ORIGINAL ARTICLE

SUICIDAL IDEATION IN DEPRESSED PATIENTS AND THERAPEUTIC ROLE OF VORTIOXETINE: SECONDARY ANALYSIS OF A LARGE PROSPECTIVE STUDY

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ABSTRACT

OBJECTIVE
To explore the association of different variables and the role of Vortioxetine in managing suicidal ideation in patients suffering from depression in Pakistan.

STUDY DESIGN
This is a secondary-analysis of a large, multi-centre, non-interventional, prospective longitudinal study with patients who were prescribed Vortioxetine.

PLACE AND DURATION OF THE STUDY
The main study was conducted in 16 Psychiatry outpatient clinics in eight cities across Pakistan. The period of study was August 2019 to June 2020.

SUBJECTS AND METHODS
A total of 498 depressed patients aged 18- 65 years participated in the study. Suicidal ideation was measured using item number 9 of the Patient Health Questionnaire (PHQ-9). Participants were assessed at baseline, 1 week, 1-month and 3-month after treatment initiation.

RESULTS
There was statistically significant reduction in reporting of suicidal ideation from 80% at baseline to 13% at outcome assessment. There was significant positive correlation between suicidal ideation and cognitive dysfunction on Perceived Deficits Questionnaire (PDQ) and suicidal ideation and depression scores on PHQ-9. There was a statistically significant difference between those who reported suicidal ideation and those who did not report suicidal ideation on the clinical global impression-severity scale both at baseline and at 3-month outcome assessment.

CONCLUSION
Suicidal ideation is common in depressed patients and this study demonstrated that suicidal ideation was reduced significantly with Vortioxetine treatment. Future research is warranted to further confirm the findings with controlled groups.

KEY WORDS
Suicidal ideations, Vortioxetine, Depression, Pakistan, Low Income Country.

INTRODUCTION

In 2015, the total number of individuals suffering from Major Depressive Disorder (MDD) was reported to be over 300 million globally.[1] There are enormous consequences of MDD in terms of lost health.[1] The World Health Organisation (WHO) has ranked it as the enormous contributor to global disability (7.5% of all years lived with disability) and is highly associated with social and occupational functional impairment.[1] MDD is a huge contributor to suicide deaths with approximately 700,000 cases per year, and most of these take place in Low and Middle Income Countries (LMICs).[2] Suicide rates in South Asia are high and suicide data from many of these countries are lacking and the available data are not reliable.[3,4] Suicide related data are officially not available from Pakistan. Both attempted and completed suicide are considered illegal acts, prohibited in the Muslim religion and socially condemned.[5] However, the evidence indicates that over the last few years, suicide rates have been gradually increasing in Pakistan with huge economic implications.[4,5]

Suicidal ideation (SI) is one of the major predictors of suicidal attempt and later suicide.[6,7] Evidence suggests that this risk is highest in patients who reported frequent thoughts of death or self-harm (on PHQ-9), they were six times more probable to attempt suicide and 5 times more likely to die by suicide in the following year than those who did not report such thoughts.[8]

Significant advancements are made to treat depressive disorder such as antidepressants and psychosocial interventions over the past five decades, leading to improved outcomes.[9,10] A number of antidepressants are available including tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs).[11] However, effective pharmacological treatments for patients with suicidal behaviours are limited; only one psychiatric medication clozapine is FDA-approved for suicidal behaviour. In a

recent review of clinical trials, it was reported that approximately 75% of the included studies excluded individuals with "clinically significant" suicidal ideation.[12,13]

Despite the extensive use of antidepressants, there is dispute that in some patients they can be linked with high risk of suicide. However, findings from a meta-analysis does not confirm this in individuals with generalized anxiety disorder (GAD) and MDD due to use of antidepressant.[14] Rather, evidence suggests antidepressant therapy reduces the risk of suicide in MDD patients.[15,16] A recent evidence shows that SI is rare among depressed patients treated with Vortioxetine.[17] Moreover, despite high prevalence of depression in LMICs, most patients with depression receive little to no treatment.[18] This massive treatment gap in Pakistan is also associated with the scarcity of mental health professionals, due to which over 90% of individuals with common mental disorders remain untreated.[19]

This study is the secondary analysis of a multi-centre prospective longitudinal study to assess how the severity of suicidal ideation varies depending on sociodemographic and psychological factors and the role of Vortioxetine in reducing suicidal ideation in depressed patients in Pakistan.

SUBJECTS AND METHODS

Design

This study is a secondary analysis of a large, multi-centre, non-interventional, prospective longitudinal study with patients who are prescribed Vortioxetine for Major Depressive Disorder.[20] The secondary analysis involved use of existing data from the previously completed study in Pakistan. This method has been used in a number of published studies and is an increasingly popular method.[21]

Study Sites

Participants for the main study were recruited from 16 collaborating outpatient departments (OPDs) of psychiatric units in seven cities (Karachi, Lahore, Multan, Faisalabad, Rawalpindi, Peshawar and Quetta) across Pakistan and the state of Azad Jammu and Kashmir.

Participants

A total of 498 participants meeting following eligibility criteria were included in the study;

Inclusion Criteria

- Meet DSM-5 clinical diagnosis of MDD (active episode) at the time of recruitment.
- Aged between 18-65 years.
- Prescribed Vortioxetine by their treating psychiatrist.

Exclusion Criteria

- Patients with concurrent or past history of Schizophrenia or other psychoses, substance or alcohol dependence, Bipolar disorder, Dementia or any other neurodegenerative disease, any mental disorder due to a general medical condition (GMC) or psychoactive substances.
- Patients having any physical health condition that could lead to cognitive dysfunction (e.g., head trauma) and chronic illnesses (such as hypertension, diabetes mellitus, anaemia, cerebrovascular accident and epilepsy etc.)
- Patient is part of the study team or of their immediate families, or is working under any study team member.
- Patients not ready to take medication or treatment on clinical evaluation by the psychiatrist.

Assessment Measures

Socio-demographics: Sociodemographic data, i.e. age, gender, marital status, living status and work status was collected using structured questionnaire. We also collected psychological variables such as previous history of self-harm, whether current episode of MDD is first episode or not etc.

PHQ-9[22]: The PHQ-9 is extensively used scale for depression severity. It is a self-administered questionnaire for depression that monitors the severity and response to treatment from the patients' perspective. It has 9 items scored as (0-not at all) to (3-nearly every day). Item number 9 of this scale assessed suicidal ideation. Total scores are computed based on how a patient is experiencing these feelings. A score of 10 or above is taken as cut-off point for depressive disorder.

Perceived Deficits Questionnaire (PDQ)[23]: It is a brief scale used to assess cognitive dysfunction in individuals with depression. The items focus on everyday situations where cognitive dysfunction can occur. It takes about 5-10 minutes to complete. It provides insights into several domains of cognitive dysfunction.

Sheehan Disability Scale (SDS)[24]: The SDS aims to assess the functional impairment of family life/home responsibilities, work/school and social life.

Clinical Global Impression-Improvement (CGI-I) Scale[25]: It is a seven-point clinician/researcher administered treatment response scale. Clinicians assess patients based on their past experience with the patient and rate the severity of illness in response to the treatment to see the improvement.

Detailed measures are reported in the main published study.[20]

Procedure

The study got full ethics approval from the Research and Ethics Committee, Rawalpindi Medical University, Pakistan (Ref R-47/RMU). Detailed procedures are described elsewhere.[19] A comprehensive participant information leaflet (PIL) was provided to all eligible patients, and a written informed consent was taken from all participants, while informed thumb impression consent was taken for

participants who were unable to read or write. The research team was trained in the Good Clinical Practice (GCP). The treating consultants assessed all eligible consented patients (n = 498) for enrolment in the study. To maintain uniformity in terms of administration of questionnaires, trained researchers read the questions to patients and recorded their response accordingly. After assessment and enrolment in the study, the medication for the study treatment period was provided to the participants (free of cost). Assessments were done at baseline, 1 week (+/- 3 days), 1-month (+/- 7 days) and 3-month (+/- 14 days) after treatment initiation.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) (V23.0) was used to carry out the analysis. This secondary analysis only used data of those participants who reported presence of SI on item number 9 of the PHQ-9 at baseline assessment. Chi-square analysis was used to assess the association between frequency of SI and gender, marital status etc. and SI. Frequencies and percentages were computed for participants reporting SI at baseline, follow-up 1, 2 and 3 (outcome).

RESULTS

No significant differences were found at baseline in sociodemographic data and history of illness related variables between those who reported SI and those who did not report suicidal ideation (Table 1). Out of 498 patients, 402 reported suicidal ideations, the percentage of male (50.5%) and female (49.5%) was almost the same. A higher percentage of married/divorced participants (72.8%) reported presence of suicidal ideation as compared to participants who were single (27.1%). Seventy eight percent of participants who reported suicidal ideation had never attempted suicide in the past, and for 46% it was their first episode of depressive illness.

Table 1
Demographic and History of illness related variations at baseline.

Suicidal ideation in the last 15 days	No (96) n	%	Yes (402) n	%	Sign. Value
Gender					
Male	52	54.2	203	50.5	.570
Female	44	45.8	199	49.5	
Marital Status					
Single	25	26.0	109	27.1	.908
Married/Divorced	71	74.0	293	72.8	
Has the patient ever attempted suicide?					
Yes	03	8.6	40	21.2	.102
No	32	91.4	149	78.8	
Status of current depressive episode					
Multiple episodes	61	63.5	217	54.0	.109
First episode	35	36.5	185	46.0	

Table 2
Frequency Analysis of change in number of patients reporting Suicidal Ideation from Baseline to 3-month Outcome assessment.

Suicidal ideation in the last 15 days	No n	%	Yes n	%
Baseline (n=498)	96	19.3	402	80.7
Follow-up-1 (n=473)	152	32.1	321	67.9
Follow-up-2 (n=456)	265	58.1	191	41.9
3-month Outcome (n=416)	362	87.0	54	13.0

Table 3
Spearman association of suicidal ideation and cognitive dysfunction (Perceived Deficits Questionnaire - PHQ-9) and depression upon treatment with Vortioxetine.

Time point	n	Correlation b/w suicidal ideation and PDQ-D	Correlation b/w suicidal ideation and PHQ-9 total score
Baseline	498	.219**	.452**
FU 1	473	.344**	.520**
FU 2	456	.394**	.534**
3-month outcome assessment	416	.450**	.494**

** Correlation is significant at the 0.01 level (2-tailed).

Table 4
Chi-Square Association between suicidal ideation and CGI - Severity categories.

Suicidal ideation in the last 15 days	No (96) n	%	Yes (402) n	%	p-value
CGI - Severity at baseline					
Normal	-	-	-	-	
Borderline + Mild (n=10)	5	50.0	5	50.0	
Moderate (n=127)	43	33.9	84	66.1	.000
Markedly ill + Severely ill (N=324)	47	14.2	293	85.8	
Extremely ill (n=21)	1	4.8	20	95.2	
CGI - Severity at Outcome	**No (362)**		**Yes (54)**		
Normal (n=117)	114	97.4	3	2.6	
Borderline + Mild (n=264)	235	90.3	29	9.7	
Moderate (n=32)	11	34.4	21	65.6	.000
Markedly ill + Severely ill (n=2)	1	50.0	1	50.0	
Extremely ill (n=1)	1	100.0	-	-	

At the baseline, 80% of the 498 participants were expressing suicidal ideation. This was reduced significantly to 13%, with only 54 participants, at the outcome assessment (Table 2).

There was significant positive correlation between SI and cognitive dysfunction (assessed through the Perceived Deficits Questionnaire and PHQ-9) at baseline, over 1, 2 and 3-month outcome assessment. Similarly, there was significant positive correlation between SI and depression scores on PHQ-9 at baseline, over 1, 2 and 3-month outcome assessment analysed using Spearman correlation coefficient (Table 3).

There was a significant difference between those who reported SI and those who did not report SI on the CGI-severity scale both at baseline and at 3-month outcome assessment (Table 4). Among the participants rated as

Table 5
Chi-Square Cross tabulation of suicidal ideation and improvement categories of CGI at 3-month outcome assessment.

Suicidal Ideation	No (362)		Yes (54)		p-value
	n	%	n	%	
CGI - Improvement					
Much improved andvery much improved (n = 381)	342	87.3	39	12.7	
Minimally improved (n = 29)	16	55.2	13	44.8	
No change (n = 2)	2	100.0	-	-	.000
Minimally worse (n = 2)	-	-	2	100.0	
Much worse and very much worse (n = 2)	2	100.0	-	-	

Table 6
Pearson Correlation of suicidal ideation and Sheehan Disability Scale (SDS).

Time point	n	Correlation b/w suicidal ideation and SDS total score
Baseline	498	.171**
FU 1	473	.272**
FU 2	456	.393**
3-month outcome assessment	416	.403**

** Pearson Correlation is significant at the 0.01 level (2-tailed).

markedly or severely ill (n = 324) by the clinicians at baseline assessment, most of them (n = 293) reported presence of suicidal ideation. There were very few participants who were rated as extremely ill (n = 21) by the clinicians at baseline assessment and amongst these all except one reported presence of SI. At 3-month outcome assessment, amongst participants who were rated as borderline and mildly ill (n = 264), only 29 participants reported presence of suicidal ideation while among those who were rated as moderately ill (n = 32) by the clinicians at 3-month outcome assessment, 21 participants reported presence of suicidal ideation.

The difference between those who reported SI and those who did not, was statistically significant on CGI-improvement categories at 3-month outcome assessment (Table 5). Amongst those who were rated as much and very much improved (n = 381), 87.3% of them reported absence of SI however, only 12.7% still reported presence of SI. There were a small number of participants who were rated as minimally improved (n = 29) by the clinicians at 3-month outcome assessment, among those 55.2% reported absence while 44.8% reported presence of SI.

There was significant positive correlation as measured using Pearson correlation method in improvement in suicidal ideation and improvement in social functioning as measured on Sheehan disability scale (Table 6).

DISCUSSION

Being married[4] and loss of marital relationship[26] are reported as risk factors of suicidal behaviours including suicidal ideation. Similar trends were observed in the present study. In this study we found no differences between male and female patients in terms of presence of SI and this is also supported by a previous research evidence.[27] Similar to the current study, the previous evidence also showed that rates of suicidal ideation were high among patients with a single episode of MDD.[27] In the current study, a higher number of participants with no previous history of suicide attempt reported presence of suicidal ideation, which is contradictory with existing established evidence of history of suicide behaviour predicting future suicide behaviour.[28] This discrepancy between current and established evidence may be because the number of participants with previous history of suicide attempt was very small (n = 43) as compared to those with no previous history of suicide attempt (n = 181), Therefore, this may warrant further investigation in this population.

It was evident from the findings that frequency of suicidal ideation was high among those with more severe illness at baseline and this frequency decreased as the severity of illness decreased at outcome assessment. Suicidal ideation is a core symptom of depression.[29,30] Suicidal ideation is reported to have a strong correlation with severity of depressive illness.[31] This finding may suggest that the description of severity of depressive illness should include suicidal behaviours. The association between severity of depressive illness and presence of suicidal ideation may be explained by predisposing risk factors that are common to both depression and suicidal ideation such as interpersonal factors,[32-34] stressful life events,[35-38] or psychological vulnerabilities including low self-efficacy,[39,40] neuroticism,[41,42] and high rumination.

Neurocognitive impairment has been reported as a risk factor for suicidal behaviour[43] and can lead to poor decision making and an increased risk of suicide because of an unhealthy appraisal of one's life.[44] Cognitive dysfunction has been found in people with a previous suicide attempts[45] and with active current SI[46]. The present study reported a strong association between cognitive dysfunction and SI in depressed patients at all assessment points. A laboratory study reported an association between neural activity in the prefrontal cortex and suicidal thoughts.[47] The prefrontal cortex is responsible for information processing such as the ability for selective attention to the information, inhibiting irrelevant stimuli, and evaluation of appropriate response, therefore, the presence of suicidal thoughts could reflect cognitive rigidity within the executive domain.[45]

The main study highlighted the efficacy of Vortioxetine for managing severity of illness,[20] and findings from this secondary analysis indicate the therapeutic role of Vortioxetine for suicidal ideation in depressed population. The existing evidence also supports that the higher use of antidepressant treatment is correlated with lower suicide

rates.[48] The major challenge with clinical trials is that most of these trials (75%) exclude patients reporting clinically significant suicidal ideation.[12] A recent systematic review has highlighted that following the year 2000 (compared to a decade before 2000), suicidal behaviours and rates of completed suicide have significantly decreased in clinical trials testing antidepressants.[49]

A very important finding from this study was that at 3-month outcome assessment, though the participants' illness was rated as borderline and mild by their treating clinician, 9.7% of these participants still reported presence of suicidal ideation. Similarly, on CGI-improvement among those who were rated as much and very much improved, 12.7% still reported presence of suicidal ideation. This finding may be explained by existing evidence that some clusters of symptoms of depression have more strong association with suicidal ideation than others.[50] In addition, evidence from RCTs also suggest that suicidal ideation does not always remit with successful treatment of depression.[51] Hence, this indicates that suicidal ideation may occur independently of depression and warrants regular risk assessment of patients who are presenting for follow-up care.

Limitations

There are some limitations of the present study that must be acknowledged, including that a self-report measure was used for assessment of suicidal ideation and as the focus was on depression, the study was not powered to investigate trajectories of suicidal ideation.

CONCLUSION

In conclusion, this study contributes to the existing literature on suicidal ideation in depressed individuals by highlighting high rates of suicidal ideation in depressed population and how Vortioxetine can benefit to manage suicidal ideation. Inquiring about suicidal ideation is fundamental to health professionals, as it is not only a significant predictor of future suicide but also patients who express suicidal ideation are trying to communicate about their inner world and level of distress. Suicidal ideation may persist for longer periods and make people with mental health problems more vulnerable. Therefore, it is hugely important to test innovative solutions to manage suicidal ideation.

Declaration of Interests

Nasim Chaudhry and Imran B. Chaudhry (IBC) report giving lectures and advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, AstraZeneca, and Janssen pharmaceuticals, for which they or their employing institution have been reimbursed. IBC reports previously being trustees of the Pakistan Institute of Living and Learning. All other authors declare no competing interests.

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REFERENCES

1. World Health Organization. Depression and other common mental disorders: global health estimates. World Health Organization; 2017.
2. World Health Organization. WHO. Suicide worldwide in 2019: global health estimates. 2021.
3. Jordans MJ, Kaufman A, Brenman NF, Adhikari RP, Luitel NP, Tol WA, Komproe I. Suicide in South Asia: a scoping review. BMC psychiatry. 2014; 14(358):1-9.
4. Shekhani SS, Perveen S, Hashmi SD, Akbar K, Bachani S, Khan MM. Suicide and deliberate self-harm in Pakistan: a scoping review. BMC psychiatry. 2018; 18(44):1-5.
5. Shahid M, Hyder AA. Deliberate self-harm and suicide: a review from Pakistan. Int J Inj Contr Saf Promot. 2008; 15(4):233-41.
6. Gelaye B, Kajeepeta S, Williams MA. Suicidal ideation in pregnancy: an epidemiologic review. Arch Womens Ment Health . 2016; 19(5):741-51.
7. Klonsky ED, May AM, Saffer BY. Suicide, suicide attempts, and suicidal ideation. Annu Rev Clin Psychol. 2016; 12:307-30.
8. Rossom RC, Coleman KJ, Ahmedani BK, Beck A, Johnson E, Oliver M, Simon GE. Suicidal ideation reported on the PHQ9 and risk of suicidal behavior across age groups. J Affect Disord. 2017; 215:77-84.
9. Yuan Z, Chen Z, Xue M, Zhang J. Application of antidepressants in depression: A systematic review and meta-analysis. J Clin Neurosci. 2020; 80(Suppl 1): 169-181.
10. Santoft F, Axelsson E, Öst LG, Hedman-Lagerlöf M, Fust J, Hedman-Lagerlöf E. Cognitive behaviour therapy for depression in primary care: systematic review and meta-analysis. Psychol Med. 2019; 49(8):1266-74.
11. Furukawa TA, Salanti G, Atkinson LZ, Leucht S, Ruhe HG, Turner EH, Chaimani A, Ogawa Y, Takeshima N, Hayasaka Y, Imai H, Shinohara K, Suganuma A, Watanabe N, Stockton S, Geddes JR, Cipriani A. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. BMJ. 2016; 6(7): 1-10.
12. Zimmerman M, Clark HL, Multach MD, Walsh E, Rosenstein LK, Gazarian D. Have treatment studies of depression become even less generalizable? A review of the inclusion and exclusion criteria used in placebo-controlled antidepressant efficacy trials published during the past 20 years. Mayo Clin Proc. 2015; 90(9):1180-6
13. Zimmerman M, Balling C, Chelminski I, Dalrymple K. Have treatment studies of depression become even less generalizable? Applying the inclusion and exclusion criteria in placebo-controlled antidepressant efficacy trials published over 20 years to a clinical sample. Psychother Psychosom. 2019; 88(3):165-70.
14. Thase ME, Gommoll C, Chen C, Kramer K, Khan A, Durgam S. Measures of suicidality in phase 3 clinical trials of levomilnacipran ER in adults with major depressive disorder. CNS spectr. 2017; 22(6):475-83.
15. Kasper S, Montgomery SA, Möller HJ, van Oers HJ, Jan Schutte A, Vrijland P, van der Meulen EA. Longitudinal analysis of the suicidal behaviour risk in short-term placebo-

controlled studies of mirtazapine in major depressive disorder. World J Biol Psychiatry. 2010; 11(1):36-44.
16. Cheung K, Aarts N, Noordam R, van Blijderveen JC, Sturkenboom MC, Ruiter R, Visser LE, Stricker BH. Antidepressant use and the risk of suicide: a population-based cohort study. J Affect Disord. 2015; 174: 479-84.
17. Inoue T, Sasai K, Kitagawa T, Nishimura A, Inada I. Randomized, double-blind, placebo- controlled study to assess the efficacy and safety of vortioxetine in Japanese patients with major depressive disorder. Psychiatry Clin Neurosci. 2020; 74(2):140-8.
18. World Federation For Health . Depression: A Global Crisis World Mental Health Day. 10 Oct, 2012; 6-7.
19. 19. Sikander S. A letter from... Pakistan. Elsevier Sci Ltd The Boulevard, Langford Lane, Kidlington, Oxford Ox5 1gb. 2020; 845-845.
20. Minhas FA, Rana RZ, Rana MH, Hamdani U. Impact of Vortioxetine on Severity, Cognitive Dysfunctions, And Functionality In Patients With Major Depression: A Real World Experience From Pakistan. J Pak Psychiatr Soc. 2021; 18(01): 22-33.
21. Cheng HG, Phillips MR. Secondary analysis of existing data: opportunities and implementation. Shanghai arch psychiatry. 2014; 26(6): 371-5.
22. Arroll B, Goodyear-Smith F, Crengle S, Gunn J, Kerse N, Fishman T, Falloon K, Hatcher S. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. Ann Fam Med. 2010; 8(4):348-53.
23. Lam RW, Lamy FX, Danchenko N, Yarlas A, White MK, Rive B, Saragoussi D. Psychometric validation of the Perceived Deficits Questionnaire-Depression (PDQ-D) instrument in US and UK respondents with major depressive disorder. europsychiatr Dis Treat. 2018; 14: 2861- 77.
24. Leon AC, Olfson M, Portera L, Farber L, Sheeehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int J psychiatry Med. 1997; 27(2): 93-105.
25. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007; 4(7): 28-37.
26. Dutta R, Ball HA, Siribaddana SH, Sumathipala A, Samaraweera S, McGuffin P, Hotopf M. Genetic and other risk factors for suicidal ideation and the relationship with depression. Psychol Med. 2017; 47(14):2438-49.
27. Fang X, Zhang C, Wu Z, Peng D, XIA W, XU J, Wang C, CUI L, Huang j, Fang Y. The association between somatic symptoms and suicidal ideation in Chinese first-episode major depressive disorder. J Affect Disord. 2019; 245:17-21.
28. Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. J Clin psychiatry. 2013; 74(9):887-93.
29. Brunoni AR, Nunes MA, Lotufo PA, Benseñor IM. Acute suicidal ideation in middle-aged adults from Brazil. Results from the baseline data of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Psychiatry Res. 2015; 225(3):556-62.
30. Akram U, Ypsilanti A, Gardani M, Irvine K, Allen S, Akram A, Drabble J, Bickle E, Kaye L, Lipinski D, Matuszyk E, Sarlak H, Steedman E, Lazuras L. Prevalence and psychiatric correlates of suicidal ideation in UK university students. J Affect Disord. 2020; 272:191-7.
31. Zimmerman M, Balling C, Chelminski I, Dalrymple K. Understanding the severity of depression: which symptoms of depression are the best indicators of depression severity?. Compr Psychiatry. 2018; 87:84-8.
32. Mackintosh K, Power K, Schwannauer M, Chan SW. The relationships between self-compassion, attachment and interpersonal problems in clinical patients with mixed anxiety and depression and emotional distress. Mindfulness (NY). 2018; 9 (3):961-71.
33. Kyron MJ, Hooke GR, Page AC. Daily assessment of interpersonal factors to predict suicidal ideation and non-suicidal self-injury in psychiatric inpatients. J Consult Clin Psychol. 2018; 86(6):556-67
34. Husain MO, Umer M, Taylor P, Chaudhry N, Kiran T, Ansari S, Chaudhry IB, Husain N. Demographic and psychosocial characteristics of self-harm: The Pakistan perspective. Psychiatry Res. 2019; 279:201-6.
35. Fakhari A, Farahbakhsh M, Azizi H, Esmaeili ED, Mirzapour M, Rahimi VA, Hashemi L, Gaffarifam S. Early marriage and negative life events affect on depression in young adults and adolescents. Arch Iran Med. 2020; 23(2):90-8.
36. Husain N, Parveen A, Husain M, Saeed Q, Jafri F, Rahman R, Tomenson B, Chaudhry IB. Prevalence and psychosocial correlates of perinatal depression: a. cohort study from urban Pakistan. Arch women's mental health. 2011; 14(5):395-403.
37. Blalock DV, Young KC, Kleiman EM. Stability amidst turmoil: Grit buffers the effects of negative life events on suicidal ideation. Psychiatry Res. 2015; 228(3):781-4.
38. Howarth EJ, O'Connor DB, Panagioti M, Hodkinson A, Wilding S, Johnson J. Are stressful life events prospectively associated with increased suicidal ideation and behaviour? A systematic review and meta-analysis. JAffect Disord. 2020; 266:731-42.
39. Christensen H, Batterham PJ, Mackinnon AJ, Donker T, Soubelet A. Predictors of the risk factors for suicide identified by the interpersonal-psychological theory of suicidal behaviour. Psychiatry Res. 2014; 219(2):290-7.
40. Liu D, Zhou Y, Li G, He Y. The factors associated with depression in schizophrenia patients: the role of self-efficacy, self-esteem, hope and resilience. Psychol health Med. 2020; 25(4):457-69.
41. Adams MJ, Howard DM, Luciano M, Clarke TK, Davies G, Hill WD, Smith D, Deary IJ, Porteous DJ, McIntosh AM, 23andMe Research Team. Genetic stratification of depression by neuroticism: revisiting a diagnostic tradition. Psychol Med. 2020; 50(15):2526-35.
42. Stefa Missagli S, Unterrainer HF, Giupponi G, Holasek SJ, Kapfhammer HP, Conca A, Sarlo M, Erbuto D, Rogante E, Moujaes Droescher H, Davok K, Berardelli I, Krysinska K, Andriessen K, Lester D. Suicide and personality traits: a multicenter study of Austrian and Italian psychiatric patients and students. Suicide Life Threat Behav. 2020; 50(1):220-32.
43. Gorlyn M, Keilp J, Burke A, Oquendo M, Mann JJ, Grunebaum M. Treatment-related improvement in neuropsychological functioning in suicidal depressed patients: paroxetine vs. bupropion. Psychiatry Res. 2015; 225(3):407-12.
44. McGirr A, Dombrovski AY, Butters MA, Clark L, Szanto K. Deterministic learning and attempted suicide among older depressed individuals: cognitive assessment using the Wisconsin Card Sorting Task. J psychiatr Res. 2012 Feb 1; 46(2):226-32.
45. Ho MC, Hsu YC, Lu ML, Gossop M, Chen VC. 'Cool'and

'Hot'executive functions in suicide attempters with major depressive disorder. J Affect Disord. 2018; 235:332-40.
46. Pu S, Setoyama S, Noda T. Association between cognitive deficits and suicidal ideation in patients with major depressive disorder. Sci Rep. 2017; 7(1):1-6.
47. Pu S, Nakagome K, Yamada T, Yokoyama K, Matsumura H, Yamada S, Sugie T, Miura A, Mitani H, Iwata M, Nagata I. Suicidal ideation is associated with reduced prefrontal activation during a verbal fluency task in patients with major depressive disorder. J Affect Disord. 2015; 181:9-17.
48. Gibbons RD, Hur K, Bhaumik DK, Mann JJ. The relationship between antidepressant medication use and rate of suicide. Arch Gen psychiatry. 2005; 62(2):165-72.
49. Khan A, Mar KF, Gokul S, Brown WA. Decreased suicide rates in recent antidepressant clinical trials. Psychopharmacology (Berl). 2018; 235(5):1455-62.
50. Keilp JG, Ellis SP, Gorlyn M, Burke AK, Oquendo MA, Mann JJ, Grunebaum MF. Suicidal ideation declines with improvement in the subjective symptoms of major depression. J Affect Disord. 2018; 227:65-70.
51. Christensen H, Farrer L, Batterham PJ, Mackinnon A, Griffiths KM, Donker T. The effect of a web-based depression intervention on suicide ideation: secondary outcome from a randomised controlled trial in a helpline. BMJ open. 2013; 3(6):1-9.

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