotective mechanisms. Clinical trials are essential to determine the efficacy and safety of Tan-IIA-based therapies in patients with AD. Expanding our understanding of the role of NEAT1 in AD could open new avenues for RNA-based therapeutic strategies.

FOOTNOTES

Author contributions: Yang LX, Luo M, and Li SY contributed to the study design, experiments, data collection, and manuscript writing; Luo M and Li SY contributed to the visualization; Li SY contributed to the resources; and all authors have read and approved the final manuscript.

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Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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SYSTEMATIC REVIEWS

Outcomes of long-acting injectable antipsychotics use in pregnancy: A literature review

Ana V Pejčić, Srdjan M Stefanović, Miloš N Milosavljević, Vladimir S Janjić, Marko M Folić, Nevena D Folić, Jovana Z Milosavljević

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Ana V Pejčić, Miloš N Milosavljević, Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Srdjan M Stefanović, Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Srdjan M Stefanović, Marko M Folić, Department of Clinical Pharmacology, University Clinical Center Kragujevac, Kragujevac 34000, Serbia

Vladimir S Janjić, Department of Psychiatry, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Vladimir S Janjić, Clinic for Psychiatry, University Clinical Center Kragujevac, Kragujevac 34000, Serbia

Marko M Folić, Center for Pharmaceutical and Pharmacological Research, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Nevena D Folić, Department of Pediatrics, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Nevena D Folić, Pediatric Clinic, University Clinical Center Kragujevac, Kragujevac 34000, Serbia

Jovana Z Milosavljević, Department of Anatomy, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Corresponding author: Ana V Pejčić, PhD, Assistant Professor, Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Svetozara Markovića 69, Kragujevac 34000, Serbia. anapejcic201502@yahoo.com

Abstract

BACKGROUND

Women with a history of serious psychotic disorders are at increased risk of disease relapse during pregnancy. Long-acting injectable (LAI) antipsychotics have been widely used to improve adherence and prevent relapse in patients with various severe psychotic disorders, but there is a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy.

AIM
To summarize relevant data on maternal, pregnancy, neonatal, and developmental outcomes from published cases of LAI antipsychotic use in pregnancy.

METHODS
A literature search was performed through November 11, 2023, using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

RESULTS
A total of 19 publications satisfied the inclusion criteria: 3 case series, 15 case reports, and 1 conference abstract. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. The use of second-generation LAI antipsychotics was reported in the majority (n = 47; 61.0%) of pregnancies. First-generation LAI antipsychotics were administered during 30 pregnancies (39.0%). Most of the women (approximately 64%) had either satisfactory control of symptoms or no information about relapse, while approximately 12% of them had developed gestational diabetes mellitus. A minority of cases reported adverse outcomes such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. However, there were no reports of negative long-term developmental outcomes.

CONCLUSION
Currently available data seem reassuring, but further well-designed studies are required to properly evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

Key Words: Antipsychotic agents; Long-acting injectable; Pregnancy; Outcome; Review

Core Tip: Considering that the currently available research on the use of long-acting injectable antipsychotics in pregnancy consists only of case reports and series, additional well-designed studies are needed to properly evaluate the risks and benefits of their use during pregnancy. Currently available data seem reassuring, given that most of the women seemed to have satisfactory control of the symptoms and that a minority of the cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns, while there were no reported negative long-term developmental outcomes.

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INTRODUCTION

Owing to their unique formulations, specific pharmacokinetic properties (*i.e.,* flip-flop kinetics), and accompanying innovations in drug delivery mechanisms, long-acting injectable (LAI) antipsychotics have been widely used in clinical practice for decades to improve adherence and prevent relapse, with the ultimate goal of reducing (re)hospitalization and mortality rates in patients with various severe psychotic disorders[1-3]. In fact, the use of these depot formulations with less frequent, more convenient dosing generally provides several relevant advantages over their oral counterparts[4-6]. By providing slow systemic absorption and continuous drug exposure with more stable blood levels, a potentially greater efficacy and acceptable safety profile are ensured, reflecting the previously mentioned beneficial effects on the main challenges regarding treatment outcomes of chronic diseases such as schizophrenia or bipolar disorder[1,7,8]. To date, several LAI antipsychotics have been approved[9,10], divided into first-generation or typical LAI antipsychotics (*e.g.,* haloperidol, fluphenazine, flupentixol, and zuclopenthixol) and second-generation or atypical LAI antipsychotics (*e.g.,* risperidone, olanzapine, aripiprazole, and paliperidone).

Women with a history of serious psychotic disorders are at increased risk of disease relapse during pregnancy, which can significantly endanger both the mother and the fetus, and satisfactory compliance with antipsychotic medications plays a key role in avoiding treatment failure[11-13]. Therefore, continuation and maintenance of antipsychotic therapy are necessary for pregnant women[14]. However, in daily clinical practice, antipsychotics are likely to be discontinued when pregnancy is confirmed for fear of possible teratogenicity or fetotoxicity[15,16]. Moreover, despite the current evidence showing that the use of oral antipsychotics is not significantly associated with poor pregnancy outcome[17,18], as well as a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy that

does not clearly support their avoidance[19-21], it has been observed that psychiatrists prefer not to start or stop the use of LAI antipsychotics, even in pregnant women with an exceptionally high risk of psychotic symptom recurrence[22].

Apart from a significantly lower potential for overdose, LAI antipsychotics appear to share an overall safety profile similar to that of their oral counterparts[23,24]. An exception is the depot formulation of olanzapine[25], which requires strict monitoring for delirium or excessive sedation for a few hours immediately after intramuscular injection[26,27]. In addition, the women with pharmacokinetic changes reflected in the increased clearance of these drugs during pregnancy may require an increase in their doses[28]. Therefore, the decision to use and the choice of an appropriate LAI antipsychotic with an optimal benefit-risk ratio for an individual pregnant woman is challenging because numerous factors need to be considered, such as: Previous compliance to drug therapy (especially psychotropic drugs); use of antipsychotics/LAI antipsychotics in previous pregnancies if any, as well as the outcomes of such pregnancies; history of recurrent psychotic manifestations, especially if they led to long and frequent hospitalizations; history of licit or illicit abuse of psychoactive substances; compliance with the approved indication related to the psychotic or affective disorder; differences in the safety profile of individual LAI antipsychotics (*e.g.*, metabolic side effects among atypical antipsychotics); need for dose escalation and length of the dosing interval during pregnancy; and a pregnant woman's decision to breastfeed[29-31].

Previous reviews published several years ago identified 12 relevant case reports of both first- and second-generation LAI antipsychotic use during pregnancy[19] and 8 case reports/series of second-generation LAI antipsychotic use during pregnancy[32]. Considering that these reviews included only selected cases published before January and March 2021, respectively, and that several case reports/series reporting outcomes of pregnancy in women using LAI antipsychotics were published in the meantime[20,33,34] or were published earlier but not included in previous reviews[35], there is a need for an updated review. Therefore, our review aims to provide an up-to-date summary of the relevant data on maternal, pregnancy, neonatal, and developmental outcomes from available published cases of LAI antipsychotic use in pregnancy to help inform clinical decision-making. We also aimed to identify whether there are ongoing clinical studies assessing LAI antipsychotic use during pregnancy.

MATERIALS AND METHODS

Electronic literature searches were conducted using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. A literature search was performed from the beginning of indexing until November 11, 2023, without language or date restrictions. A detailed search strategy for each database is presented in Table 1.

Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. LAI antipsychotics included first- (fluphenazine, haloperidol, zuclopenthixol, and flupentixol) and second-generation (aripiprazole, olanzapine, paliperidone, and risperidone) antipsychotics. Conference abstracts were included only if they contained sufficient data for analysis. Reviews, meta-analyses, commentaries, guidelines, "*in vitro*" studies, and animal studies were excluded. The eligibility of the retrieved publications was reviewed based on their titles and abstracts. When the title and information available in the abstract were insufficient for evaluating whether the publication properly corresponded to the research topic, we tried to retrieve and evaluate the full text. Publications were included that all the authors agreed met the eligibility criteria. Disagreements between the individual judgments were resolved by consensus.

Additionally, backward and forward citation searches were performed for publications that met the eligibility criteria. Backward citation searching was performed by inspecting the references cited in these publications, while forward citation searching was performed using the Google Scholar citation index on November 21, 2023, to identify publications that cited these publications.

We extracted the following data: type of publication, country, number of women, number of pregnancies, maternal age, information about alcohol/tobacco/illicit drug use during pregnancy, psychiatric diagnosis, information about LAI antipsychotic medication (name, dosage, and duration of treatment during pregnancy) and other medications used during pregnancy, maternal treatment outcomes (information about efficacy of LAI antipsychotic use and relapse of symptoms), gestational diabetes mellitus, pregnancy hypertension, premature rupture of membranes, delivery mode, live birth, stillbirth, spontaneous abortion, preterm birth, gestational age at birth, gender of the newborn, birth weight, Apgar score (at 1, 5, and 10 minutes), admission of the newborn to special care nursery or neonatal intensive care unit, neonatal and developmental outcomes, and main conclusions. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

To identify ongoing clinical studies aimed at assessing the use of LAI antipsychotics during pregnancy, we searched the ClinicalTrials.gov database on January 23, 2024. We performed a search by entering previously mentioned LAI antipsychotics in the intervention/treatment search field, and pregnancy in the condition/disease search field.

RESULTS

Results of the literature search

Our search strategy identified 142 publications in PubMed/MEDLINE, 67 publications in Scopus, and 47 publications in Web of Science, and 200 total publications were screened for eligibility after duplicates were removed. Of these 200 publications, 17 met the inclusion criteria, and 183 were excluded (172 irrelevant publications, 6 review/consensus

Table 1 A detailed search strategy for each database

Database	Search strategy
PubMed/MEDLINE	(("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotic" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotically" [All Fields] OR ("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "antipsychotic" [All Fields] OR "antipsychotics" [All Fields] OR "antipsychotic s" [All Fields] OR "antipsychotically" [All Fields]) OR ("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "neuroleptic" [All Fields] OR "neuroleptics" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptically" [All Fields] OR "neuroleptization" [All Fields]) OR ("antipsychotic agents" [Pharmacological Action] OR "antipsychotic agents" [MeSH Terms] OR ("antipsychotic" [All Fields] AND "agents" [All Fields]) OR "antipsychotic agents" [All Fields] OR "neuroleptic" [All Fields] OR "neuroleptics" [All Fields] OR "neuroleptical" [All Fields] OR "neuroleptically" [All Fields] OR "neuroleptization" [All Fields]) OR ("aripiprazole" [MeSH Terms] OR "aripiprazole" [All Fields] OR "aripiprazol" [All Fields] OR "aripiprazole s" [All Fields]) OR ("fluphenazine" [MeSH Terms] OR "fluphenazine" [All Fields]) OR ("haloperidol" [MeSH Terms] OR "haloperidol" [All Fields] OR "haloperidol s" [All Fields] OR "haloperidole" [All Fields]) OR ("flupenthixol" [MeSH Terms] OR "flupenthixol" [All Fields] OR "flupentixol" [All Fields]) OR ("clopenthixol" [MeSH Terms] OR "clopenthixol" [All Fields] OR "zuclopenthixol" [All Fields]) OR ("olanzapine" [MeSH Terms] OR "olanzapine" [All Fields] OR "olanzapin" [All Fields] OR "olanzapine s" [All Fields]) OR ("paliperidone palmitate" [MeSH Terms] OR ("paliperidone" [All Fields] AND "palmitate" [All Fields]) OR "paliperidone palmitate" [All Fields] OR "paliperidone" [All Fields] OR "paliperidone s" [All Fields]) OR ("risperidon" [All Fields] OR "risperidone" [MeSH Terms] OR "risperidone" [All Fields] OR "risperidone s" [All Fields])) AND ("long-acting" [All Fields] OR ("inject" [All Fields] OR "injectability" [All Fields] OR "injectant" [All Fields] OR "injectants" [All Fields] OR "injectate" [All Fields] OR "injectates" [All Fields] OR "injected" [All Fields] OR "injectible" [All Fields] OR "injectibles" [All Fields] OR "injecting" [All Fields] OR "injections" [MeSH Terms] OR "injections" [All Fields] OR "injectable" [All Fields] OR "injectables" [All Fields] OR "injection" [All Fields] OR "injects" [All Fields]) OR ("depot" [All Fields] OR "depots" [All Fields])) AND ("pregnancy" [MeSH Terms] OR "pregnancy" [All Fields] OR "pregnancies" [All Fields] OR "pregnancy s" [All Fields] OR ("pregnant" [All Fields] OR "pregnants" [All Fields]))) NOT ("mice" [MeSH Terms] OR "mice" [All Fields] OR "mouse" [All Fields] OR "mouse s" [All Fields] OR "mouses" [All Fields] OR ("mice" [MeSH Terms] OR "mice" [All Fields]) OR ("rats" [MeSH Terms] OR "rats" [All Fields] OR "rat" [All Fields]))
Web of Science	In all databases and all collections (Web of Science Core Collection; KCI-Korean Journal Database; Preprint Citation Index; ProQuest™ Dissertations & Theses Citation Index; SciELO Citation Index): TS = (antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR fluphenazine OR haloperidol OR flupenthixol OR flupentixol OR zuclopenthixol OR olanzapine OR paliperidone OR risperidone) AND TS = (long-acting OR injectable OR depot) AND TS = (pregnancy OR pregnant)
Scopus	TITLE-ABS-KEY ((antipsychotic OR antipsychotics OR neuroleptic OR neuroleptics OR aripiprazole OR fluphenazine OR haloperidol OR flupenthixol OR flupentixol OR zuclopenthixol OR olanzapine OR paliperidone OR risperidone) AND (long-acting OR injectable OR depot) AND (pregnancy OR pregnant))

guidelines, 3 publications with unavailable full text, 1 conference abstract of an already included publication, and 1 conference abstract with incomplete data on pregnancy and delivery outcomes). We identified 2 additional publications *via* citation search; therefore, 19 publications satisfied the inclusion criteria: 3 case series[20,21,33], 15 case reports[34-48], and 1 conference abstract[49]. One case series reported aggregate data[20], while all others reported individual data.

Main characteristics of included pregnant women

An overview of the included publications/cases is presented in Table 2. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. The age of the pregnant women ranged from 20 to 43 years, and most were diagnosed with schizophrenia (n = 43; 58.1%), followed by schizoaffective disorder (n = 8; 10.8%), bipolar disorder (n = 5; 6.8%), and psychosis (n = 3; 4.0%). The exact diagnosis in 15 women (20.3%) reported by Eleftheriou *et al*[33] was not specified (either a bipolar or psychotic disorder). The majority of the women were from Australia (n = 39; 52.7%), followed by Italy (n = 15; 20.3%), Spain (n = 9; 12.2%), Turkey (n = 3; 4.0%), the United States (n = 3; 4.0%), Japan (n = 1; 1.3%), Portugal (n = 1; 1.3%), Serbia (n = 1; 1.3%), South Korea (n = 1; 1.3%), and Sweden (n = 1; 1.3%). Smoking, alcohol consumption, and the use of illicit drugs some point during pregnancy were reported in 33 (44.6%), 3 (4.0%), and 3 (4.0%) women, respectively.

Characteristics of prescribed LAI antipsychotics

In the majority (n = 47; 61.0%) of pregnancies, the use of second-generation LAI antipsychotics was reported [aripiprazole was used in 26 (33.8%); paliperidone in 14 (18.2%); risperidone in 6 (7.8%); and olanzapine in 1 (1.3%)]. First-generation LAI antipsychotics were used in 30 (39.0%) pregnancies [zuclopenthixol in 14 (18.2%); flupentixol in 9 (11.7%); fluphenazine in 5 (6.5%); and haloperidol in 2 (2.6%)]. The dosage and duration of LAI antipsychotic treatment during pregnancy varied considerably among individual medications, and this information is presented in Table 2. During more than half of the pregnancies, women reported using medications other than LAI antipsychotics (n = 46; 59.7%).

Maternal outcomes

Relapse/worsening of the patients' condition during pregnancy, after delivery, and both during pregnancy and after delivery were reported in 15 (19.5%), 7 (9.1%), and 1 (1.3%) pregnancies, respectively. One patient (1.3%) required hospitalization for psychosis relapse after stillbirth, while another patient (1.3%) discontinued LAI antipsychotic use without consulting a clinician and was hospitalized for an acute psychotic attack. Improvement or partial control of symptoms was reported in 3 (3.9%) pregnancies. The remaining 49 (63.6%) had satisfactory symptom control or no information about relapse. Gestational diabetes mellitus was reported in nine (11.7%) pregnancies (two during the use of first-generation LAI antipsychotics and seven during the use of second-generation LAI antipsychotics). Elevated blood

Table 2 An overview of included publications/cases

No.	Ref.	Maternal age (yr)	Type of publication, No. of women/pregnancies	Psychiatric diagnosis	LAI-AP medication (dosage, duration of treatment during pregnancy); other medications used during pregnancy	Maternal treatment outcomes	Pregnancy and delivery outcomes (gestational age, gender, birth weight, Apgar score 1/5/10 min)	Neonatal and developmental outcomes
1	Donaldson and Bury[36], 1982	29	Case report, 1/1	Hebephrenic schizophrenia	Fluphenazine enanthate (25 mg/month, entire pregnancy); dicyclomine hydrochloride, doxylamine succinate and pyridoxine hydrochloride (from 45 to 101 d of gestation), ferrous sulphate, folic acid (from day 101 to near delivery), paracetamol (from day 165 to near delivery), sodium amytal (from day 250 to 255)	Her symptoms improved during pregnancy	Labor was induced surgically and proceeded to forceps delivery (36 wk, male, 2520 g, 9/NR/NR)	Born with a short sloping forehead, wide metopic suture, persistent metopic fontanelle, telecanthus, ocular hypertelorism, nystagmoid eye movements, bilateral cleft lip and palate, imperforate anus, rectourethral fistula, bifid scrotum, unusual penis with hypospadias, and neutrophil polymorphs with numerous nuclear projections. His overall progress was good, with the rectourethral fistula divided and anoplasty performed soon after delivery and the cleft lip and palate repaired at 7 months
2	Cleary[37], 1977	32	Case report, 1/1	Schizophrenia	Fluphenazine decanoate (2 cc every 3 wk, entire pregnancy); benztropine mesylate sporadically	Latent homicidal ideas were noted late in pregnancy, and her behavior continued to be bizarre, explosive, and unpredictable. Two months after delivery, she developed somatic delusions, became agitated and paranoid, and was readmitted to a psychiatric hospital. After discharge and some months later, she indicated the persistence of a schizophrenic thought disorder	Delivered by cesarean section 9 d after the expected date following the failure of oxytocin to induce labor (40 wk and 9 d, male, 3380 g, 8/10/NR)	Born healthy. Possible minor extrapyramidal manifestations 4 wk after delivery (or withdrawal symptoms from fluphenazine) that responded to diphenhydramine elixir. Apparently well-nourished, well-developed, and alert child at 24 months
3	O'Connor *et al* [38], 1981	22	Case report, 1/1	Schizophrenia	Fluphenazine decanoate (50 mg fortnightly from 14 to 24 wk /increased over three wk to this dose/, then 100 mg fortnightly from 24 wk to delivery); chlorpromazine (from 12th week of pregnancy to delivery)	Her suicidal behavior gradually abated after the LAI-AP dosage increase, but she continued to exhibit denial of pregnancy, extreme unpredictability, and total resistance to obstetric examination	Delivered by cesarean section after spontaneous onset of labor (39 wk, male, 3530 g, 10/10/NR)	Excellent condition at delivery. Initial progress was good. On the 21st d after birth, he developed many neurological signs (*e.g.*, excessive irritability, choreiform and dystonic movements involving mainly the upper limbs, jittery behavior, and hypertonicity) which persisted for 9 months and were mainly treated with diphenhydramine. The symptoms were consistent with LAI withdrawal effects. Follow-up at 15 months of age revealed no abnormalities
4	Collins and Comer[39], 2003	35	Case report, 1/1	Schizoaffective disorder	Haloperidol decanoate (200 mg/2 wk, throughout the pregnancy – last dose 3 wk before delivery); not specified	She had an acute psychotic episode before induced delivery	Induced vaginal delivery (full term, female, 3880 g, 9/9/NR)	At birth was noted to be "jittery", then developed diarrhea and metabolic acidosis, and was transferred to NICU at 3rd d. She became increasingly irritable, and on day 8 had an episode of tonic-clonic movements in

								all extremities with tongue thrusting and torticollis (possible tardive dyskinesia or withdrawal dyskinesia). Tonic-clonic episodes continued up to the 14th d of life (successfully treated with clonazepam). On day 21, she was discharged to foster care with no tremulous movements noted
5	Janjić *et al* [40], 2013	35 at 1st pregnancy, 38 at 2nd pregnancy	Case report, 1/2	Schizophrenia	Zuclopenthixol decanoate (in 1st pregnancy initially 400 mg/2 wk, then upon discovery of the pregnancy at 13 wks' gestation dose was decreased to 200 mg/month and this dose was also used during entire 2nd pregnancy); not specified	Maternal psychiatric status during both pregnancies, after each delivery, and during the follow-up period was favorable (continued to be rated as "borderline mentally ill"), with no exacerbations	Delivery method not specified for both pregnancies. 1st pregnancy/child: (39 wk, female, 3750 g, 9/NR/NR); 2nd pregnancy/child: (40 wk, female, 3700 g, 9/NR/NR)	Both girls were healthy without obvious congenital malformations. The brain ultrasound of the first child revealed some clinically insignificant periventricular hyperechogenicity. Both had been normally developing 3.5 yr and 6 months after delivery
6	Ballester-Gracia *et al* [41], 2019	43	Case report, 1/1	Bipolar disorder	Aripiprazole LAI (400 mg/month for first 2-3 wk of pregnancy, then decreased to 300 mg/month, entire pregnancy); not specified (probably none)	No recurrence of her illness or significant mood fluctuations during pregnancy. Two days after hospital discharge after delivery, she came as an outpatient and was euthymic, so LAI-AP dose was increased to 400 mg/4 wk	Spontaneous vaginal delivery without complications (40 wk and 4 d, female, 3500 g, 9/10/10)	No congenital malformations at birth or development abnormalities at five months after delivery
7	Sole *et al*[49], 2020	30	Conference abstract, 1/1	Schizophrenia	Aripiprazole LAI (400 mg/28 d, entire pregnancy), not specified	No psychiatric complications due to pregnancy and puerperium were reported. No bounding disorder was detected	Delivered without obstetric complications (41 wk, female, 3465 g, 9/10/NR)	No neonatal complications
8	Fernández-Abascal *et al* [21], 2021	35 (table), 39 (text)	Case series, 1/1	Paranoid schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 8th week, 300 mg/28 d from 8th week until delivery); not specified	Throughout pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained	Uncomplicated eutocic/vaginal delivery (38 wk and 5 d, gender?/male in text; female in table/, 3300 g, 9/10/NR)	During the first 6 wk of follow-up postural plagiocephaly and hypertonia were noted, that finally were resolved with physiotherapy. He developed normally during a 3-yr follow-up
9	Fernández-Abascal *et al* [21], 2021	29 (table), 32 (text)	Case series, 1/1	Schizophrenia, schizotypal personality disorder	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 20th week, 300 mg/28 d from 20th week until delivery); not specified	Adherence was maintained throughout the pregnancy with psychopathological stability and good adherence. She had clinical worsening 3 months after delivery	Admitted to ED for spontaneous delivery – eutocic/vaginal delivery, right medial episiotomy (31 wk and 5 d, female, 1800 g, 10/10/NR)	Remained in an incubator for 1 month due to prematurity. No congenital malformations were observed at delivery or during the postpartum period. She developed normally during a 2-yr follow-up
10	Fernández-Abascal *et al* [21], 2021	35 (table), 36 (text)	Case series, 1/1	Paranoid schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 5th week, 300 mg/28 d from 5th week until delivery); not specified	Psychopathological stability and proper treatment adherence were maintained throughout the pregnancy	Eutocic/vaginal delivery (39 wk and 6 d, male, 3140 g, 9/10/NR)	No congenital malformations were observed at birth, and the postpartum period proceeded without relevant events. Normal development at 2 months
11	Fernández-Abascal *et al* [21], 2021	31	Case series, 1/1	Schizophrenia	Aripiprazole LAI (160 mg/28 d from beginning of pregnancy until delivery); occasional budesonide inhalation	Throughout the pregnancy, the patient remained psychopathologically stable, and treatment adherence was maintained	Uncomplicated eutocic/vaginal delivery (39 wk and 5 d, male, 3102 g, 10/10/NR)	Born healthy. In the 2-yr follow-up he remained in good health and developed normally

12	Fernández-Abascal *et al* [21], 2021	38 (table), 39 (text)	Case series, 1/1	Schizophrenia	Aripiprazole LAI (300 mg/28 d from beginning of pregnancy until delivery); not specified	Throughout the pregnancy, she remained psychopathologically stable, and treatment adherence was maintained	Eutocic/vaginal delivery (39 wk, male, 2940 g, 8/10/NR)	Born healthy. In the 1-yr follow-up, he remained in good health and developed normally
13	Fernández-Abascal *et al* [21], 2021	30	Case series, 1/1	Schizophrenia	Aripiprazole LAI (400 mg/28 d from beginning of pregnancy to 8th week); when pregnancy was confirmed the prescription dose of benzodiazepines was adjusted downwards until they were withdrawn along 4 wk, levothyroxine	To ensure psychopathological stability and to detect warning signs of decompensation, the patient was closely monitored weekly during pregnancy (no worsening was reported)	Eutocic/vaginal delivery (40 wk, male, 3400 g, 9/10/NR)	Born healthy. He has been followed for 18 months, and no malformation, developmental abnormalities, or growth retardation were detected
14	Eleftheriou *et al*[33], 2023	38	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment, interruption of treatment at 23 wk); folic acid	Postpartum hospitalization for psychosis relapse	Cesarian section (31 wk, NR, 1995 g, 6/8/NR)	Down's syndrome, fetal hydrops complicated by septic shock, massive anuria, and death in 10 d. This syndrome cannot be considered a drug-induced malformation
15	Eleftheriou *et al*[33], 2023	25	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	Postpartum hospitalization for psychosis relapse	Vaginal delivery (40 wk, female, 3300 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
16	Eleftheriou *et al*[33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment, interruption of treatment at 14 wk); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Spontaneous abortion (miscarriage) at 15th week	Not applicable
17	Eleftheriou *et al*[33], 2023	35	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Spontaneous abortion (miscarriage) at 9th week	Not applicable
18	Eleftheriou *et al*[33], 2023	34	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (200 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, carbamazepine (in first trimester, stopped at 10 wk)	Postpartum hospitalization for psychosis relapse	Cesarian section (40 wk, male, 2900 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
19	Eleftheriou *et al*[33], 2023	28	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, oral aripiprazole (in first trimester)	No hospitalization for psychosis relapse	Cesarian section (40 wk, female, 3140 g, 7/9/NR)	Live birth with no malformations. No adaptation disorders after delivery

20	Eleftheriou *et al*[33], 2023	43	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid.	No hospitalization for psychosis relapse	Vaginal delivery (40 wk, male, 2300 g, 10/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
21	Eleftheriou *et al*[33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Vaginal delivery (40 wk, male, 3500 g, 8/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
22	Eleftheriou *et al*[33], 2023	20	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (in first trimester)	Hospitalization for psychosis relapse after stillbirth	Stillbirth at 26th week	Not applicable
23	Eleftheriou *et al*[33], 2023	31	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Aripiprazole LAI (400 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, paroxetine (in first trimester)	No hospitalization for psychosis relapse	Vaginal delivery (38 wk, female, 3120 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
24	Manouilenko *et al*[42], 2018	35	Case report, 1/1	Psychosis	Olanzapine pamoate (405 mg/4 wk, from 25th week, reduced to 300mg/4 wk from 29th week and ultimately due to sedation to 210 mg/2 wk at 39th week, exposure until delivery); oral olanzapine for 4 d and promethazine injections before initiation of LAI-AP	Improved rapidly on LAI-AP, but she was hospitalized at pregnancy week 40 since she reported fatigue and depression	Vaginal delivery was induced by amniotomy (40 wk, female, 2930 g, 9/10/10)	Fully developed infant. The child's somatic and psychomotor development up to 3 yr of age was normal
25	de Azevedo Avelar *et al* [43], 2020	26	Case report, 1/1	Schizophrenia	Paliperidone palmitate (263 mg every three months twice during pregnancy, the last one approximately 2 months before birth – exposure during entire pregnancy); none	She was doing well on this LAI-AP (asymptomatic on follow-up)	Presented to ED with abdominal pain, found to be in labor – pregnancy was not planned nor monitored (unknown gestational age, male, 2420 g, 9/10/10)	Approximately 1 yr after birth no health or developmental issues
26	Zamora Rodríguez *et al*[44], 2017	34	Case report, 1/1	Bipolar schizoaffective disorder	Paliperidone palmitate (100 mg/4 wk initially, then reduced to 50 mg/4 wk, she was pregnant for 2 wk when it was initiated, and dosage reduced at 5 wk of pregnancy and remained at this dosage until and after delivery); venlafaxine and clonazepam for first 5 wk, which were then changed to fluoxetine and	No psychotic or affective symptoms except for a slight period of anxiety in the days immediately after discovering she was pregnant, and a mild and self-limited depressive relapse from days 7 to 9 after giving birth	Term birth, delivery mode not specified (40 wk, male, 2440 g, 9/10/10)	Clinical status of the newborn was normal. No diseases or malformations were detected in the first year of follow-up

					lorazepam, omeprazole and yodocefol			
27	Özdemir *et al* [45], 2015	37	Case report, 1/1	Schizophrenia	Paliperidone palmitate (100 mg monthly, from beginning until week 28 of gestation – last dose given at the 28th week); haloperidol orally from 29th week until delivery	Developed psychotic symptoms despite regular injections of LAI-AP 2 wk before a change to haloperidol was made (her symptoms subsided 3 wk afterwards)	Cesarean section without complications (39 wk, male, 3000 g, 9/NR/NR)	The baby has been followed for 4 months, and no malformation or growth retardation was detected
28	Binns *et al* [46], 2017	28	Case report, 1/1	Chronic paranoid schizophrenia	Paliperidone palmitate (150 mg/4 wk, entire pregnancy); not specified	Good control of psychosis was maintained	Pregnancy was complicated by polyhydramnios, induced labor followed by cesarean section due to fetal distress (39 wk, male, 3840 g, 9/9/NR)	Neonatal clinical examination confirmed a minor correctable congenital anomaly, bilateral talipes equinovarus, which was managed conservatively but was otherwise normal. The early postnatal course was uncomplicated
29	Iwata *et al* [34], 2021	30	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, first dose was given at 34 wks' gestation, and she electively gave birth at 38 wks' gestation); initially from beginning of pregnancy olanzapine orally (problems with adherence) up to 32nd week, then risperidone orally for 7 d during 33rd week of pregnancy	Doing well on LAI-AP (after its initiation at the third trimester she had a notable improvement in positive and negative symptoms, and the delivery was performed without any issues)	Uneventful cesarean section (38 wk, male, NR, NR/NR/NR)	Transient tachypnea of the newborn that was managed with nasal continuous positive airway pressure. He was discharged 29 d after the delivery. Normal growth and neuropsychological development at 12 months after birth
30	Erdoğan *et al* [35], 2017	25	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, from beginning of pregnancy, last dose given at 22nd week); not specified	She discontinued LAI-AP use without consultation with a clinician. At the 29th week of pregnancy, she was hospitalized with an acute psychotic attack	Normal vaginal delivery (40 wk, male, 3200 g, 9/10/NR)	Born healthy baby. Normal neurobehavioral development according to BSID-III (subscales of cognitive, motor, and language developments were in normal ranges at 2, 6, 12, 18, and 24 months of age)
31	Erdoğan *et al* [35], 2017	32	Case report, 1/1	Schizophrenia	Paliperidone palmitate (150 mg/monthly, entire pregnancy); not specified	No information about worsening of her condition during treatment. Four months after delivery she gave baby to ward of state	Normal vaginal delivery (41 wk, female, 2980 g, 9/10/NR)	Normal neurobehavioral development according to BSID-III (subscales of cognitive, motor and language developments were in normal ranges at 2, 6, 12, and 18 months of age)
32	Eleftheriou *et al*[33], 2023	26	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (50 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, lorazepam (first trimester)	Postpartum hospitalization for psychosis relapse	Cesarian section (39 wk, female, 3020 g, 9/9/NR)	Live birth with no malformations. No adaptation disorders after delivery
33	Eleftheriou *et al*[33], 2023	32	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Cesarian section (40 wk, male, 3250 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery

34	Eleftheriou *et al*[33], 2023	30	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	Postpartum hospitalization for psychosis relapse	Cesarian section (39 wk, male, 3650 g, 10/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
35	Eleftheriou *et al*[33], 2023	25	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (100 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid	No hospitalization for psychosis relapse	Cesarian section (40 wk, female, 3255 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
36	Eleftheriou *et al*[33], 2023	33	Case series, 1/1	Bipolar or psychotic disorder (exact diagnosis not specified)	Paliperidone LAI (50 mg/month, pregnancy started on LAI treatment which was continued until delivery); folic acid, haloperidol (first trimester)	No hospitalization for psychosis relapse	Cesarian section (39 wk, female, 3100 g, 9/10/NR)	Live birth with no malformations. No adaptation disorders after delivery
37	Clinebell *et al* [47], 2017	32	Case report, 1/1	Bipolar disorder	Risperidone LAI (50 mg/2 wk, entire pregnancy); risperidone orally, citalopram, and benztropine (entire pregnancy)	She was doing well	Intrauterine growth restriction, and, due to concerns for placental insufficiency, she had induction of labor (35 wk, male, 2098 g, 8/8/9)	Born healthy, but with bilateral supernumerary nubs/digits on his hands that were removed after birth (this anomaly was a paternal family trait). The child has met developmental milestones at 16 months
38	Kim *et al*[48], 2007	35	Case report, 1/1	Schizophrenia	Risperidone LAI (25 mg/2 wk, entire pregnancy); not specified	Her psychotic symptoms improved markedly with LAI-AP treatment. No information about relapse	She delivered vaginally 3 h after premature rupture of membranes (36 wk and 6 d, female, 2230 g, 9/9/NR)	No evidence of congenital malformation at birth and no developmental abnormalities were found 8 months postnatally
39	Nguyen *et al* [20], 2022	Mean±SD: All: 30.3±5.5; FGA: 31.0±6.0; SGA: 29.1±4.5	Case series, 36/38	Schizophrenia (25/69.4%); Schizoaffective disorder (6/16.7%); Bipolar affective disorder (3/8.3%); Unspecified psychosis (2/5.6%)	FGA (24/38): zuclopenthixol– 12 (100 mg fortnightly– 2, 150 mg fortnightly– 2, 200 mg fortnightly– 5, 200 mg monthly– 1, 300 mg fortnightly– 1, 300 mg monthly– 1); flupentixol– 9 (20 mg fortnightly– 1, 30 mg fortnightly– 1, 40 mg fortnightly– 5, 40 mg monthly– 1, 100 mg fortnightly– 1); fluphenazine– 2 (50 mg fortnightly); haloperidol– 1 (dose missing). SGA (14/38): aripiprazole– 8 (300 mg monthly– 1; 400 mg monthly– 7), risperidone– 4 (37.5 mg fortnightly– 1; 37.5 mg monthly– 1, 50 mg fortnightly– 2); paliperidone– 2 (100 mg monthly). First trimester exposure data only on 35/38 pregnancies, with 1/38 having a third	Psychiatric relapse reported in 9 (40.9%) pregnancies in women on FGA and 3 (27.3%) pregnancies in women on SGA LAI-AP. Note: Valid% reported due to missing data	All pregnancies: spontaneous delivery in 13 (34.2%), emergency cesarean section in 11 (28.9%), premature birth (< 37 wk) in 6 (15.8%). Induction in 16 (66.7%) on FGA and 7 (50.0%) on SGA, emergency cesarean section in 8 (33.3%) on FGA and 3 (21.4%) on SGA, premature birth (< 37 wk) in 5 (20.8%) on FGA and 1 (7.1%) on SGA. Note: Valid% reported due to missing data. For all babies the mean gestational age was 38.25 wk (SD = 2.19) and mean birth weight was 3.18 kg (SD = 0.76). Gender and Apgar score were NR	Admission to a special care nursery was reported in a total of 18 *i.e.*, 47.4% of babies (13 *i.e.*, 54.2% and 5 *i.e.*, 35.7% whose mothers received FGA and SGA, respectively). Congenital malformations were recorded in 2 babies, and with data available on first-trimester exposure in only 35 pregnancies, this gives a 5.7% rate. One baby had undescended testes whose mother was treated with risperidone LAI, and the other was a patent ductus arteriosus in a baby of a woman who received flupentixol LAI. Both babies were managed conservatively. The authors were not able to assess for neonatal extrapyramidal syndrome (not recorded in their data)

	trimester exposure and first trimester data were missing for 2/38. Nearly half (n = 17, 44.7%) were on LAI-AP as the sole medication while the rest had exposures to other oral medications including olanzapine, quetiapine, diazepam, chlorpromazine, risperidone, benztropine, venlafaxine, aripiprazole, fluoxetine, escitalopram, desvenlafaxine, lamotrigine)	

AP: Antipsychotic(s); BSID-III: Bayley Scales of Infant and Toddler Development 3rd Ed; ED: Emergency department; FGA: First-generation antipsychotics; LAI: Long-acting injectable; NICU: Neonatal intensive care unit; NR: Not reported; SD: Standard deviation; SGA: Second-generation antipsychotics.

pressure during pregnancy was reported in 5 (6.5%) pregnancies (all were treated with first-generation LAI antipsychotics). One case series[20] reported that pregnant women treated with LAI antipsychotics were more likely to have obstetric complications, including gestational diabetes and pregnancy hypertension, than the general population. They also had elevated rates of psychiatric admission during pregnancy and statutory child protection involvement, while the outcomes were similar for first- and second-generation LAI antipsychotic exposures[20].

Pregnancy and delivery outcomes

Premature rupture of membranes was reported in six pregnancies (7.8%): Four involved the use of first-generation LAI antipsychotics and two the use of second-generation LAI antipsychotics. The use of cesarean section as a delivery method was reported in 24 pregnancies (31.2%): 10 involved first-generation and 14 involved second-generation LAI antipsychotic use. One (1.3%) pregnancy ended in stillbirth, whereas two (2.6%) ended in spontaneous abortion (miscarriage), all of which involved the use of aripiprazole LAI. Preterm birth (< 37 wk) was reported in 11 (14.3%) pregnancies (6 and 5 involved first- and second-generation LAI use, respectively). The reported birth weight of babies ranged from 1800 to 3880 g, while 7 (9.5% of 74 live births) were specified as having a low birth weight (< 2500 g), all of whom were exposed to second-generation LAI antipsychotics (3 to aripiprazole, 2 to risperidone, and 2 to paliperidone). The average Apgar scores at 1, 5, and 10 min were 8.9, 9.7, and 9.8, respectively.

Neonatal and developmental outcomes

Admission to a special-care nursery or neonatal intensive care unit was reported in 21 babies (28.4% of 74 live births); 14 and 7 were exposed to first- and second-generation LAI antipsychotics, respectively. One case series[20] reported that pregnant women treated with LAI antipsychotics were more likely to have special care nursery admissions for their babies than the general population, while outcomes were similar for first- and second-generation LAI antipsychotic exposure[20].

Of the five babies who were exposed to fluphenazine LAI, one was born preterm in the 36th week with a normal karyotype but with multiple congenital anomalies (*e.g.*, bilateral cleft lip and palate, imperforate anus, and rectourethral fistula) requiring surgical interventions[36], while two experienced neurological manifestations at 3[37] and 4 wk[38] after

delivery, but afterwards were doing well on follow-up. Neurological manifestations included possible minor extrapyramidal manifestations or withdrawal symptoms, which responded well to diphenhydramine, and this baby was apparently well developed at the 24-month follow-up[37], while the other baby developed symptoms consistent with withdrawal effects (*e.g.*, excessive irritability, choreiform and dystonic movements, jittery behavior, and hypertonicity), which persisted for 9 months and required treatment with diphenhydramine[38]. The baby did not show any abnormalities at the 15-month follow-up[38].

Of the two babies exposed to haloperidol LAI, one[39] developed possible tardive dyskinesia or withdrawal dyskinesia 8 days after birth, which continued until the 14th day of life and was successfully treated with clonazepam.

No significant anomalies or problems were reported in the 14 babies exposed to zuclopenthixol LAI[20,40]. Brain ultrasound revealed clinically insignificant periventricular hyperechogenicity in only one baby, but she was normally developed at the 3.5-year follow-up[40].

Of the nine babies exposed to flupentixol LAI, patent ductus arteriosus was reported only in one baby who was managed conservatively[20].

Of the 23 babies born alive who were exposed to aripiprazole LAI, one[21] experienced postural plagiocephaly and hypertonia during the first 6 wk of life that resolved with physiotherapy (he developed normally during the 3-year follow-up), one[21] remained in the incubator for 1 month due to prematurity (but developed normally during the 2-year follow-up), and one[33] was born preterm with Down's syndrome, developed fetal hydrops complicated by septic shock and massive anuria, and died within 10 d (but this syndrome cannot be considered a drug-induced malformation).

One baby exposed to olanzapine LAI developed normally during the 3-year follow-up[42].

Of the 14 babies exposed to paliperidone LAI, one[34] experienced transient tachypnea that was managed with nasal continuous positive airway pressure (he developed normally during the 12-month follow-up), while another[46] was born with a minor correctable congenital anomaly, bilateral talipes equinovarus, which was managed conservatively (he was otherwise normal and the early postnatal course was uncomplicated). The average maternal plasma concentration of paliperidone in the latter case[46] was 13.8 ng/mL (15 h before delivery, 12.7 ng/mL; 9 h before delivery, 15.0 ng/mL), while the umbilical vein concentration was approximately half of the average maternal concentration (7.3 ng/mL), implying appreciable fetal exposure to the drug. However, it was also noted that the relationship between the baby's bilateral talipes equinovarus and paliperidone exposure is uncertain, considering that antipsychotic drug exposure in pregnancy has not been previously recognized as an association[46].

Of the six babies exposed to risperidone LAI, one[20] had undescended testes and was managed conservatively, while another[47] had intrauterine growth restriction and was born healthy but preterm with bilateral supernumerary nubs/digits on his hands that were removed after birth (this anomaly was a paternal family trait). This child met developmental milestones at 16 months[47].

Ongoing clinical studies

We identified only one currently recruiting study ("Long-acting Injectable Antipsychotics for Mental Ill-Health in Pregnancy and Postpartum" – NCT05766007) that specifically aims to assess safety and clinical outcomes of LAI antipsychotic use during pregnancy and postpartum[50]. This study also aims to determine the magnitude of changes in pharmacokinetics during pregnancy, assess the extent of fetal exposure at delivery, describe breastmilk pharmacokinetics of selected LAI antipsychotics, the extent of breastfed infant exposure, and the sources of variability in maternal and fetal/breastfed infant LAI antipsychotic exposure[50]. The study population includes pregnant and postpartum women aged at least 18 years receiving maintenance doses of LAI antipsychotics (risperidone, paliperidone palmitate, fluphenazine decanoate, flupenthixol decanoate, and zuclopenthixol decanoate)[50]. This observational prospective cohort study is being conducted in Nigeria and is sponsored by the University of Liverpool[50]. The study started on August 01, 2023 and is estimated to be completed in August 2025[50]. The estimated number of participants enrolled is 125[50]. We also found three currently recruiting studies that aim to evaluate outcomes of antipsychotic treatment during pregnancy, but these are not restricted to LAI antipsychotic use: "Maternal And Infant Antipsychotic Study" (NCT06049953)[51] being conducted in the United States since 2023, "National Pregnancy Registry for Psychiatric Medications" (NCT01246765)[52] being conducted in the United States since 2008, and "The National Register of Antipsychotic Medication in Pregnancy" (NCT00686946)[53] being conducted in Australia since 2005.

DISCUSSION

The currently available research on the use of LAI antipsychotics during pregnancy consists only of case reports and series, which are small and not generalizable. It is difficult to adequately interpret the data from these publications because many of the women who were evaluated had concurrent prescriptions for LAI and oral antipsychotics or other medications at some point throughout their pregnancy, and no control group was available for comparison. However, most of the women included in our review (about 64%) either had satisfactory control of the symptoms or no information about relapse, while about 12% had developed gestational diabetes mellitus (mostly on second-generation LAI antipsychotics). It is also important to note that a minority of cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. Stillbirth and spontaneous abortion were reported only during the use of aripiprazole LAI, whereas low birth weight was reported only in newborns exposed to second-generation LAI antipsychotics. Preterm birth was reported with both first- and second-generation LAI antipsychotics. Neurological manifestations in newborns, including possible minor extrapyramidal manifestations, withdrawal symptoms, tardive dyskinesia, and withdrawal dyskinesia, were

reported only for first-generation LAI (fluphenazine and haloperidol). Multiple congenital anomalies, such as bilateral cleft lip and palate, imperforate anus, and rectourethral fistula requiring surgical intervention, were reported in only one baby exposed to fluphenazine LAI. Other reported congenital anomalies were mostly managed conservatively. Only one neonate born preterm and exposed to aripiprazole LAI died 10 d after birth. However, the baby was born with Down's syndrome, which cannot be considered a drug-induced malformation, and developed fetal hydrops, septic shock, and anuria. In addition, no negative long-term developmental outcomes following exposure to LAI antipsychotics during pregnancy were reported.

As previously noted, in terms of the use of LAI formulations in pregnancy as compared to that of oral formulations, there are currently no data in the literature that can be generalized; therefore, whether the risks of LAI antipsychotic use are the same, or more or less concerning, or if there are completely different risks involved compared to those of oral antipsychotics remains unclear[19,32]. However, more constant plasma drug levels associated with the use of LAI formulations may reduce fetal exposure to the highly fluctuating plasma drug levels associated with the use of oral formulations[32,54]. One case series[20] found that pregnant women treated with LAI antipsychotics were more likely to have obstetric complications and special care nursery admission for their babies compared to the general population, and outcomes were similar between first- and second-generation LAI antipsychotic exposure. Determining whether the outcomes are due to illness or medication factors (class of medication or long-acting formulations) remains an ongoing problem in this area[20]. In addition, some studies on the use of oral antipsychotics during pregnancy indicate a possible increased risk for complications like gestational diabetes[55-59], preterm birth[56,60-62], congenital malformations[63-65], withdrawal symptoms[66], and neonatal hospitalization[66-69]. Nevertheless, many of these findings have not been consistent across studies[60,62,70-75]. Furthermore, these studies are inherently confounded by indications as most have examined the use of medications during pregnancy[19,76]. It is also difficult to distinguish the effects of maternal illness from those of antipsychotic medications because there is documented evidence that the offspring of women with psychotic illness are highly likely to be at an increased risk of adverse outcomes due to higher rates of smoking, alcohol consumption, illicit substance use, maternal obesity, and reduced serum folate levels related to low dietary vitamin intake [77-80].

Another interesting observation in our review was that stillbirth and spontaneous abortion were only reported with the use of aripiprazole LAI. However, no causal relationship between these adverse pregnancy outcomes and the use of aripiprazole LAI could be established based on these data. One large nationwide cohort study found that women exposed to oral antipsychotics during pregnancy had a 34% higher risk of spontaneous abortion than unexposed women; however, the risk was similar to that in women exposed before (but not during) pregnancy[81]. In addition, the risk did not increase in exposed pregnancies compared with unexposed pregnancies in the same women[81]. Risk estimates were also rather similar for several types of antipsychotic medications, but the confidence intervals were wide, and the numbers were too small to perform adjusted analyses for most drugs[81]. Previous smaller studies did not find an increased risk of spontaneous abortion after prenatal exposure to atypical antipsychotics[82,83], therefore, the authors suggested that the overall higher risk of spontaneous abortion initially observed could be due to factors related to the underlying disease rather than antipsychotic medications[81]. In contrast, in the same study, the risk of stillbirth was twofold higher in pregnancies exposed to antipsychotics; however, owing to the small number of cases, they could not simultaneously adjust for multiple confounders[81]. A previous study found that the number of stillbirths was within the reference range (0 in 561 pregnant women exposed to second-generation antipsychotics and 2 in 284 pregnant women exposed to first-generation antipsychotics)[82].

Although most of the women included in our review (approximately 64%) either had satisfactory control of symptoms or no information about relapse, one case series[20] reported that pregnant women treated with LAI antipsychotics had elevated rates of psychiatric admissions during pregnancy and statutory child protection involvement, suggesting potential destabilization in the mental state associated with pregnancy or compounding psychosocial comorbidities[20].

For women on LAI antipsychotic treatment who become pregnant, it can be difficult to decide whether to continue with LAI or to switch to an oral form of the same antipsychotic, particularly considering that the discontinuation of antipsychotics during pregnancy is linked to an increased risk of bipolar and schizophrenia episode recurrence[84]. Each situation needs to be individually weighed on a case-by-case basis, and clinicians should plan, evaluate, and tailor treatment and management strategies during pregnancy, considering the patient's medical history, current treatment, and symptomatology[32]. Further well-designed research (*e.g.*, prospective longitudinal, observational, and database studies) is needed to properly evaluate the risks and benefits of continuing LAI *vs* switching to oral antipsychotics[19,32]. A shared large database, i.e., registers, for monitoring outcomes of mothers and their children over time could make significant progress in this area, and clinicians could incorporate planned longitudinal follow-up following discharge in their clinical practice to systematically collect all clinical variables of newborns exposed to LAI antipsychotics during pregnancy and the postpartum mental health status of women[32]. Our review identified only one ongoing observational prospective cohort clinical study conducted with the specific aim of assessing the safety and clinical outcomes of LAI antipsychotic use during pregnancy[50]. We hope that this study will provide further insights into the risks and benefits of LAI antipsychotic use during pregnancy.

CONCLUSION

Most of the women included in our review had either satisfactory symptom control or no information about relapse. A minority of the cases reported adverse outcomes, such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns, and there were no reported negative long-term

developmental outcomes. Further well-designed studies are required to evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

ARTICLE HIGHLIGHTS

Research background

Long-acting injectable (LAI) antipsychotics have been widely used to improve adherence and prevent relapse in patients with various severe psychotic disorders, but there is a lack of high-quality data from previous research on the safety of LAI antipsychotics during pregnancy.

Research motivation

Considering that previous reviews on this topic included only selected cases published before January and March 2021, respectively, and that several case reports/series reporting outcomes of pregnancy in women using LAI antipsychotics were published in the meantime or were published earlier but not included in previous reviews, there is a need for an updated review.

Research objectives

We aimed to provide an up-to-date summary of the relevant data on maternal, pregnancy, neonatal, and developmental outcomes from available published cases of LAI antipsychotic use in pregnancy.

Research methods

A literature search was performed through November 11, 2023, using three online databases: PubMed/MEDLINE, Scopus, and Web of Science. Case reports or case series that reported information about the outcomes of pregnancy in women who used LAI antipsychotics at any point in pregnancy, with available full texts, were included. Descriptive statistics, narrative summation, and tabulation of the extracted data were performed.

Research results

A total of 19 publications satisfied the inclusion criteria: 3 case series, 15 case reports, and 1 conference abstract. They reported the outcomes of LAI antipsychotic use in 74 women and 77 pregnancies. Most of the women (approximately 64%) had either satisfactory control of symptoms or no information about relapse. A minority of cases reported adverse outcomes such as stillbirth, spontaneous abortion, preterm birth, low birth weight, congenital anomalies, and neurological manifestations in newborns. However, there were no reports of negative long-term developmental outcomes.

Research conclusions

Currently available data seem reassuring, given that most of the women seemed to have satisfactory control of the symptoms and that a minority of the cases reported adverse outcomes.

Research perspectives

Considering that the currently available research consists only of case reports and series, additional well-designed studies are needed to properly evaluate the risks and benefits of LAI antipsychotic use during pregnancy.

FOOTNOTES

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Country/Territory of origin: Serbia

ORCID number: Ana V Pejčić 0000-0003-1741-0025; Srdjan M Stefanović 0000-0003-2206-2037; Miloš N Milosavljević 0000-0002-1786-1507; Vladimir S Janjić 0000-0001-6072-085X; Marko M Folić 0000-0002-0807-3488; Nevena D Folić 0000-0001-9494-881X; Jovana Z Milosavljević 0000-0001-9660-6709.

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