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. There are enormous consequences of MDD in terms of lost health. 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. 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). Suicide rates in South Asia are high and suicide data from many of these countries are lacking and the available data are not reliable. 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. However, the evidence indicates that over the last few years, suicide rates have been gradually increasing in Pakistan with huge economic implications.

Suicidal ideation (SI) is one of the major predictors of suicidal attempt and later suicide. 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.

Significant advancements are made to treat depressive disorder such as antidepressants and psychosocial interventions over the past five decades, leading to improved outcomes. 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). 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.\textsuperscript{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.\textsuperscript{14} Rather, evidence suggests antidepressant therapy reduces the risk of suicide in MDD patients.\textsuperscript{15,16} A recent evidence shows that SI is rare among depressed patients treated with Vortioxetine.\textsuperscript{17} Moreover, despite high prevalence of depression in LMICs, most patients with depression receive little to no treatment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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)\textsuperscript{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)\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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

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
Being married and loss of marital relationship are measured on Sheehan disability scale (Table 6).

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 **

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).

The main study highlighted the efficacy of Vortioxetine for managing severity of illness, 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.

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** Table 5 **

<table>
<thead>
<tr>
<th>CGI - Improvement</th>
<th>No (362)</th>
<th>Yes (54)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Much improved and very much improved (n = 381)</td>
<td>342</td>
<td>87.3</td>
<td>39</td>
</tr>
<tr>
<td>Minimally improved (n = 29)</td>
<td>16</td>
<td>55.2</td>
<td>13</td>
</tr>
<tr>
<td>No change (n = 2)</td>
<td>2</td>
<td>100.0</td>
<td>-</td>
</tr>
<tr>
<td>Minimally worse (n = 2)</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Much worse and very much worse (n = 2)</td>
<td>2</td>
<td>100.0</td>
<td>-</td>
</tr>
</tbody>
</table>

** Table 6 **

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

** Pearson Correlation is significant at the 0.01 level (2-tailed). **
The major challenge with clinical trials is that most of these trials (75%) exclude patients reporting clinically significant suicidal ideation. 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.

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. In addition, evidence from RCTs also suggest that suicidal ideation does not always remit with successful treatment of depression. 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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