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Addresses

Editorial office
Dr. Shahul Ameen
St. Thomas Hospital, Kurisummoodu PO,
PIN - 686 104, Kottayam Dt., Kerala, India
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Guest Editorial

Do Asians Patients Require Only Half of the Clozapine Dose Prescribed for Caucasians? A Critical Review

The article by de Leon *et al*.[1] raises several important issues regarding treating Asian patients with clozapine. Historically and traditionally, physicians have prescribed antipsychotic drugs by starting with low doses and slowly increasing the dose based upon the patient's individual response and balancing adverse side effects. The "start low and go slow" approach continues to be used by prescribers independent of the patient's ethnic background. Over the last 30 years, significant medical developments occurred that influence regulatory agencies today, affecting drug labels. These developments include pharmacogenomics, modeling simulations, and analytical and imaging technologies that allow drugs in psychiatry to be more accurately individualized to treat patients. Clozapine represents a unique category among antipsychotic medications as it is approved for treatment-resistant patients with schizophrenia by regulatory agencies.[2]

Clozapine has many challenges with patient management because of its well-known adverse effect profile.[2,3] The evidence of clozapine doses being about only half in Asians compared to Caucasians presented by de Leon *et al*.[1] is reasonable, logical, and based upon published studies. This commentary presents additional information warranting clozapine dosage requirements be lower in Asians.

Clozapine disposition has considerable interpatient variability and is dependent upon many individual factors such as sex, smoking, and pharmacogenomics. Therapeutic monitoring of clozapine plasma or serum concentrations provides clinicians information about dosing, drug interactions, and patient response. The recommended clozapine plasma concentrations are >350 ng/mL,[4] with a possible "ceiling effect" range of 600–838 ng/ml.[5] Upon a closer examination of two studies,[6,7] the relationship between clozapine dose and plasma concentrations reveals this interesting finding in a Caucasian population (N = 148) where the data presented was clozapine dosed at 3 mg/kg and 6 mg/kg. The mean (±S.D.) body weight (kg) for the male and female Caucasian groups were 77.6 ± 15.9 and 69.9 ± 12.6, respectively.[6] Those results would translate to mean clozapine daily doses of 232.8 mg (3 mg/kg) and 465.6 mg (6 mg/kg) for the males and 209.7 mg (3 mg/kg) and 419.4 mg (6 mg/kg) for the females, respectively. The corresponding clozapine plasma concentrations for greater than 90% of the male and female patients were <200 ng/ml and <400 ng/ml, respectively. The clozapine study in Taiwanese patients (N = 162) did not separately analyze the differences between males and females.[7] However, clozapine daily doses of 200–250 mg and 400 mg yielded the corresponding mean ± (S.D.) clozapine plasma concentrations (ng/ml) of 320 ± 163 and 591 ± 325, respectively. Collectively, these two studies and subsequent other studies support that Taiwanese and Chinese patients had a clozapine plasma level/dose factor of 1.50 higher than Caucasians. A recent study comparing Chinese (N = 126, from Beijing) to a previously published Caucasian Italian outpatient sample (N = 152) also reported a clozapine concentration/dose (C/D) ratio of 1.57, higher among the Asian group.[8]

Clozapine metabolism has been elucidated and involves mainly hepatic cytochrome P450 CYP1A2.[9] Although other CYPs are involved in clozapine metabolism, CYP1A2 remains the predominant metabolic pathway. Clozapine disposition significantly correlates (r = 0.84, P < 0.0024) with caffeine demethylation (used as a measure of CYP1A2 activity).[10] Smoking and sex are factors that influence CYP1A2 activity, which can then impact clozapine plasma concentrations.[5,6,11] Medications that are CYP1A2 inhibitors (e.g., fluvoxamine) or inducers (e.g., carbamazepine) can lead to significant clozapine drug–drug interactions, impacting patient care.[12]

The CYP1A2 drug-metabolizing enzyme is found in a cluster with CYP1A1 and CYP1B1 located on chromosome 15 and comprises about 13% of all CYP hepatic protein content. The CYP1A2 enzyme structure is well known, with over 100 drug and endogenous substrates.[13] CYP1A2 activity between Swedish (N = 194) and Korean (N = 150) populations

using a caffeine 100 mg test dose for phenotyping and single nucleotide polymorphism (SNP) genotyping was analyzed.[14] Smoking and oral contraceptive (OC) use were the other main factors between the two groups included in the analysis. The overall findings revealed significantly higher CYP1A2 activity in Swedes than Koreans when considering smoking, OC use, and genotype. The difference between Caucasians and Asians could be clinically relevant for medications that CYP1A2 substrates with a narrow therapeutic index.[13] Another study reported that median CYP1A2 activity is lower among South Asians compared to those with European ancestry, where multiple linear regression analysis reported that 41% of the variability could be explained by diet, lifestyle, and genetics.[15]

However, CYP1A2 is not the only cause for CYP enzyme-linked metabolic differences between Asians and Caucasians. The CYP2C subfamily and CYP2D6 are also known to differ between East Asians and Caucasians.[16] Although clozapine is primarily metabolized by CYP1A2, other CYPs such as CYP2C19 and CYP2D6 are also involved, which can contribute towards the extensive interpatient variability.[17] The incidence of poor metabolizers (PMs) for CYP2C19 is highest among Asians (12–23%) compared to Caucasians (2–5%).[18] A recent study reported that CYP2C19 PMs ($N = 8$) did not appear to be associated with the higher clozapine C/D ratio when patients were stratified by sex and smoking status.[8] Yet, the CYP2C family and CYP2D6 status can contribute towards the wide interpatient variability.

A larger question emerges of what the designation of the ethnic term "Asian" really signifies. The FDA guidance for clinical trials included countries from the Far East, Southeast Asia, and the Indian subcontinent.[19] A perspective commentary reported that according to the Asian Diversity Project, over 40 different populations, ethnic minorities, and indigenous subgroups exist in the Asian category.[20] Further analysis by SNPs from the Pan-Asian study showed that modern genetics identify individuals from specific Asian groups (e.g., Chinese versus Mainland Japanese versus Okinawans).[20] The Indian population alone was shown to have its own genetic diversity with geographical regions (e.g., North versus South).[21] Therefore, Asians are a heterogeneous population with many genetic subpopulations.

Based upon the evidence, Asians represent a distinct population from Caucasians, Africans, and other ethnic groups based upon genetic polymorphisms. So, do Asians require only half of the clozapine doses prescribed for Caucasians? The indications are that lower clozapine doses are found in Asians compared to Caucasians with relatively similar plasma concentrations that include the various factors such as smoking that influence these drug levels. Genetic polymorphism for clozapine metabolism can account for the wide interpatient variability where ethnicity can be incorporated. Every patient differs in clozapine disposition. Prescribers have the tools to assist in drug dosing, such as CYP pharmacogenomics testing, patient information (e.g., sex and smoking history), and analytical support to measure clozapine concentrations. Each of these tools should be employed to maximize clozapine's use.

Michael W. Jann

Department of Pharmacotherapy, University of North Texas System College of Pharmacy, Fort Worth, TX, USA

Address for correspondence: Dr. Michael W. Jann University of North Texas Health Science Center. 3500 Camp Bowie, Blvd., Fort Worth, TX 76107, USA.
E-mail: michael.jann@unthsc.edu

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Review Article

Do Asian Patients Require Only Half of the Clozapine Dose Prescribed for Caucasians? A Critical Overview

Jose de Leon[1,2], Anto P. Rajkumar[3,4], Arun R. Kaithi[5], Georgios Schoretsanitis[6], John M. Kane[6,7], Chuan-Yue Wang[8], Yi-Lang Tang[9], Shih-Ku Lin[10], Kyung Sue Hong[11], Saeed Farooq[12], Chee H. Ng[13], Can-Jun Ruan[14], Chittaranjan Andrade[15]

ABSTRACT

Since 1997, studies have found that Asians need lower clozapine doses than Caucasians. Caucasians with average clozapine metabolism may need from 300 to 600 mg/day to reach the therapeutic range (350 ng/ml). Thus, serum clozapine concentration-to-dose (C/D) ratios typically range between 0.60 (male smokers) and 1.20 (female non-smokers). A 2019 systematic review of clozapine levels demonstrated weighted mean C/D ratios of 1.57 in 876 East Asians and 1.07 in 1147 Caucasians ($P < .001$). In Asian countries, average clozapine doses are lower than 300 mg/day. After sex and smoking stratification in 5 Asian samples with clozapine concentrations, the clozapine dose required to reach 350 ng/ml in female non-smokers ranged from 145 to 189 mg/day and in male smokers, from 259 to 294 mg/day. Thus, in Asian patients with

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[1]Mental Health Research Center, Eastern State Hospital, Lexington, Kentucky, USA, [2]Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain, and Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain, [3]Department of Psychiatry, Christian Medical College, Vellore, Tamil Nadu, India, [4]Institute of Mental Health, University of Nottingham, Nottingham, United Kingdom, [5]Hazelwood Center, Louisville, Kentucky, [6]Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, [7]Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA, [8]Department of Psychiatry, The National Clinical Research Centre for Mental Disorders and Beijing Key Lab of Mental Disorders and Beijing Institute for Brain Disorders Center of Schizophrenia, Beijing Anding Hospital, Capital Medical University, Beijing, China, [9]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia, and Substance Abuse Treatment Program, Atlanta VA Medical Center, Decatur, Georgia, USA, [10]Department of General Psychiatry, Taipei City, Psychiatric Center, Taipei, Taiwan, and Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan, [11]Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Korea, [12]School of Primary, Community and Social Care, Faulty of Medicine and Health Sciences, Keele University, Staffordshire, and Midlands Partnership NHS Foundation Trust, Staffordshire, United Kingdom, [13]Department of Psychiatry, The Melbourne Clinic and St Vincent's Hospital, The University of Melbourne, Melbourne, Victoria, Australia, [14]Laboratory of Clinical Psychopharmacology & The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China, [15]Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Jose de Leon
Room 3A15A, Mental Health Research Center, Eastern State Hospital, 1350 Bull Lea Road, Lexington, Kentucky 40511, USA.
E-mail: jdeleon@uky.edu

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average metabolism (with no inducers other than smoking, with no inhibitors, and in the absence of extreme obesity), the dose needed for clinical response may range between 150 mg/day for female non-smokers to 300 mg/day for male smokers. Clozapine levels may help personalize dosing in clozapine poor metabolizers (PMs) and ultrarapid metabolizers (UMs). Asian PMs may need very low doses (50-150 mg/day) to obtain therapeutic concentrations. About 10% (range 2-13%) of Asians are genetic PM cases. Other PMs are patients taking CYP1A2 inhibitors such as fluvoxamine, oral contraceptives, and valproate. Temporary clozapine PM status may occur during severe systemic infections/inflammations with fever and C-reactive protein (CRP) elevations. Asian UMs include patients taking potent inducers such as phenytoin, and rarely, valproate.

Key words: *Asian continental ancestry group/genetics, blood, CYP1A2, clozapine, drug labeling, India, pharmacokinetics, sex, smoking*

This review article proposes that the clozapine package insert (or drug labeling) and psychiatric literature should inform physicians that Asian patients with average clozapine metabolism are likely to need between 150 and 300 mg/day of clozapine to reach therapeutic concentrations, in contrast with Caucasian patients with average clozapine metabolism who need 300 to 600 mg/day.

WHAT IS THE EVIDENCE?

A reader familiar with United States psychiatric textbooks[1] or review articles[2] or British textbooks[3] or guidelines[4] may find the title of this article surprising. A British textbook[3] states, "The range [for clozapine dosing] is approximately 250 mg/day (female non-smoker) to 550 mg/day (male smoker)" and makes no reference to Asian patients.

Average response in randomized clinical trials (RCTs) is used by pharmaceutical companies to provide recommended average doses, but this approach is misguided when statistical heterogeneity is present and when the mean does not represent the heterogeneous sample well.[5] As a matter of fact, the question asked in a Cochrane review, "What is the optimal dose for clozapine in schizophrenia?"[6] is an irrelevant question because there is no average clozapine dose that is "best". The right dose depends on the clozapine clearance of the individual patient, which is mainly mediated by CYP1A2 and is significantly influenced by ethnicity, smoking status and sex, all of which have major influence on CYP1A2 activity.[7] A better question therefore is to ask what dose is optimal for specific sub-groups: 1) Asian non-smoker females, 2) Asian non-smoker males, 3) Asian smoker females, 4) Asian smoker males, 5) non-Asian non-smoker females, 6) non-Asian non-smoker males, 7) non-Asian smoker females, and 8) non-Asian smoker males.[8]

These questions are at the heart of clinical practice but were not asked when clozapine was introduced in the market. Traditionally, drug studies for approval focused on Caucasian subjects, predominantly male, but this state of affairs is no longer satisfactory. The current need is to understand how different racial and ethnic ancestry can lead to differences in efficacy and safety in the use of various drugs.

WHO ARE ASIANS?

According to the Food and Drug Administration (FDA), the Asian phenotype includes people whose ancestral origins range geographically from Pakistan to Japan.[9] Within that group is a more homogeneous genetic group called East Asians, who comprise of Chinese, Korean, Japanese, and Mongolian people. This classification is largely driven by the history of genetic evolution.[10] This means that people from Western Asia[11] are genetically different from other Asians and are closer to Caucasian Europeans;[10] it also means that the original people from the Americas[10] have actually descended from East Asians and are likely to be genetically close to East Asians. In this review, we report clozapine levels from Vellore, which probably reflects a population from Southern India, while the Northern India population probably includes a more complex mix.[12]

THE EVIDENCE FROM CLOZAPINE BLOOD LEVELS

Although clozapine prescribers in Western countries are not aware that Asians need lower clozapine doses, this is not a new concept. In 1997, Chang *et al*.[13] and Chong *et al*.[14] showed that Chinese patients who used half the clozapine dosage had concentrations similar to Caucasians. Moreover, in 2005, Ng *et al*.[15] found that 20 Singaporean Asians (from 3 ethnic groups: Chinese, Indian, and Malay) had higher clozapine concentration-to-dose (C/D) ratios than 20 Australian Caucasians.

The clozapine C/D ratio is a measure of clozapine drug clearance, which can be influenced by genetic, personal, and environmental factors.[16] The clozapine C/D ratio can be used to distinguish patients based on clozapine metabolism. Thus, patients with a very low clozapine C/D ratio belong to an ultrarapid metabolizer (UM) phenotype, while those with a very high C/D ratio belong to a poor metabolizer (PM) phenotype. In 2015, a review[16] proposed that in US schizophrenia patients, Caucasians with average clozapine metabolism usually need 300-600 mg/day to reach the lowest part of the therapeutic range (350 ng/ml). US male smokers usually reach a therapeutic concentration of ≥350 ng/ml with a dosage of 600 mg/day; this corresponds to a C/D ratio of 0.58 (350/600). US female non-smokers usually reach a concentration of ≥350 ng/ml with a dosage of only 300 mg/day. This corresponds to a C/D ratio of 1.17 (350/300). Therefore in the US, clozapine C/D ratios typically range between approximately 0.60 and 1.20.[16]

Based on the limited published data on Chinese patients,[13-15] and the fact that clozapine follows linear kinetics, the review[16] also proposed that East Asians may have clozapine C/D ratios that are twice as high, ranging from 1.20 to 2.40, which means that they need only half the clozapine dosage of US Caucasians.[16] In 2019, a systematic review of clozapine levels supported that conclusion,[8] since the clozapine C/D ratio was higher when comparing weighted mean values of 1.57 in 876 East Asians and 1.07 in 1147 Caucasians ($P < 0.001$). Interestingly, a Mexican study[17] which provided no information on patient ethnicity described clozapine C/D ratios similar to East Asians.

THE EVIDENCE FROM CLOZAPINE DOSING IN ASIAN COUNTRIES

In 1998, Farooq[18] reported his clinical observation that Pakistani psychiatrists also used lower doses similar to those used by Chinese psychiatrists, and proposed that Pakistanis also have lower clozapine clearance than Caucasians, but similar to Chinese. However, these comments on the need for low clozapine doses in Chinese and Pakistani patients were largely ignored in Western countries.

Clozapine is widely used in China. In 2012, Wang and Li[19] stated that the mean dose reported in Chinese studies was 216 mg/day, which was much lower than the 431 mg/day reported in the non-Chinese literature. A dosing study with >3,000 samples from the Japanese clozapine database described a mean dose of 186 mg/day.[20] In a survey of 117 Indian psychiatrists, Shrivastava and Shah[21] indicated that almost all (86%) of their patients were stabilized on clozapine doses lower than 300 mg/day. A recent Asian review described clozapine daily dosing in single samples from several different countries. In countries with no published blood levels, the sample average doses (in mg/day) were 368 in Sri Lanka, 364 in Malaysia, 245 in Thailand, 193 in Myanmar, 182 in Vietnam, 158 in Pakistan, 142 in Bangladesh and 58 in Indonesia.[22]

DOSING RECOMMENDATION FOR ASIANS IN THE ABSENCE OF BLOOD LEVELS

If the psychiatrist has access to blood levels, the best way to personalize clozapine dosing[23] is to use a dose that provides a trough steady-state clozapine concentration of at least 350 ng/ml.[24] Alternatively, the data from the five Asian samples[25] after sex and smoking stratification can be used to orient Asian clinicians who have no access to an assessment of blood levels. The five samples were from Beijing,[8,26] Taipei,[27] Seoul,[28] and Vellore.[29] In these 5 Asian samples, the clozapine dose required to reach at least 350 ng/ml in female non-smokers ranged from 145 to 189 mg/day and in male smokers, from 259 to 294 mg/day.

These clozapine dosing guidelines are based on patients with average metabolism who are not using inducers (other than smoking) or inhibitors and do not have extreme obesity. The dose needed for clinical response in Asian patients with average clozapine metabolism ranges between 150 mg/day for female non-smokers and 300 mg/day for male smokers. After reaching these doses, when a psychiatrist is faced with the need to ascertain whether the patient is not going to respond to clozapine, they may want to reach at least 200 mg/day in an Asian female non-smoker before declaring her to be non-responsive; likewise, an Asian male smoker will need at least 350 mg/day. Asian female smokers and Asian non-smoking males will need intermediate doses.

THE IMPORTANCE OF USING CLOZAPINE BLOOD LEVELS IN ASIANS

This review has so far focused on Asian non-smoking females or Asian smoking males with average metabolism, but not all patients are average for clozapine metabolism. Clozapine PMs and UMs exist, and they can be genetic or non-genetic PMs or UMs.

In the 5 Asian samples,[25] approximately 10% (range 2-13%) of possible genetic clozapine PMs needed very low clozapine doses of approximately 50-125 mg/day to reach 350 ng/ml. In Vellore, the PM percentage appeared

to be 2%. Moreover, phenoconversion by environmental and personal variables can make a normal clozapine metabolizer appear to be a phenotypical clozapine PM. Fluvoxamine is an extremely powerful inhibitor of clozapine metabolism that makes most patients resemble clozapine PMs,[30] and should never be co-prescribed with clozapine in the absence of access to blood levels. Other powerful inhibitors of clozapine metabolism that are likely to make a patient a clozapine PM are: ciprofloxacin, oral contraceptives, and high doses of caffeine. Phenothiazines, tricyclic antidepressants, and high doses of sertraline can also phenoconvert patients to clozapine PM.[30] Valproic acid in some patients may also inhibit clozapine metabolism.[29,31]

More importantly, using the clozapine C/D ratio in the Vellore sample, we estimated that a clozapine PM male smoker who was taking valproic acid would only need 105 mg/day to get therapeutic concentrations.[25]

Clozapine deposits in fat tissue,[32] and this decreases clozapine clearance. After combining four Asian samples with measures of weights, we found that 1.1% (5/429) of patients appear to be phenotypic clozapine PMs due to extreme obesity.[25]

The most common cause of clozapine phenotypic PM status may be a severe infection or severe inflammation with systemic manifestations that include fever and/or elevations of C-reactive protein (CRP). The inflammation releases cytokines that inhibit CYP1A2 and other CYPs, thereby increasing clozapine levels.[33] Most clinicians are not aware that pneumonia can be lethal in clozapine patients because it can lead to clozapine intoxication.[34] Halving the clozapine dose when pneumonia is diagnosed, or when any serious inflammation/infection with fever and/or CRP elevation occurs, may avoid the development of clozapine intoxication.[33,34] The complexities involved in diagnosing fever in clozapine patients are reviewed in a recent article.[35]

Patients taking a potent inducer such as rifampicin or one of the three potent antiepileptic inducers, phenytoin or phenobarbital, can become clozapine UMs and require much higher clozapine doses.[30] Valproic acid, instead of being an inhibitor of clozapine metabolism, can be an inducer in some patients. Studies suggest that when valproic acid acts as an inducer, it mainly induces norclozapine metabolism[31,36-38] but can sometimes contribute to the patient becoming a UM who needs very high clozapine doses.[39] Norclozapine is clozapine's main metabolite and has no antipsychotic efficacy but may contribute to adverse drug reactions.[40] In summary, in some clozapine patients, valproic acid can act as an inhibitor of clozapine metabolism and in others, as an inducer, particularly of norclozapine metabolism.[41] During early titrations, it is important to consider the risk of inhibition.

Mild CYP1A2 inducers are omeprazole and intake of cruciferous vegetables such as broccoli. These latter compounds and the polycyclic aromatic hydrocarbons (PAH) found in the smoke of tobacco bind to the aryl hydrocarbon receptor (AhR), inducing CYP1A2 expression.[42] The same PAH in barbecued food can act as it does in tobacco smoke, but one would have to consume great quantities of barbecued food to gain the same effect as daily smoking. More importantly, in people from India or Sri Lanka,[43] high coffee intake has been associated with induction of CYP1A2 expression, possibly because of the way the coffee beans are roasted. Using the clozapine C/D ratio in the Vellore sample, we estimated that a particular clozapine UM would need 1029 mg/day of clozapine to reach a clozapine level of 350 ng/ml. She was a non-smoking female who reported consuming 10 cups of coffee/day, much higher than other patients. Assuming that her single clozapine level was not contaminated by lack of adherence, she appeared to be a clozapine UM explained by the high induction produced by the roasting of coffee beans.[25]

In conclusion, the best way of personalizing dosing for clozapine PMs and UMs, whether genetic or non-genetic by source, is to measure clozapine blood levels.[23]

THE NEED FOR STARTING WITH LOWER DOSES AND SLOWER TITRATION IN ASIAN PATIENTS

Asian patients need half the dose to which Caucasian patients are usually up-titrated. Therefore to prevent myocarditis, in Asians, it may be desirable to start with 12.5 mg/day and, if tolerated, to reach 50 mg/day at day 7, 100 mg/day at day 14, and 150 mg/day at day 21. Then, after reaching a steady-state (five days later), a trough clozapine level could be obtained to personalize dosing. It is preferable to require a normal CRP level for starting clozapine, or else systemic inflammation-related reduction in clozapine metabolism may compromise the safety of the titration.[23,44] Weekly CRP can be measured with the white blood count (WBC). If the CRP is elevated, clozapine should be stopped until the CRP normalizes because this may be an initial sign of clozapine-induced inflammation that can progress to myocarditis.[23,44] Frequently, clozapine up-titration is conducted in the background of a prior antipsychotic, and so delaying clozapine titration until CRP normalizes is safe. If the patient is not already taking another antipsychotic, an additional antipsychotic can

be given until it is determined that the patient can tolerate a slower clozapine up-titration.

Two articles have independently proposed that clozapine-induced myocarditis is a hypersensitive reaction similar to lamotrigine-induced Stevens-Johnson syndrome that is produced by rapid up-titration.[45,46] Normal titration may lead to myocarditis in clozapine PMs, such as those taking valproic acid.[47] If the clozapine up-titration is too fast for a specific patient, a clozapine-induced inflammation will develop, manifested as CRP elevation. This will further reduce clozapine metabolism and predispose to myocarditis. The high incidence of clozapine-induced myocarditis in Australia may be partly explained by the use of Caucasian-level titration in patients of Asian ancestry, considering the increase in Asian emigration to Australia in the last ten years.[8]

INTERPRETING CLOZAPINE BLOOD LEVELS

Clinicians frequently fail to understand that a single clozapine level must be viewed with caution and that a pattern change across several levels is easier to interpret. Laboratory, technical, and natural variations can cause some day-to-day variations in clozapine levels, even after assuming the stability of all possible confounding factors such as trough (early morning before medication intake) and steady-state levels (≥5 days with no clozapine dose change), drug interactions, smoking, and caffeine intake.[48] The most important changes in clozapine levels in outpatients are due to a lack of compliance.[49] Based on an RCT in an inpatient setting with very strict control over compliance and many levels every other week for months,[50] we have suggested that only a change by a factor of 2 is probably meaningful from the clinician's perspective. This means that if an individual has a clozapine level of 500 ng/ml, the next one under the same stable conditions should not be >1000 or <250 ng/ml. However, a change from 500 to 400 ng/ml is probably not significant.[48]

CONCLUSION

This review article proposes that Asians, defined as people whose ancestral origins range geographically from Pakistan to Japan, and who comprise up to 50% of the world's population, may need half the clozapine dosage used in Western countries. Psychiatrists in India, and more widely, in Asia, need to be aware that the clozapine doses needed by Asian patients are half those needed by Caucasian patients.

Based on the evidence presented in this article, Asian psychiatrists should encourage their hospitals and facilities, where possible, to developing laboratories that can allow obtaining clozapine levels to become routine practice. This would help personalize clozapine dosing. Asian pharmaceutical companies should consider developing clozapine formulations that allow lower doses, such as 12.5, 10, or even 5 mg. These low doses are far more appropriate for starting clozapine in Asian patients. This article estimates dosing for Asians based on linear kinetics and the estimation that the lower therapeutic range is 350 ng/ml, but this value is mainly based on studies in Caucasians and response-plasma levels in Asians are needed. Future studies in Asian patients need to establish whether or not this value (350 ng/ml) needs to be modified in Asians.

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Conflicts of interest

In the last 3 years, Drs. de Leon, Rajkumar, Kaithi, Schoretsanitis, Wang, Tang, Lin, Hong, Farooq, Ruan and Andrade have had no conflicts of interest. In the last 3 years, Dr. Kane reports personal fees from Alkermes, personal fees from Allergan, personal fees from Bristol-Myers Squibb, personal fees from IntraCellular Therapies, personal fees from Janssen, personal fees from Lundbeck, personal fees from Minerva, personal fees from Neurocrine, personal fees from Otsuka, personal fees from Pierre Fabre, personal fees from Reviva, personal fees from Sunovion, personal fees from Takeda, personal fees from Teva, other outside the submitted work from LB Pharma, MedAvante and The Vanguard Research Group. In the last 3 years, Dr. Ng reports being a consultant for Grunbiotics, Lundbeck, Servier, and Janssen-Cilag, and received research speaker honoraria from Servier, Janssen-Cilag and Pfizer.

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Review Article

Vitamin D and Depression: A Critical Appraisal of the Evidence and Future Directions

Vikas Menon, Sujita Kumar Kar[1], Navratan Suthar[2], Naresh Nebhinani[2]

ABSTRACT

Background: Growing evidence points to the role of vitamin D in the pathobiology and treatment of depression. However, the evidence is inconsistent in many aspects. The objectives of this narrative review were to evaluate the state of the evidence, synthesize the knowledge gaps, and formulate recommendations for more enhanced research in this growing area. **Methods:** Electronic searches of MEDLINE via PubMed, Cochrane Library, and Google Scholar databases were carried out from inception till February 2019 to identify relevant English language peer-reviewed articles. Abstracts generated were systematically screened for eligibility. Included articles were grouped under three broad themes: The association between vitamin D and depression, its biological underpinnings, and trials evaluating the efficacy of vitamin D supplementation in depression. Relevant data were extracted as per a structured proforma. **Results:** A total of 61 articles were included in the present review. Overall findings were that there is a relationship between vitamin D and depression, though the directionality of this association remains unclear. The association appears to be driven by the homeostatic, trophic, and immunomodulatory effects of vitamin D. Evidence from supplementation trials suggest a more robust therapeutic effect on subjects with major depression and concurrent vitamin D deficiency. **Conclusion:** Serum vitamin D levels inversely correlate with clinical depression, but the evidence is not strong enough to recommend universal supplementation in depression. Enriching depression treatment trials with subjects having concurrent vitamin D deficiency appears to be a potential step forward in identifying subgroups who may maximally benefit from this approach.

Key words: *Depression, immune system, inflammation, psychiatry, vitamin D*

Depression is a common and disabling mental illness, prevalent worldwide across all ages, genders, and races. In 2015, 4.4 per cent of the world's population was suffering from depression.[1] The condition is associated with increased morbidity and mortality, owing to increased risk for stroke, cardiovascular events, and suicide as well as lifestyle-related disorders such as diabetes and hypertension.[2-4] It also has significant

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Department of Psychiatry, Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER), Dhanvantri Nagar, Puducherry, [1]Department of Psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, [2]Department of Psychiatry, AIIMS, Jodhpur, Rajasthan, India

Address for correspondence: Dr. Vikas Menon
Department of Psychiatry, JIPMER, Puducherry - 605 006, India. E-mail: drvmenon@gmail.com

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economic and social consequences, such as decreased productivity and increased health care utilization costs.[5,6] Compounding the issue further, depression is associated with a high burden of nonresponse to conventional treatment options.[7,8]

Given the above scenario, clinicians and researchers are constantly looking to expand the therapeutic options to tackle depression. The last quarter of a century has seen research attention being increasingly centred on inflammation as a possible pathophysiological mechanism in depression. Several trials of anti-inflammatory agents have shown promise, but the evidence, so far, is not strong enough to guide clinical recommendations.[9,10]

Parallel to these developments, the role of vitamin D in depression has also received increasing research focus. Currently, there are at least three lines of evidence to support this association: first, an increased region-specific expression of vitamin D receptors (VDRs) in brain areas (such as prefrontal and cingulate cortices) known to play a key role in mood regulation;[11] second, the modulatory role proposed for vitamin D in the association between depression and inflammation (through a possible immune-modulatory mechanism)[12,13]; last, the emerging insights about the neuroprotective properties of vitamin D (by virtue of its anti-inflammatory effects).[14,15]

Against this background, we carried out the present narrative review to summarize the literature and clarify the evidence in three areas: association between vitamin D and depression, its underlying biological links, and therapeutic effects of vitamin D on depression. Accordingly, we had our objectives: - 1) to describe the evidence for association between vitamin D and depression and outline the underlying biological mechanisms, 2) to synthesize the evidence base for effect of vitamin D supplementation in depression, and 3) to highlight the knowledge gaps in these areas and formulate recommendations that seem most relevant for future research.

METHODS

Search strategy

We carried out an electronic search of MEDLINE through PubMed, Cochrane Library and Google Scholar databases (all up to February 2019) for articles on vitamin D and depression. For PubMed search, the following MeSH or free text terms were used: 'vitamin D', 'vitamin d', '25-hydroxyvitamin d 2', '25-hydroxyvitamin d 3', 'calcifediol', 'depression' or 'depressive symptoms' along with the Boolean operators AND and OR in a sequential MeSH and all fields search, as follows: ((((('vitamin d'[MeSH Terms] OR 'ergocalciferols'[MeSH Terms]) OR ('vitamin d'[MeSH Terms] OR 'vitamin d'[All Fields] OR 'ergocalciferols'[MeSH Terms] OR 'ergocalciferols'[All Fields])) OR ('25-hydroxyvitamin d 2'[MeSH Terms] OR ('25-hydroxyvitamin d 2'[MeSH Terms] OR '25-hydroxyvitamin d 2'[All Fields] OR '25 hydroxyvitamin d 2'[All Fields]))) OR ('calcifediol'[MeSH Terms] OR ('calcifediol'[MeSH Terms] OR 'calcifediol'[All Fields] OR '25 hydroxyvitamin d 3'[All Fields]))) AND (('depressive disorder'[MeSH Terms] OR 'depression'[MeSH Terms]) OR ('depressive disorder'[MeSH Terms] OR ('depressive'[All Fields] AND 'disorder'[All Fields]) OR 'depressive disorder'[All Fields] OR 'depression'[All Fields] OR 'depression'[MeSH Terms])).

Search terms were adapted to suit the search needs of other databases as appropriate. Additionally, hand searches of the reference lists of the generated articles were done in order to ensure a comprehensive search. The searches were done by three independent reviewers, all of whom were qualified psychiatrists.

Study selection and data extraction

The initial search yielded 879 hits. We included only English language articles published in peer-reviewed journals. Editorials and commentaries were not included in the main review but only to support some recommendations, we make at the end. We also included systematic reviews and meta-analyses addressing focused research questions related to the focus areas, and the original articles included in these reviews were not examined separately. Based on these criteria and after eliminating duplicates, 148 articles were identified for potential inclusion, and after their full texts were examined, 61 papers were included in the present review after elimination of articles other than original research papers or those not relevant to the focus areas of the present review. All the three authors participated in study selection and reached a consensus regarding the papers to be included in the review. We neither performed a risk of bias assessment for individual studies nor computed effect estimates, as this was meant to be a narrative review.

Selected studies were categorized under three broad themes: studies that looked at the biological basis of the association between vitamin D and depression, studies that dealt with quantifying the association between vitamin D and depression, and trials that evaluated the effect of supplementing vitamin D in depression. Accordingly, in this review, we will discuss our search results under these three headings, and finally, we end with a discussion on knowledge gaps in these areas and recommendations to enrich and enhance future research.

RESULTS

Of a total of 148 full-text articles assessed, 116 (78.37 per cent) were published in the last ten years and 82 articles (55.41 per cent) were published in the last five years. These percentages clearly indicate the increasing research focus on the role of vitamin D in depression in the last decade. Totally, 61 articles were included in the present review. Of these, 46 were original articles, 13 were reviews/meta-analysis papers, and two were commentaries.

Vitamin D and depression: Biological underpinnings

The exact biological mechanisms linking vitamin D and depression are not fully understood. However, possible pathways include an imbalance in the calcium homeostasis of intracellular and extracellular compartments and a possible fallout of disequilibrium between glutamate, an excitatory neurotransmitter, and GABA, an inhibitory neurotransmitter. This, in turn, affects cellular signalling. Vitamin D may have a potential role in restoring this calcium and neurotransmitter imbalance by regulating intracellular calcium stores and cellular signalling and impacting the onset of depression favourably.[16]

Research has uncovered a possible neurotrophic and immunomodulatory role for vitamin D, leading many researchers to label it as a neurosteroid hormone.[17,18] Preclinical studies have shown that administration of vitamin D modulates the levels of inflammatory cytokines in the animal models of multiple sclerosis, a neurodegenerative condition with an inflammatory basis.[19] This is important because evidence suggests that depression is also a condition with elevated levels of systemic inflammation.[20,21] Increased region-specific expression of VDRs has been noted in the prefrontal and cingulate cortices, thalamus, amygdala, and hippocampus, all key brain areas implicated in the pathophysiology of depression.[22]

Furthermore, vitamin D modulates the hypothalamic-pituitary-adrenal axis, which regulates the production of the monoamine neurotransmitters epinephrine, norepinephrine, and dopamine in the adrenal cortex and also protects against the depletion of dopamine and serotonin.[23,24] Figure 1 summarizes the possible biological links between depression and vitamin D.

The possibility of reverse causality too has been pointed out by prior investigators.[25,26] Certain factors related to depression can further increase the risk of vitamin D deficiency in an individual suffering from depression. Depressed individuals may avoid outdoor activity for prolonged periods of time (reducing sunlight exposure); poor appetite may lead to nutritional (and vitamin D) deficiency; metabolic derangements and increased demand for vitamin D (for restoring the calcium homeostasis) might further increase the risk of vitamin D deficiency in depression.

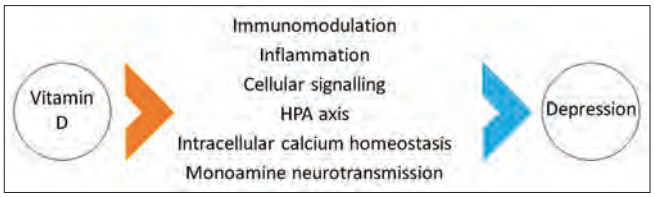

Figure 1: Postulated biological links between vitamin D and depression. HPA: Hypothalamo-pituitary-adrenocortical

Evidence for the association between vitamin D and depression

Several cross-sectional studies,[27-31] few cohort studies,[32-34] and one case-control study[35] have examined the association. All the studies found that depressed subjects had lower levels of vitamin D compared to controls, and those with the lowest vitamin D levels had the greatest risk of depression (odds ratios 1.31, 95 per cent confidence interval [CI] 1.00–1.71). These values, though statistically significant, do not establish clinical relevance beyond doubt.

While both hospital-based[29,30,33,36] and community-based[27,37] trials show a link between low vitamin D levels and presence and severity of depressive symptoms, it is important to examine if these associations hold good after controlling for relevant demographic, lifestyle, and geographical factors. Encouragingly, community-based trials that controlled for age, gender, smoking, and body mass index have also found an inverse correlation between serum levels of 25(OH)D and levels of depression.[27,28]

These findings are partly tempered by the conclusions from two negative studies among the elderly; one a large Chinese epidemiologic study (n = 3,262) of men and women aged 50–70 years[38] that did not show any association between vitamin D and depression; and the other, a cohort study from Hong Kong (n = 939, all aged more than 65 years),[32] where no relationship was observed between baseline vitamin D level and depression status at four-year follow-up. Notably, both these studies showed that the odds ratios turned insignificant after adjusting for several key confounders.

Evidence for Vitamin D supplementation in depression

Vitamin D supplementation for depression in adults

Vitamin D metabolites are capable of crossing the blood–brain barrier,[39] and as mentioned before, VDRs are widespread in key brain areas implicated in

depression, including the hippocampus.[17] Hence, it could be speculated that vitamin D supplementation may confer additional therapeutic benefits in depression.

Building on this premise, a number of trials with different methodologies have evaluated the efficacy of vitamin D supplementation in depression in the last decade. However, the findings have been somewhat inconsistent.[40-42] Partly, the reason may lie in the heterogeneity of trials with respect to sample size, study setting and design, the age range of participants, vitamin D dosing protocols, duration of the intervention, and the outcome measures used.

As studies using heterogeneous designs may be difficult to compare, it becomes important to examine results from randomized controlled trials (RCTs). Four RCTs[43-46] have evaluated the efficacy of supplemental vitamin D in patients with clinical depression. While three of them evaluated the efficacy of supplemental vitamin D, the fourth one studied the efficacy of vitamin D as an adjunct to standard anti-depressant therapy. All four trials demonstrated benefits for vitamin D, with effect sizes varying from moderate to large. On a discordant note, two recent RCTs[47,48] found no evidence of any beneficial effect of vitamin D3 supplementation on depressive symptoms or mood-related outcomes. Interestingly, both these negative studies were done on healthy population and not clinically depressed subjects.

Clinical improvement in depressive symptoms with vitamin D supplementation appears to vary depending on several methodological considerations. Spedding[49] noted that therapeutic benefits of vitamin D were more pronounced in studies with fewer 'biological' flaws (such as suboptimal dosing of vitamin D), and worsening in depressive symptoms with vitamin D supplementation was noted in studies with methodological flaws. These perspectives are supported by findings that higher dosages of vitamin D had a greater impact on mental health and wellbeing.[40,50,51]

Vitamin D supplementation in depression during pregnancy or peripartum period

Researchers have found a relationship between low serum vitamin D concentration during pregnancy and elevated postpartum[52,53] as well as antepartum depression.[54] On a conflicting note, a large nested case-control study (605 women with postpartum depression [PPD] and 875 controls) found a greater probability of postnatal depression with an increase in 25-hydroxyvitamin D concentration.[55]

An Iranian RCT on pregnant women found that consuming 2,000 IU vitamin D3 daily during late pregnancy was effective in mitigating perinatal depressive symptoms.[56] In a cross-sectional study from Japan, higher dietary vitamin D intake was independently associated with a lower prevalence of depressive symptoms during pregnancy.[57]

One association study showed a significant inverse association between vitamin D levels and risk of antepartum (at 21 weeks, adjusted odds ratios [AOR] 0.54, 95 per cent CI 0.29–0.99) and PPD (at three days, AOR 2.72, 95 per cent CI 1.42–5.22).[58] Similarly, levels of vitamin D in early pregnancy were found to be a marker for elevated depression scores both in early and late pregnancy.[59] These results, though not conclusive, suggest a relationship between serum vitamin D levels and antepartum and PPD.

Vitamin D supplementation in depression in childhood and adolescence

Results from a review of 25 observational and eight longitudinal studies concluded a role for vitamin D in the pathogenesis of several child and adolescent psychiatric conditions, including attention deficit hyperactivity disorder and autism spectrum disorders (ASD).[60] A case series of 54 adolescents with depression found a positive association between vitamin D levels and wellbeing and a greater improvement in depression with vitamin D supplementation.[61]

Only one completed RCT is available in this population. This six-month study, done on children with ASD aged 2–12 years, did not find significant benefits for daily oral supplementation of 2,000 IU of vitamin D on autism scores.[62] An RCT aimed at assessing the efficacy of vitamin D supplementation in children and adolescents with depressive disorder is currently underway.[63]

The salient features of supplementation trials described in this section are shown in Table 1. Overall, the available literature supports a relationship between vitamin D and depression in adults as well as children and adolescents. But, on a closer examination, there are several gaps in the evidence, which we outline below.

Gaps in understanding of the relationship between vitamin D and depression

Gaps in understanding of the association between vitamin D and depression

Much of the evidence linking vitamin D with depression in adults comes from cross-sectional studies.[64] Cohort or case-control studies are few and RCTs, considered superior for establishing causality, are even fewer.

Table 1: Salient features of vitamin D supplementation trials

Author, year, place	Type of study/ sampling	Sample size and characteristics	Intervention details	Main findings	Special remarks (if any)
Jorde *et al*., 2008 Norway[40]	Randomized controlled trial	441 subjects aged 21-70 years	Trial of 20,000 or 40,000 IU vitamin D per week versus placebo for 1 year	In the two groups given vitamin D, but not in the placebo group, there was a significant improvement in BDI scores after 1 year	Subjects with serum 25(OH)D levels <40 nmol/L scored significantly higher on the BDI total and the BDI subscale than those with levels >40 nmol/L
Kjærgaard *et al*., 2012 Norway[41]	Randomized controlled trial	357 subjects aged 30-75 years with serum 25(OH)D levels below 55 nmol/l (*n*=243), those with serum 25(OH)D levels above 70 nmol/l (*n*=114) served as nested controls	Participants with low 25(OH) D levels were randomised to either placebo or 40 000 IU vitamin D(3) per week for 6 months	In the intervention study, no significant effect of high-dose vitamin D was found on depressive symptom scores when compared with placebo	Participants with low 25(OH)D levels at baseline were more depressed than participants with high 25(OH)D levels
Yalamanchili and Gallagher, 2012 United States[42]	Randomized controlled trial (secondary data)	489 community dwelling elderly post-menopausal women aged 65-77 years	Three interventions: Hormonal therapy (conjugated equine estrogens with or without medroxyprogesterone acetate), calcitriol or combination therapy (HT plus calcitriol) and matching placebos for 3 years	There was no effect of hormone therapy, calcitriol or hormone therapy with calcitriol on depression	In post-menopausal women, there was no effect of hormone therapy and calcitriol either individually or in combination with depression.
Khoraminiya *et al*., 2013 Iran[43]	Randomized controlled trial	42 outpatients aged 18-65 years with a diagnosis of MDD without psychotic features	Daily oral 1,500 IU of vitamin D3 plus 20 mg fluoxetine or placebo plus 20 mg fluoxetine for 8 weeks	Depression severity decreased significantly in the intervention group compared to controls.	Combination therapy was superior to fluoxetine alone in controlling mood symptoms from the fourth week of treatment
Mozaffari-Khosravi *et al*., 2013 Iran[44]	Randomized controlled trial	120 subjects aged 20-60 years with depressive symptoms and vitamin D deficiency	Two single intramuscular injections equivalent to 300,000 IU (G300) and 150,000 IU (G150) of vitamin D were compared with a no treatment group (NTG) for 3 months	Significant improvement on Beck depression inventory scores was noted between G300 and NTG, but not between G150 and NTG groups	Correction of vitamin D deficiency also improved the depression state
Sepehrmanesh *et al*., 2016 Iran[45]	Randomized controlled trial	40 patients aged 18-65 years with a diagnosis of MDD	Single capsule of 50,000 IU vitamin D per week (n=20) or placebo (n=20) for 8 weeks	A trend towards a greater decrease in the BDI was observed in the vitamin D group but not the placebo group	No statistically significant differences were observed
Wang *et al*., 2016 China[46]	Randomized controlled trial	726 dialysis patients with depression	52-week treatment of oral 50,000 IU per week of vitamin D3 versus a placebo control group	Depressive symptoms and BDI scores were not significantly improved in the test group versus the control group	Authors found a beneficial effect on the subtype of vascular depression
Choukri *et al*., 2018 New Zealand[47]	Randomized controlled trial	152 healthy young adult women aged 18-40 years	50, 000 IU of oral vitamin D3 or placebo once per month for 6 months	No benefits were noted in the intervention group with regard to depressive or anxiety outcomes over controls	
Jorde and Kubiak, 2018 Norway[48]	Randomized controlled trial	408 healthy adult subjects aged 40 and above	Vitamin D 100,000 IU as a bolus dose (capsule) followed by 20,000 IU per week versus placebo for 4 months	BDI scores did not differ significantly between the vitamin D and placebo group	
Dumville *et al*., 2006 United Kingdom[50]	Randomized controlled trial	2117 women aged 70 years or more	Daily oral supplementation of 800 IU if vitamin D plus information sheet on increasing calcium in diet versus only information sheet in controls	No significant differences were observed between the two groups on subjective psychological wellbeing scores	

Contd...

Table 1: Contd...

Author, year, place	Type of study/ sampling	Sample size and characteristics	Intervention details	Main findings	Special remarks (if any)
Vieth *et al*., 2004 Canada[51]	Randomized controlled trial (two sequential partly overlapping studies)	Study 1: 64 outpatients with 25(OH)D <61 nmol/L) Study 2: 117 patients with serum 25(OH)D <51 nmol/L	Study 1: low dose supplementation (600 IU/day) versus high dose supplementation (4,000 IU/day) of vitamin D versus no supplementation for 2-6 months Study 2: Only supplementation arms were compared	In Study 1, wellbeing score improved more for the 100 mcg/day group than for the lower-dosed group. In Study 2, wellbeing scores improved with both doses of vitamin D	High dose supplementation was superior to low dose supplementation in subjects with average higher levels of serum vitamin D
Vaziri *et al*., 2016 Iran[56]	Randomized controlled trial	169 pregnant women aged 18 years or older with gestational age of 26-28 weeks and EPDS score of 0-13	Intervention group received 2,000 IU vitamin D3 daily from 26 to 28 weeks of gestation until childbirth Control group received two placebo pills composed of starch daily for same period	Intervention group had greater reduction in depression scores than control group at 38-40 weeks of gestation and at 4 and 8 weeks after birth	Supplementation of vitamin D3 daily during late pregnancy was effective in decreasing perinatal depression levels
Föcker *et al*., 2018 Germany[63]	Randomized controlled trial (protocol only)	200 inpatient children and adolescents (aged 11-18.9 years) with vitamin D deficiency and BDI score >13	Intervention group will receive 2,640 I.E. vitamin D3 daily for 28 days along with TAU while placebo group will receive only TAU. After 28 days, both groups receive 1,000 I.E vitamin D daily for next 11 months	Awaited	Tests the hypothesis that delaying vitamin D supplementation in placebo group will impact improvement of depression scores
Azzam *et al*., 2015 Egypt[62]	Randomized controlled trial	21 children with ASD aged 2-12 years	Intervention group received daily oral dose of 2,000 IU vitamin D3 versus no supplementation in placebo group (6-month study)	No significant differences between groups on ASD outcome scores	Limitation was that baseline 25(OH) D levels were lower in intervention group and levels did not rise following supplementation

BDI: Beck depression inventory; MDD: Major depressive disorder; EPDS: Edinburg postnatal depression scale; TAU: Treatment as usual; ASD: Autism spectrum disorder

As the bulk of the literature is from observational studies, several questions remain. Chief among them is the issue of small and unrepresentative samples, varying measures of depression (self-report vs. clinician-rated), and the potential problem of reverse causality. Given that two of the important negative studies came from China and Hong Kong, the issue of latitude moderating the association between vitamin D and depression needs further examination.

Owing to several sources of bias in existing studies and the danger of publication bias impacting the literature on vitamin D and depression, the possibility of a meta-analysis answering this question with finality remains bleak. More RCTs are therefore needed to examine the efficacy of supplemental vitamin D on prevention and treatment of depression.

Knowledge gaps in biological underpinnings between vitamin D and depression

Our understanding of the effect of vitamin D on neuronal brain function and behaviour is largely based on animal studies, and there are practically very few human studies. Studies examining the behavioural impact of VDR knock-out in mice have reported an increase in behaviours suggestive of heightened anxiety and psychosis, but not depression (such as greater immobility in tail suspension test).[65,66] Indeed, research attention on the effect of vitamin D on brain function has been more substantive in schizophrenia than depression.

The impact of vitamin D on monoamines involved in the pathobiology of depression is not well understood either. Vitamin D may upregulate genes involved in the synthesis of tyrosine hydroxylase, an enzyme involved in the synthesis of catecholamines.[18] A protective role for vitamin D in reducing the negative effects of dopaminergic toxins, possibly by increasing glial cell-line derived neurotrophic factor, has been proposed.[67,68] This may reciprocally affect serotonin transmission in the brain, given the links between dopaminergic and serotonergic systems. Preclinical models also point to a cross-talk between vitamin D and glucocorticoid receptors, and this may hold significance given the dysregulated hypothalamo-pituitary axis in depression.[69] Evidently, more human studies and animal models are required to further our understanding

of biological links between vitamin D and depression. This will not only advance our understanding of the various pharmacological therapies but also, potentially, open up new therapeutic targets in depression.

Gaps in understanding the effect of vitamin D supplementation in depression

As summarized earlier, several trials that sought to evaluate the effect of supplemental vitamin D on depression have been published in the last five years. Two subtly different meta-analyses have attempted to summarize the existing data in this regard—one by Gowda *et al.*[70] that synthesized trials where the outcome of interest was subsyndromal depressive symptoms and the other by Vellekkatt and Menon[71] that only included trials on syndromal or clinical depression. The results were illuminating. The pooled effect size (standardized mean difference) in the first meta-analysis was 0.28 (95 per cent CI = –0.14 to 0.69) while in the second one, it was 0.58 (95 per cent CI = 0.45 to 0.72). This clearly indicates that adjunctive vitamin D may be more beneficial for subjects with clinical depression than subsyndromal depressive symptoms.

Interestingly, in the Gowda *et al.* paper, effects remained non-significant in subgroups stratified on serum 25(OH)D levels (cut-off of 50 nmol/l), vitamin D dosing used (cut-off of 4,000 IU/day), and whether vitamin D was used together with other supplements or anti-depressants, implying that these parameters may not be significant moderators in the relationship. Of note, there were limited trials in the Vellekkatt and Menon paper, with one trial contributing disproportionate weight in the meta-analysis. Several sources of bias, such as lack of allocation concealment and blinding, were also noted by the authors. As such, the garbage in, garbage out phenomenon cannot be ruled out.

From the above, it is clear that there are several unknowns in the literature. First, there is a need for larger and more rigorous trials to answer the question of whether the beneficial effects of vitamin D are different in subjects with subsyndromal depression versus syndromal major depression. Second, the biological plausibility that the beneficial effects of vitamin D may be higher in clinically depressed subjects with concurrent vitamin D deficiency emphatically merits further investigation.

And last, there is very little evidence among special populations like pregnant women or postpartum mothers. The available evidence is mostly cross-sectional, and we were able to find only one interventional study[56] in this group. Nevertheless, the positive results of this trial and another related trial that linked prenatal supplementation of vitamin D to a decrease in risk of schizophrenia in the offspring's life[72] are encouraging. Thus, whether supplemental vitamin D may exert benefits on primary prevention of depression is a question that needs to be systematically examined. Further, the directionality of the association between vitamin D and PPD is inconsistent because both high and low vitamin D levels have been shown to be associated with a risk of PPD.[73]

Other important gaps in evidence include a lack of clarity on whether a change in vitamin D levels parallels that of depressive symptoms following treatment. This would be expected if, indeed, vitamin D and depression share a cause–effect relationship. Studying the relationship between change in inflammatory marker status and vitamin D levels in major depression will throw more light on the three-way association and aid understanding of the mediating mechanisms involved in the purported benefits of vitamin D in depression.

Recommendations for future research

Based on the above, we propose the following recommendations that may be kept in mind by prospective researchers who intend to study the preventive and therapeutic roles of vitamin D in depression:

1. Use standard doses/duration/frequencies/route of administration of vitamin D: Preliminary evidence shows that oral and parenteral routes are comparable in efficacy, but compliance is likely to be of greater concern in oral supplementation. Parenteral supplementation may be more efficient in this regard, and there are supporting studies showing beneficial effects of a single adjunctive parenteral dose of vitamin D in depression[44]
2. Address key methodological issues: Based upon the findings from an interesting meta-analysis[49], which found a significantly higher effect size for vitamin D in depression when combining trials without methodological flaws, a few important recommendations can be made. First, researchers must avoid ineffective interventions, which in this context means those that do not change the vitamin D status of the patient. Second, researchers must strive to measure vitamin D levels of depressed subjects at baseline and target subjects with vitamin D deficiency (defined as levels less than 20 ng/ml) rather than vitamin D insufficiency (defined as 21–29 ng/ml) when the aim is to evaluate the therapeutic effects of supplemental vitamin D in depression.[74] Ethno-specific desirable reference ranges for vitamin D need to be computed, keeping in mind the effect of confounders such as age, sex, and ultraviolet B (UVB) radiation.[75] Whenever

possible, the goal of supplementation must be to change the vitamin D status of the trial participant. As substantiated earlier, it also appears to be a sound idea to enrich vitamin D trials with depressed subjects also having concurrent vitamin D deficiency. Based on the available evidence, it appears that, for favourable benefits in depression, a supplemental dose of ≥800 IU daily for 4–6 weeks or a single parenteral dose of 3,00,000 IU of vitamin D should be given along with initiation of antidepressant treatment. The question of how long to continue supplementation is less clear, but it is probably beneficial to give until there is a change in vitamin D status of the patient (from deficient or insufficient to normal)

3. Use uniform assay procedures and outcome measures: This is necessary to facilitate inferences. Researchers must develop standard protocols for vitamin D assay and supplementation in clinical practice. The recommended assay to measure different types of vitamin D is the chromatographic procedure of liquid chromatography-tandem mass spectrometry (LC-MS/MS).[76] Uniform instruments must be used to assess depression outcomes of interest. Adhering to these steps would, undoubtedly, enhance cross-cultural comparability of findings
4. Identify depression subgroups that would benefit maximally from supplemental vitamin D: Just as there appears to exist an inflammatory biotype of depression,[77] it also seems plausible that there is a subset of patients with depression who may benefit maximally from vitamin D supplementation. The challenge for us is to find out that subpopulation, and enriched trials certainly appear to be a step forward to achieve this. From the available literature, it appears that patients who are obese, elderly, adolescent, or homebound and those with chronic illness may be more likely to benefit from vitamin D-based interventions, and this merits further study
5. Estimate concurrent changes in vitamin D, inflammatory markers, and depression: Researchers should try to evaluate whether changes in vitamin D levels and systemic inflammatory markers parallel that of depression scores. This will provide further evidence to support the links between vitamin D and depression and also give valuable insights into the biological mechanisms behind this association
6. Investigate the benefits of suprathreshold dosing of vitamin D: Thus far, the available trials have only looked at using supplementation to correct preexisting vitamin D deficiency. It may be worthwhile to check if additional supplementation helps with residual symptom management in depression and prevention of further episodes

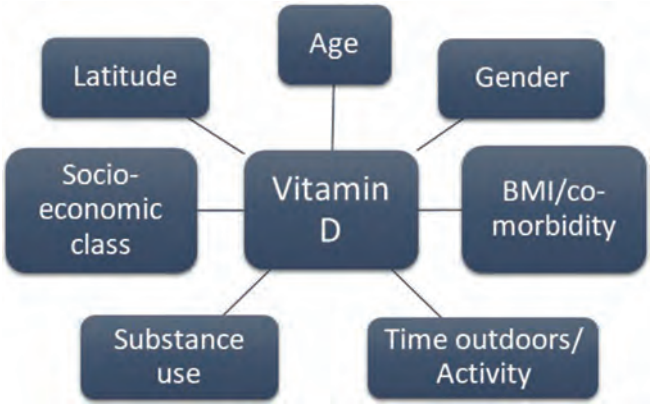

Figure 2: Key confounders in the relationship between vitamin D and depression

7. Adequate adjustment for confounding factors: This is important, to avoid the danger of spurious associations. There are many important confounders that researchers should be aware of, and these include both demographic and lifestyle factors. Additionally, in special populations such as postpartum mothers, controlling for variables including, but not limited to, social support, the gender of the baby, and the educational status of the mother assumes significance. Figure 2 depicts the key confounding factors in the relationship between vitamin D and depression.

CONCLUSION

The evidence clearly supports a relationship between vitamin D and depression, though the directionality of the association can be contested. This is partly because most of the evidence comes from cross-sectional studies. The biological links between the two can be explained on the basis of the homeostatic, immunomodulatory, and neuroprotective roles of vitamin D. Pooled evidence from RCTs suggest superior therapeutic benefits of vitamin D supplementation in clinical, rather than subsyndromal, depression. Many gaps in evidence remain, and this must be addressed through future trials that employ uniform assays, dosing protocols, and outcome measures. Adequate control of confounders and enriching depression trials with subjects also having concurrent vitamin D deficiency appear to be key steps forward in delivering results that would be scientifically sound, valid, and translational.

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Conflicts of interest

There are no conflicts of interest.

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Review Article

Repurposing Potential of Ketamine: Opportunities and Challenges

C. S. Gautam, Sonia S. Mahajan, Jatin Sharma, Harmanjit Singh, Jagjit Singh

ABSTRACT

Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor which also interacts with various other receptors that account for its myriad actions. Originally approved as a general anesthetic, it is being explored to be repurposed for numerous other indications such as depressive disorders, suicidal ideation, substance-use disorders, anxiety disorders, chronic pain, refractory status epilepticus, and bronchial asthma exacerbations. Numerous trials are ongoing for the same. The nasal spray of esketamine, a more potent S (+) enantiomer of ketamine, has been approved by the United States Food and Drug Administration (USFDA) for treatment-resistant depression along with the oral antidepressants. However, there are concerns about its safety on long term use, given its psychedelic effects and potential abuse. In this review, we discuss repurposing ketamine for potential therapeutic use and about the safety concerns related to ketamine and esketamine.

Key words: *Depression, esketamine, repurposing, safety*

Ketamine, a phencyclidine derivative, was developed in the year 1962 to overcome the psychotomimetic side effects and abuse potential of the parent drug phencyclidine.[1] It is a racemic mixture of two enantiomers S (+) and R (–), and its S isomer esketamine is more potent than the racemate ketamine having fewer side effects.[2] It was approved in 1970 by the United States Food and Drug Administration (USFDA) for use in humans as an intravenous anesthetic agent.[3] Drug repurposing or re-profiling, for new potential therapeutic areas, holds a great advantage over conventional drug development in reducing the cost, saving time, and the requirement of less data since such candidates have already undergone the tests for toxicity and regulatory work-up.[4]

Ketamine, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor, acts on numerous other receptors, contributing to its legion effects and uses. It has antagonistic actions at L-type, voltage-gated Ca^{2+} channels; nicotinic and muscarinic acetylcholine receptors; hyperpolarization-activated cyclic nucleotide-gated (HCN) channels; voltage-sensitive sodium channels, and large-conductance, K_{Ca}

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Department of Pharmacology, Government Medical College and Hospital, Chandigarh, Punjab, India

Address for correspondence: Dr. Harmanjit Singh
Department of Pharmacology, Government Medical College and Hospital, Chandigarh, Punjab, India. E-mail: harman_gmcp@yahoo.com

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channels (BK channels). Also, it causes activation of μ and δ opioid, α-amino-3-hydroxy-5-methyl-4-isoxazo lepropionic acid, (AMPA) and γ –aminobutyric acid A ($GABA_A$) receptors.[3]

This review article focuses on the repurposing potential of ketamine, its therapeutic uses and the safety concerns related to ketamine and esketamine.

The current evidence and ongoing trials available regarding the use of ketamine in various approved and potential therapeutic indications are given in Table 1. Given its myriad actions and great repurposing potential, it is approved or is being investigated for the following conditions.

Anesthesia

Ketamine is an agent used for induction of general anesthesia, particularly in patients who are hemodynamically unstable or having bronchospasm, and in geriatric and pediatric patients.[5] It is used in doses 0.5–1.5 mg/kg intravenously (i.v.), 4–6 mg/kg intramuscularly (i.m.), and 8–10 mg/kg per rectum for induction, and as an i.v. infusion of 25–100 μg/kg/minute for maintenance of anesthesia.[6] It produces profound analgesia, amnesia, and unresponsiveness to commands but does not produce complete unconsciousness (dissociative anesthesia). (S)–ketamine also induces sedation at doses 3–9 mg/kg intranasally.[7]

Analgesia

In subanesthetic doses, ketamine is an effective analgesic for postoperative pain. It is efficacious for management of high levels of chronic as well as acute postoperative pain in doses 0.15–0.25 mg/kg i.v. It also reduces the opioid requirement in these patients.[8] Further, preliminary evidence suggests that ketamine may also be used in these doses for acute post -traumatic pain management as an alternative to opioids.[9]

It is used as a third-line drug or adjuvant for cancer pain not responding to standard drugs like opioids, amitriptyline, gabapentin, and nonsteroidal antiinflammatory drugs. However, evidence regarding its efficacy and safety in cancer pain is insufficient.[10-13] A Phase I/Phase II, prospective, single-group, open-label clinical trial (NCT03146806)[14] is recruiting participants to evaluate the safety and utility of intranasally administered ketamine for the treatment of cancer pain. A phase II single-arm, open-label trial to evaluate the effectiveness of continuous intravenous infusion of ketamine in terminally ill cancer patients is in the patient recruitment stage (NCT03362073).[15]

Ketamine is also used as an adjuvant drug for intractable chronic noncancer pain, complex regional pain syndrome (CRPS), and refractory neuropathic pain.[16-18] NMDA antagonism in the brain and spinal cord is the main mechanism of its analgesic effect.

Table 1: Current evidence for the repurposing potential of ketamine

Approved/Potential Therapeutic Use	Proposed Mechanism of Action	Evidence
Cancer pain	NMDA antagonism in the brain and spinal cord	Lauretti *et al*., 1999[10] Finkell *et al*., 2007[11]
Treatment Resistant Depression*	Increase in the signaling of mTOR, increased protein synthesis via dephosphorylation of eukaryotic translation elongation factor 2 and increase in BDNF, TrkB and GSK-3-associated pathways in TRD	Murrough *et al*., 2013[23] Philips *et al*., 2019[24] Zheng *et al*., 2019[25] Singh *et al*., 2016[32]* Daly *et al*., 2017[33]*
Cocaine Use Disorder	Improved prefrontal cortex glutamate homeostasis causing synaptic improvements	Dakwar *et al*., 2017[38]
Opioid Use Disorder	Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements	Krupitsky *et al*., 2002[40] Krupitsky *et al*., 2007[41] Jovaisa *et al*., 2006[42]
Alcohol Use Disorder	Improved prefrontal cortex glutamate homeostasis, causing synaptic improvements	Wong *et al*., 2015[45]
Suicidal Ideation	Increased signaling via mTOR, BDNF and GSK-3 pathways	Canuso *et al*., 2018[48] Grunebaum *et al*., 2018[49] Grunebaum *et al*., 2017[50] Fan *et al*., 2017[28]
Anxiety Disorders (SAD, GAD)	Increased BDNF signaling in hippocampus	Taylor *et al*., 2018[55] Glue *et al*., 2018[56]
Refractory Status Epilepticus	NMDA antagonism and reduction in NMDA induced neurotoxicity	Rosati *et al*., 2012[62] Ilvento *et al*., 2015[63]
Bronchial Asthma	Inhibition of inflammatory cascade, reduction in markers of inflammation and bronchodilatation	Esmailian *et al*., 2018[67] Tiwari *et al*., 2016[68]

*Esketamine has been recently approved for use in patients with treatment resistant depression. BDNF – Brain-derived neurotrophic factor, GAD – Generalized anxiety disorder, GSK-3 – Glycogen synthase kinase-3, mTOR – Mammalian target of rapamycin, NMDA – N-methyl-D-aspartate, SAD – Social anxiety disorder; TRD – Treatment resistant depression, TrkB – Tropomyosin-related kinase B

Ketamine increases the inhibitory serotonergic signal and thus enhances the endogenous antinociceptive system.[19]

Depressive disorders

Ketamine has shown a rapid antidepressant response in the treatment of unipolar depression and treatment-resistant depression (TRD).[20] Its action is seen within 24 hours, lasting for 4–7 days (transient effect) after single intravenous administration of subanesthetic doses (0.5 mg/kg). High response rates with minimal side effects are observed with its use.[21,22] Further, it was observed that with the administration of repeated (six) infusions of ketamine to patients of TRD, cumulative and sustained antidepressant effects were obtained.[23,24] In a meta-analysis of randomized controlled trials (RCTs), ketamine given along with other anesthetic agents conferred a short term improvement in patients at early stages of electroconvulsive therapy (ECT).[25] However, ketamine has shown low antidepressant efficacy in elderly, with mild and transient adverse effects.[26]

Probable mechanisms responsible for rapid antidepressant effects of ketamine are increase in the signalling of mammalian target of rapamycin (mTOR), increased protein synthesis via dephosphorylation of eukaryotic translation elongation factor 2, and increase in brain-derived neurotrophic factor (BDNF). Various pathways associated with the action of ketamine are tropomyosin-related kinase B (TrkB) pathway, associated downstream phosphatidylinositol-3-kinase (P13K)-Akt pathway, and glycogen synthase kinase-3 (GSK-3)-associated pathways. Enhanced glutamate signalling via the AMPA receptors in the prefrontal cortical regions and subsequent increase in synaptogenesis and synaptic functioning also contribute to its antidepressant effects.[27,28]

A phase III randomized, initially double-blind, then open-label clinical trial (NCT03742557),[29] aimed to provide clinical evidence of responses in the form of neurological basis or underlying biomarkers of response after a series of ketamine administrations in patients with TRD, is currently in recruitment stage. Another phase II single-arm open-label trial evaluating the cortical neurophysiological functions after ketamine administration in patients of TRD is also in progress (NCT02935595).[30] Recently, Esketamine nasal spray has been approved by the USFDA for TRD. Esketamine, due to its safety concerns and potential for misuse and abuse will be available only through a restricted distribution system. Moreover, it is to be self-administered under the supervision of a healthcare provider, and the patient must be monitored for at least two hours after the dose due to the risk of sedation and dissociation.[31]

Esketamine is more potent, 0.40 mg/kg i.v. dose as comparable to 0.5 mg/kg i.v. ketamine. Antidepressant efficacy of intravenous esketamine is demonstrable at doses 0.2 mg/kg and 0.4 mg/kg, with better tolerability at low doses.[32] A recent clinical trial has demonstrated the rapid antidepressant effects of intranasal esketamine in patients of TRD in doses 56 mg and 84 mg and a safety profile comparable to i.v. ketamine.[33] A randomized, double-blind, non inferiority clinical trial making a neck to neck comparison of antidepressant efficacy of single intravenous infusion of 0.25 mg esketamine and 0.5 mg ketamine in patients with TRD is ongoing.[34] Current antidepressants take around 2–3 weeks for producing a response, and remission is seen in around 70% of patients (30% of patients did not respond).[35] Therefore, a rapid action of esketamine could be useful. Intranasal esketamine has also shown a transient impairment of cognitive performance in healthy individuals, which is manifested as slow performance time or with more rate of causing errors,[36] and it has been given a black boxed warning regarding risk for sedation; difficulty with attention, judgment, and thinking (dissociation); abuse, and suicidal thoughts, and behavior.[31]

Substance use disorders (SUDs)

Ketamine has been found to be efficacious in cocaine, heroin, and alcohol use disorders. In cocaine-dependent participants, ketamine (0.41 mg/kg) significantly increased the motivation to quit cocaine compared to lorazepam and also caused a significant reduction in cocaine craving.[37] Ketamine also caused a significant reduction (66%) in the rates of cocaine self-administration.[38] A phase III, randomized, double-blind, placebo-controlled trial (NCT03344419) is being conducted to evaluate the efficacy of ketamine infusion in cocaine use disorder is recruiting participants.[39]

High-dose ketamine (2 mg/kg) showed statistically significant improvement in the abstinence rates and reduced craving in patients with heroin dependence and nearly double the participants showed abstinence up to one year after multiple doses (up to three) as compared to a single dose of ketamine.[40,41] Ketamine effectively suppresses the physiological response to opioid withdrawal by decreasing mean arterial pressure, heart rate, and serum cortisol levels.[42] A phase III randomized controlled trial NCT03345173, in the recruiting stage, will evaluate the efficacy of ketamine in facilitating rapid naltrexone induction for acute detoxification of opioid users.[43]

It also improved the one year abstinence in patients of alcohol use disorder.[44] Ketamine reduced the requirement of benzodiazepines when used as an adjunct to them in the management of alcohol withdrawal symptoms.[45] Two Phase-2, placebo-controlled RCTs, NCT02649231 and NCT02461927, evaluating the efficacy of ketamine in alcohol use disorder are presently recruiting participants.[46,47]

Suicidal ideation

Ketamine, as well as esketamine, were found to be efficacious in reducing suicidal ideation and behavior in patients of major depression, bipolar disorder, and cancer. A single i.v. administration of sub anesthetic dose (0.5 mg/kg) ketamine produces rapid amelioration of suicidal thoughts and behavior within few hours, with sustained effect up to a week. Beneficial effects of ketamine have been observed for up to 6 weeks when combined with standard pharmacotherapy.[28,48-50] Although these results seem promising, psychotomimetic side effects and concerns regarding long term use of ketamine have to be kept in mind. An RCT (NCT01892995), yet to start recruiting, has been planned to evaluate the effect of ketamine in patients with acute suicidal ideation.[51] Another phase III RCT (NCT02418702), still in the prerecruitment phase, will evaluate the effect of ketamine on suicidal thinking of military persons.[52]

Anxiety disorders

The anxiolytic effects of ketamine in patients of major depression have been elucidated.[53,54] In a randomized, double-blind placebo-controlled trial in patients of a social anxiety disorder (SAD), it was observed that ketamine infusion, compared to placebo, showed a significant benefit in SAD symptoms in the first 14 days.[55] However, there is a need for active (e.g., midazolam) controlled trials to substantiate the anxiolytic effects and optimal dosing of ketamine. Weekly doses of ketamine 1 mg/kg given subcutaneously were well tolerated, and the dissociative symptoms were found to decrease after repeated dosing, thus helpful in maintenance of SAD.[56] Mechanism of its antianxiety effect is similar to that of its anti depressant effect, i.e., by activating synaptic plasticity, by increasing BDNF translation and secretion, and by inhibiting GSK-3, and activating mTOR signaling.[56,57]

A phase IV, midazolam controlled clinical trial (NCT02579928)[58] to evaluate the tolerability and short-term efficacy of ketamine for adolescents with medication refractory anxiety disorders (SAD, panic disorders, generalized anxiety disorder [GAD] and/or separation anxiety disorder) is currently ongoing. Another phase IV, double-blind RCT (NCT03043430)[57] is in progress (in recruiting stage) to evaluate the efficacy of intranasal ketamine for anxiolysis in pediatric patients.

Refractory status epilepticus

Evidence suggests that the activity as well as the number of NMDA receptors is increased in refractory status epilepsy. Ketamine reduces NMDA receptor-induced neurotoxicity and also has a neuroprotective role; hence, it could be effective for the treatment of refractory convulsive status epilepticus (RCSE).[59,60] Evidence also suggests that ketamine, at usual doses, has an epileptogenic potential and should be avoided in patients with epilepsy.[61]

In a small, open-label, uncontrolled study, it was observed that ketamine appears effective and safe for the treatment of status epilepticus in children.[62] However, large scale controlled trials are required to substantiate these findings.[62] Ketamine can be effectively used to treat RCSE as an alternative to general anesthetics and also avoids the need for endotracheal intubation in these patients.[63]

A phase III RCT (NCT02431663)[64] has been planned to evaluate the efficacy of intravenous administration of ketamine in children with RCSE while NCT03115489,[65] another phase II/III RCT, is investigating the efficacy of ketamine as a first-line agent for refractory status epilepticus. Both the trials are in the recruitment stage.

Exacerbation of severe bronchial asthma

Evidence shows that inhalational ketamine is effective for the treatment of severe exacerbations of asthma.[66] It leads to improved outcomes and a reduction in the need for mechanical ventilation. It inhibits inflammatory cascade, reduces inflammatory markers, and causes bronchodilation. Systemic effects like anxiolysis and decrease in mechanical work of breathing also contribute to this effect.[66]

In an RCT, i.v. ketamine in 0.4–0.5 mg/kg doses, followed by an infusion for 30 minutes produced a significant reduction in the peak expiratory flow rate (PEFR) among patients with mild-to-moderate bronchial asthma.[67] Ketamine has shown comparable efficacy to aminophylline in children with bronchial asthma poorly responding to standard therapy.[68]

A pilot study (NCT03338205)[69] is ongoing to assess the safety and utility of ketamine as adjuvant therapy in pediatric patients with acute status asthmaticus not responding to standard therapy.

Role as an immunomodulator

Ketamine has an immunomodulatory role as it interferes with the production of early mediators of immunity, reduces the proinflammatory influences, and prevents the extension of local inflammation.[6] Its antiinflammatory effect is thought to be due to inhibition of high mobility group box 1 (HMGB1) induced activation of endothelial cells.[70] It also increases mTOR signalling and subsequently suppresses autophagy and helps in amelioration of inflammation in ischaemia/reperfusion in the brain and in airway allergy.[71] However, ketamine also increases the levels of cytokines IL–6 and IL–1beta in mice hippocampus and has potential to cause neuroinflammation leading to neurodegeneration.[72]

CHALLENGES IN REPURPOSING KETAMINE: SAFETY, CAUTIONS, AND WARNINGS

The side effects of ketamine are dose-related.[2] Psychotomimetic phenomena like euphoria, dysphoria, psychomotor retardation, hallucinations, vivid dreams, and nightmares are common adverse effects.[73] Subanesthetic doses of ketamine can cause impairment of attention, memory, and judgement.[2] At higher anesthetic doses, tonic-clonic movements are very common (>10%).[2] Ketamine, in induction doses, can increase heart rate, blood pressure, and cardiac output and increases myocardial oxygen demand, making it unsuitable for the patients at risk of myocardial ischaemia.[74]

Ketamine should be used cautiously in patients with a history of psychiatric disorders, cerebrovascular accidents, epilepsy, glaucoma, hypertension, or ischaemic heart disease.[2]

Following toxicities are the concerns with long term use of ketamine and pose challenges in repurposing ketamine.

Neurotoxicity

Ketamine causes potent cerebral stimulation, especially in patients of seizure disorders, in whom it activates subcortical seizure activity.[75] It triggers clinical or electroencephalogram (EEG) seizure activity at doses >2 mg/kg intravenously.[75] It can cause subpial vacuolar myelopathy; focal lymphocytic vasculitis in medullary tissue, nerves, and leptomeninges of the spinal cord; and gliosis when administered intrathecally.[76,77] It increases cerebral blood flow and intracranial pressure; this raises the alarm regarding its use in patients with compromised intracranial compliance. However, the cerebral perfusion is not adversely affected. It should be avoided only in patients with structural obstruction to cerebral blood flow.[78]

Ketamine produced a dose- and duration-dependent increase in the levels of proinflammatory cytokines like IL–6 and IL–1β in the mice hippocampus, and this suggested that ketamine may lead to neurodegeneration.[72] An increased expression of Toll-like receptor–4 (TLR–4) by ketamine causes the subsequent increase in the proinflammatory cytokines.[72]

Cognitive impairment

Ketamine administration in healthy volunteers may produce central nervous system depression and/or intoxication, perceptual alterations, referential ideas or delusion, and negative symptoms such as mild-to-moderate alogia and increased latency of responding.[79] In a preclinical study, it was observed that a single subanesthetic dose of ketamine might cause protein damage and lipid peroxidation in the hippocampus.[80] This consequently affects the memory acquisition and retrieval. However, no reduction in memory consolidation was observed.[80]

Urinary tract toxicity

Evidence suggests that long term use of ketamine is associated with the urinary tract toxicity.[81] It can cause symptoms such as frequency and urgency of micturition, urge incontinence, dysuria, and irritation. These generally settle after a few weeks of stopping ketamine. Findings such as bladder instability, detrusor overactivity, interstitial cystitis, vesicoureteric reflux, hydronephrosis, papillary necrosis, and renal impairment are observed during urinary tract investigations. Irreversible damage may lead to renal failure.[82,83] The mechanism behind this is still not clear; however, *in vitro* studies have revealed that there was a direct interaction between ketamine and urinary bladder.[84]

Abuse potential of ketamine

Ketamine is generally abused as a recreational drug and carries a strong reinforcing effect. It is mostly used intranasally, which produces rapid effects, and there is a need to tightly regulate its availability in the market.[85] The primary psychological effects of ketamine are anesthesia and sedation. When abused, it produces relaxation at low doses and a dream-like state at high doses. Acute use produces ethanol-like effects, and chronic use produces positive and negative symptoms of schizophrenia. It is hypothesized that, increased dopamine release due to ketamine-induced blockade of NMDA receptors on GABA neurons in the reticular nucleus of the thalamus is the basic mechanism of its abuse.[85] A single subanesthetic dose of ketamine has

been shown to increase the level of dopamine in the prefrontal cortex of rats.[86]

CONCLUSION

Ketamine appears to hold a promising repurposing potential for the treatment of various conditions like major depression, generalized and social anxiety disorders, refractory status epilepticus, substance use disorders, and bronchial asthma exacerbations. In addition, esketamine has been recently approved for TRD. However, given its recreational effects, abuse potential, and potential safety concerns, long term use of ketamine may pose a problem and should be carefully watched for. There is a need to do tremendous research and generate a high level of evidence to ascertain its efficacy and safety for these indications.

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There are no conflicts of interest.

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Original Article

Resting State Quantitative Electroencephalogram Power Spectra in Patients with Depressive Disorder as Compared to Normal Controls: An Observational Study

Jnanamay Das, Shailly Yadav

ABSTRACT

Introduction: A significant number of quantitative electroencephalogram (qEEG) studies indicate that increased spectral activities distinguish patients with depressive disorder from control subjects. But they did not yield consistent findings in the delta, theta, alpha, or beta bands. **Methods:** A total of 30 drug-naïve or drug-free subjects with a depressive episode or recurrent depressive disorder were compared with 30 age, sex, education, and handedness-matched healthy controls using qEEG power spectra in six frequency bands (delta, theta, alpha, beta, slow beta, and fast beta) and total activities separately. Spectral analysis was performed on a section of 180 s of qEEG digitized at the rate of 512 samples/s/channel, and absolute powers were log-transformed before statistical analysis. **Results:** Statistically significant differences between the patients and normal controls were found in the delta and the total bands, while Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) score predicted the fast beta spectral power at the left temporal region. In the entire region of the brain, in the theta band, lesser absolute spectral power was found in patients than normal controls, whereas in the fast beta band, it was greater. In other bands, greater powers of spectral activities were found in patients than normal controls consistently in the parietal and occipital regions. **Conclusion:** Various findings of qEEG absolute power spectra could demonstrate a difference between the patients with depressive disorder and the normal controls independently and efficiently. However, all the differences collectively showed stronger evidence. The findings may steer future studies to differentiate the patients with depressive disorder from controls.

Key words: *Depression, qEEG, power spectra, healthy controls, resting state*
Key messages: *qEEG absolute power spectra differed between patients with depressive disorder and the normal controls.*

Earlier studies with electroencephalogram (EEG) described various changes in depression in the form of background frequencies and sleep-related abnormalities.[1,2] But later studies based on computerized quantitative EEG (qEEG) provided objective as well as reliable data, and the possible

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Department of Psychiatry, ESI Hospital, Sector-15, Rohini, New Delhi, India

Address for correspondence: Dr. Jnanamay Das
135, Modern Apartments, Sector-15, Rohini, New Delhi - 110 089, India. E-mail: drjdas@hotmail.com

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psychiatric diagnostic utility of these methods of assessment has already been evaluated.[3,4] But various qEEG studies in depressive disorder exhibited a wide range of findings. Depressed patients presented with increased beta activity: more precisely, increased fast beta activity was found in frontal areas in patients of major depression with melancholia.[5,6] For the alpha frequencies, unipolar patients with depressive disorder had symmetrical or increased power on the left side compared to the right.[7] Although patients with depressive disorder exhibited greater alpha blocking, euthymic recovered depressed subjects showed greater alpha amplitudes, whereas unmedicated currently depressed patients exhibited elevated EEG alpha and beta.[8-10] In delta and theta bands, increased absolute powers of the right hemisphere were found in drug-free depressed patients compared to controls, and no change was noted after clinical improvement.[11] But patients with depression had also shown decreased alpha activity and increased delta, theta, and beta activity but no interhemispheric asymmetry.[12] A significant increase in spectral power in theta (4–7.5 Hz), alpha (7.5–14 Hz), and beta (14–20 Hz) frequency bands was found in depressed patients at parietal and occipital sites, both in eyes closed and eyes open conditions. An increase in slow (theta and alpha) activity in the EEG pattern reflected a decreased cortical activation in these brain regions, and enhancement of beta power correlated with anxiety symptoms which were suggested as playing an important role in the onset of depressive disorder.[13]

However, a few recent studies point toward the involvement of anterior cingulate and prefrontal cortices in depression. Subjects of major depressive disorder (MDD) showed significantly elevated current density in the delta, theta, alpha, beta1 (13–18 Hz), and beta2 (19–21 Hz) frequency bands relative to controls in anterior cingulate and prefrontal cortices when qEEG data were analyzed using low-resolution electromagnetic tomography method.[14] The importance of the intrinsic functional connectivity of the left dorsolateral prefrontal cortex (DLPFC) with the subgenual cingulate area in depression has already been established.[15] The MDD group, and particularly the depressed males, displayed increased overall frontal and parietal alpha power and left mid-frontal hypoactivity associated with increased theta2 (6–8 Hz) activity in the anterior cingulate cortex (ACC), whereas females with MDD had increased right parietal activity, suggesting increased emotive arousal. It was proposed that altered theta in the ACC might reflect emotion regulation abnormalities in MDD.[16] Concurrent measurements of brain electrical activity by EEG and glucose metabolism by positron emission tomography showed that the rostral ACC was the largest cluster with positive correlations followed by right frontotemporal regions in theta band only. The results pointed toward a link between theta and cerebral metabolism in the ACC as well as disruption of functional connectivity within frontocingulate pathways in depression.[17] ACC plays a key role in treatment outcome in depression as dorsolateral prefrontal and dorsal cingulate regions are implicated in cognitive control.[18]

A magnetic resonance imaging (MRI) study confirmed structural changes in the brain of depressed subjects, demonstrating significantly lower gray matter volume in the left and right DLPFC.[19] However, evidence related to peripheral growth factors, proinflammatory cytokines, endocrine factors, and metabolic markers are still growing to contribute to the understanding about the pathophysiology and to provide a biological signature of depressive disorder.[20] But in electrophysiology, though a significant number of qEEG studies indicated that increased spectral activities distinguished depressed from control subjects, they did not yield consistent findings in the delta, theta, alpha, and beta bands.[21] This study was an attempt to assess the profile of the absolute spectral activities in patients with depressive disorder as a group compared to normal healthy controls.

METHODS

This study was conducted at the Central Institute of Psychiatry (C.I.P.), Ranchi, India. It is a postgraduate teaching hospital having bed strength of 673 and imparts training in psychiatry, clinical psychology, psychiatric social work, and psychiatric nursing. The study was approved by the Institute Ethics Committee and written informed consent was taken from all the participants (and their legally qualified representatives in case of patients) before enrolling them for the study. The subjects were recruited by purposive sampling technique over a period of 10 months from November 1, 1996 to August 31, 1997.

Data collection and participants

The subjects who constituted the sample were outpatients and inpatients with a diagnosis of a depressive episode or recurrent depressive disorder according to the Diagnostic Criteria for Research of International Classification of Diseases 10th edition.[22] Both male and female patients aged between 18 and 60 years formed the patient group. Only those patients who were drug-naive completely or psychotropic-drug-free for at least 4 weeks were included. Patients with a diagnosis of schizoaffective disorder, mixed affective state or depression as a part of bipolar affective disorder, or organic mood disorder (depressed type) and the patients who received electroconvulsive therapy within 6 months before the EEG study were excluded. Female patients

who were in menstrual period were also excluded to avoid the changes in electrical activities of the brain due to altered hormone levels. The control group consisted of age, sex, education, and handedness-matched healthy subjects. In the control group, subjects with a history of any psychiatric illness, any major physical illness, neurological illness, significant head injury, or family history of psychiatric illness in first-degree relatives were also excluded.

Clinical assessment

Relevant sociodemographic and clinical data of all the participants were collected in a specially designed sociodemographic and clinical data sheet. The patients were assessed on various psychiatric rating scales on the day of qEEG recording procedure: Structured Interview Guide for the Hamilton Depression (SIGH-D) rating scale,[23] Hamilton Anxiety (HAM-A) rating scale,[24] the Brief Psychiatric Rating Scale (BPRS),[25] to assess the severity of depression, the anxiety associated with depression, and the general psychopathology, respectively. Hindi version of Sidedness Bias Schedule was used to assess the hand preference in both the patient and the control groups.[26] Healthy controls were screened with the General Health Questionnaire (GHQ-5).[27]

EEG recording

The patients, as well as the normal controls, were informed regarding the qEEG recording procedure in detail to remove any apprehensions so that the artifacts were reduced to a minimum. If electromyogram (EMG) related artifacts were present in the qEEG recording, the recording was discontinued, and the patients underwent Jacobson's Progressive Muscular Relaxation (JPMR) training. If the EMG-related artifacts still persisted, the particular qEEG and the patient both were excluded from the study. Among the included patients, six underwent JPMR training, but none of the control group required JPMR training. The participants were advised to avoid the use of tea, coffee, or nicotine for at least 1 hour before the recording. qEEG was recorded for 15–20 min, while subjects rested with their eyes closed in an alert state in a soundproof, light-attenuated room, using 25 monopolar electrodes placed according to the international 10–20 system and referred to link earlobes. A four-pole filter with a 70 Hz cut-off frequency and a low-pass band filter with 0.1 Hz was used. The time constant was 0.1 s, and the electrode-skin impedance was kept below 5 kΩ. The qEEGs were digitized at 512 samples/s/channel using Neurofax EEG 2100K (Nihon Kohden, Japan).

Spectral power analysis

First 180 s epochs of artifact-free EEG data were visually selected from each recording after carefully excluding segments with eye movement, blink, electrocardiogram (ECG), EMG, movement, electrode, and perspiration artifacts or changes related to drowsiness. Selected EEG epochs were recomputed against a common average reference. qEEGs from 21 electrodes: FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, FZ, CZ, PZ, T1, and T2 were used for analysis to calculate spectral power, expressed in μV, by fast-Fourier transformation (FFT) using Welch's averaged periodogram method.[28] Frequencies between 1.5 and 35 Hz were analyzed, divided into delta (1.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz), beta (whole, 13–35 Hz), slow beta (13–20 Hz), and fast beta (20.5–35 Hz) bands along with total spectral activities (1.5–35 Hz). Rhythm version 10.1 software (Stellate Systems, Canada) was used for qEEG analysis.

Statistical analysis

Descriptive analysis was performed to calculate the percentage, mean, and standard deviation of the clinical data of the experimental group and demographic data of both the groups. Calculated powers of absolute spectral activities were extracted from the bound files with (dot). BND extension created as a result of FFT. As the absolute spectral power was not normally distributed (Shapiro–Wilk test), normalization was achieved by log-transformation as recommended by "neurometrics."[29,30] *Post-hoc* classification of the sample was done on the basis of patients with depressive disorder as a group as compared to normal subjects. To compare the power spectral activities of the depressive disorder group and the control group, a separate multivariate analysis of variance (MANOVA) was conducted for each qEEG band, and if a significant relationship was found, it was followed by an ANOVA for the spectral powers at each electrode region. A linear regression analysis for patients with depressive disorder (n = 30) with SIGH-D, HAM-A, and BPRS scores as predictor variables for spectral power (in areas where significant variations across normal subjects were found) were performed using separate entry method. Subsequently, we computed Pearson correlation coefficients for patients with depressive disorder (n = 30) between SIGH-D, HAM-A, and BPRS scores and significant spectral measures separately. $P < 0.05$ was considered as statistically significant. Statistical analysis was done using Statistical Package for Social Sciences of International Business Machines Corporation, New York, USA (SPSS v 23).

RESULTS

Sociodemographic and clinical data

Though qEEG recording was done in case of 36 patients, six patients were excluded from the analysis due to the presence of various artifacts (ECG, EMG, eye

movement, sweat). Among 30 patients, 21 were drug-naive. Complete profiles of both the groups and the scores of various rating scales have been given in Table 1.

Spontaneous (<35 Hz) spectral power

MANOVA [Table 2] for comparison of the patient group and the healthy control group showed a significant difference for the spectral power in the delta band and the total band. A similar trend was observed in case of the theta band, though it did not reach the significance level of <0.05. No significant interaction was found for alpha band × group, beta band × group, slow beta band × group, fast beta band × group. Supplementary one-way ANOVA showed a significant difference between the patients and the healthy controls in delta band spectral power [Table 3a] at FP1, P3, FZ, and CZ electrode regions, and a trend toward significance was found at FP2 region. However, in ANOVA, no statistically significant difference was found in spectral powers over any of the electrode regions in theta and total bands.

In the delta band [Table 3a] at almost all the electrode regions except at T2, F7, F4, and P4, the values of the means were greater in the patient group than the normal subjects, indicating more delta power in drug-free patients with depressive disorder than the controls. In the theta band [Table 3a] at all the electrode regions, the mean values of spectral powers were lesser in the patient group, indicating lesser theta power in the patients with depressive disorder than the control group. In the alpha band [Table 3a] at most of the electrode regions except at T2, F7, T1, T3, and F4, the mean values of spectral powers were greater in the patients, indicating more alpha power in the drug-free patients with depressive disorder than the control group. In the beta (whole) band [Table 3b] at most of the electrode regions, the mean values of spectral powers were greater in patients than the control group except at T1, T2, FZ, and PZ electrode regions, indicating more beta power in the drug-free patients with depressive disorder than the normal controls. In slow beta band [Table 3b], mean values of spectral activities were found to be greater at FP2, T4, T6, C4, P4, O2, F3, C3, P3, O1, and FZ electrode regions and lesser at F8, T2, FP1, F7, T1, T3, T5, F4, CZ, and PZ electrode regions than the control group, indicating increased and decreased slow beta power, respectively, in patients with depressive disorder than the normal controls. In the fast beta band [Table 3b] at all the electrode regions, the mean values of spectral activities were greater in patients with depressive disorder, indicating higher fast beta power in the drug-free patients with depressive disorder than the normal control group. In the case of total spectral activities [Table 3b] at most of the electrode regions, the mean values were greater in patients with depressive disorder than that of control group except at T2, F7, T1, and F4 electrode regions, indicating increased total spectral power in the drug-free patients with depressive disorder than that of the normal control group.

Regression and correlation analysis

Linear regression analysis found SIGH-D score ($r = 0.448$; constant = 0.105; $P < 0.05$) as a predictor variable for the fast beta (beta2) spectral power at T3 electrode region (left temporal region) in patients with depressive disorder ($n = 30$). SIGH-D score also showed a significant correlation with the spectral power of the fast beta band at T3 electrode region ($r = 0.448$; $P < 0.05$). Figure 1 shows the scatter plot. No significant correlation between any of the HAM-A

Table 1: Details of both the groups

	Drug free patients with depressive disorder (Group A)	Normal control (Group B)
Total no (*n*)	30 (Drug naïve: *n*=21)	30
Male/Female	M=21, F=9	M=21, F=9
Mean age	31.77±10.10 years	32.07±8.76 years
Mean of total period of education	7.27±5.95 years	7.67±5.72 years
Handedness	Right handed: *n*=30, Left handed: *n*=0	Right handed: *n*=30, Left handed: *n*=0
Details of the drug free patients with depressive disorder		
Total duration of illness	Mean=36.59±68.48 months	
Duration of current episode	Mean=39.07±44.80 weeks	
Duration of episode	9 months or less: *n*=19 (63.3%)	
	More than 9 months: *n*=11 (36.7%)	
Number of episodes of depression	Single episode: *n*=21 (70%)	
	More than one episodes maximum up to 5: *n*=9 (30%)	
Family history of psychiatric disorders	Present: n=15 (50%) [8 patients (26.7%) had a history of affective disorder]	
	Absent: *n*=15 (50%)	
Structured interview guide for the hamilton depression (SIGHD)	Mean=27.30±5.59	
Hamilton anxiety rating scale score (HAM-A)	Mean=18.53±3.75	
Brief psychiatric rating scale score (BPRS)	Mean=18.13±5.32	

and BPRS scores and spectral power values of any other bands were found.

Table 2: Details of MANOVA (Wilks' Lambda) comparing the absolute powers of the drug-free patients with depressive disorder and the control group

Band	*F* (df=21,38)	*P*	Partial η^2
Delta	3.035	0.001	0.626
Theta	1.816	0.054	0.501
Alpha	1.547	0.119	0.461
Beta	1.612	0.098	0.471
Slow beta	1.164	0.333	0.392
Fast beta	1.479	0.144	0.450
Total	3.922	<0.001	0.684

DISCUSSION

In this study, the absolute power of spectral activities was found to be greater on both the sides in delta band in drug-free patients with depressive disorder than normal controls in almost all the areas of the brain. MANOVA showed a significant difference between the two groups (P = 0.001). Moreover, ANOVA revealed a significant difference between the two groups at the left frontal, left parietal, and especially the central regions. In previous qEEG studies in depression also, increased delta has been found.[11,12,14] This points toward decreased cortical activation in these brain

Table 3a: Mean, S.D. and *F* Ratio (ANOVA) of absolute powers of the drug free patients with depressive disorder and the control group

Electrode	Group	Delta		Theta		Alpha	
		Mean±S.D.	*F* (ANOVA)	Mean±S.D.	MANOVA	Mean±S.D.	MANOVA
FP2	A	1.66±0.20	3.46	1.16±0.23		1.49±0.42	
	B	1.57±0.19		1.25±0.40		1.44±0.49	
F8	A	1.57±0.23	0.73	1.12±0.21		1.41±0.37	
	B	1.52±0.24		1.22±0.40		1.40±0.50	
T2	A	1.50±0.24	0.21	1.23±0.23		1.51±0.36	
	B	1.53±0.30		1.32±0.38		1.54±0.46	
T4	A	1.29±0.27	0.49	1.05±0.26		1.42±0.36	
	B	1.24±0.29		1.12±0.42		1.39±0.43	
T6	A	1.35±0.26	0.23	1.30±0.39		1.93±0.46	
	B	1.31±0.38		1.40±0.52		1.88±0.56	
FP1	A	1.64±0.20	5.81	1.14±0.24		1.49±0.44	
	B	1.52±0.16		1.25±0.38		1.45±0.47	
F7	A	1.50±0.26	0.00	1.08±0.26		1.43±0.41	
	B	1.50±0.26		1.23±0.41		1.45±0.48	
T1	A	1.58±0.39	0.02	1.25±0.30		1.55±0.35	
	B	1.57±0.34		1.34±0.42		1.56±0.46	
T3	A	1.35±0.28	0.57	1.05±0.25		1.42±0.37	
	B	1.29±0.29		1.18±0.42		1.45±0.44	
T5	A	1.31±0.25	2.98	1.21±0.33		1.70±0.45	
	B	1.18±0.33		1.26±0.46		1.65±0.48	
F4	A	1.09±0.36	0.85	0.84±0.28	NS	1.20±0.45	NS
	B	1.16±0.22		1.00±0.42		1.20±0.49	
C4	A	0.83±0.35	1.51	0.46±0.28		0.88±0.47	
	B	0.72±0.33		0.50±0.42		0.80±0.47	
P4	A	0.86±0.28	0.33	0.68±0.31		1.27±0.57	
	B	0.91±0.39		0.77±0.49		1.20±0.57	
O2	A	1.47±0.23	1.89	1.39±0.33		1.98±0.51	
	B	1.37±0.35		1.44±0.53		1.91±0.55	
F3	A	1.15±0.31	0.99	0.88±0.30		1.28±0.47	
	B	1.06±0.32		1.03±0.46		1.22±0.47	
C3	A	0.50±0.33	0.06	0.36±0.30		0.86±0.46	
	B	0.48±0.25		0.43±0.42		0.76±0.48	
P3	A	0.90±0.37	4.74	0.66±0.32		1.15±0.46	
	B	0.71±0.32		0.67±0.52		1.07±0.59	
O1	A	1.50±0.24	2.90	1.37±0.35		1.95±0.51	
	B	1.37±0.34		1.41±0.52		1.91±0.56	
FZ	A	1.33±0.35	11.05	1.06±0.27		1.40±0.44	
	B	1.08±0.21		1.15±0.50		1.34±0.52	
CZ	A	0.92±0.31	4.67	0.66±0.30		0.99±0.39	
	B	0.76±0.28		0.70±0.43		0.93±0.46	
PZ	A	0.87±0.35	1.37	0.61±0.32		1.05±0.51	
	B	0.78±0.26		0.66±0.52		1.05±0.57	

Group A: Drug free patients with depressive disorder; Group B: Controls; NS – MANOVA not significant

Table 3b: Mean, S.D. and *F* Ratio (ANOVA) of absolute powers of the drug free patients with depressive disorder and control group

Electrode	Group	Slow Beta		Fast Beta		Beta		Total Activities	
		Mean±S.D	MANOVA	Mean±S.D	MANOVA	Mean±S.D	MANOVA	Mean±S.D	F (ANOVA)
FP2	A	0.77±0.33		1.01±0.37		1.22±0.35		2.09±0.23	0.86
	B	0.75±0.28		0.88±0.23		1.14±0.23		2.02±0.30	
F8	A	0.69±0.32		0.82±0.30		1.08±0.29		1.98±0.23	0.21
	B	0.73±0.34		0.77±0.24		1.06±0.27		1.97±0.32	
T2	A	0.77±0.30		0.84±0.26		1.11±0.27		2.00±0.23	0.52
	B	0.84±0.30		0.80±0.25		1.13±0.29		2.05±0.32	
T4	A	0.80±0.35		0.93±0.36		1.18±0.35		1.91±0.24	0.51
	B	0.78±0.29		0.78±0.22		1.09±0.23		1.86±0.32	
T6	A	0.90±0.34		0.96±0.31		1.24±0.31		2.21±0.35	0.05
	B	0.90±0.38		0.84±0.32		1.19±0.34		2.18±0.45	
FP1	A	0.74±0.34		0.98±0.34		1.19±0.23		2.06±0.23	0.60
	B	0.75±0.27		0.89±0.25		1.13±0.24		2.01±0.28	
F7	A	0.68±0.33		0.82±0.29		1.06±0.30		1.95±0.27	0.13
	B	0.74±0.32		0.73±0.25		1.05±0.28		1.98±0.33	
T1	A	0.76±0.33		0.86±0.28		1.12±0.30		2.07±0.31	0.02
	B	0.87±0.31		0.80±0.30		1.15±0.29		2.08±0.35	
T3	A	0.82±0.35		1.04±0.43		1.26±0.39		1.95±0.26	0.06
	B	0.85±0.30		0.83±0.28		1.16±0.27		1.93±0.32	
T5	A	0.80±0.32		0.85±0.29		1.14±0.29		2.05±0.31	0.28
	B	0.85±0.29		0.78±0.25		1.12±0.27		2.00±0.37	
F4	A	0.51±0.42		0.72±0.44		0.94±0.43		1.71±0.33	0.02
	B	0.54±0.30	NS	0.63±0.24	NS	0.89±0.26	NS	1.72±0.34	
C4	A	0.30±0.32		0.36±0.31		0.59±0.37		1.39±0.31	0.97
	B	0.28±0.31		0.30±0.30		0.59±0.32		1.31±0.33	
P4	A	0.41±0.30		0.45±0.30		0.71±0.34		1.63±0.38	0.05
	B	0.37±0.37		0.34±0.31		0.65±0.36		1.60±0.41	
O2	A	0.96±0.34		1.04±0.38		1.32±0.35		2.30±0.36	0.08
	B	0.93±0.36		0.87±0.32		1.21±0.34		2.22±0.43	
F3	A	0.54±0.39		0.74±0.41		0.95±0.42		1.75±0.33	0.01
	B	0.54±0.32		0.66±0.22		0.93±0.23		1.74±0.36	
C3	A	0.29±0.31		0.32±0.31		0.56±0.37		1.26±0.36	0.22
	B	0.26±0.30		0.28±0.29		0.55±0.32		1.21±0.34	
P3	A	0.39±0.31		0.44±0.30		0.70±0.35		1.57±0.33	0.88
	B	0.35±0.36		0.34±0.34		0.65±0.36		1.48±0.43	
O1	A	0.95±0.32		0.97±0.36		1.27±0.34		2.27±0.35	0.33
	B	0.93±0.35		0.89±0.30		1.22±0.32		2.21±0.45	
FZ	A	0.61±0.40		0.77±0.43		1.02±0.40		1.90±0.31	1.18
	B	0.56±0.35		0.64±0.27		0.92±0.28		1.80±0.39	
CZ	A	0.26±0.36		0.48±0.41		0.65±0.44		1.50±0.30	0.85
	B	0.29±0.30		0.36±0.30		0.63±0.32		1.42±0.33	
PZ	A	0.30±0.32		0.33±0.31		0.60±0.34		1.50±0.34	0.10
	B	0.32±0.33		0.28±0.32		0.61±0.34		1.47±0.39	

Group A: Drug free patients with depressive disorder; Group B: Controls; NS – MANOVA not significant

regions.[13,31] Interestingly, none of the studies we reviewed on qEEG in depression evaluated the total effect of all the frequency bands. Here, MANOVA showed a significant difference between the drug-free patients with depressive disorder group and normal control group ($P < 0.001$) in the total frequency band, though no significant difference was found in ANOVA in any individual electrode region.

The higher power of the total spectral activities in most of the areas of the brain was almost similar to the findings of delta and alpha bands and was also comparable to previous qEEG studies in affective disorders and depression.[2,3,10,32,33] On the contrary, in theta band, in the entire region of the brain, both on the right and the left sides, lesser powers of spectral activities than that of normal controls were found, indicating that power of theta decreases as a whole in patients with unipolar depression, especially if they are untreated. MANOVA also showed a trend toward significance ($P = 0.054$) Abnormalities in theta band had been found in previous quantitative EEG studies in depression, and it was linked to cerebral metabolism in the ACC.[11,17,34-36] However, the findings were inconsistent. In contrast to our findings, increased absolute theta power has been found in patients with depression compared to healthy controls in "the entire region of the brain" too.[12]

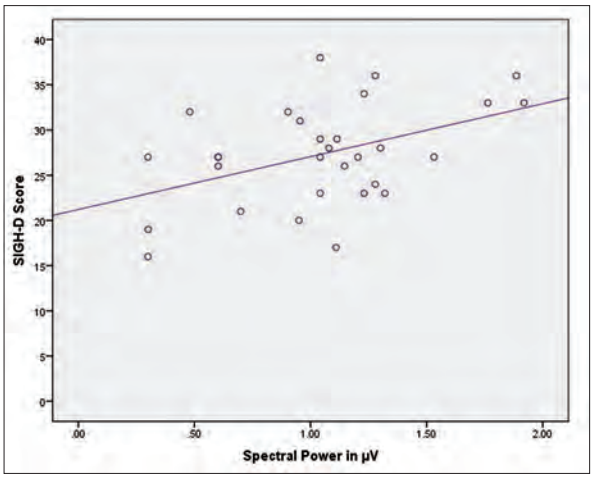

Figure 1: Scatter plot showing the correlation between Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (SIGH-D) Score and Spectral power of Fast Beta Band at T3 electrode region in patients with depressive disorder. SIGH-D: Structured Interview Guide for the Hamilton Depression Rating Scale

Moreover, in yet another study, depressed subjects also showed significantly lesser theta activity as well as no significant difference compared to healthy controls in the ACC activities.[17,37] This may be due to the difference in methodology or different technique used for assessment.

In most areas of the brain, especially in parietal and occipital regions, the powers of spectral activities of alpha, beta (whole), and slow beta bands were found to be greater in drug-free patients with depressive disorder than the normal controls. In the alpha band, similar findings were found in most of the qEEG studies.[7,8,10,14,34,38-40] But decreased absolute alpha power was also reported in one study in patients with depression compared to healthy controls in all brain areas except in right parietal and occipital channels.[12] In beta (whole) band too, the findings of our study are comparable to previous qEEG studies in depression.[5,10,12] In slow beta band again, findings of our study repeated those of previous studies where a significant increase in spectral power in beta frequency band was found in depressed patients at parietal and occipital sites.[13,14,31,34] In the entire region of the brain and on both sides, the powers of fast beta activities were found to be greater in drug-free patients with depressive disorder than the normal controls. SIGH-D score predicted the fast beta spectral power at the left temporal region. Moreover, SIGH-D score was also found to be correlated with the fast beta power in the temporal region of the left side. This suggests that the fast beta spectral power at left temporal region was related to the severity of depression. In a previous study, though the depressed subjects showed significantly elevated current density in 19–21 Hz (beta2) frequency band relative to controls in anterior cingulate and prefrontal cortices, no significance was found in 22–30 Hz (beta3) band.[14] An increase in slow alpha activity in the EEG pattern might reflect a decreased cortical activation in these brain regions, but the enhancement of beta power might correlate with anxiety symptoms that most likely played an important role in the onset of depressive disorder.[13,31]

The present study has got the following significant new findings which were not found in any of the previously published studies: (a) statistically significant differences between the patients with depressive disorder and normal controls were found in the delta band and the total qEEG band. A similar trend was found in the theta band too. Moreover, SIGH-D score or severity of depression predicted the fast beta spectral power at the left temporal region. (b) The theta band as a whole demonstrated a difference between the patients with depressive disorder and normal controls; in the entire region of the brain, the power of spectral activities was found to be lesser in patients with depressive disorder. (c) The fast beta band too as a whole could show the difference between the patients with depressive disorder and normal controls; in all the areas of the brain, the power of spectral activities was found to be greater in patients with depressive disorder. (d) In all other bands including total spectral activities, the power of the spectral activities was found to be greater in patients with depressive disorder consistently in parietal and occipital regions, which could also illustrate the difference between the two groups.

On the basis of these findings, it can be suggested that the future qEEG studies in depression should preferably compare the absolute spectral power of the same subjects in the depressed state with that of their treated state to search for a biomarker of depression.[18,20] Moreover, future qEEG studies should explore whether the patterns "decreased theta absolute power," or "greater power in the fast beta band" or "the combination of lesser power in theta band and greater power in the fast beta band" in all the areas of the brain can be demonstrated in cases of other psychiatric disorders or not when compared with healthy controls before declaring them specific for depression. As fast beta band showed significant changes in cases of depression, future studies should be designed to include gamma band (EEG beyond 35 Hz) also to get additional information.

STRENGTHS AND LIMITATIONS OF THE STUDY

Using age, sex, education, and handedness-matched control group in the present study formed two relatively homogeneous groups, overcoming the problem of heterogeneity. There is evidence that drugs such as antidepressants, antipsychotics, carbamazepine, sodium valproate, and other psychotropic drugs,

even when given for brief periods, can induce slight EEG disturbances.[10,41-43] Also, the use of common reference for estimation, low sampling rate for qEEG data acquisition, analysis of less than half a minute qEEG segments, and statistical analysis without log transformation of spectral activities remain as issues in some studies. Drug-free or naïve status before EEG recording in our patients, use of averaged reference for estimation of spectral activities, the high resolution offered by qEEG digitized at the rate of 512 samples/s/channel, analyzing 180 s of qEEG power spectra in six frequency bands along with total activities separately, and log-transformed absolute powers before statistical analysis, making them more homogeneous and more normally distributed, added credibility to our findings.

Limited sample size, recruitment of an unequal number of male and female subjects, and applying JPMR in a few patients to reduce EMG artifacts are the major limitations of this study. Future studies with larger sample size, evenly divided gender groups, and clustering analysis or classification analysis to differentiate the two groups might provide more robust evidence for the association between depression and qEEG absolute spectral activities.

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Conflicts of interest

There is no conflict of interest.

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Original Article

Depression Outcome Expectancy in Primary Care in Singapore: Symptom Severity as a Mediating Determinant

Shannon Chin, Kokkwang Lim, Chee Khong Yap[1], Meiyin Wong[1]

ABSTRACT

Background: Depression has been identified as the most common mental illness in Singapore. To address this growing concern, the current study focused on the population within the primary care setting since depression has been demonstrated to be highly prevalent in these patients. This study examined the possible predictors of outcome expectancy based on illness perception and depression severity. **Methods:** One hundred and one adult patients with depressive symptoms in primary care were recruited for a cross-sectional study. Positive outcome expectancy was measured using the Depression Change Expectancy Scale, and illness perception was measured using the Illness Perception Questionnaire Mental Health. Depression severity was derived from the Patient Health Questionnaire-9 scores extracted from the participants' medical records. Regression and mediation analyses were applied to explore possible predictors of positive outcome expectancy. **Results:** Regression analysis demonstrated that symptom severity, and specific dimensions under illness perception (i.e., perception of chronicity, perception of personal control, and perception of treatment control) were the most significant predictors of positive outcome expectancy. Mediation analysis found that symptom severity partially mediated the relationship between perception of chronicity and positive outcome expectancy. **Conclusions:** Pharmacotherapy, interventions from allied health professionals, and psychotherapeutic interventions (e.g., strategies from positive psychology, solution-focused therapy, and strengths-based cognitive behavioral therapy) that aim to directly alleviate depressive symptoms as well as improve the perceptions of chronicity, personal control, and treatment control could potentially enhance treatment benefits in primary care patients with depression.

Key words: *Change/outcome expectancy, depression, illness perception, primary care, symptom severity*

Key messages:

- *Patients' optimism about their recovery is associated with their depression severity, perceived chronicity, and overall sense of control.*
- *Depression severity partially mediated the relationship between perceived chronicity and positive outcome expectancy.*

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Department of Psychology, James Cook University, [1]Psychology Services, National Healthcare Group Polyclinics, Singapore

Address for correspondence: Mr. Chee Khong Yap
22, Jln BS3/7, Bukit Serdang, 43300 Seri Kembangan, Selangor, Malaysia. E-mail: yapcheekhong@gmail.com

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Depression has been rising in prevalence globally. The estimated number of people diagnosed with depression worldwide surged by 18.4% between 2005 and 2015.[1] In Singapore, depression was reportedly the most common mental illness, with a lifetime prevalence of 5.8%.[2] Per-capita studies showed that depression was associated with increases in both medical costs (e.g., outpatient and inpatient) and non-medical expenses (e.g., transport and social services).[3]A recent study in Singapore estimated the mean annual total costs per patient to be $7,638, with the indirect costs (e.g., productivity loss attributable to depressive disorder) dominating the total costs for the society.[4]

Depression in primary care

Primary care is, by design, the first line of healthcare for the community, and general practitioners (GPs) have been described as the gatekeepers to mental health services.[5] In Singapore, primary care is provided at polyclinics under the government healthcare facilities and private clinics in the community. A national survey found that, out of 500 respondent GPs, nearly 70% indicated that they were seeing patients with mental illness, and 62% indicated that patients with mental illness comprised only 1-5% of their monthly caseload. Among the GPs who were seeing patients with mental illness, depression (23%) was one of the most common mental illnesses attended to.[6] These findings were admittedly conservative estimates of the local prevalence of depression since studies have indicated that in Asian societies, somatic symptoms of depression may be more salient to patients and could be mistakenly reported merely as symptoms of organic ailments.[7]

Contributing factors to effective treatment

Studies have shown that treatment adherence and positive treatment outcomes could be predicted by patients' perception of their illness, the severity of their illness, and their expectation that the illness will improve with treatment.[8-12] Similar findings have also been reported for depression, where patients' beliefs about depression and its treatment, the severity of their depression, and their outcome expectancy were clearly associated with treatment adherence and outcome.[13-16]

Ironically, it may be the pessimism which depressed patients characteristically experience that often obstructs their own treatment adherence and recovery.[17,18] Reasons for nonadherence to an early termination of treatment includes negative beliefs about antidepressants (e.g., "I can become addicted to antidepressants") and discouragement with the treatment if there is no readily perceived progress.[19,20]

Outcome expectancy

Outcome or change expectancy refers to patients' optimism that their illness will improve in the future and has been shown to be a crucial mechanism for positive change for many forms of psychotherapy.[21] Research also indicates that, unlike other pre-treatment variables such as age, gender, or comorbidity, outcome expectancy can be modified through interventions. In particular, in depressed patients' prior to treatment, positive expectations about the treatment effectiveness predicted their active engagement in therapy, which in turn predicted their relative improvement.[22,23]

Illness perception

Illness perception refers to patients' perception of the characteristics of their illness with or without treatment and is based on the self-regulation model (SRM), which assumes that people actively engage in problem-solving based on their perception of the problem.[24] This model describes three distinct phases in patients' self-regulation: (1) perception formation, (2) coping reaction, and (3) appraisal of the coping reaction. The present study focused on the first phase, i.e., perception formation.

Leventhal *et al*.[25] proposed five dimensions that makeup patients' perception of their own illness such as *identity*, *timeline*, *causes*, *consequences*, and *controllability*. *Identity* refers to the labels an individual uses to characterize the illness and its symptoms. For depression, this would be recognized as symptoms (e.g., having difficulty in sleeping) and how they interpret these symptoms (as a reaction to events, a symptom of depression, an expression of their personality, a result of their lifestyle, etc.). *Timeline* refers to the perceived length of the illness (the duration of the depressive episode, time to recover, predictability of their episodes, etc.). *Causes* refer to the perceived causes of the illness (genetic, social, situational, etc.). *Consequences* refer to the real and imagined impact of the illness. Finally, *controllability* refers to the degree to which patients believe that their illness can be controlled with their self-efficacy or the effectiveness of a given treatment. These dimensions determine patients' overall experience of their illness, which could later influence their coping responses.

Symptom severity

Russell and Kazantzis[26] showed that greater depressive symptomatology was associated with treatment nonadherence. Symptom severity can refer to the overall number of symptoms present, the frequency of occurrence of each symptom, or the intensity of distress from each symptom. The severity of patients' depression may reflect their subjective distress or functional impairment and could further entrench any

negative perceptions of their depression or expectations about treatment outcomes.

The empirical literature on psychological treatment for depression has focused on potential predictors of treatment outcome. However, there are limited studies from Asia that sought to clarify possible contributors to these predictors of treatment outcome. Optimism has frequently been examined as a predictor and overlaps with outcome expectancy thereby associated with patients' hope for mental health recovery.[27] From these studies on optimism, it is possible to make inferences on the relationships among outcome expectancy, illness perception, and symptom severity. In a psychiatric sample, it was found that, a model consisting of high self-esteem, high capacity for leisure activities, low depression score, and low belief that one's problems constitute an illness explained 51% of the variance in the patients' optimism scores.[27] These findings indicated that depression severity and some aspects of illness perception might contribute to outcome expectancy for patients undergoing treatment for depression.

This study explored possible associations among outcome expectancy, illness perception and depression severity, with a view to increasing our understanding of optimal interventions for fostering positive outcome expectancy for depressed patients in primary care.

METHODS

Design and participants

This cross-sectional study involved 101 participants (37 males and 64 females) who were patients seeking psychological services at five polyclinics, i.e., primary care clinics in the community.

Power analysis for multiple regression with 13 predictors was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, and medium effect size (*f2*) of 0.15. The desired sample size was 131 initially; however due to time and human resource limitations for data collection, the sample size obtained for the current study was 101.

Measures

There were two versions (English and Mandarin) of each of the questionnaires used. The Mandarin versions of the questionnaires were first translated from the English version and then reverse-translated for accuracy check. Mandarin-speaking participants were administered the Mandarin versions of the questionnaires, and English-speaking participants were administered the English questionnaires only. The following Likert-based questionnaires were administered:

Depression Change Expectancy Scale (DCES)[21]: The participants' levels of positive outcome expectancy were measured with the DCES, which contains items such as "Even though I try, nothing seems to help improve my mood" and "I have had some success in reducing my depressive symptoms."

Illness Perception Questionnaire Mental Health (IPQ-MH)[24]: The participants' perceptions of their mood disturbance were measured with the IPQ-MH which comprised the *identity*, *structure*, and *cause* scales.

The *identity* scale addressed the participants' characterizations of their concerns, e.g., 'sadness', 'anger', and 'sleeping problems'. This scale also asked the participants to rate the degrees to which their complaints were related to the following parameters: (1) circumstances or events (2) a symptom of depression (3) expression of personality, and (4) their daily routine life.

The *structure* scale addressed the participants' perception of their concerns with respect to seven subscales: (1) the duration of the problem (*timeline chronic*); (2) any recurrent nature of the problem (*timeline cyclical*); (3) the severity of any consequences of the problem (*consequences*); (4) any personal control over the problem (*personal control*); (5) any control that they might gain in treatment over the problem (*treatment control*); (6) how full an understanding they might have about the problem (*coherence*); and (7) any associated emotional distress (*emotional representation*).

The *cause* scale assessed the participants' attributions of the causes of their concerns with respect to four subscales, i.e., biological, psychosocial, structural, and stress-related causes.

Patient Health Questionnaire 9 (PHQ-9)[28]: The level of the severity of the participants' depression was measured with the PHQ-9 by their clinical psychologists. It contains emotions such as "feeling down, depressed, or hopeless" and "feeling tired or having little energy." In addition, the PHQ-9 has been demonstrated to be valid and reliable for screening depression in Singapore for primary care settings.[29]

Procedure

The co-investigator from a university in Singapore collaborated with a team of clinical psychologists from various polyclinics to receive ethical approval from the polyclinics' review board, followed by an acknowledgment from the university's ethics committee.

The clinical psychologists in each polyclinic selected participants among patients who were referred to them by the polyclinic's general practitioners. The clinical psychologists screened each patient's eligibility for the study based on the PHQ-9. The minimum cut-off used in the study was any score ≥1. The eligible patients were then invited to participate in the study. The clinical psychologists also explained and obtained written informed consent from the patients who expressed an interest in participating in the study. Thereafter, the participants were interviewed individually by the co-investigator in a private area of the clinic, to maintain confidentiality. The co-investigator verbally administered the combined questionnaire in the participant's preferred language (i.e., English or Mandarin). The participants were encouraged to ask questions to clarify any items in the combined questionnaire throughout the administration process. Each interview lasted approximately 30 minutes.

Statistical analyses

The data were first screened for missing or erroneous values which was then entered into the Statistical Package for the Social Sciences (SPSS) and sorted with relevant numerical limits for each item on the questionnaire. Missing or erroneous values were manually identified and removed from the data set. Subsequently, checks on assumptions of normality and multicollinearity were conducted. Based on their standardized skew and kurtosis, none of the variables was found to be abnormal at $P < 0.001$. There were no univariate outliers found at $P < 0.001$. None of the variables displayed multicollinearity. The assumption of independence of error was assessed using the Durbin-Watson value. The Durbin-Watson was 2.02, close to 2, satisfying the assumption of independence of error. With all assumptions being met, the data were deemed suitable for multiple regression analysis.

RESULTS

The participants' mean age was 45 years ($SD = 18.5$). The major ethnic group represented Chinese ($n = 84$) along with other groups; Indian ($n = 4$), Malaysian ($n = 7$), and others ($n = 6$). Additional demographic details, such as marital status and employment status, are presented in Table 1.

For the severity scores on the PHQ-9, about 20% of patients ($n = 20$) reported a minimal range of symptoms, 46% ($n = 46$) reported a mild range of symptoms, 23% ($n = 23$) reported a moderate range of symptoms, 10% ($n = 10$) reported a moderately severe range of symptoms, and only about 2% ($n = 2$) reported a severe range of symptoms.

Correlation analysis

There were eight individual IPQ-MH subscales that significantly correlated with positive outcome expectancy: *identity* ($r = -0.40$, $P < 0.001$), *timeline chronic* ($r = -0.66$, $P< 0.001$), *consequences* ($r = -0.43$, $P < 0.001$), *personal control* ($r = 0.61$, $P < 0.001$), *treatment control* ($r = 0.64$, $P < 0.001$), *emotional representation* ($r = -0.28$, $P = 0.005$), *psychosocial cause* ($r = -0.29$, $P = 0.004$), and *structural cause* ($r = -0.29$, $P = 0.003$). Depression severity and positive outcome expectancy were also significantly correlated ($r = -0.41$, $P < 0.001$).

None of the demographic variables were found to be significantly correlated with positive outcome expectancy. Therefore, these variables were excluded from the regression analysis.

Multiple regression

The results of the regression indicated that the correlates explained 67.3% of the variance of positive

Table 1: Descriptive statistics for participant demographic (*n*=101)

Participant Demographic	Frequency	Percent
Age (in years)		
21-39	41	40.6
40-59	37	36.6
60-69	9	8.9
70+	14	13.9
Gender		
Male	37	36.6
Female	64	63.4
Ethnicity		
Chinese	84	83.2
Malay	7	6.9
Indian	4	4
Others	6	5.9
Language		
English	77	76.2
Mandarin	24	23.8
Education		
No formal education	2	2.0
Primary	10	9.9
Secondary	37	36.6
Tertiary	33	32.7
Missing data	19	18.8
Marital status*		
Single	41	40.6
Married	44	43.6
Separated	12	11.9
Divorced	4	4.0
Employment status*		
Student	11	10.9
Employed	57	56.4
Unemployed	32	31.7

*Missing data from one participant

outcome expectancy (R^2 = 0.67, F (9,91) = 20.77, P < 0.001). Depression severity (β = -0.22, P = 0.001), *timeline chronic* (β = -0.24, P = 0.008), *personal control* (β = 0.29, P < 0.001), and *treatment control* (β = 0.29, P = 0.001) significantly predicted positive outcome expectancy.

Mediation analysis

The relationship between *timeline chronic* and positive outcome expectancy was partially mediated by depression severity [Figure 1]. The predictor variable (*timeline chronic*) was significantly correlated with both proposed mediator (depression severity; β = 0.33, P=0.001) and outcome variable (positive outcome expectancy; β = -1.78, P < 0.001). Furthermore, depression severity was significantly correlated with positive outcome expectancy (β = -1.10, P < 0.001). A hierarchical regression was conducted with depression severity and *timeline chronic* as predictor variables and positive outcome expectancy as the outcome variable. The model with *timeline chronic* as the sole predictor explained 43% of the variance [R^2 = 0.43, F (1, 99) = 74.61, P < 0.001] while the model with *timeline chronic* and depression severity both as predictors explained 47.3% of the variance [R^2 = 0.47, F (2, 98) = 44.05, P < 0.001]. The additional variance explained by depression severity was 4.4% [R^2 change = 0.044, sig. F change < 0.01] which reflected a partial mediation. None of the other correlations were found to be mediated by depression severity.

DISCUSSION

Illness perception and outcome expectancy

The regression analysis identified three subscales of illness perception as significant predictors of outcome expectancy: *personal control*, *treatment control*, and *timeline chronic*. The first two variables showed positive correlations with outcome expectancy, while the last variable showed a negative one. These results indicated that, the more influence the patients believed that they themselves or their treatment had on their depressive symptoms; the more optimistic they would be about their condition. This is supported by past findings that mood in depressed patients could be improved by reducing learned helplessness and cultivating an adaptive sense of control.[30] Thus, a fundamental process of depression recovery seems to be a progressively stronger sense of self-efficacy or confidence in the course of treatment. The current findings on chronicity suggest that the more the patients believed that their depressive symptoms might improve only after an extended length of time, the less optimistic they would be about their eventual recovery.

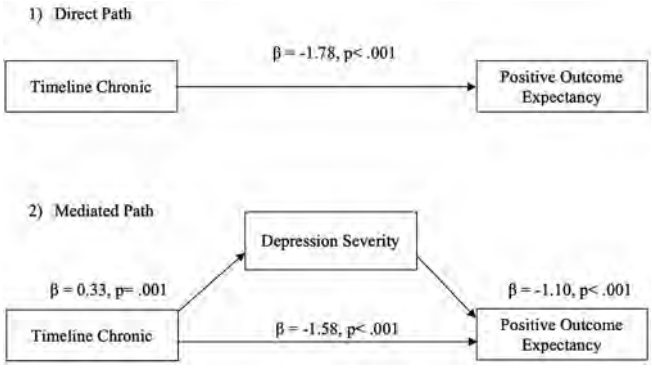

Figure 1: Model testing hypothesis that depression severity mediates the relationship between timeline chronic and positive outcome expectancy

Depression severity and outcome expectancy

Depression severity was negatively associated with positive outcome expectancy. Korn*et al*.[31] conducted a study with patients with major depressive disorder (MDD) who were given more desirable information and less undesirable information. Compared to the control group, the MDD patients did not engage in optimistically biased updating, despite having received more information that would warrant an optimistically biased view about future life events. Thus, providing depressed patients with general encouragement and positive reinforcements may not be sufficient in promoting positive outcome expectancy. Interventions with a more sustained and in-depth focus on inducing positive biases such as those from positive psychology and cognitive bias modification may prove to be more impactful.[32]

Depression severity in its various forms (e.g., duration and severity of individual depressive episodes, number of previous episodes, and comorbidity) has been noted as a salient predictor of chronicity.[33] similarly in this study, depression severity acted as a partial mediator for the relationship between the perception of chronicity and outcome expectancy. This mediation mechanism suggests that outcome expectancy is influenced not only by subjective perception but also by objective symptomatology and functional impairment. Thus, while psychotherapy is often beneficial, an appropriate range of physically active interventions could also be crucial in consolidating depressed patients' optimism about their recovery. These somatic interventions that directly target symptom reduction and hence symptom severity (e.g., pharmacotherapy and occupational therapy for patients needing physical rehabilitation) may then leverage on this mediation mechanism in encouraging patients' confidence about their eventual recovery. It is then recommended that especially for primary care, in the spirit of primary and secondary

prevention, therapeutic services from medical doctors and allied health professionals trained in mental health should be made available to depressed patients.

In essence, psychosocial services that are most impactful to depressed patients in primary care provide: (1) accurate assessment of the overall severity of the patients' depression, (2) psycho educational information and advice that maximally inspire hope that is justified by the assessment results, and (3) interventions that deliberately deflate the outlook that depression is inevitably protracted and elicit an expectancy that depression could be readily contained with evidence-based strategies. In particular, strengths-based cognitive-behavioral therapy (SB-CBT) has structured activities that guide patients to minimize negative biases in their expectations,[34] and solution-focused therapy (SFT) has conversational strategies that accentuate the patients' own resourcefulness (including their positive utilization of treatment) and direct their attention to even small signs of success which could then decrease any illness perception with a chronicity bias.[35]

Limitations

As the participants were recruited from patients who were already attending their appointments, they might have possessed relatively positive outcome expectancy for their depression. It is possible that these patients were more likely to be optimistic about their condition to begin with, leading to a probable selection bias. It would have been interesting to test the hypotheses with a sample that included patients with depression who had either discontinued or refused treatment. Additionally, a majority of the patients were found to have relatively low depression severity, with only about 12% reporting moderately severe to severe symptoms. Although this may not be unusual in a primary care setting, where many patients are functioning relatively well in their daily lives in spite of their symptoms, it may have contributed to a more positive bias in the sample. Therefore, the current study could not be generalized to a more severely depressed population.

This study also did not measure the possible presence of comorbidity. While the participants were instructed to restrict their responses to the context of their depression, the responses from participants with additional mental health conditions or physical diseases might have been complicated by the more varied stressors in their lives. Moreover, clinical details such as the prior number of depressive episodes, family psychiatric history, and individual psychiatric history were not included in the scope of the present study. These are additional factors that may have potentially confounded the results of the regression analysis. Future studies may analyze these factors together with outcome expectancy which may reveal additional insights into treatment adherence.

In addition, due to time and human resource limitations for data collection, the sample size for the current study was limited to 101, rather than the desired 131. The scales used in the Mandarin versions of the questionnaires were also not validated after the translation process due to the study's limited timeframe. This lessened the sensitivity of the statistical analyses and decreased the likelihood of detecting possible effects.

CONCLUSIONS

Patients' confidence in their own recovery from depression appears to be linked to their beliefs about how long their depression would last as well as how much they can boost their recovery by themselves and through their treatment. Interventions from SB-CBT, SFT, and positive psychology can assist the patients in developing an adaptively optimistic attitude as they work toward recovery. The patients' subjective perception of their depression seems to influence their objective symptomatology, which may, in turn, influence their subjective outcome expectancy. In primary care, this mediating mechanism could be expeditiously curbed with psychotropic medication prescribed by family physicians or general practitioners as well as somatic interventions from occupational therapists or physiotherapists for depressive symptoms that interfere with physical functioning, while psychotherapy aims to ameliorate underlying psychosocial elements for more integrated and sustainable recovery.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Sexual Dysfunction in Women with Depression: A Hospital-Based Cross-sectional Comparative Study

R. Mrinalini Reddy, R. Arul Saravanan, Samir Kumar Praharaj[1], M. Thirunavukarasu

ABSTRACT

Background: There is a need to explore the sexual functioning of women with depression as one part of sexuality is that it helps in developing an intimate emotional and physical relationship with another person, and this relationship may serve as a buffer against life stresses. Our aim was to study the prevalence and types of sexual dysfunction in depressed women patients and to compare them with non-depressed women. **Materials and Methods:** A total of 270 participants who attended a teaching hospital were selected for the study – 135 cases and 135 controls. Sociodemographic and clinical details were collected. Mini International Neuropsychiatry Interview (M.I.N.I), Hamilton Depression Rating Scale (HAM-D), Arizona Sexual Experiences (ASEX) scale, and Female Sexual Functioning Index (FSFI) scale were used. Sexual dysfunction was assessed in both groups. **Results:** Among the cases, 47.40% had mild depression, 44.44% had moderate depression, and 8.15% were severely depressed. On the ASEX, 46.66% of the cases had sexual dysfunction, while it was only 8.89% among the controls. The difference in sexual dysfunction among cases and controls was statistically significant. Using the FSFI, 40% of the cases had female sexual dysfunction (FSD), and it was only 11.1% in controls. **Conclusion:** Sexual dysfunction was more common in females with clinical depression than in those without depression. Numerous factors can operate in the causation of FSD. This study underlines the importance of screening females with depression for FSD, for its early diagnosis and management.

Key words: *Depression, sexual dysfunction, women*
Key messages: *Sexual dysfunction is more commonly seen in women with clinical depression.*

Depression is a common disorder and is mainly characterized by depressed mood, decreased energy, and loss of interest in previously pleasurable activities. Sexual dysfunctions are "impairments in the sexual response cycle or the presence of pain associated with sexual intercourse."[1] The prevalence of female sexual dysfunction (FSD) in Western countries is reported to be between 17% and 55%. FSD is considered a

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Department of Psychiatry, SRM Medical College and Research Centre, Kattankulathur, Kancheepuram, Tamil Nadu, [1]Department of Psychiatry, Kasthurba Medical College, Manipal, Karnataka, India

Address for correspondence: Dr. R. Arul Saravanan
403, New B Block, SRM Medical Staff Quarters, Potheri, Kattankulathur, Kancheepuram - 603 203, Tamil Nadu, India.
E-mail: arulpsg@gmail.com

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multidimensional entity with various biological and psychosocial dimensions.[2] FSDs can occur in the form of Hypoactive sexual desire disorder (HSDD), sexual aversion disorder, female sexual arousal disorder, female orgasmic disorder, dyspareunia, and vaginismus. Furthermore, there are newer disorders identified recently, such as persistent genital arousal disorder.

The risk factors for sexual dysfunction include age, education level, emotional ill health and stress, and sexual abuse.[3] Pregnancy also plays a role in sexual dysfunction. The sexual functioning is considerably lower in the last trimester of pregnancy.[4] In a study, middle-aged women of 40–65 years with a lower socioeconomic and lower level of education showed the highest rates of FSD.[5] A study from Brazil reported that the prevalence of sexual dysfunction was 28% and 49%, respectively, in females across selected social groups. The prevalence rate was between 18% and 29.3% for female orgasmic disorder and 26.7% for HSDD.[6,7] Furthermore, the study also showed that women seeking professional help for sexual disturbances were only 18.8%.[8] FSD is physically disconcerting, emotionally distressing, and socially disruptive for those who suffer from it.[9]

A few earlier studies have suggested that depression increases the risk for the development of FSD. In women who had depression, HSDD was reported to be the most common type of FSD.[10] The chief complaint of patients with depression may include loss of sexual desire, and conversely, the presence of lower sexual desire may lead to depression. A few studies have shown that FSD was more common in depressed women than in patients with no depression.[11] The loss of sexual desire was found to have greater prevalence than disorders of arousal or orgasm, and in other studies, HSDD was the most prevalent in depressed patients.[12] The Study of Women's health Across the Nation (SWAN), in the United States, showed recurrent depression to be associated with reduced arousal and pleasure.[13] Yet, depressed female patients are very reluctant to talk about sexual dysfunction even when they are in the hospital for the treatment of depression.

There is a paucity of studies in India on FSD. FSD is also one of the grossly underreported health conditions in India due to various social and cultural taboos. There is a further reduction in the interest and desire for sexual activities with the partner when clinically depressed. Increase in depression is leading to increased prevalence of HSDD as part of depressive symptomatology.[14] Yet, like the women from the United States who were part of SWAN study, this dual malady is probably silently suffered by Indian women too. We undertook the study to determine whether sexual dysfunction in those with depression was more when compared with those without depression, using ASEX and FSFI.

MATERIALS AND METHODS

This hospital-based, cross-sectional comparative study was conducted at a Medical College Hospital between January 2017 and December 2018. Female patients who attended the Psychiatry outpatient (OP) of the tertiary care teaching hospital were approached for the study.

Sample

Using a previous Indian study by Roy *et al.*, the expected proportion of women with FSD was considered as 70.3% among people with depression and 43.3% among women without depression.[15] Power of study at 90% and two-sided alpha error of 5% yielded a sample size of 119. Allowing for an additional 10% excess, a final sample size of 135 in each group was arrived at.

Purposive sampling was used to select patients who received a diagnosis of mild, moderate, or severe depressive episode as per International Classification of Diseases, Tenth Revision (ICD-10). Both new and follow-up cases were included. The inclusion criteria for cases included women age 18–45 years who are sexually active, attended the psychiatric OP department, are diagnosed with depression, are with or without anti-depressant medications, and are willing to give consent to participate in the study. The exclusion criteria included reporting menopausal symptoms and having serious medical comorbid conditions that required hospitalization more than once in the past.

The control group consisted of females who accompanied patients to our hospital and those who came for work in the institution. Females, matched for age in 1:1 ratio to that of cases, were approached. Subjects who did not have depression or any major mental illness, never had any history of psychotropic medication use, and consented to participate in the study were included in the control group.

The participants were approached and briefed about the study and written informed consent was obtained. The interview and assessment were conducted by a female psychiatrist in the privacy of her office room.

Tools

Sociodemographic and clinical details were collected. The following tools were used: Mini International Neuropsychiatry Interview (M.I.N.I),[16] Hamilton Depression Rating Scale (HAM-D-17 item),[17] Arizona Sexual Experiences (ASEX) Scale,[18] and Female Sexual

Functioning Index (FSFI) scale.[19] The overall time taken was an hour for each participant.

MINI is a short, structured diagnostic interview schedule for ICD-10 and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) psychiatric disorders. It has a short administration time of 15 min. The structured questions are answered in yes or no format. It is widely used in many clinical trials and epidemiological studies in psychiatry. Its validity and reliability varied between good and very good when compared with Composite International Diagnostic Interview and the Structured Clinical Interview for DSM-IV.[20,21] MINI was used because of its brevity and accuracy.

HAM-D or HDRS is a 17-item depression assessment scale. It is clinician-rated and takes about 20 min to administer. Eight items have a 0 (not present) to 4 (severe) score, and nine items have a 0–2 score. It has a sensitivity of 90% and specificity of 63% at a cut-off score of 7. It is one of the most widely used scales for assessment of severity and change of the depressive symptoms in adult patients.[22]

ASEX is a five-item, easy-to-use, rating scale designed to screen for sexual dysfunction. It quantifies the five domains of sex drive, arousal, vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm. The questions are short, easy to understand, and less intrusive. The total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. Studies have shown that it is a reliable, valid, and sensitive tool to measure sexual dysfunction in both males and females.[18]

FSFI is a 19-item, self-reported questionnaire for assessing the key dimensions of sexual function in women. It is easy to administer and psychometrically sound. The FSFI rating scale was based on clinical interpretations of a principal components analysis, which gave a six-domain structure identified as desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.

Both the ASEX and FSFI scales were translated into Tamil language by the first and second authors independently. A consensus questionnaire was arrived at after comparing the translations. An independent language expert back-translated this consensus questionnaire into the English version, which was compared with the original and found to be satisfactory. In case of discrepancy, the fourth author's suggestion was accepted. The final vernacular version was used. As sexual dysfunction is a sensitive problem with added stigma, some of the questions were tempered based on the cultural context. The briefer ASEX was given first to check the sexual activity/functioning of each individual, and later, FSFI was used for assessing the domains of sexual functioning. MINI was used as a screening tool to rule out other comorbid mental illness in the study group and to screen the control group for mental illness.

Statistical analysis

The ASEX and the FSFI total scores were considered as the primary outcome variables. Other scores and computed results from the study were secondary outcome variables. The study group was the primary explanatory (dependent) variable. Demographic variables such as age, gender, and marital status were considered as other explanatory (independent) variables. Descriptive analysis was done and presented as mean and standard deviation (SD) for continuous variables and frequency and proportions for categorical variables. Independent sample *t*-test and Chi-square tests were carried out to test for significance. IBM SPSS version 16 was used for statistical analysis.

Ethics approval

The Institutional Ethical Committee approved the study. Written informed consent was obtained from all the participants after providing detailed information about the study and voluntary nature of participation. The confidentiality of the study participants was maintained throughout the study.

RESULTS

A total of 281 females were approached for the study purpose. Eleven females were excluded from the study as they had menopausal symptoms. Four out of these 11 perimenopausal females had reported to be sexually inactive. Finally, a total of 135 females with depression and 135 females in the control group were studied. The mean age ± SD was 32.09 ± 5.68 years in the cases and 32.04 ± 5.58 years in the control group. The majority were housewives, were from middle socioeconomic status, had completed schooling, were Hindu by religion, and were from semi-urban domicile [Table 1]. The case and control groups did not show any statistically significant difference in the above-mentioned demographic data.

We assessed severity of depression using the HAM-D. Severe depression was seen in 8.15% of the cases. The proportion of cases with mild depression was 47.40%, while 44.44% had moderate depression. The mean ASEX score was 19.6 ± 4.65 in the cases, while it was 15.27 ± 4.13 in the controls. This mean difference was statistically significant ($t = 4.33$, 95% CI, $P < 0.001$).

Poor sex drive was reported in 64.8% (n = 87) of cases. Difficulty in sexual arousal and lubrication difficulty was reported by 54.8% (n = 74) and 68.9% (n = 93), respectively. Difficulty in reaching orgasm was seen in 71.9% (n = 97) of the cases, and 69.7% (n = 94) reported unsatisfying orgasms. The severity of depression was associated with sexual dysfunction, which was statistically significant ($\chi^2 = 68.03$, df = 24, $P = 0.000$).

The mean FSFI rating scale score was 27.79 ± 3.38 in cases, and it was 31.09 ± 3.65 in controls. The difference was statistically significant (t = 3.30, 95% CI, $P < 0.001$). In our study, according to the FSFI rating scale, 40% of the cases had FSD and it was only 11.1% in controls [Table 2].

In this study, 22.22% of the cases had a positive history of antidepressant medication, while only 7.4% among the controls had a positive history of any medication use. This difference in proportions among cases and controls was statistically significant. There was a statistically significant difference between the cases and the control group with respect to the use of medicines and FSD ($\chi^2 = 11.73$, df = 1; $P = 0.001$). In cases who had positive current medication history (n = 30), FSD was reported in 20%.

Table 1: Sociodemographic comparison of cases and controls

Variables		Cases n=135		Controls n=135	
		Frequency	%	Frequency	%
Education	Up to secondary school	41	30.37	43	31.85
	Graduate	89	65.92	87	64.44
	Postgraduate	5	3.70	5	3.70
Occupation	Employed	47	34.81	49	36.29
	Student	14	10.37	14	10.37
	Housewife	74	54.81	71	52.59
	Unemployed	0	0	1	0.74
Socioeconomic status	Lower	33	24.44	35	25.92
	Middle	82	60.74	76	56.29
	High	20	14.81	24	17.77
Domicile	Rural	44	32.59	39	28.88
	Semi Urban	63	46.66	64	47.40
	Urban	28	20.74	32	23.70
Religion	Hindu	74	54.81	74	54.81
	Christian	32	23.70	31	22.96
	Muslim	29	21.48	30	22.22
Marital status	Single	25	18.51	24	17.77
	Married	104	77.03	104	77.03
	Divorced	5	3.70	5	3.70
	Widow	1	0.74	2	1.48
Family type	Nuclear	79	58.51	74	54,81
	Extended	45	33.33	45	33.33
	Joint	11	8.14	16	11.85

DISCUSSION

FSD is one of the underdiagnosed disorders across the world and especially in developing countries like in India with complex cultural barriers and taboo regarding an open discussion about sexual health. Across the world, it is often underreported or underdiagnosed compared with male sexual dysfunction.[23] The prevalence of FSD in non-depressed women reported in Indian studies varies from 33.3% to 73.2%.[24,25] The varying rates were reported to be due to vastly different study samples, methodological differences, and cultural variations in sexual practice in India.[25] Even fewer studies have been done on FSD in women who are depressed.

This study was done to assess sexual dysfunction in females with depression. A total of 135 cases of depression and 135 age-matched controls were studied. A statistically significant difference was observed in sexual dysfunction between cases and controls.

The mean age of the study population was 32 years in both groups. Sexually active married women formed the majority (77.03%) of the study sample. The baseline parameters of our study sample were comparable with that of Sreelakshmy *et al.*,[26] Roy *et al.*,[17] and Kendurkar *et al.*[27]

In our study, the mean ASEX score was more in cases than in controls, and the difference was statistically significant. As per ASEX, 46.66% of our cases had SD, while only 8.89% of controls had SD. This difference in SD among the cases and controls was statistically significant. Our finding was consistent with the study done by Roy *et al.*,[17] who observed that on ASEX

Table 2: Comparison of the female sexual dysfunction using ASEX scale and FSFI rating scale in the two study groups (n=270)

Sexual dysfunction		Group		Chi-square	*P*
		Cases (n=135)	Control (n=135)		
ASEX scale	No SD (<14)	21 (15.55%)	50 (37.03%)	50.42 (df=3)	<0.001
	Probable (14-21)	51 (37.77%)	73 (54.07%)		
	SD (>21)	63 (46.66%)	12 (8.89%)		
FSFI rating scale	FSD (below 26)	54 (40%)	15 (11.1%)	29.61 (df=2)	<0.001
	No FSD (score 26 and above)	81 (60%)	120 (88.9%)		

ASEX – Arizona Sexual Experiences; FSFI – Female Sexual functioning Index; SD – Sexual dysfunction; FSD – Female sexual dysfunction

scale, 73.3% of participants were showing sexual dysfunction in the study group, but it was only 20% in the controls. As in our study, the difference in proportion between cases and controls was statistically significant.

Our study showed that there is a significant association between depression and FSD. The psychomotor and cognitive symptoms of depression, along with low self-esteem, depressive cognitions like hopelessness and helplessness, contribute significantly to this outcome.[2] Apart from neuro-humoral changes that affect the hormonal levels, the antidepressant medications themselves also significantly contribute to FSD, making it worse.[28]

In our study, the mean HAMD score was 14.60. This is because the majority of the cases were from the OP department and had mild to moderate depression. Similar to our study, Roy *et al.*, in their study done at a medical college hospital in Mysuru, Karnataka, reported a mean HAMD score of 19.13, which is comparable. However, a study done at France in a community setting showed that 52% of their subjects had moderate depression, while 34% had severe depression. They had used the Montgomery and Åsberg Depression Rating Scale (MADRS), and the majority were on antidepressants for a longer time.[29] That study did show a clear relationship between the prevalence of sexual dysfunction and severity of depression, independent of antidepressant drug treatment.

Though all components of sexual functioning were affected in our study, in the depressed group, the majority reported lubrication dysfunction, pain, and orgasmic dysfunction. Low desire, low arousal, and low satisfaction were also reported more in the cases than in the controls; however, this was not statistically significant.

The other area studied was the use of medications and their association with FSD, which showed significant difference between the women with depression and the healthy control group. The existing literature also confirms sexual dysfunction as a possible adverse event of all antidepressants.[30] Strategies to mitigate this include reducing the antidepressant dose, switching to a different antidepressant with lower sexual side effect, and addition of hormones and/or antidotes.[28] When compared with other Indian studies [Table 3], the overrepresentation of the mild and moderate depressive cases in our study sample is perhaps the reason for the slightly lower FSD in ASEX and FSFI.

Limitations

Our study was a cross-sectional descriptive study and the causal association could not be established. Furthermore, the selection of purposive samples of cases and controls from the institution precludes the generalization of the findings. Lack of validation of the translated ASEX and FSFI is another limitation. A more detailed clinical information of the cases in terms of onset, number of episodes, and duration would have added more strength to the analysis and to the generalizability of the results. We could not analyze and compare the effect of classes of antidepressants upon FSD because of the small sample.

CONCLUSION

Our study is an attempt to address the often-neglected area of FSD in depressed females, done at a tertiary care teaching hospital. Even though the study sample contained mostly of patients with mild and moderate depression, women with depression had significantly higher sexual dysfunction.

Table 3: Comparison of Indian studies on FSD

Study	Location	Study sample	Instrument used	Remarks	Prevalence of FSD
Kar and Koola[31]	South India	61 women	Sexual Function Questionnaire	Postal questionnaire to English-speaking women	OD 28%
Avasthi *et al*.[32]	Chandigarh, North India	100 women	Brief Index of Sexual Functioning for Women; Sex Knowledge and Attitude Questionnaire II	Women attending pediatric unit	OD 9%, LD 5%, PD 7%
Singh *et al*.[25]	Tamil Nadu, South India	149 women	FSFI	Women attending medical OP clinic	73.2% FSD
Abhivant and Sawant[2]	Solapur, North India	49 women with depression	ASEX, FSFI	Psychiatric OPD	67.34%
Roy *et al*.[15]	Karnataka, South India	30 cases 30 controls	ASEX, FSFI, HAM-D	Psychiatric OPD	73.3% (ASEX); 70% (FSFI)
Sreelakshmy *et al*.[26]	South India	40 patients	FSFI, HAM-D	Obstetrics and gynecology OPD	90% FSD
This study	Tamil Nadu, South India	135 cases; 135 controls	ASEX, FSFI, HAM-D	Psychiatry OPD	46.6% (ASEX); 40% (FSFI)

FSD – Female sexual dysfunction; OD – Orgasmic disorder; LD – Lubrication disorder; PD – Pain disorder; ASEX – Arizona Sexual Experiences; FSFI – Female Sexual functioning Index; HAM-D – Hamilton Depression Rating Scale

Sexual functioning and dysfunction are still a sensitive and stigmatized area, even among educated adult females. Though they seek treatment for somatic and psychological symptoms of depression, adult females are hesitant to seek out help for sexual dysfunction. This study underlines the importance of screening depressed female patients for sexual dysfunction.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Psychiatric Morbidity, Cultural Factors, and Health-Seeking Behaviour in Perinatal Women: A Cross-Sectional Study from a Tertiary Care Centre of North India

Shweta Goyal, Bandna Gupta, Eesha Sharma[1], Pronob K Dalal, Yashodhara Pradeep[2]

ABSTRACT

Background: Poor mental health of the mother affects her physical health and the neonate's health and development. Studies from Southern India place different estimates of perinatal mental ill-health. Cultural variables affect health-seeking behaviour and are thus important to study in perinatal women with psychiatric morbidity. **Methods:** A total of 281 perinatal women were screened on Edinburgh Postnatal Depression Scale (EPDS), Perinatal Anxiety Screening Scale (PASS) and Mini International Neuropsychiatric Interview version 6.0 (MINI), assisted with a clinical interview to identify psychiatric illnesses. The cultural formulation interview (CFI) of DSM-5 was applied on perinatal women having psychiatric illnesses and their caregivers. **Results:** A psychiatric diagnosis was present in 10.3% of perinatal women. Depression and anxiety disorders were seen in 7.12% and 1.41%, respectively. Marital discord ($P < 0.0001$), psychosocial stressors ($P < 0.0001$), and past history of psychiatric disorder ($P < 0.001$) were significantly higher in perinatal women with a current psychiatric diagnosis. On CFI work-related stress, the gender of the infant, low education and conflict across generations were identified as the negative aspects of the culture associated with psychiatric illness during and after pregnancy. Religion and social support were the major coping strategies, while stigma and financial problems were the major barriers to help-seeking. **Conclusion:** The high prevalence of psychiatric disorders and the strikingly low help-seeking are noteworthy. These findings can help in planning treatment and prevention programs for timely detection and intervention for perinatal psychiatric disorders.

Key words: *Culture, help-seeking, perinatal, psychiatric illness*
Key messages: *Though they have a high prevalence of psychiatric morbidity, help seeking is poor in perinatal women.*

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Departments of Psychiatry and [2]Obstetrics and Gynecology, King George's Medical University, Lucknow, Uttar Pradesh, [1]Department of Child and Adolescent Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Bandna Gupta
Department of Psychiatry, King George's Medical University, Lucknow - 226 003, Uttar Pradesh, India. E-mail: drbandna@yahoo.co.in

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Mental ill-health has not really been a priority in the context of reproductive health and poses a global burden and disability.[1] The transition to motherhood involves major psychological and biological changes and makes pregnancy and postpartum period vulnerable to ill-health.[2-4] The perinatal period is identified as a risk factor for the occurrence or recurrence of psychiatric disorders in women.[5] According to DSM-5,[6] perinatal psychiatric disorders include conditions that occur during pregnancy and up to four weeks after delivery. Common mental health problems seen in the perinatal period include postpartum blues, depression, anxiety, and psychosis. Various studies[7-10] have identified factors associated with antenatal psychiatric morbidity. Past history of depression was found to be the strongest predictor of antenatal depressive symptoms,[7] along with unmarried status, polygamy, past history of stillbirth, and perceived lack of social support.[8] Other factors are psychosocial stress, domestic violence, chronic medical illness and young age of the mother[9] and quality of the marital relationship.[10] Risk factors for post-partum depression in a meta-analysis,[11] included depression and/or anxiety during pregnancy, stressful life events, low social support, past history of depression and poor marital relationship.[12,13]

Poor maternal mental health can cause delayed prenatal growth of the foetus, preterm delivery and low birth weight.[14-16] Sub-optimal mother-child interaction and bonding can cause an increased incidence of developmental disorders such as Attention Deficit Hyperactivity Disorder.[17-19]

Only a few studies are available on prevalence, risk factors, and obstacles to care. Data from India has mostly come from the southern part of the country, revealing wide range (11-23%) of perinatal mental morbidity, primarily depression.[20-23] Studies do not mention details about help-seeking behaviour and its cultural determinants but report significant number of antenatal depressed mothers remaining depressed 6 weeks or months postpartum. This indicates low help-seeking. Reasons for not seeking help included the belief that a 'good mother' should be able to cope on her own, stigma, guilt, and denial.[24] Complex and poorly understood cultural and regional variables can affect help-seeking.

The current work was planned to study psychiatric morbidity, its prevalence and cultural factors influencing illness understanding, help-seeking behaviour and barriers to care in perinatal women, thereby helping in planning and implementation of services for perinatal mental health issues.

METHODS

This was a cross-sectional study conducted from September 2014 to July 2015. The sample was drawn from women attending the antenatal and postnatal care services of the Department of Obstetrics and Gynaecology at a tertiary health care centre of North India by purposive sampling technique. For the purpose of this study, perinatal psychiatric disorders were defined as in DSM-5, i.e., "Psychiatric disorders occurring during pregnancy and/or up to four weeks after delivery". Participants fulfilled the following inclusion criteria: a) women currently pregnant or up to four weeks post-partum, b) Age >18 years, c) Willing to give written informed consent, and d) accompanied by a caregiver. For the purpose of the study, the caregiver was operationally defined as, "a family member who is living in the same household most of the time and shouldering the responsibility of the caring for the subject most of the time." Women were excluded if they reported the onset of the current psychiatric disorder prior to pregnancy or if they had any co-morbid medical illnesses requiring priority medical management. The Institutional Ethics Committee (IEC) approved the study.

Procedure and instruments

Written informed consent was taken, and a semi-structured proforma was used for collecting sociodemographic and clinical information, including menstrual, sexual and reproductive history and information on psychosocial stressors and marital discord. M.I.N.I. International Neuropsychiatric Interview, version 6.0.0 (MINI),[25] was applied to identify psychiatric illnesses. Edinburgh Postnatal Depression Scale (EPDS)[26] and the Perinatal Anxiety Screening Scale (PASS)[27] were applied on all the participants. The participant and a primary caregiver were interviewed using the Cultural Formulation Interview (CFI) of DSM-5.[6]All assessments were done by a single investigator, from the Department of Psychiatry, who was sufficiently trained for the purpose.

Edinburgh postnatal depression scale (EPDS)[26]

It is a 10-item questionnaire to identify postpartum depression. The EPDS can be used up to eight weeks postpartum and has been reliably applied for depression screening during pregnancy.[28] The cut-off scores vary in different cultures.[29] In Indian studies, the cut-off score used in the majority was 12.[20,21]

Perinatal anxiety screening scale[27]

It is a valid and reliable 31-item instrument to screen for problematic anxiety in antenatal and postpartum women, applied as a self-report assisted by the interviewer. The scale was translated into Hindi

(a formal translation and back-translation exercise was not done), and a mental health professional fluent in the Hindi language validated the translation.

Discussion of cultural formulation interview[6]

It was introduced with DSM-5. It includes 16 questions about the impact of culture on key aspects of an individual's clinical presentation and care, specifically, illness understanding, help-seeking behaviour, and barriers to care. The CFI can be used regardless of the cultural background of the individual or the clinician. Two sites in India participated in the validation of CFI, one in New Delhi at Post Graduate Institute of Medical Education and Research (PGIMER)-Dr Ram Manohar Lohia Hospital, and the other in Pune at King Edward Memorial (KEM) Hospital.[30]

Statistical analysis

Independent (unpaired) samples T-test and Chi-square/Fisher's exact test were used for group comparisons, for continuous and categorical variables, respectively. The sample size was calculated by the following formula $Z.^2 P (1\text{-}p)/d^2$. In this case, $Z = 1.96$ standard normal variate (at 5% type 1 error, i.e., $P < 0.05$). The expected proportion in population based on previous studies[20-23] (P) was kept as 23%, and the absolute error or precision (d) was kept as 5%. The sample size calculated was 272, and we planned to recruit more than this figure for our study.

RESULTS

Socio-demographic and clinical characteristics of the sample

A total of 315 women were screened for the study, of whom 281 satisfied the inclusion criteria and were included in the study. The mean age of the sample was 25.9 ± 4.04 years, with the majority (54.8%) in the age group 18-25 years. The sample was largely urban (72.24%), married (99.29%), college graduates (34.87%), and housewives (94.25%), Hindu (80.07%), living in a joint family (58.36%), and with a monthly family income more than INR 10,000 (49.11%). Only a small percentage of women were illiterate (11.39%). Most of the women were antenatal (88.61%), mostly in the third trimester of pregnancy (45.2%). Nearly 60% of the women were multigravida. Complications during current pregnancy were present in 19.2%, the commonest being a post-dated pregnancy (3.56%). Concurrent medical disorders were present in 58.7%, the commonest being anaemia (52.3%). About 40% of women had a past history of complicated pregnancies, abortion being the commonest (11.74%).

Psychiatric assessment of study sample (n = 281)

Table 1 depicts the results of psychiatric assessment with MINI. In this sample, 10.3% of perinatal women had a current psychiatric diagnosis. The commonest diagnosis was Major Depressive Disorder, which was present in 7.12% (n = 20) women. Thus, 70% of the psychiatric morbidity in this sample was contributed by Major Depressive Disorder. Other disorders found in this sample included Anxiety Disorder Unspecified (1.41%), Brief Psychotic Disorder (0.71%), Bipolar Affective Disorder (0.36%), Obsessive Compulsive Disorder (0.36%), and Adjustment Disorder (0.36%). Past history of psychiatric illness was present in 3.56%, again predominantly depression (reported by 3.2%). Four women (1.41%) had a family history of psychiatric illness – two had a history of bipolar affective disorder in father, one had a history of depression in sister, and one had a history of psychosis in sister. EPDS and PASS were applied on the sample and none of the women without a psychiatric co-morbidity scored above the cut-off. Thus both EPDS and PASS, which are specifically designed to pick-up depression and anxiety in pregnancy and postpartum phase, respectively, reported similar findings as that by MINI [Table 2].

Comparison of the socio-demographic and clinical variable between the groups with and without Psychiatric Illness

60 women (21.35%) reported psychosocial stressors in their lives. Of them, 38 (13.51%) reported marital discord, 12 (4.27%) reported financial difficulties. The remaining 10 women reported other stressors, e.g., ill-health of the child, health issues in other family members, etc. Sociodemographic variables did not differ between women with and without current psychiatric morbidity. Among the clinical variables, psychosocial stressors ($P < 0.01$), marital discord ($P < 0.01$), and a past history of psychiatric illness ($P < 0.01$) were significantly more in perinatal women with psychiatric morbidity [Table 3].

Assessment of the study sample on CFI

Of the 29 women with a current psychiatric diagnosis, 2 had psychotic symptoms and could not be assessed

Table 1: Psychiatric assessment of study sample (n=281)

Variable	Observation [n (%)]
Presence of psychiatric diagnosis as per DSM-5	29 (10.32%)
Type of Psychiatric disorder	
Major Depression	20 (7.12)
Anxiety unspecified	04 (1.41)
Brief psychotic disorder	02 (0.71)
Bipolar affective disorder	01 (0.36)
Adjustment disorder	01 (0.36)
Obsessive compulsive disorder	01 (0.36)
Past h/o psychiatric disorder	10 (3.56)
Family h/o psychiatric disorder	04 (1.41)

on CFI. Thus, presented here are the results of CFI on 27 perinatal women with psychiatric morbidity. Tables 2 and 4 depict the distribution of thematic interpretations of participants' and caregivers' responses to questions in the CFI that explore illness understanding, help-seeking behaviour, and barriers to care.

Illness understanding in the CFI [Table 4] comprises of a cultural definition of the problem, cultural perception of the cause, context, and support, and the role of cultural identity. More than 85% of women used words/phrases descriptive of emotional/behavioural symptoms (low mood, reduced sleep, crying spells) to describe their problems. However, when it came to communicating their problems to others or what aspect of their problem troubled them the most, there was a slight shift in focus towards interpersonal stress, pregnancy-related worries, reduced ability to work, and physical health. Almost 25-30% of women gave responses consistent with these themes. Similar kind of responses were given by the caregivers too for the above questions.

When asked about their perceptions of the cause, the women gave mixed responses, the commonest being pregnancy/physical health (33.3%), interpersonal stress (29.6%), and psychological attribution (22.2%).

According to patients, their family/community members attributed the problem to pregnancy/physical illness (51.8%), psychological factors (40.7%) and interpersonal stress (11%). Rest other responses included witchcraft (14.8%) and destiny (7.4%). The caregivers gave responses similar to the above, with slight emphasis on witchcraft.

When asked about the kind of support that makes their problem better, the majority of the women reported social support (70.3%), followed by spiritual support (25.9%) and faith healing (3.7%). Work-related stress was reported by the majority of women (77.7%) as the most important factor causing worsening of their symptoms. Other factors were family issues, financial difficulties and marital discord. Caregivers' responses on social support were the same, but they reported work-related stress and marital discord as almost equally responsible for worsening of the symptoms.

Women and their caregivers reported religion and ethical and cultural values received from their elders and society as the most important aspect of their culture and acknowledged education as an important aspect of their identity. When asked about the cultural factors that could have a bearing on their existing problem, various factors like social support, religion, moral values, cultural factors, marital discord, destiny, and low socio-economic status were reported by both the women and the caregivers. Other factors like intergenerational conflict, low education, the gender of the infant and poverty were identified as negative aspect of their culture responsible for causing concern or any other difficulty.

Help-seeking behaviour in CFI [Table 5] was explored by two sets of questions. The first set asked about past help-seeking and coping, while the second explored current help-seeking. Religion was the most common coping strategy reported by both the women (44.4%) and the caregivers (25.9%). Coping by self and by seeking social support were other prominent means of coping. Caregivers' responses laid more emphasis on self-coping and faith healing. Help-seeking in the past was majorly by non-medical means such as social support, prayer, and faith-healing. Medical help was

Table 2: Assessment of study sample on EPD and PASS

Assessment on EPDS/PASS	Psychiatric disorder	
	Present	Absent
No. of women scoring>12 (cut-off score)	20 (68.97%)	0
No. of women with scores≤12 (Subsyndromal)	07 (24.14%)	112 (44.44%)
No. of women scoring>26 (cut-off score)	01 (3.45)	00
No. of women with scores≤26 (Subsyndromal)	26 (89.66)	160 (63.49)

EPDS – Edinburgh Postnatal Depression Scale, PASS – Perinatal Anxiety Screening Scale

Table 3: Comparison of socio-demographic and clinical variables between thegroups with and without Psychiatric Illnesses

Variables	Psychiatric disorder		t/X^2
	Present (*n*=29)	Absent (*n*=252)	
Presence of psychosocial stressors	19 (65.52)	41 (16.27)	X^2=37.56
Marital discord	18 (62.07)	20 (7.94)	df=1
			P<0.0001
Financial	00	12	
Others	01	09	
Presence of Marital discord	18 (62)	20 (7.93)	X^2=65.18
			df=1
			P<0.0001
Family h/o psychiatric illness	02 (6.90)	02 (0.79)	0.054 (Fisher's Exact test)
Past h/o psychiatric illness	05 (17.24)	05 (1.98)	*P*=0.001 (Fisher's Exact test)

Table 4: Assessment of perinatal women with psychiatric morbidity (*n*=27), and their caregivers, on the CFI – Illness understanding

Theme	Investigators' thematic interpretations from participants responses	Perinatal women with psychiatric morbidity (*n*=27)	Caregivers (*n*=27)	Examples of patient and informants verbteims
Cultural definition of the problem				
What problem brings you here today?	Behavioral/emotionalsymptoms or acknowledgement of mental illness	23 (85.19%)	24 (88.89%)	"Mann udaasrahatahai" "Uljannhotihai"
	Interpersonal/social stress	04 (14.81%)	03 (11.11%)	"Sasural wale pareshankartehai"
How would you describe your problem to other people?	Behavioral/emotional symptoms or acknowledgement of mental illness	20 (74.07%)	18 (66.67%)	"Mann dukhirahatahai" "Dimagkamjorhai/dilkamjorhai"
	Interpersonal/social stress, Destiny, pregnancy	07 (25.93%)	09 ()	"Gharmeiladaijhagdahotahai"
What troubles you most about your problem?	Behavioral/emotionalsymptoms	17 (62.96%)	20 (74.07%)	
	Worries related to Pregnancy, reduced ability to work, Interpersonal stress, Physical Health	10 ()	07 ()	Neendnaiaati" "Rona aatahai" "Kaamnaikarpaate" "Pati se ladai ho gai hai"
Cultural perception of cause, context and support of the CFI				
Why do you think this is happening to you? What do you think are the causes of your [PROBLEM]?	Pregnancy/Physical illness	09 (33.33%)	09 (33.33%)	"Pregnancy"
	Interpersonal stress	08 (29.63%)	08 (29.63%)	"Shareer se kamjorhai"
	Psychological attribution/ Acknowledgement of psychiatric illness	06 (22.22%)	04 (14.81%)	"Kismatkharabhai" "Sasuralwalo se ladai k kaaran"
	Others: Destiny, "No idea", Witchcraft	04 (%)	06 (%)	
What do others in your family, your friends, or others in your community think is causing your [PROBLEM]?	Pregnancy/Physical illness	14 (51.85%)	07 (25.93%)	"Pregnancy"
	Psychological attribution	11 (40.74%)	00 (%)	"Shareer se kamjorhai"
	Others: Witchcraft, Destiny, Interpersonal stress	09 (%)	20 (%)	"Gharkiladaijagdekiwajah se" "Kisi ne kuchkaradiyahai" Answers were not mutually exclusive
Are there any kinds of support that make your [PROBLEM] better, such as support from family, friends, or others?	Social support	19 (70.37%)	20 (74.07%)	"Maykemeigharwalo se baatkarlena"
	Spiritual support	07 (25.93%)	06 (22.22%)	"Patikesaath"
	Faith-healing	01 (3.70%)	01 (3.70%)	"Bhagwan se prarthanakarna" "Jardwaifukwaikaraana
Are there any kinds of stresses that make your [PROBLEM] worse, such as difficulties with money, or family problems	Work-related stress	21 (77.78%)	10 (37.04%)	"Kaambahutjaadakarnapadtahai"
	Family issues, Financial difficulties, Marital discord, Pregnancy-related, Sarcasm from neighbours	12 (%)	17 (%)	"Paisekikammi" "Pati se ladai hone par" "Bacchekichintahona
Role of cultural identity				
For you, what are the most important aspects of your background or identity?	Religion, cultural values, society, education, stamina			Humaradharm" "Samaj" "Sanskriti" "Reetiriwaz"
Are there any aspects of your background or identity that make a difference to your [PROBLEM]?	Social support	O2 (7.41%)	02 (7.41%)	"Samaaj"
	Religion	09 (33.33)	07 (25.93%	"Sanskriti"
	Culture, Moral values, Marital discord, Destiny, Low socioeconomic status	16	18	"Dharam" "Rudiwaadhi" "Paiseki kami" "Ladkihona
Are there any aspects of your background or identity that are causing other concerns or difficulties for you?	Inter-generational conflict	06 (22.22%)	07 (25.93%)	Saas bahu meianbanhona
	low education, Gender related issues, Culture or society related, poverty	21 (%)	20 (%)	Jyadapadelikhenahona Ladkihona Purushpradhansamaj Ladke kapaidha hone kichaha

CFI – Cultural formulation interview

reported by less than one-third of the patients and caregivers.

On questions about current help-seeking, counselling/ medication and social support were acknowledged as

Table 5: Assessment of perinatal women with psychiatric morbidity (*n*=27), and their caregivers, on the CFI – Help-seeking behavior and Barriers to Care

Theme	Investigators' thematic interpretations from participants responses	Perinatal women with psychiatric morbidity (*n*=27)	Caregivers (*n*=27)	Examples of patient and informants verbatims
Self copingand past help seeking				
What have you done on your own to cope with your [PROBLEM]?	Religion	12 (44.44%)	07 (25.93%)	"Bhagwan ka aasra"
	Social support, Self, Medical support, Delivery, Faith-healing	15 (%)	20 (%)	"Gharwalo ka sath" "Apne se koshishkarna" "Jardwanafukwana
In the past, what kinds of treatment, help, advice, or healing have you sought for your [PROBLEM]?	Socialsupport	08 (29.63%)	11 (40.74%)	Gharwalo ka sahaara"
	Faithhealing, Medical help, Prayers	19 (%)	16 (%)	"Pooja karna" "Dua taabeejkarana" "Dawaikarwana
Current help-seeking				
"What kinds of help do you think would be most useful to you at this time for your [PROBLEM]?"	Counselling/medication, Social support	17 (40.74%)	20 (44.44%)	Kisi kesamjhane se" "Dawaai se"
	Improvement in interpersonal relationship, Faith-healing, Delivery, Time, No idea	10 (14.81%)	07 (11.11%)	"Rishto kasudhar jane se" "Dua taabeej se" "Baccha ho jaanekebaad"
"Are there other kinds of help that your family, friends, or other people have suggested would be helpful for you now?"	Faith healing	09 (33.33%)	14 (51.85%)	Dua taabeej se"
	Medication/counselling	04 (14.81%)	00 (%)	"Kisi kesamjhane se"
	Social support, Religion, Delivery, Care, Marital related, Self, 2nd baby, Male child	14 (7.41%)	13 (%)	"Dawaai se" "Rishto k sudar jane se" "Bhagwankikripa se" "ladka ho jaanekebaad"
Have you been concerned about this and is there anything that we can do to provide you with the care you need?	Psychological/pharmacological help	24 (88.89%)	21 (77.78%)	"Dawaai"
	Social support, Nothing, Don't know, Understanding, Access to services	03 (3.70%)	06 (%)	"Baatcheetkejarariyesualhkarwade" "Patanai" "Soojhbhooj"
Barriers to care				
Has anything prevented you from getting the help you need?	Stigma	08 (29.63%)	08 (29.63%)	"Logon ko patanachaljaye"
	Financial problems	07 (25.93%)	07 (25.93%)	"Hichkichahat"
	Work related, Health issues/Pregnancy, No factor, Interpersonal stress, Family commitments, Distance	12 (%)	10 (%)	"Paiseki kami" "Kaammeivyasth hone kiwajah se"

CFI – Cultural formulation interview

helpful by around 50% of the women and caregivers. Interestingly, the women and caregivers reported that they had been advised faith-healing and resolution of marital discord by others as remedial measures for the current symptoms.

Barriers to care were explored by a single question in CFI [Table 5]. Stigma (29.63%), and financial problems (25.93%) were the major barriers to seeking help in both the women and the caregivers. Other factors were busy work schedule, family commitments and poor accessibility of health care facilities.

DISCUSSION

Prevalence of psychiatric morbidity

The primary aim of the study was to detect the prevalence of psychiatric disorders in perinatal women. A meta-analysis of the point prevalence of non-psychotic common mental disorders in developing countries reported values of 15.6% during pregnancy and 19.8% postpartum.[31] In our study, 10.3% of perinatal women had a current psychiatric diagnosis. Among them, most (≈80%) had a diagnosis of major depressive disorder.

The literature reveals that after the postpartum blues, which is usually self-remitting, postpartum depression is the common psychiatric disorder in perinatal women.[32-34] The average prevalence rate of non-psychotic postpartum depression based on a meta-analysis of a large number of studies, is 13%.[11] Although individual studies and systematic reviews[35-41] have estimated different rates of perinatal depression, prevalence estimates are affected by the nature of the assessment method and the length of the postpartum period under evaluation.[11] The prevalence studies done in this area in our country[40] are mostly from the southern part. In our study, there is a 7.12% point prevalence of depressive episodes. Our findings revealed a greater number of women with antepartum depression, that is, out of 20 (7.12%) women with a

depressive episode, 19 were in antenatal period and only one woman had postpartum depression. This could be because antenatal women formed the majority (89%) of our sample.

A cohort study by Chandran *et al*. in 2002[22] in rural Tamil Nadu reported that, of the 71 women with depression, 38 (54%) had an antenatal onset, suggesting that antenatal depression is a predictor for postpartum depression. Similar findings were also observed in a study done in Goa in 2002.[42] A study on the prevalence of women at risk for peripartum depression using the Edinburgh Postnatal Depression Scale (EPDS) found 31 (6%) out of 506 women being at risk of peripartum depression.[40] That lower prevalence compared to our study could be due to the fact that they did not use any diagnostic tool to confirm the diagnosis; so, some of the cases would have been missed.

Sociodemographic and clinical profile in women with and without psychiatric illness

In our sample, there was no significant difference in the socio-demographic profiles of perinatal women with or without a current psychiatric diagnosis, similar to a cohort study by Chandran *et al*.[22] However, in our study, marital discord, psychosocial stressors and a past history of psychiatric disorders were significantly higher in perinatal women with a current psychiatric diagnosis.

There is a significant presence of psychosocial stressors in women with psychiatric illness in our study, implying the role of the psychosocial factors in the onset and prevalence of psychiatric illnesses. Similar findings were found by Patel *et al*. in a study done in South India, where 78% of the depressed mothers had a history of psychological stressors in the antenatal period.[43] Among psychosocial factors, financial difficulties, experiencing a stressful life event, having a family member with chronic illness, lack of support from family networks or friends, and having conflicts with in-laws, especially the mother-in-law, were found to be important risk factors in a review of perinatal depression in Asian women.[36] Our findings about psychosocial stressors are very similar to those observed in the above review.

Marital discord was significantly more present in women with psychiatric illness and emerged as an important factor associated with psychiatric illnesses in perinatal women, similar to the findings by Chandran *et al*.[22] A review of risk factors for depression during pregnancy in Asian countries found that marital discord and poor support from the husband are important risk factors and that conflict with mother-in-law and dissatisfaction with the infant's gender are more specific to the Asian cultures.[36]

History of psychiatric illness in the past was significantly more positive in patients with psychiatric illness. In a population-based study, Rich-Edwards *et al*.[44] found that a past history of depression was the strongest predictor for antenatal depressive symptoms, and very similar findings were observed in a study done in Canada.[45] A review by Ryan, about depression in pregnancy, reported that past history of depression is a substantial biologic risk factor.[33]

Discussion of cultural formulation interview

The cultural context of the illness experience is essential for effective diagnostic assessment and clinical management. DSM 5 introduced CFI, which is a set of 16 questions that clinicians can use to obtain information about the impact of culture on key aspects of an individual's clinical presentation and care.

Most of the perinatal women and caregivers identified the nature of their symptoms as emotional and behaviour problem, and stated varied factors as the cause for their problem, like pregnancy/physical illness, destiny, stress due to interpersonal problems, and witchcraft. A multicentric qualitative study[46] about postnatal depression across countries and culture found that loneliness, lack of emotional and social support, poor relationships with partners, family conflict, and tiredness emerged strongly as themes across all 15 centres as causes of unhappiness following delivery, and most centres saw a lack of social support, family conflict, and sleeplessness as causes of postnatal depression.

Culture has a great influence on one's practices and understanding. Women with psychiatric illness and their caregivers acknowledged education, religion, and ethical, moral, and cultural values as an important aspect of their cultural identity. Similar findings were reported by two studies done in the southern part of our country.[22,23]

Religion and social support were found in our study as a major moderating factor, similar to the findings by Oates *et al*.[46] Stigma as a prejudice[47] is commonly faced by women in relation to marriage and childbirth,[48] and due to this fear, pregnant women often do not reveal their problems to others and do not seek medical help.[49] In our study, one-third of the women and caregivers identified stigma and financial problems as the major barriers to help-seeking.

A wide range of services was used by the subjects, varying from professional care to faith healers. Trust, easy availability and accessibility, recommendations by the significant others and belief in supernatural causation of illness were important reasons for choosing

a particular facility. Therefore, socio-cultural factors appeared to influence the help-seeking behaviour.[29] The majority of patients and caregivers were ready to accept psychological or pharmacological help to overcome their problems.

Strength and limitations of the study

Psychiatric morbidity in perinatal women has been studied widely, but studies on cultural factors affecting illness understanding and help-seeking behaviour are very few. Thus, studying cultural factors and help-seeking behaviour in a validated structured manner is the strength of our study.

However, there are certain limitations. The sample size was small and the study was conducted at a tertiary care centre. Therefore, its results have limited generalizability. Another limitation was that the scales EPDS and PAS were translated into Hindi (a formal translation and back-translation exercise was not done) and were interviewer-assisted. No structured tool was used to assess psychosocial stressors and marital discord, and these variables were recorded only on the socio-demographic proforma. Also, the CFI used does not have pre-defined interpretations. We were unable to interview two psychotic patients on CFI because of the nature of their illness. Hence their data could not be provided.

CONCLUSION

Psychiatric morbidity is significant in perinatal women attending antenatal and postnatal services, depression being the most common. Psychosocial stressors, marital conflict, and past history of psychiatric illness are significant in the group of perinatal women with current psychiatric illnesses. So, if psychological support is provided to these women on time, it could significantly reduce the occurrence of depression in them. Cultural aspects need to be addressed while planning future preventive and treatment programs for proper detection and treatment of perinatal psychiatric disorders.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Short-Term Impact of Hematopoietic Stem Cell Transplantation on Psychiatric Morbidity and Quality of Life in Hematological Malignancies in Adults

Deeksha Elwadhi, S. K. Khandelwal[1], Lalit Kumar[2], Atul Sharma[2]

ABSTRACT

Background: Hematopoietic stem cell transplantation (HSCT) is an established treatment for a number of malignancies. Quality of life (QOL) is an important marker for assessing arduous treatment modalities. Diagnosis of cancer, HSCT, and the physical and psychosocial sequelae of the intensive treatment lead to a deficit in the QOL of the recipient. This study aimed to assess the impact of HSCT on psychiatric morbidity and QOL in patients with hematological malignancies. **Methods:** A longitudinal pre-post study was conducted at a cancer research center. Thirty patients with hematological malignancies were assessed at three different time points for psychiatric symptoms and QOL. Sociodemographic and clinical variables were collected using a semi-structured questionnaire. Comprehensive psychopathological rating scale was used to assess the psychiatric symptoms. WHO QOL Bref and cancer-specific European Organisation for Research and Treatment of Cancer Quality of life Questionnaire (EORTC-QLQ) were used to measure the quality of life. **Results:** The mean (SD) age of the sample was 42.3 (12.8) years, with 24 males and 6 females. Most patients reported anxiety and depressive symptoms, reaching a peak at 3 week post-HSCT. The maximum deficit in QOL scores was seen at 3 weeks, with further improvement at 3-month post-transplant. **Conclusions:** HSCT leads to an increase in symptoms and a decrease in QOL during the acute phase. In the long run, it leads to improvement in physical and psychological wellbeing, with improvement in QOL. The recent surge in the long-term survivors of the procedure calls for further research in this direction so as to aid in their full recovery.

Key words: *Hematological malignancies, Hematopoietic stem cell transplantation, psychiatric morbidity, quality of life*

Key messages:

- *Hematopoietic stem cell transplantation is an arduous but life-saving procedure*
- *Acute hospitalization is the period of maximum physical and psychological dysfunction*
- *Overall, it leads to a decrease in symptoms and improvement in quality of life.*

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Department of Health Research, [1]Department of Psychiatry, Holy Family Hospital, [2]Department of Medical Oncology, AIIMS, New Delhi, India

Address for correspondence: Dr. Deeksha Elwadhi
India Red Cross Society Building, 1 Red Cross Road, New Delhi - 110 001, India. E-mail: elwadhideeksha@gmail.com

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Hematopoietic stem cell transplantation (HSCT) is an established treatment modality for a number of hematological malignancies, such as chronic myeloid leukaemia, acute myeloblastic leukaemia, and multiple myeloma. Hematopoietic progenitor cells emerging from bone marrow, peripheral blood, or umbilical cord are injected intravenously to re-establish hematopoiesis in patients with defective bone marrow. High rates of physical complications have been reported with HSCT, the most common being opportunistic infections and graft-versus-host disease.[1] In addition, studies have shown that HSCT may be associated with significantly elevated rates of depression, anxiety, and cognitive difficulties.[2-4] A prospective study of 220 transplant recipients showed a total prevalence of psychiatric disorders to be 44.1%.[5] The complications of this procedure are likely to affect the Quality of Life (QOL) of the cancer survivors, among whom such issues are already of great concern because of the severity of the illness.[6]

World Health Organization (WHO) defines QOL as an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards, and concerns.[7] Prospective studies assessing QOL in HSCT patients showed physical functioning to be the most severely affected domain.[8-10] The majority of the studies have reported improved QOL 1-year post-HSCT.[11,12]

There is a dearth of data from low-income countries regarding psychiatric morbidities and QOL in hematological malignancies, and none in patients receiving HSCT.[13,14] The few studies regarding the prevalence of psychiatric disorders and QOL in malignancies pertain to either pediatric age group[15] or solid tumors like cancers of breast, cervix, and head and neck.[16,17]

This study aimed to assess the impact of HSCT on psychiatric morbidity and QOL in patients with hematological malignancies and to determine any correlation between the presence of psychiatric morbidity and the QOL.

MATERIALS AND METHODS

The study had a pre-post design, and the participants were assessed at three time points. Baseline interview was conducted one week prior to the HSCT, followed by assessments at three weeks and three months after the HSCT. All inpatients admitted for their first HSCT in the bone marrow transplant ward of the hospital were contacted 1 week prior to the procedure. They were provided with a brief description of the purpose of the study. Informed written consent was taken from those who expressed willingness to participate.

A convenience sample of 30 adult subjects admitted for HSCT, of either gender, who could understand the local language (Hindi) were recruited. Patients who were unwilling to take part in the study, were unable to understand the test questions, or had concurrent substance use disorder other than nicotine dependence were excluded from the study. Patients whose clinical condition made them unfit to sit through the interview, due to extreme pain or weakness, and those who had severe side effects from induction treatment regime were also excluded.

All participants were allowed to ask questions throughout the study and were free to withdraw at any point in time. Participant anonymity and confidentiality were guaranteed. Ethical clearance was taken from the Institute Ethics Committee.

A semi-structured proforma was used to collect the sociodemographic details and cancer-related clinically relevant information. Cognitive impairment was screened using the Hindi Mental State Examination (HMSE).[18] The HMSE is an Indian adaptation of the Mini Mental State Examination (MMSE), developed for the Hindi speaking population, and has a maximum score of 30. HMSE was preferred over MMSE, keeping in mind the relevant context of the study population. It is a highly sensitive (94%) and specific (98%) instrument to detect cognitive impairment, especially in the Indian populace,[19] and is freely available in the public domain for use in research. HMSE was used as a screening tool to exclude any cognitive deficits that could hamper further interviewing.

Comprehensive Psychopathological Rating Scale (CPRS)[20] was used to assess the psychiatric morbidity. It has 65 items, covers a wide range of psychiatric symptoms (depression, schizophrenia, obsessive compulsive disorder, and mental distress in connection with severe physical illness) and has high inter-rater reliability.[21] In addition to the full scale, two of its subscales – Brief Scale for Anxiety[22] and Montgomery Asberg Depression Rating Scale[23] – were also used, to assess anxiety and depression, respectively. Both these scales have a high degree of concordance.[24] The CPRS assesses symptoms and observed behavior and does not provide categorical diagnoses.[20]

QOL was assessed using two instruments. The first was the generic World Health Organization Quality of Life Questionnaire (WHOQOL- BREF) Hindi Version[7] – a 26-item, internationally applicable, cross-culturally comparable, multilingual, and multidimensional

instrument to measure QOL. In the study, four broad domains of QOL were assessed: physical health, psychological health, social relationship, and environment.

The second assessment instrument was the Hindi version of EORTC-QLQ (European Organization for Research in Treatment of Cancer Quality of Life Questionnaire) C30-version 3.0,[25] which is an integrated system for assessing the health-related QOL specifically of cancer patients. The QLQ C30-version 3.0 has five functional scales, three symptom scales, a global health status/QOL scale, and six single items. The total score in each domain ranges from 0 to100. Translations are available in 43 languages including Hindi. It is freely downloadable for research purposes. The two instruments were used to capture the cancer-specific effects on QOL in addition to the overall QOL.

The analysis was done using SPSS 20.0. Descriptive analysis of sociodemographic variables and outcome variables (scores in HMSE, CPRS, WHOQOL-BREF, and EORTC) was done. A comparison of the change in the mean scores of the variables over the three assessment points was done using repeat measure analysis of variance (ANOVA). The within-subject differences were taken into consideration, and in case Mauchly's test of Sphericity indicated that the assumption of sphericity has been violated, Greenhouse-Geisser correction was used to report the effect size. Correlation between the sociodemographic parameters and the outcome variables was assessed using Pearson's product–moment correlation analysis.

Table 1: Sociodemographic and clinical variables

Variables	Mean (SD) or frequency (%)
Age (years)	42.3 (12.8)
Gender	
Male	24 (80%)
Female	6 (20%)
Education	
Primary	7 (23.3%)
Middle	3 (10%)
High school	10 (33.3%)
Graduate	6 (20%)
Post graduate	4 (13.3%)
Occupation	
Professional	3 (10%)
Skilled worker	10 (33.3%)
Unskilled worker	4 (13.3%)
Student	5 (16.7%)
Homemaker	2 (6.7%)
Unemployed	6 (20%)
Marital status	
Married	8 (26.7%)
Unmarried	22 (73.3%)
Diagnosis	
Multiple myeloma	21 (70%)
Hodgkin's lymphoma	4 (13.3%)
Non-Hodgkin's lymphoma	2 (6.7%)
Acute Myelogenous lymphoma	3 (10%)
Duration of the Disease (years)	1.967 (1.07)
Type of HSCT	
Autologous	23 (76.7%)
Allogeneic	7 (23.3%)
Past-treatment received	
Chemotherapy	30 (100%)
Radiotherapy	12 (40%)
HSCT	0
Immunotherapy	0
Comorbidities	
Medical*	4 (13.3%)
Psychiatric†	1 (3.3%)

*Three had hypertension, whereas one had diabetes, †Adjustment disorder (6 months prior to the study); HSCT – Hematopoietic stem cell transplantation

RESULTS

Sociodemographic and clinical characteristics

The mean (SD) age was 42.3 years, and 24 (80%) were male. Multiple myeloma was the most common diagnosis (n = 21; 70%). Hodgkin's (4), non-Hodgkin (2), and AML (3) constituted the remaining 30%. Mean duration from the initial diagnosis to the first assessment point was around 2 years (6 months to 6 years). Twenty-three patients received autologous HSCT, while seven received allogeneic transplant with donor being HLA matched siblings. One patient was diagnosed with adjustment disorder 6 months prior to inclusion in the study and was not receiving any psychiatric treatment at the time of assessment.

The rest of the parameters are given in Table 1.

Psychiatric morbidity

The mean HMSE scores at all the three assessment points were within the normal range, indicating no cognitive deficits in the study population. The maximum mean HMSE score was at 3-month post-transplant, whereas the minimum was at 3 weeks post-transplant. The difference in means of the HMSE scores over three assessment points using repeat measure ANOVA [$F = 23.65$ $\eta^2 = 0.449$; $P < 0.001$], as shown in Table 2, was statistically significant. However, no clinical relevance can be inferred as none of the scores, at any of the assessment points, were below the threshold for cognitive deficits.

The mean total CPRS score was highest at three weeks post-transplant and lowest at three months post-transplant. Mean scores for anxiety and depression subscales showed a similar pattern.

At baseline, 19 patients (63%) had scores indicating mild depression. The most commonly reported CPRS items were inner tension, lassitude, and fatigability,

Table 2: RM ANOVA statistics of serial comparisons over three assessment points

Scale	Pre-transplant, mean scores (SD)	Three-week post-transplant, Mean scores (SD)	Three-month post-transplant, Mean scores (SD)	*F**	Effect size**	*P*
HMSE	30.37 (0.76)	29.70 (0.96)	30.83 (0.38)	23.65	0.449	<0.001
CPRS						
CPRS Total score	11.617 (4.5)	14.03 (5.33)	8.383 (4.19)	23.06	0.443	<0.001
Anxiety subscale	4.30 (2)	5.167 (2.52)	2.517 (1.63)	19.47	0.402	<0.001
Depression subscale	8.950 (4.44)	10.217 (4.64)	4.717 (3.27)	31.25	0.519	<0.001
WHOQOL-BREF						
Total	47.91 (6.14)	46.06 (5.2)	49.43 (4.22)	19.77	0.405	<0.001
Physical	44.978 (10.65)	36.232 (8.46)	47.716 (7.82)	24.42	0.457	<0.001
Psychological	49.391 (13.61)	48.275 (12.31)	50.801 (9.07)	1.68	0.055	0.19
Social relationship	52.081 (16.04)	51.807 (14.6)	59.033 (13.23)	12.77	0.306	<0.001
Environmental	53.02 (11.62)	51.562 (10.85)	51.562 (12.33)	5.89	0.169	0.005
EORTC						
Total	60 (13.2)	57.498 (13.02)	71.388 (12.32)	12.26	0.297	<0.001
Physical functioning	61.111 (15.96)	50.215 (14.52)	66.222 (14.54)	13.69	0.321	<0.001
Role functioning	69.445 (20.57)	50.556 (19.32)	60.556 (14.83)	12.51	0.301	<0.001
Emotional functioning	60 (15.7)	54.445 (15.43)	63.611 (12.85)	6.34	0.179	0.003
Cognitive functioning	80 (16)	67 (13.84)	75 (15.63)	9.62	0.249	<0.001
Social functioning	69.442 (27.36)	50 (29.03)	70 (26.41)	9.83	0.253	0.001

HMSE=Hindi mental state examination; CPRS=Comprehensive psychopathological rating scale, WHOQOL- Bref=World Health Organisation Quality of Life questionnaire - Bref; EORTC=European Organization for Research in Treatment of Cancer Quality of Life Questionnaire, *Degrees of freedom (within groups) = 29, **In case Mauchly's test for spherical assumption ruled no sphericity assumed, Greenhouse Geisser correction used

with no reports of sadness of mood. At three weeks post-transplant, 22 patients (73%) had scores suggestive of mild depression, and one had moderate depression. At 3 months post-transplant, six patients (20%) met the cut-off for mild depression. Difficulty in concentration was the most reported symptom at the latter two assessments. None of the subjects reported psychotic symptoms or suicidal ideations. ANOVA for mean total CPRS scores showed significant difference at the three time points [$F = 23.06\ (1, 29)$; η^2=0.443; $P < 0.001$].

Quality of life

The maximum deficit in all the four domains of WHOQOL Bref was seen at 3 weeks, with improvement at 3-month post-transplant. The highest scores out of the four domains at all the time points were seen in the social relationship, and the lowest scores, in physical functioning.

Overall QOL showed a statistically significant rise at 3-week and 3-month post-transplant as compared to the baseline. In separate scales (physical, role, cognitive, and social functioning), a statistically significant fall at 3 weeks and an increase at 3-month post-transplant were noted. In the emotional functioning scale, the fall from 3-week to 3-month post-transplant was statistically significant. Similar pattern was found in both WHOQOL Bref and EORTC QLQ.

In the EORTC symptom scales, fatigue, nausea and vomiting, pain and dyspnea, sleep difficulties, appetite difficulties, and constipation were maximum at 3-week post-transplant and showed a significant fall at 3-month post-transplant. Financial problems showed a rising curve with the passage of time. Overall, 3-week period appears to be the period of maximum symptoms, with significant improvement at 3-month post-transplant.

Correlation analysis

A correlation analysis was done to explore the direction and strength of the linear association within the same outcome variables at different time points and also between the different outcome variables. It was assumed that the *P* value achieved 'statistical significance' at $P < 0.01$ considering multiple measurements. The CPRS score at baseline was positively correlated with scores at 3 weeks ($r = 0.47$, $P = 0.008$) and negatively correlated with the role functioning domain of EORTC QLQ at baseline ($r = -0.50$, $P = 0.005$). The CPRS score at 3 weeks had a strong positive correlation with CPRS total score at 3-month post-transplant ($r = 0.73$, $P < 0.001$). The HMSE score at baseline and at 3-week post-transplant did not show any statistically significant correlation with each other. However, the HMSE scores at three months post-transplant were positively correlated with the EORTC global health domain at three months. The WHOQOL Bref mean scores at baseline were positively correlated with the scores at 3-week and 3-month post-transplant. Also, they were correlated with the EORTC global health domain and role function subdomain at pre-transplant. Further, WHOQOL Bref scores at three weeks post-transplant were significantly correlated with the mean scores at the three months post-transplant ($r = 0.87$; $n < 0.001$)

indicating that an earlier improvement heralds a later improvement in QOL. A statistically significant positive correlation was seen between various subdomains of EORTC QLQ at various assessment points, as shown in the supplementary file.

An important point of note was the statistically significant negative correlation seen between a particular combination of WHOQOL Bref and EORTC QLQ, that is, WHOQOL Bref scores at 3 weeks and EORTC global health domain at 3 months, even though intuitively one may expect a positive correlation between these two.

DISCUSSION

This study assessed the impact of HSCT on psychiatric morbidity and QOL in hematological malignancies in a pre-post design. It is the first of its kind in an Indian setting.

No mortality was reported in our small sample during the follow-up period of 3 months. The majority (23, 76.7%) were recipients of autologous HSCT, which is not associated with graft versus host disease a nd has lower mortality rates.

None of the study participants had any cognitive deficits at any assessment point. Some studies have shown that the deficits in cognition do occur in HSCT recipients as a long-term sequelae.[26] This could not be commented upon in our study, as we followed up patients only for 3 months.

CPRS has been used in many studies to assess the impact of various interventions on psychiatric symptoms and offers the advantage of objective assessment like "observation of sad mood." In our study, 63% of the subjects were rated to have mild baseline depression on CPRS, which increased to 73% at 3 weeks. These rates are higher than the prevalence found in other studies, which were in the range of 20%–40%.[2,27,28] The higher rates could be due to the differences in the patient population, treatment protocols and the instrument used, as none of the previous studies had used CPRS. Interestingly, none of our subjects reported sadness of mood, and observed sadness was present in only one patient at 3-week assessment. The vegetative symptoms such as sleep and appetite disturbances may have led to higher scores on CPRS in these patients.

The trajectories for the total scores, as well as the depression and anxiety subscales of CPRS, were similar. All three showed maximum scores during hospitalization, with a decrease thereafter, as found in previous studies.[29-31] Patients recover from the acute effects of HSCT in 4–6 weeks. Post-transplant patients are isolated (usually for the first two weeks) to prevent opportunistic infections, which may give them less chance for allaying their fears and anxieties regarding the outcome. Once the acute period is over, patients are discharged and nursed in more comfortable and less stringent settings at home, and the pain and dysfunction caused by malignancy also improve, which aids in the decrement of the scores. Some previous studies have also shown improvement in psychiatric outcomes with the passage of time after the procedure.[9,32]

Two instruments were used to assess the QOL. WHO QOL Bref assessed the generic overall QOL, whereas EORTC was used to measure cancer-specific QOL, bringing the effect of malignancy and side effects of treatment in its fold. QOL is an important parameter to be assessed, especially in cases with a terminal diagnosis and in arduous procedures such as HSCT, to judge the overall effect of the treatment.

The mean overall QOL score in both the scales decreased from baseline to reach a nadir at three weeks post-transplant, with a significant increase at three months post-transplant. Physical functioning was the most affected domain and psychological/emotional functioning, the least. In previous studies too, the physical functioning had declined rapidly immediately after transplantation, reaching its lowest at 30 days.[33,34] Wettergren *et al*.[12] found physical functioning at 8- to 12-month post-transplantation to be as good as prior to the procedure. In our study, social relationships improved with time, which was also seen in one of the first prospective studies.[10] Mc Quellon *et al*.[9] showed a parabolic curve in QOL, which was also seen in the physical and social relationship domains of our sample. Chang *et al*.[2] showed a linear improvement in the QOL at six- and twelve-months post-transplant. A linear trend was seen in the environmental domain, but it was a worsening than an improvement; satisfaction with the environment decreased over time. Return to the home increases the interaction and functioning of the individual but adds to the difficulties in going back for tertiary care.

Role functioning was maximum before HSCT, with a significant decrease at 3 weeks after it ($P < 0.001$), corresponding to the period of acute side effects. The poor role fulfillment may be a result of various factors such as the patient's poor physical health, over-involvement from the family leading to role reversal, precautions as advised by the oncologist, apprehensions regarding the long-term success, and reluctance to join back normal functioning after a long break due to the malignancy and its treatment.

Emotional functioning also was seen to improve with the passage of time. HSCT exerts a toll on the recipients early in the process. Emotional functioning for survivors is most compromised before transplantation and immediately after the procedure.[9,33] As in our study, significant improvement was seen in a previous study as early as at hospital discharge to 100-day post-HSCT,[35] with stabilization over time.[36]

All symptom scale items showed maximum dysfunction at 3-week post-transplant. The financial problem showed a linear increase until three months post-transplant. With limited role function and continuing medical care costs, the financial situation worsens in these patients. The worsening financial situation can be a major impeding factor in overall QOL. The increased financial burden can also lead to the advent of anxiety and depressive symptoms in the patients. Both prospective and cross-sectional studies have shown greater financial difficulties at varied time points ranging from 1- to 7-year post-transplant.[8,37]

A negative correlation was found between the mean duration of disease before the assessment and CPRS scores at baseline (−0.44). It can be inferred that longer the duration of the malignancy, the psychiatric symptoms decrease, as the patient accepts the diagnosis and the prognosis. Due to acceptance, the patient's anxiety and concerns start falling, which leads to better coping. However, in a study by Rodrigue *et al*.,[38] significant positive association was found between disease duration and depression.

A correlation between the CPRS score at baseline and the scores at 3-week and 3-month post-transplant can indicate that patients with better coping skills and good functioning at baseline might tolerate the effects of the procedure better as compared to the others. This calls for liaison between psychiatry and oncology, as a baseline assessment and intervention early in the course could lead to a better overall outcome. Frequent contact with a trained therapist can ensure good psychological recovery and better QOL.

A negative correlation was found between the CPRS scores at baseline and the EORTC role functioning subdomain scores at baseline (−0.50). Higher scores, signifying more psychiatric symptoms, lead to a higher toll on the QOL of the individual and a restriction in the fulfillment of roles, which can explain the negative correlation.

We may not be able to tender a concrete response as to how a statistically significant negative correlation between WHOQOL Bref scores at 3 weeks and EORTC global health domain at three months was seen, but we suppose that the small sample size of our study might have contributed to this, which is a major limitation of our study. In addition, it might be that the focus of WHO QOL Bref is to evaluate the overall generic QOL, whereas EORTC QLQ specifically focuses on cancer-specific domains.

Even though the biological correlates of psychiatric morbidity in HSCT have not been adequately described, a few possible mechanisms can be inferred. First, in many conditions of chronic stress, an imbalance in the hypothalamic-pituitary-adrenal axis underlies the development of psychiatric symptoms, which could also lead to such a development in malignancies.[39] HSCT itself is quite a tenuous procedure and can lead to significant stress to the body. Second, the chemotherapy regimen for immunosuppression prior to the procedure might lead to changes in the immune system, which might lead to the development of psychiatric symptoms.[40] All the more, isolation periods essential in the prevention of infections post-HSCT might lead to under-stimulation and can lead to cognitive deficits or development of psychiatric symptoms, in a similar way to the development of ICU psychosis.

The longitudinal assessment, with a baseline measure pre-transplant, is the major strength of this study. Assessment time points represented different landmarks for the transplant recipients – admission, discharge, and follow-up. Validated instruments were used for the assessment of outcome variables, and no attrition was reported in the above sample.

Small sample size, the fact that the group was heterogeneous in terms of type and diagnosis, and a short follow-up period are the limitations of this study. In addition, neuropsychological assessment could not be done in this study, due to time constraints. Even though a single-arm pre-post study design is a well-accepted methodology, the study could have been made more robust by including a control group. As it was an exploratory study, further research can take that into consideration.

This study infers that HSCT leads to an increase in psychological symptoms and a decrease in various domains of QOL during the acute phase, with significant improvement in the long run.

With the advancement in technology, newer procedures have forayed into the medical practice. It has become increasingly important to assess the impact of these procedures, not only on the underlying disease but also on the other important aspects of the patient's life. It is prudent to assess whether these procedures unintentionally increase morbidity in the race to

decrease it. Studies with a larger, homogeneous sample should be followed up for a longer period to corroborate the above findings further. Descriptive studies addressing the main concerns of the patient and finding the locus of distress should be undertaken for designing targeted psychological interventions.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Stress and its Social Determinants – A Qualitative Study Reflecting the Perceptions of a Select Small Group of the Public in Sri Lanka

Buddhika Senanayake, Sumudu Indika Wickramasinghe[1], Sisira Edirippulige[2], Carukshi Arambepola[3]

ABSTRACT

Background: Exposure to stress, especially for prolonged periods, can result in physical and mental disorders. To attribute causality to its associated disease profile, social determinants need to be identified at the population level. The objective of this study was to explore perceptions regarding stress and its probable social determinants, among a purposeful cohort of the public from Colombo district, Sri Lanka. **Methods:** A qualitative study using focus group discussions (FGDs) was conducted among adults. Purposive sampling was used to recruit 8--10 participants into homogenous groups. Data were collected until information saturation. A semistructured FGD guide was used to facilitate the discussions. Content analysis methods were used to analyze data. **Results:** Six FGDs consisting of 59 participants were conducted. Participants included primary healthcare workers, community members, village leaders, private and public sector employees, unemployed individuals, homemakers, self-employed persons, slum dwellers, and persons from affluent communities. Three main themes emerged: social, economic, and cultural factors. Social factors consisted of four sub-themes: social role or status, generation gap, disability, and unsafe environment. Economic factors included three related subthemes: poverty, unemployment, and job insecurity. Cultural factors included three subthemes: superstitious beliefs, religion and caste, marriage and dowry. **Conclusion:** Elements regarding stress and its social determinants among the public in Sri Lanka seem to be an amalgam of interconnected sociocultural and economic factors. However, addressing these social determinants in isolation (at an individual level) may not be feasible, as most causes appear to be outside the scope of the individual.

Key words: *Health perception, social determinants, stress disorders*

Key messages: *Social determinants were interconnected, often across sociocultural and economic domains. Most of these factors were outside the scope of the individual's personal purview and therefore, holistic national policy initiatives will be required to assist those affected at the population level.*

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Senior Registrar in Community Medicine, Post Graduate Institute of Medicine, University of Colombo, [3]Senior Lecturer, Department of Community Medicine, Faculty of Medicine, University of Colombo, Colombo, Sri Lanka, [1]Medical Officer, Ministry of Health, Sri Lanka and PhD Candidate, Centre for Online Health, School of Medicine, The University of Queensland, Brisbane, [2]Programme Director (e-Healthcare), Centre for Online Health, The University of Queensland, Brisbane, Australia
Buddhika Senanayake: ORCID Number - 0000-0002-2278-2889

Address for correspondence: Dr. Buddhika Senanayake
160, Prof. Nandadasa Kodagoda Road, Colombo, Sri Lanka. E-mail: buddhikaoffice@gmail.com

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Stress is a basic psychobiological process. It is based on the existence of and exposure to stressors (events perceived as causing stress) and a subsequent chain of escalating events leading to a "stress response." However, how every person responds to each situation is different, and the stress response varies according to the way the stimulus is appraised as a threat. Therefore, stress and its subsequent response experienced by humans is almost always the result of a cognitively mediated subjective experience.[1]

Different aspects of stress have been studied by researchers over time. Extreme entities of stress response such as burnout and post-traumatic stress disorders (PTSDs) have been explored extensively. Burnout has been studied in various occupational categories, including healthcare workers.[2,3] Studies of PTSD have examined the consequences of traumatic events at length.[4,5] However, stress has often been studied in depth combined with a specific physical or a psychosocial disorder.[6-8]

The social determinants of health are defined as conditions, which influence the way people are born, grow, work, live, and age. It further includes the health system they access to attain care.[9] These aspects interact in determining the distribution of health among populations in relation to both communicable and noncommunicable diseases.[10] Studies from several countries have shown that the prevalence of common mental health conditions, including stress, invariably follows a social gradient.[11-13] These determinants are also narrowly correlated to the immediate environment of an individual such as underprivileged social conditions of low income, lower level of education, unemployment, insecure housing, unsafe home and neighborhood conditions, unsafe employment, childhood experiences (e.g., abuse), and poor relationships and social support.[14]

Exposure to social stressors for a protracted period can result in accrual of stress, with probable mental health consequences.[15] Short-term and chronic social stressors have also been identified and illustrated as root causes (social determinants) of mental health disorders.[16] Psychological distress has also been recognized as a significant health-related risk factor for Aboriginal and Torres Strait Islander adults in Australia. Their social determinants of psychological distress were identified as negative perceptions of the residential neighborhood, lack of social support from family, and social and civic distrust.[17] Determinants of psychological stress among Chinese dessert oil workers were occupational stress, burnout, and personality.[18] A study on stress and social determinants of maternal health revealed poverty, food insecurity, lack of access to quality education, and unsafe environments as significant life stressors.[19] However, these determinants are population and context (locale) specific and most likely will differ between countries. Hence, stress (and its social determinants) should be ideally studied relative to the country or the community, with specific knowledge on its traditions, history, culture, belief systems, social norms, and values. Although studies are available to identify stress among populations after a catastrophe such as floods,[20] the stress accrued over the years among seemingly normal populations have not been explored up to now.

Sri Lanka is an island with a population of approximately 21 million, located to the south of the Indian peninsula. In recent times, it is beset with high suicide rates among its population, and the burden of mental illnesses has been recognized as a national priority.[21] Widening income inequality, general rising costs of living (inflation), and the changing social fabric may be some of the reasons for these high suicide rates and also increased stress levels. Although the effects of stress are usually not seen outwardly, they may gradually culminate in increasing numbers of mental health disorders and noncommunicable diseases. Therefore, identifying the social determinants that could lead to stress (hence a predisposition to mental disorders) is crucial, and preventive strategies could be provisioned to minimize the harm caused by these. To date, no study has explored stress and its social determinants among the general public in Sri Lanka. However, it is also important to study these aspects in close relation to the living environments of the population, as it would provide a snapshot of the true state of events. Therefore, we aimed to explore perceptions regarding stress and its probable social determinants among a cohort of the public from the Colombo district in Sri Lanka.

MATERIALS AND METHODS

A qualitative methodological approach was used to conduct this study, as it allowed to understand the contexts of the participant's life in relation to developing stress. The subsequent analysis used thematic analysis through analyzing (transcribed interview) content.[22] Focus group discussions (FGDs) were used as the preferred method of interview, to generate in-depth information on social determinants of stress. The FGDs provided an opportunity for diverse views and experiences of individuals to be outlined and generated a rich understanding of participants' experiences and beliefs. This method also allowed relatively passive individuals (participants), through positive group dynamics, to have the confidence to express themselves.[23]

The study was approved by the Ethics Review Committee (EC-13-180).

Inclusion and exclusion criteria

This study was conducted among adults (>18 years of age) residing for more than 1 year in the district of Colombo. Institutionalized adults (for psychological, correctional, or other reasons), pregnant females, lactating mothers, adult visitors to the area, those with severe psychotic illnesses, and adults experiencing acute stressful events during the 1 month preceding the study were excluded.

Participant recruitment and sampling

Participants were recruited purposefully from a community-health outreach service, conducted by research assistants with the help of local community health workers in selected areas within Colombo district. The smallest administrative unit in Colombo district was (conveniently) selected to include a population subgroup from each socioeconomic sector (identified from administrative data on subdivision of communities for Colombo district): highly urban, urban, and rural. FGDs were conducted in each of these selected administrative units, among a homogenous group of 8--10 adults.

Once a group of 15--20 prospective participants was selected (purposively) by the local community health workers, the research assistants selected every second client for inclusion in the study. As the clinic participant numbers were too large, at the beginning of the study, we decided to include every second client (to have a manageable number for each group). Several of the prospective participants were also included through referrals by community health workers, prior to the outreach service. In this context, purposive sampling was considered suitable in selecting the prospective group of participants, as it helps augment theoretical diversity by selecting information-rich participants related to the phenomenon of interest.[24,25] "Homogeneity" of selected participants was mainly based on their level of education, and this helped to reduce variation in intelligence-level, to simplify analysis, and to facilitate group interviewing.[26] The final number of FGDs depended on the saturation of data, which was determined by the point at which the researcher acquired sufficient information to make a meaningful explanation on the subject of interest.[27] The FGDs were carried out among adults from different socioeconomic groups, as it was useful for substantiation and triangulation of the qualitative data from the different sources, to improve validity.[28]

Interview guide

An interview guide was developed by the research team, with the assistance of subject experts, to conduct each FGD in an open-ended manner *(*online-only supplementary material 1*)*. This guide was useful for the interviews to be repetitively conducted (and data to be collected) similarly across the different domains of inquiry.[28] The panel of subject experts comprised of public health specialists, psychiatrists, psychologists (two each), and a medical anthropologist.

Focus-group discussions

Each focus group was conducted by one facilitator, one cofacilitator, and one or two note takers (research assistants). A place convenient for the participants (either the community center or local government administration office), with minimum disturbance, was arranged for each FGD with the help of local community health workers, on the same day of recruitment. The FGDs lasted between 60 and 90 min (average of 75 min). Discussions were audio-taped and subsequently transcribed verbatim. All questions in the focus group guide were written on an easel pad for participants to refer to during the discussion. During the sessions, the facilitator read each question and followed the interview guide with frequent prompts for probing in order to make sure that important aspects were fully deliberated.

Analysis

Content analysis methods were used to explore the perceptions of the study participants and to identify themes.[29] The discussion transcripts were coded in an open-ended manner by hand, after reading carefully, to gain a deeper understanding of the contexts. These initial codes were reviewed closely and categories generated. Finally, the categories were reviewed for developing overall themes. Suitable quotations were selected and extracted to illustrate the main findings. A final review of codes, categories, and themes was conducted to exclude any oversight of any important information.[30] During open coding of the comments made by the participants, a list of social determinants affecting stress was identified (directly or through interpretation). Findings are described narratively.

RESULTS

Six FGDs were held, with a total of 59 participants. The participants included village leaders (n = 4; 6.8%), retired private and public sector employees (n = 6; 10.2%), unemployed individuals (n = 6; 10.2%), housewives (n = 12; 20.3%), self-employed adults (n = 7; 11.8%), slum dwellers (n = 8; 13.5%), adults representing the affluent communities (n = 6; 10.2%), primary healthcare workers (n = 5; 8.5%), and other members from the community (n = 5; 8.5%). The

mean age of participants was 42 years (SD +/− 10.2), and the majority of them were females (52.5%). The education level was either secondary education or less in nearly half (50.8%) of the participants. Only 14% belonged to the older age group (of 60 years or above).

Social determinants of stress

A list of the key social determinants, as identified by the participants as probable causes for their stress, is provided in Table 1. Short verbatim quotations from the participants are presented as evidence for the interpretation of data.

Themes

Content analysis of the focus group interviews identified three main themes related to the social determinants of stress as identified by the participants. These were social factors, economic factors, and cultural factors. Within each theme, several subthemes were also identified [Table 2]. The comments made by the participants were grouped into these themes and subthemes [Table 3].

Theme 1: Social factors

Four subthemes were identified within this theme. They were social roles or status, generation gap, disability, and unsafe environment.

Social roles or status

Participants described how "immediate society" (extended family, neighbors, or work community) defined individuals by the type of work they engaged in. This meant that some participants felt constrained (or uncomfortable) to interact with others outside their immediate environment. Therefore, the type of occupation was clearly identifiable as a stressor when interacting in society, especially for those occupied in taboo (or low-level manual) work. Participants representative of occupations such as three-wheel drivers, masonry workers, and garbage collectors stated that they felt society was judgemental (often negatively) of them, purely on the basis of their occupation. The type of household, assets owned, and commuting in a "luxury" vehicle were perceived as symbols of high social status. Many of the participants made attempts to fit into the expected roles and status within their immediate "high" society, disregarding the basic needs of their family. This meant that some participants endured significant stressors when realizing their aspiration to be included in the "igh" social status group. Those who were of the view that they had lower social status complained about reduced social interactions they had, due to the perception that they were ignored (as inferior) by others.

Table 1: Social determinants of stress as reported by participants

Probable determinant of stress	Example (Quote or interpretation)
Poor living conditions	"Stress depends on the place you are born and the place you live. A person in a developed country lives longer than a person living in an African country. The difference may be (even) one or two decades. Not only among countries, but also within countries there is a marked difference in life expectancy among different regions"- 52-year-old male working as a clerk in a public sector institution
Social problems	"I do not wish to live with my husband anymore. He is a severe drug addict. I can have a separate independent life with my children. But my parents, close relatives, and friends force me to continue the marriage." - 31-year-old mother of two children
Childcare responsibilities	"I am a widow and I am looking after three (grand) children. Two of them are going to school. They belong to my son. My son is working as a laborer in a construction site. He visits home once a month. Children's mother (daughter-in-law) is abroad (working) for the last three years and there has been no communication from her in the past 1 year. I am going to take care of these children as long as I can. But what will happen to these children after my death?" - A 70-year-old grandmother from the rural sector
Use of harmful narcotic substances (and illegal alcohol)	"My husband works as a manual laborer in a rubber state. He drinks "kassipu" (a local illicit liquor product) - half a bottle every day during last 2--3 years. He does not provide adequate money for household work and for children's education. Therefore, I work as a domestic servant (maid) in a close by house to help with the basic expenses. - A mother of two children (aged 9 and 5) from a rural area
Health services	"In the 18th and 19th centuries, the TB caseload was very high in Western Europe and North America. The number of cases has reduced drastically with the improvement of personal hygiene and socioeconomic status of these societies, even before the first anti-TB drug was discovered' - 68-year-old retired male doctor
Inconsistent educational policies	Educational policy reforms should be encouraged at national or at provincial levels. Participants critiqued education policy. "The competitiveness of people for survival was initiated from this education system. They develop individuals who can compete well, but who lack socio-environmental and life skills. The competitiveness of the current society may be due to the poor educational system. They fail to meet the demands of employment skills and needs. As I know, persons who passed G.C.E A/Levels are working as laboratory attendants. Graduates who have completed a degree are posted to receptionist posts in public institutions. This is a waste of national money and resources."- A retired bank executive.
Poor governance	Good governance was identified as a key determinant for the socioeconomic, cultural and political stability of a country. The demise of law and order of the country could adversely affect health outcomes. Most participants stated that law enforcement in their area on most occasion, was poor. "Equitable law and order with good governance is a must."
Inconsistent government policies and programmes	Consistent economic, health, social, and educational policies should be established with immediacy to minimize the undesirable effects social determinants of stress have on the general public. "Not having a consistent policy is bad, anyone can do whatever they want and justify it without any accountability and scientific basis." - A retired school principal

Table 2: Social determinants of stress: Themes and subthemes

Themes	Subthemes
Social factors	Social roles or status
	Generation gap
	Disability
	Unsafe environment
Economic factors	Poverty
	Unemployment
	Job insecurity
Cultural factors	Superstitious beliefs
	Religion
	Cast, marriage and dowry

Participants described how in Sri Lankan society, traditionally the social role defined for females was to be a "home-maker," that is, to prepare meals, care for the children, and to carry-out household chores. Many female participants found it difficult to deviate from this traditional and set role. Furthermore, many of them were economically dependent on their husbands, who in turn expected their wives to fulfill the traditional role of being a housewife. Furthermore, most women participants did not have the opportunity to engage in any gainful employment, due to a lack of relevant skills or opportunity. This traditional role for females in society meant that their financial vulnerability was higher.

Generation gap

The "generation gap," the age difference between parents and their adult children, was a reason for some disagreements. The related disputes sometimes included extended family as well. For some female participants, a conflict with in-laws, when living within the extended family setting, was a concern. Constant arguments and disagreements led to the accrual of stress (and anger), and during acute periods of disharmony, stress levels were intense. According to some participants, the social norm was that "the extended family should be promoted with mutual understanding among all family members." However, many female participants found disharmony within the family often, attributing it to the difference in perceptions stemming mostly from the age difference between older adults and the younger generation (generation gap).

A 34-year-old lady stated,

> "We are living with my husband's parents, and they interfere too much into our family issues. I do not have any freedom to cook what I want or to decorate the home as I would like."

Disability

Participants with a disability felt that they were unfairly discriminated in society due to their incapacities, and this was stress-causing. Their routine activities of daily living (shopping, banking, going to the cinema, etc.) were compromised (or difficult) as the access to premises (public and private) was difficult, owing mostly to poor facilities. One participant with disability stated that though regulations and policies supported favorable infrastructure to be developed for disabled people to access public buildings easily, facilities were yet to "catch up."

Another factor for stress among disabled participants was the type of disability. Disability subsequent to diseases with an attached stigma element, such as elephantiasis, was alienating for some, especially when outside their home environment.

> "I have a heavy right leg due to filariasis. It makes it difficult to perform my daily activities. When I go to a public place, everyone looks at my leg and try to ignore me."

Some participants also identified issues related to sexual and reproductive health as another factor causing stress. Sexual dysfunction was identified as a reason for discriminating the male partner within the family unit, a major obstacle for the psychological well-being and marital harmony of one participant.

Unsafe environment

Insecure living environment (in slums or in new developments close to slum areas) was cause of stress for many participants from urban communities. New developments for housing or establishment of an industrial estate in an already highly urbanized region created significant stress for the long-term occupants of the area. These new developments made the inhabitants of the area feel insecure and (somewhat) discriminated. Adverse and illegal activities within the slum environments (narcotic drug trade, illegal liquor trade, etc.) made some settings insecure and socially undesirable (described as "notorious areas of trouble"). Parents had concerns for their children when living in or close to insecure environments, as it sometimes led to discrimination of their children when outside their community, for example, when the children were at school. Furthermore, the social connectedness within such communities was nominal as people feared interactions or community activity.

Theme 2: Economic factors

Various views related to economic factors affecting participants were clustered in this theme. Three related subthemes were also identified. These were poverty, unemployment, and employment insecurity.

Poverty

Participants commented on the constant difficulty in being financially secure. This was identified as one of

Table 3: Social determinants of stress as reported by participants

Probable determinant of stress	Quote(s) or interpretation(s)
Social factors	
Social roles or status	"As a professional, I have to maintain my social status. Everyone expects that. Therefore, I have constructed a big house (three floors) with all modern facilities and bought a brand new vehicle. I took a housing loan and a vehicle loan from two private banks. A large portion of my salary is deducted from the bank loans and therefore, I have to work overtime. I work from early morning until late evening and this routine schedule has been continuing for the past 6-8. People may think that we have money, but most of the things we got are from bank loans." - A 45 year old male professional
Generation gap	"I married four years ago and I do not have any children yet. I worked as a management assistant in a state ministry before marriage. After marriage, I resigned from the job. My husband influenced me a lot to do so, as he feels it would affect our family life. We are living with his parents and they interfere too much with our family issues. I do not have any freedom to cook what I want and to decorate the home as I would like."
Disability	"All my family members including my grandmother, mother, and sisters are obese. I have undergone extensive diet schedules and several treatment plans. I got discouraged as people used to laugh at me and made comments when I exercised. People use nicknames to identify me in the workplace. During busy hours, even bus conductors were reluctant to let me use the public transport." "I met with an accident three months back and fractured my right leg. I can't walk now and I am using a wheelchair. I am unable to use public transport and public premises (hospitals, government officers) because they do not provide separate access to wheelchairs." - A 40-year-old businessman living in an urban area
Unsafe environment	"I have a teenage daughter and a teenage son. They want to go and play in the park. But I cannot send them out because of the unwanted things happening near the park. Some people are drunk and some make bad remarks to young people. There are illegal drug distributing centres and narcotic drugs are also exchanged. I strongly oppose their request to play in the park. I have to protect my children." - 36-year-old mother from low-income setting in a highly urban area
Economic factors	
Poverty	"I am a widow and I am looking after three children. Two of them are going to school and they belong to my son. My son is working as a laborer in a construction site. He visits home once a month. Children's mother (daughter-in-law) is abroad working as a domestic servant in a middle east country for the last three years and there has been no communication from her in the past one year. I am going to take care of these children as long as I can. But what will happen to these children after my death?" - A 70-year-old grandmother from the rural sector "My husband works as a manual labourer in a rubber state. He drinks "kassipu" (a local illicit liquor product) - half a bottle every day during last 2-3 years. He does not provide adequate money for household work and for children's education. Therefore, I work as a domestic servant in a close by the house to help with the basic expenses. - A mother of two children (aged 9 and 5) from a rural area
Unemployment	"I graduated from a leading state university in Colombo two years ago. I have tried my best to find a job according to my academic qualifications. I have applied for more than 1,000 jobs in the past 18 months with no success. I am frustrated because I was unable to find a job according to my credentials. People suggest me to go behind politicians and try to find a job. I cannot plan my life without a permanent job." - A 30-year-old male from rural area
Job insecurity	"I have done three jobs for the last 1 year. I worked as a three wheel driver for two months, part-time sales man for three months and I am currently working as a helper for a construction site. All of these jobs are contract basis, part-time, or freelance. I do not have a permanent income and currently receiving a low wage. These jobs lack pension plans, sick day leaves, predictable income, or anticipated schedules of work." - A 33-year-old male from semi-urban area
Cultural factors	
Superstitious beliefs	"I have three children. Two of them got married. My main concern is my daughter who is still unmarried and will be 33 this year. She is pleasant, well-educated, and working in a private firm. My main issue is to find a partner for her. My family astrologist said that according to her horoscope, it would be a difficult task to find a suitable partner for her. My husband advised me to go ahead with marriage without considering this horoscope or astrological guidance, but I am reluctant to do against that." A 58-year-old mother living in an urban area "I am the only son in my family and did my secondary education in the science stream. I strongly oppose astrology as a science and consider it a myth. When I got married two years back, I intentionally did not match the horoscopes and did not believe in any auspicious time prepared by the astrologer. I changed those auspicious times according to my convenience and got married. My first son was born 1 year back and on the same day, my father got a heart attack and died the next day. After three weeks, my mother also passed away. A lot of my relatives point their finger at me for the cause of these sudden deaths. So, now I have a guilty feeling about myself." A young man from a semi-urban area (30 years of age)
Religion	"According to the culture of our ethnic group, several families are living in one household. We do not have the independence to carry out family-related matters according to our plans as all other members interfere with it. Not only that, the privacy for us is also less". A young female (26 years) from a minority ethnic group
Caste, marriage and dowry	"I do not wish to live with my husband anymore. He is a severe drug addict. I can have a separate independent life with my children. But my parents, close relatives and friends force me to continue the marriage." - 31-year-old mother of two children "I am a member from a lower caste. People treat us inferiorly; neglect our rights; do not value our services; they won't allow us to come to certain social functions. Our children are neglected from school and ultimately they dropout from education system. The caste system makes people exposed to prejudice, stereotyping, etc, and it is a social evil. This cannot be eradicated without changing the mind-set of the people in the society." "I got married three years ago. My father did not have much money to give as a dowry. Before marriage my husband did not expect any financial benefits from me. But few months after the marriage my husband started harassing me to provide a dowry. He shouted/screamed at me. It was a severe physical and emotional abuse. I got divorced six months back and I lost my whole life. I never expected that" - 27-year-old mother of one child

the main (or the most important) determinants of stress. A perception of being inferior was seen among the poor with a feeling of not being in control of their life. People living in poverty (as identified by themselves) described how they struggled to pay for food, accommodation, clothing, education, healthcare, transport, or recreation. It was described as an "unending struggle" to meet the competing demands with a limited income.

> "My husband is a part-time manual laborer, and we have three children. We do not have enough income to live. We are struggling for the survival of our family."

In extreme circumstances of poverty, some parents willingly involved their children in manual labor, during some aspects of their work (e.g., masonry, cleaning services). This meant that these children were sometimes exposed to risks such as physical or sexual abuse, especially during times when parents were unavailable.

Unemployment

Participants described unemployment as a "most devastating experience" as they felt insecure and discriminated. Being unemployed was described as directly associated with economic instability and stress.

> "I completed my degree 8 months back and ever since, I am looking for a job. Currently, I am spending all day searching online for job opportunities and more short-term ways to make money. I fear that if I stop the search and watch TV, I'll miss some job opportunities."

Unemployment made some participants feel uncomfortable to interact with their immediate social environment and embarrassed when with family. It led to isolation and severe psychological distress. Some participants described situations where it had sometimes led to severe consequences such as depression and suicide among friends.

Job insecurity

Employment insecurity was identified as an important workplace stressor by many participants. They expressed that job insecurity, which is a subjective perception, is due to labor-hire factors in their current workplaces. Some argued that it was due to the mismatch between employee capabilities and employer expectations. This issue had serious consequences for some, as it led to feelings of insecurity and dissatisfaction. Some participants stated that job insecurity was also linked to issues related to productivity and profits. These perceptions were also associated with low employment satisfaction, poor psychological wellbeing, and increased physical symptoms (weight gain, headache, etc.).

> "I have been working for a private company, on a contract basis, for 3.5 years. They do not have any intention to make my appointment permanent. I do not have the luxury of gaining the benefits the company provides their permanent staff. Actually, I lost interest in this job and have started searching for a new one."

Theme 3: Cultural factors

Superstitious beliefs

Cultural practices related to superstitious beliefs were also identified as important determinants of stress among the participants. They stated that, traditionally, Sri Lankan society placed faith in astrology and horoscopes (charts) for predicting the future for individuals, communities, country, and even the "whole universe." Several participants assumed that it was vital to consider the astrological perspectives (assuming that it was a "time-tested science for centuries") prior to engaging in any important activity. This meant that planned actions were often directed by astrologers, and for the non-believers, this created significant stress. Even though the majority of participants interviewed were believers of astrology, a few were strongly against these concepts and said that it destroyed motivation of an individual and allowed the mistaken belief that an "alien planet" from far away could influence them. The believers argued that the potential risks of challenging the cultural norms and values far out-weighed the simplicity of simple acceptance.

> "If you challenge (astrology), you should get ready to face the consequences and repercussions."

Religion

Religions with strict regulations were also a stressful issue for some participants. Younger generation was increasingly reluctant to submit to these religious regulations, and they made them feel stressed. The pressure from elders, religious leaders, and religious (or faithful) peers forced them to conform to certain religious traditions such as attending prayer, appropriate dress, leisure activities, etc. Most of the participants in the rural sector believed in a broad pantheon of gods and that some spirits and demons helped them during stressful times.

Participants (especially from the Buddhist faith) believed that actions (good or bad) in the past trailed one as "karma," with a potential to significantly change their lives in the future. They stated that good karma would lead to a prosperous future and that bad karma could cause harm (at least eventually). Some participants had used several cultural approaches to assess their "karma level" (through astrologers) and to seek advice from gods "to make their lives happy" and

to minimize stress. A few participants described how they had learned from their parents to place faith in fate and karma since their childhood.

Caste, marriage, and dowry

Participants described how culturally and traditionally accepted concepts such as "caste" and "dowry" also were a causality to stress, mostly during times of marriage of young females. Since marriage was often considered a family event, the stressors associated with the marriage (costs, preparation of dresses, etc.) included all family members. However, this extended process often led to the isolation of the young female within the family (without being able to express personal feelings) at a time of need for guidance. Participants described that in the Sri Lankan context, marriage was considered an important social phenomenon, dissimilar to Western societies where the concept of divorce, separation, and living together prior to marriage are considered typical occurrences.

Informal norms of society forced married partners to stay together even during incompatibility or disharmony, by emphasizing the importance of responsibility and respect. Mothers who had young children were especially bound by these informal norms, as it was seen as their responsibility to look after the children and separation from the partner was not encouraged. This led to some females feeling isolated within their marriages even though their partner was simply "physically present."

Although discrimination according to caste is relatively less in the modern era, it is still prevalent in some communities when social events such as marriage and related cultural gatherings are concerned. Some participants from lower castes (as identified by themselves) felt that they were often discriminated in society. They felt that the type of employment they were in (e.g., garbage collectors) made them inferior to the others. Participants expressed that an isolation from the rest of the community was also a cause for stress.

DISCUSSION

This is the first qualitative study of this type conducted in Sri Lanka. We attempted to identify the social determinants of stress among the general public in Sri Lanka. The study identified social factors (social status, generation gap, disability, and unsafe environment), economic factors (poverty, unemployment, and job insecurity) and cultural factors (superstitious beliefs, religion, caste, marriage, and dowry) causing stress among adults.

Previous studies conducted in other, mostly developed, countries have shown that psychological distress was greater in the lowest wealth quintile, wealth inequalities correlated with distress.[31,32] Although in developed countries the higher level of stress was well allied to the lower social strata, this study showed that in Sri Lanka, both upper and lower extremities of social strata experienced high-stress circumstances, though the issues escalating stress for either social strata were dissimilar. One of the reasons for the low social strata to live with high stress could be the low financial safety net (benefits) and poor social security systems in developing countries. Continuity in work (often long hours in manual labor) was necessary for the poor to maintain a good quality of life as compared with the richest quintile, which often adversely affected their family ties and social relationships. Furthermore, individuals from the poorest quintile may be chronically stressed due to this social deprivation and poor social capital. "Social status index" developed by De Silva makes an attempt to measure social status according to the Asian cultural context.[33] De Silva *et al*. showed that a traditional healer in a rural village had a higher social status despite having poor financial income compared with an illegal drug seller with multiple financial assets. This example clearly shows that social status needs a deeper inquiry, interpreted with caution, considering prior knowledge, culture and social background of a particular individual. Similarly, intergenerational poverty and racism are identified as unique social determinants of stress among indigenous people living in Australia.[34]

Unemployment is another social determinant closely linked with stress.[35] A vicious cycle is created when unemployment leads to poverty, with a well-correlated dose--response relationship between income and health.[36] Our study showed that poverty and unemployment were significant determinants for stress among the communities included. Previous research has shown that unemployment leads to illness and premature deaths.[37] Furthermore, undesirable consequences of poverty affect early childhood development and have the potential to thereby influence subsequent generations.[38] Investment in poverty reduction is uniformly identified as a successful preventive strategy for psychological stress.[39] Some participants of this study clearly described unemployment as the most devastating experience in the matrix of factors affecting stress. Therefore, from the perspective of governance, strategies for poverty reduction and employment placement through training and retooling of the labor force are imperative for mitigating stress among citizens.

One of the most important findings identified through this study was that marriage and its related

factors (caste and dowry) were stress-causing to both the individual and the family. Caste is a way of cultural segregation of people, and it is traditionally determined by birth. This segregation creates an internalization of prejudice and long-lasting discrimination, with impaired individual self-esteem.[40] This traditional concept is increasingly challenged in modern society, possibly due to rapid globalization and the importance placed on individual skills and work performances.[41] Our study showed that these traditional practices were still persistent in some Sri Lankan communities, causing substantial stress to some participants. Policies such as equity in education and equal employment opportunities may minimize these cultural barriers in times to come. In this context, legal policy makers (at the local and national level) should recognize the depth of self-depreciation which adversely affects society and remedial measures should be taken through legislative protections.[40] Research shows "dowry" as another complex culturally determined concept that has led to sex-selective abortions, female infanticides, and neglect of daughters.[42] In some cases, it directly relates to domestic violence and severe psychological stress, resulting in mental disorders.[43] This is observed not only among females of this study but also in previous studies where African American men had identified race, ethnicity, and marital traditions as crucial cultural determinants for their stress.[44] Importantly, evidence shows that legislative prohibition *per se* is ineffective in tackling these complex problems. A holistic approach using human behavioral ecology could provide positive motivations in contesting these cultural barriers.[42]

This study identified an unsafe environment (neighborhood) as a determinant of stress among the participants. Weich and Lewis showed how insecure housing conditions could cause extensive psychological morbidity.[45] The effects of the built environment and the quality of relationships between people of the neighborhood are a crucial determinant of stress.[46] This was further supported by a study conducted among Australian aboriginal communities, where negative perceptions of the residential neighborhood, lack of social support from family, and social and civic distrust had caused significant community stresses.[17] Resultantly, the National Aboriginal Health Strategy Working Group recognized how indigenous communities living in rural Australia required self-esteem, dignity, justice, and control over the physical environment as crucial determinants for mitigating stress.[47] Furthermore, strategic urban planning is well-identified as a policy level solution to create safe environments and minimize community stress levels.[48]

This study has many strengths. This was a study on perceptions of social determinants of stress in a multiethnic, multicultural district in Sri Lanka. The participants represented all social strata of the community, representing both urban and rural sectors. The qualitative study method was useful as it allowed the participants to express their feelings freely, unlike in a closed assessment. The data gathered in the focus groups achieved informational saturation, and therefore, the findings from this study could be described as an accurate representation of the community perceptions of social determinants of stressors affecting adults in the community. This information may be applicable to other countries in the region through common links shared on the identified social determinants. Importantly, the results of this study will enhance support to policy formulation in relation to health as well as non-health sectors to gain positive health outcomes at the population level.

One limitation of this study was the purposeful sampling. This increased some bias, as it is likely that "health-seeking" clients were identified. However, participants who were frank in stating their opinion needed to explore the perceptions accurately. Another limitation would be that all areas of Sri Lanka could not be included (resource limitation). Since the focus groups were conducted in the local language (Sinhala), participants who were not fluent had to be excluded.

CONCLUSION

Social determinants were interconnected, often across sociocultural and economic domains. However, several of these factors were outside the scope of the individual's personal purview, requiring management of societal expectations. This means that individuals suffering from stress might not be able to mitigate stress-causing events by themselves alone. Therefore, strong social support programs, inclusive economic development programs, public counseling services (free of charge at the point of delivery), and holistic national policy initiatives will be required to assist those affected.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Perceived Stress and its Epidemiological and Behavioral Correlates in an Urban Area of Delhi, India: A Community-Based Cross-Sectional Study

Ruchira Pangtey, Saurav Basu, Gajendra Singh Meena, Bratati Banerjee

ABSTRACT

Background: Increasing stress has been recognized as a major public health problem in the developing world accelerated by an ongoing demographic, economic, and sociocultural transition. Our study objectives were to validate a Hindi version of the 10-item Perceived Stress Scale (PSS-10) and to also assess the extent of perceived stress and its correlates among an adult population in an urban area of Delhi. **Methodology:** A community-based cross-sectional study was conducted in an urban resettlement colony of Delhi among 480 adult subjects aged 25--65 years, during the period from January to December 2015. The PSS-10 was translated into Hindi and validated in the study population. Data was analyzed using IBM SPSS Version 25. **Results:** A total of 243 (50.6%) men and 237 (49.4%) women were enrolled. The scale had an acceptable level of internal consistency (Cronbach's alpha = 0.731). A principal component analysis was run on the PSS-10 data, based on which a three-component structure was accepted, which explained 61% of the total variance. The mean PSS score was 19.25 (SD = 4.50) years. Perceived stress was highest in the 35--50 age group. On multivariate analysis, low socioeconomic status and a white-collar occupation were found to be associated with increased perceived stress ($P < 0.001$). **Conclusion:** A high burden of perceived stress exists in residents of a low-income urban population in India.

Key words: *Hindi, India, PSS-10, stress*
Key messages: *The Hindi version of the PSS-10 is a valid and reliable instrument for measuring perceived stress in the community.*

Growing stress in the developing world is indicative of unresolved physical and emotional tensions accentuated by the fast-changing demographic, economic, and sociocultural landscape. Chronic stress negatively influences health and well-being in relation to mental health, cardiovascular disease, diabetes, obesity, etc.[1-5]

Stress is a dynamic concept influenced by the relationship between the environment and the individual and its effect upon the individual varies

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Department of Community Medicine, Maulana Azad Medical College, New Delhi, India

Address for correspondence: Dr. Saurav Basu
Department of Community Medicine, Maulana Azad Medical College, New Delhi, India. E-mail: saurav.basu1983@gmail.com

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with his or her ability in coping with it.[6] Perceived stress is a measure of the degree to which situations in one's life are appraised as stressful and is comprised of sociocultural context dependent on medical, physical, psychological, and psychosocial aspects.[7] The appraisal of this perceived stress is considered to supersede the assessment of stressful life events.[8]

Previous studies have shown that sociodemographic factors (like educational level, socioeconomic status, neighborhood profile, and gender) and behavioral risk factors (like smoking and alcohol consumption) are also associated with perceived stress.[9-14] However, most Indian studies on perceived stress have been conducted within specific population subgroups, but there is a lack of data regarding perceived stress and associated factors in the general population.[15-18] Understanding the factors associated with stress in Indian populations can enhance the development of community-based interventions for stress reduction. Furthermore, early identification of individuals and subgroups with an accumulation of stress-related risk factors may provide opportunities for early strategic intervention for prevention of adverse behavioral and health outcomes.[11]

Perceived Stress Scale (PSS), developed by Sheldon Cohen, is used as a self-appraisal measure for individuals to assess the extent of the perceived stressfulness of their various life situations.[19] Various studies in India have used the scale, but to our knowledge, it has not been previously validated in a predominantly Hindi speaking population.

Our study objectives were to validate a Hindi version of the PSS and to also assess the extent of perceived stress and its correlates among an adult population in an urban area of Delhi.

METHODOLOGY

A community-based cross-sectional study was conducted in an urban resettlement colony in the Gokalpuri area located in the North-East district of Delhi, India during the period from January to December 2015. The population of the area was approximately 23,187 (December 2013). The study site was chosen as it is the field practice area of the Department of Community Medicine of a premier medical college in Delhi. The study area is a resettlement colony of an urban slum and comprises a densely populated, low-income population.

Adult individuals aged from 25 to 65 years who were residing in the area for a minimum period of 6 months and could understand and converse in Hindi were included in the study. Those who, at the time of the interview, were suffering or recuperating from serious illnesses which had required hospitalization were excluded.

We conducted a secondary analysis of data collected originally for a study ascertaining the burden of behavioral risk factors related to select non-communicable diseases in 480 subjects.[20]

The sampling unit for the present study was a household. Systematic random sampling was applied for selection of houses. Every ninth house was selected. If the selected house was found to be locked, it was visited three more times. In the eventuality that data could not be collected from the same house or no eligible individual was available in the household, the next house was selected. From each familial household, a maximum of two individuals, each of the opposite sex, were enrolled in the study. If multiple eligible individuals were available in the same household, the study subjects were selected randomly by a draw of lots. A maximum of 10 individuals were enrolled in a day.

Data were collected from the subjects using a semi-structured patient interview schedule. The perceived stress was measured using PSS.[19] The scale was linguistically validated into the local language Hindi. The translation process included: (1) Forward translation of the original PSS into Hindi was done by a native speaker, (2) the back-translation into English was done by another native speaker, (3) this forward and back-translation process was continued until the back-translated version matched with the original English version of the scale, (d) the translated version was pretested in 10 adults who were not included in the study [Supplement 1]. The PSS was verbally administered to those subjects who were illiterate or lacked functional literacy or on their request.

The PSS has been widely used and psychometrically validated as a reliable measure of psychological stress estimated over the previous 4 weeks.[19] It comprises of 10 items measured on a five-point Likert scale (0: never, 1: almost never 2: sometimes 3: fairly often 4: very often). The PSS construct demonstrates a two-factor structure; the first being "general stressors" and the second being "the ability to cope."[21] The PSS score is obtained by summing the scores of all the items, with reverse coding for items 4, 5, 7, and 8 as they are positively stated. The PSS score ranges from 0 to 40, with the 40 point score representing the highest perceived stress level. The PSS does not have any diagnostic cutoff to differentiate between the stressed and not stressed individuals.

The socioeconomic status of the subjects was assessed using the modified Kuppuswamy classification updated

for 2014 income criteria.[22] Current daily smokers were defined as those who were currently smoking cigarettes, bidis, or hookah daily in the previous 7 days. Current daily smokeless tobacco users were defined as those who were currently using chewable tobacco products like gutka, naswar, khaini, or zarda paan daily in the previous 7 days. Heavy drinking was defined as a quantity of alcohol consumption that exceeds an established threshold value which in the present study was set at more than 14 drinks per week for men (or >4 drinks per occasion) and more than seven drinks per week for women (or >3 drinks per occasion).[23] Weight and height of the subjects were also recorded to calculate the body mass index (BMI). The Asia-Pacific classification of BMI, which has a lower cutoff for overweight and obesity, was accepted for this study.[24]

Ethics: Ethical clearance was obtained from the Institutional Ethics Committee of the medical college. All subjects gave their written and informed consent before their enrolment in the study.

Statistical analysis: The data was analyzed using IBM SPSS Version 25.

A principal component analysis (PCA) was run on the 10-item PSS to ascertain its construct validity. The present dataset satisfied the PCA requirements regarding the linear relationship between variables and adequacy of sample size. The Cronbach alpha and the Spearman-Brown split-half reliability coefficient were calculated to establish the reliability of the PSS.

Categorical variables were expressed as frequency and proportion, while continuous variables were expressed as mean and standard deviation. The Mann--Whitney U test and the Kruskal--Wallis H test were used to determine if there was a statistically significant median difference in perceived stress levels between two or more groups, respectively. A multiple regression analysis was run to predict the PSS score (dependent variable) from the independent variables that showed statistically significant association with higher PSS scores on bivariate analysis. There was linearity as assessed by partial regression plots and a plot of studentized residuals against the predicted values. There was homoscedasticity as assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. There was no evidence of multicollinearity, as assessed by tolerance values greater than 0.1. The assumption of normality was met, as assessed by a Q-Q Plot.

Due to the multiple comparisons involved, the Bonferroni correction was applied (0.05/11) and a P value <0.004 was considered as statistically significant.

RESULTS

The mean (±SD) age of the subjects was 37.9 (11) and ranged from 25 to 64 years. A total of 243 (50.6%) men and 237 (49.4%) women were enrolled. The socioeconomic class of the subjects was lower in a majority (62) of the subjects, with 113 (23.5%) belonging to the lower middle class and 279 (58.1%) to the upper lower class [Table 1].

The mean PSS score was 19.25 (SD = 4.5) years. The scale had an acceptable level of internal consistency, as determined by a Cronbach's alpha of 0.731. The Spearman-Brown split-half reliability coefficient was also adequate (0.71). The translated Hindi version of PSS is provided as online supplementary material.

PCA of the PSS-10 was conducted. The suitability of PCA was assessed before analysis. Inspection of the correlation matrix showed that all variables had at least one correlation coefficient greater than 0.3. The overall Kaiser--Meyer--Olkin (KMO) measure was 0.633, classifications of "mediocre" according to Kaiser, while the individual KMO values for all the items were greater than 0.4, which suggested retaining all the items of the

Table 1: Sociodemographic characteristics of study sample (*n*=480)

Variable	*n* (%)
Age	
18-34	225 (47)
35-50	156 (32.4)
>50	99 (20.6)
Sex (Gender)	
Men	243 (50.6)
Women	237 (49.4)
Marital status	
Married	346 (72.1)
Unmarried	123 (25.6)
Divorced	11 (2.3)
Family type	
Nuclear	288 (60)
Joint	192 (40)
Educational status	
No schooling	101 (21)
<10 years	159 (33.2)
≥10 years	220 (45.8)
Occupation	
Professional	45 (9.4)
Semi-Professional	23 (4.8)
Clerical/shop owner	54 (11.3)
Skilled worker	42 (8.8)
Semi-skilled	54 (11.3)
Unskilled	142 (29.6)
Housewife	120 (25)
Socioeconomic Status	
Upper	22 (4.6)
Upper middle	47 (9.8)
Lower middle	113 (23.5)
Upper Lower	279 (58.1)
Lower	19 (4)

PSS-10. Bartlett's Test of Sphericity was statistically significant (χ^2 = 1526.04, df = 45, P < 0.001), indicating that the data was likely factorizable.

PCA revealed three components that had eigenvalues greater than one, which explained 34.2%, 16.6%, and 10.1% of the total variance, respectively. Component loadings of the rotated solution are shown in Table 2. Visual inspection of the scree plot with a cutoff of an eigenvalue ≥1 also indicated that the three components should be retained [Figure 1]. Strong loadings of items relating to "perceived helplessness" were present in component 1 (items 1, 2, 6), "perceived distress" in component 2 (items 9, 10), and "self-efficacy for coping" in component 3 (items 5, 7, 8).

On bivariate analysis, subjects of lower education level (less than 10 years), of lower socioeconomic status, who were married, or having diabetes were observed to show significantly higher median PSS scores (P < 0.004). A Kruskal--Wallis H test was conducted to determine if the PSS score in the subjects differed by age and BMI [Table 3]. A post-hoc analysis using the Mann--Whitney U test revealed that the increase in the median PSS scores from 0--34 to 35--50 age group was statistically significant (P < 0.001). Furthermore, the increase in the median PSS score from underweight to overweight (P = 0.001) and the decrease from normal to obese (P = 0.001) were also statistically significant.

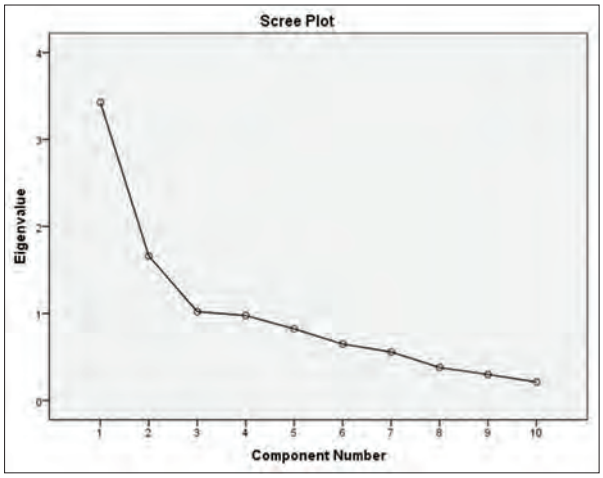

Figure 1: Scree Plot of the Perceived Stress Scale-10

The multiple regression model statistically significantly predicted PSS, F (8, 471) = 13.8, P < 0.0005, adjusted R^2 = 0.18. The variables socioeconomic status (coded high/middle = 1, lower = 0), employment type (coded 1 = white collar, 0 = non-white collar), and marital status (coded 1 = married, 0 = unmarried) added statistically significantly to the prediction (P < 0.004). The regression coefficients and standard errors are reported in Table 4.

Self-rated health status was reported as *excellent* by 66 (13.8%), *very good* by 112 (23.3%), *good* by 180 (37.5%), *fair* by 93 (19.4%), and *poor* by 29 (6%) subjects. Furthermore, adherence to healthy lifestyle habits was reported as *excellent* by 48 (10%), *very good* by 143 (29.8%), *good* by 164 (34.2%), *fair* by 113 (23.5%), and *poor* by 12 (2.5%) subjects.

DISCUSSION

The present study assessed the reliability and factor structure of the PSS-10 in a general population in an urban area in Delhi. The study findings of the Hindi PSS-10 revealed a three-component structure which is in variance with previous studies which had supported a two-component structure comprising of "perceived helplessness" and "perceived self-efficacy for coping."[25,26] The three-component structure in our study additionally indicates the presence of "distress."

The amount of total variance explained by the two-component structure was 51%, which is consistent with previously published studies on PSS-10.[25-26] Furthermore, the three-component structure of our study explained 61% of the total variance.

Table 2: Rotated Structure Matrix for PCA with Varimax rotation of a three component (PSS-10) questionnaire*

	Component		
	1	2	3
PSS 1 felt upset because of something that happened unexpectedly?	0.792	0.112	0.040
PSS 2 felt unable to control the important things in your life?	0.668	0.320	0.007
PSS 3 felt nervous and "stressed"?	0.737	0.282	0.166
PSS 4 felt confident about your ability to handle your personal problems?	−0.627	0.326	−0.033
PSS 5 things were going your way?	0.083	−0.121	0.907
PSS 6 felt could not cope with all the things that you had to do?	0.61	0.515	0.030
PSS 7 felt able to control irritations in your life?	0.23	0.340	0.632
PSS 8 felt you were on top of things?	−0.17	0.478	0.629
PSS 9 angered because of things that were outside of your control?	0.078	0.710	0.109
PSS 10 felt difficulties were piling up so high that you could not overcome them?	0.342	0.636	0.152

*Varimax rotation with Kaiser Normalization. PCA - Principal component analysis, PSS - Perceived stress scale

Table 3: Association between perceived stress score and sociodemographic variables (*n*=480)

Variable	Mean (SD)	*n* (%)	PSS median score (IQR)	*P*
Age		-		
18-34	37.9±	225 (47)	19 (5)	<0.001*
35-50	11.0	156 (32.4)	21 (5)	
>50		99 (20.6)	19 (5)	
Sex (Gender)				
Men	-	243 (50.6)	19 (6)	0.02**
Women		237 (49.4)	20 (4)	
Education (years)				
<10	8.0±5.2	260 (54.2)	20 (4)	<0.001**
≥10		220 (45.8)	18 (5)	
SES				
Upper/Middle	-	182 (38)	17 (5)	<0.001**
Lower		298 (62)	20.5 (5)	
Marital status				
Married	-	346 (72.1)	20 (5)	<0.001**
Unmarried		134 (27.9)	18 (6)	
Family type				
Nuclear	-	288 (60)	20 (5)	0.02**
Joint		192 (40)	19.5 (5)	
Employment type				
White collar	-	122 (25.4)	20 (5)	0.37**
Others		346 (72)	20 (5)	
Daily tobacco smoking				
Present	-	53 (11)	20 (8)	0.42**
Absent		427 (89)	19 (5)	
Daily smokeless tobacco use				
Present	-	60 (12.5)	20 (5)	0.02**
Absent		420 (87.5)	19 (6)	
Heavy drinking				
Present	-	113 (23.5)	20 (4)	0.14**
Absent		367 (76.5)	20 (6)	
BMI				
Normal	21.3±4.8	150 (31.3)	20 (6)	<0.001*
Underweight		154 (32.1)	18 (6)	
Overweight		134 (27.9)	21 (3)	
Obese		42 (8.8)	17 (5)	
Diabetes				
Present	-	42 (8.8)	21 (4)	0.004**
Absent		438 (91.3)	19 (6)	
Hypertension				
Present	-	91 (19)	20 (4)	0.11**
Absent		389 (81)	20 (6)	

*Kruskal-Wallis H Test, **Mann-Whitney U Test. SES - Socioeconomic status, BMI - Body mass index

Table 4: Summary of Multiple Regression Analysis

Variable	B	95% CI	*P*
Intercept	16.73		< 0.001
Age (Years)	0.02	-0.02 - 0.06	0.26
Male sex	0.72	-0.18 - 1.16	0.11
≥10 years education+	1.65	0.59 - 2.7	0.002
Married+	1.98	0.94 - 3.0	< 0.001*
Nuclear family+	0.28	-1.09 - 0.53	0.50
White collar occupation+	3.34	2.16 - 4.53	< 0.001*
Upper SES+	-5.5	-6.85 - (-4.1)	< 0.001*
BMI	-0.02	-0.10 - 0.06	0.62

*$P<0.001$; B=unstandardized regression coefficient; +Sex (1=male, 0=female), education (1 = ≥ 10 years, 0 = < 10 years), marital status (1=married, 0=unmarried), employment type (1=white collar, 0=others), SES (high/middle=1, lower=0). SES - Socioeconomic status, BMI - Body mass index

Our study found that mean perceived stress level measured by the PSS-10 was 18.69 in men and 19.75 in women. The mean PSS score was also lower in young people aged below 35 years. Large population-based studies conducted in the general population of the developed world had also found higher mean PSS scores among women compared with men, but the mean PSS scores were found to be much lower. A cross-sectional study in Denmark reported mean PSS scores of 11.7 in 5,346 women respondents and 10.2 in 4,676 men respondents.[11] Three national-level surveys in the United States (US) also found higher mean PSS scores among women than men, but in contrast to the present study, reported an increase in the PSS scores with decreasing age.[10] The US surveys also showed that mean PSS scores increased in men from 12.07 to 15.52 from 1983 to 2009 and in women from 13.68 to 16.14 during the same period. Mean PSS scores in a five-country Western European study in the elderly population was 17.6.[27] Developed countries with much higher human development indices, overall material prosperity, and relative lack of economic insecurity are expected to show lower stress levels in their populations compared with populations in the developing world. Nevertheless, the perceived stress levels in our study are only slightly higher compared with those in the US study. This could be due to the phenomenon of relative deprivation in which, despite the lack of absolute deprivation, the perceptions of inequality could translate into stress.[28]

Low educational level was not found to be a significant predictor of increased stress in the present study. Although a high educational level can also act as a stressor, it has been suggested that the ability to cope with stress improves with education.[11] Furthermore, similar to previous studies, we also found higher PSS scores in subjects belonging to the lower socioeconomic classes.[9-11]

Unemployment or the lack of a means of employment in those who desire to work has been previously reported to be associated with increased perceived stress due to the likelihood of lack of financial autonomy.[10] However, in our study, those with a white-collar job reported higher perceived stress. This could be due to the large number of homemakers in our sample whose perceived stress levels differed from those of the unemployed.

In the present study, married participants reported increased levels of perceived stress compared with those who were unmarried, although marriage is usually considered to lower perceived stress levels.[29] However, it is also known that factors related to economic

deprivation can contribute towards stress spillover in marriages.[30]

The strengths of the present study are that it is one of the first studies from India that validated the PSS-10 scale and assessed the perceived stress in the general population from a low-income community. However, there are certain limitations to our study. First, it is a cross-sectional study due to which temporal relationship between perceived stress and the various stressor variables cannot be determined. Second, the study did not take into account several factors like social isolation and neighborhood profile, which can influence perceived stress levels among individuals in a community.[11,14,29] Third, our study did not include elderly subjects (aged ≥65 years) who are known to experience greater perceived stress.[31] Finally, the study was conducted in a single community in Delhi, which limits its external validity.

In conclusion, perceived stress in a low-income urban Indian population was high, with low socioeconomic status and lack of white-collar employment being its covariates. Future studies should assess the role of social networks in the Indian context for coping with perceived stress.

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Conflicts of interest
There are no conflicts of interest.

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ONLINE SUPPLEMENTARY MATERIAL

Hindi translation of the Perceived Stress Scale – 10 item

इस सूचकांक के सभी प्रश्न इस बात से सम्बंधित हैं कि पिछले माह इस प्रकार के विचार तथा भावनाएं आप में कितनी बार उत्पन्न हुए

कृपया प्रत्येक परिस्थिति में गोला लगाके उचित उत्तर निर्देशित करें

नाम

तिथि

आयु

लिंग 1 . पुरुष 2 . स्त्री

0 कभी नहीं 1 लगभग नहीं के बराबर 2 कभी कभी 3 कई बार 4 अनेक बार

1. पिछले माह कितनी बार आप के साथ कुछ अप्रत्याशित घटना घट जाने से आप परेशान हुए?
2. पिछले माह, आपको कितनी बार लगा कि जीवन की आवश्यक चीज़ों को आप नियंत्रित नहीं कर पाएं?
3. पिछले माह, आपने कितनी बार घबराहट तथा तनाव महसूस किया?
4. पिछले माह, कितनी बार आप अपनी व्यक्तिगत समस्याओं से सामना करने के लिए आत्मविश्वास पूर्ण लगा?
5. पिछले माह, कितनी बार आपको लगा कि चीज़े आप के पक्ष में जा रही हैं?
6. पिछले माह, कितनी बार आपने यह पाया कि जो सारी चीज़ें आपको करनी पड़ रही है, उन्हें आप निपटा नहीं पा रहे हैं?
7. पिछले माह, कितनी बार आपको लगा कि आप अपने जीवन में चिढ़चिढ़ाहट को काबू कर पाए?
8. पिछले माह, आपको कितनी बार लगा कि सभी चीज़े आप के नियंत्रण में है?
9. पिछले माह, कितनी बार आपको इस बात पर गुस्सा आया कि चीज़े आपके नियंत्रण के बाहर है?
10. पिछले माह, कितनी बार आपको लगा कि मुसीबतों का अम्बार लगता जा रहा है, जिस पर आप जीत प्राप्त नहीं कर सकते है?

Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress.. J Health Soc Behav. 1983;24:386-96.

Original Article

Preoperative Anxiety in Adult Patients Undergoing Day Care Surgery: Prevalence and Associated Factors

Meghna Jiwanmall, Stephen A. Jiwanmall[1], Aparna Williams, S. Kamakshi[2], Lovisal Sugirtharaj[2], K. Poornima[3], Kuruthukulangara S. Jacob[1]

ABSTRACT

Background: There is a paucity of data related to anxiety levels in patients undergoing day care surgery in India. **Methods:** Preoperative anxiety was assessed using Amsterdam Preoperative Anxiety and Information Scale (APAIS) 1 day before surgery and on the day of surgery, and the patients were categorized as cases (APAIS score ≥13) and controls (APAIS score <13). Sociodemographic characteristics, clinical features, and fears associated with anesthesia and surgery were also noted. **Results:** Out of the 399 patients recruited, 58.1% experienced significant preoperative anxiety. The fear of needles ($P = 0.002$), fear of waking up during the surgery ($P < 0.001$), and the patient's need of additional information regarding anesthesia and surgery ($P < 0.001$) were significantly associated with preoperative anxiety. **Conclusion:** A significant proportion of patients scheduled for day care surgery have preoperative anxiety. A preanesthetic workup of a patient with adequate clarification about their doubts and fears related to anesthesia and surgery is recommended to bring down the level of anxiety.

Key words: *Anxiety, risk factors, day care surgery, preoperative*

Key messages: *(1) Preoperative anxiety does exist in a significant proportion of patients scheduled for day care surgery. (2) The factors significantly associated with preoperative anxiety were fear of injection or needles, fear of waking up during the surgery, and the patient's need for additional preoperative information regarding anesthesia and surgery. (3) A preanesthetic workup of a patient with adequate clarification about their doubts and fears related to anesthesia and surgery is recommended to bring down the level of anxiety.*

Day care surgery has witnessed an exponential increase both globally and in India over the past few years.[1,2] Numerous patients, with multiple comorbidities,

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Departments of Anaesthesiology, [1]Psychiatry, [2]Nursing and [3]Biostatistics, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence: Dr. Stephen A. Jiwanmall
Department of Psychiatry, Christian Medical College, Vellore, Tamil Nadu, India.
E-mail: stephenjiwanmall@yahoo.com

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previously deemed unfit for day care surgery, are now undergoing day care surgical procedures. The advantages of day care surgery include shorter hospitalization times, shorter waiting time, decreased risk of infections, early mobilization, lower costs, and reduced bed occupancy. The other presumed advantages include less stress for the patients due to avoidance of prolonged hospital stay and decreased time of separation from the family and home environment.

Day care surgery seems to be an attractive option for many patients, but recent studies have shown that preoperative anxiety is observed more frequently in day care patients when compared with in-patients undergoing fast-track surgery.[3] Some authors recommend that anxious patients and those who wish strongly for inpatient treatment should be excluded from day care surgical procedures.[3,4] Wetsch *et al.* have reported that day care surgery also has additional stress and that all patients may not be fit for shortened hospitalization.[3]

Preoperative anxiety is a real concern for many patients undergoing anesthesia and surgery.[5,6] Literature reports that 60%–92% of patients experience significant preoperative anxiety.[6] Autonomic response associated with increased anxiety may cause tachycardia, hypertension, and arrhythmias and increase the risk of intraoperative hypothermia.[6] Preoperative patient anxiety in the day care setup is especially relevant as sedative premedication is often omitted. Other factors contributing to patient stress and anxiety may include time pressures associated with the surgery in 1 day's time, waiting time in the ward prior to surgery, interaction with the hospital staff (nurses, anesthetists), and arranging an accompanying person and monetary resources. In addition, patients may have fears regarding anesthesia, surgery, and adverse events in the recovery period. There is a dearth of data from India in this field. Therefore, this study attempted to examine the prevalence and factors associated with preoperative anxiety in patients undergoing day care surgical procedures.

METHODOLOGY

Design

This was a cross-sectional study to evaluate the prevalence of anxiety in patients posted for day care surgery. However, a case–control framework was used to assess the factors associated with preoperative anxiety.

Setting

The study was conducted in a medical college with tertiary and specialist surgical departments.

Sample

Consecutive patients posted for day care surgery were recruited for the study after obtaining informed written consent. The inclusion criteria were as follows: (i) adults within the age group of 18–70 years, (ii) with or without a history of previous surgery, and (iii) American Society of Anaesthesiologists (ASA) Class 1–2, scheduled for elective surgery.

The exclusion criteria were as follows: (i) patients with a known history of anxiety or depressive disorders, (ii) people with mental retardation or with difficulties in speech and hearing, resulting in impaired communication, and (iii) patients who had taken an anxiolytic medication within 24 h prior to surgery.

Assessments

The following instruments were used to evaluate the patients:

(i) *Amsterdam Preoperative Anxiety and Information Scale* (APAIS)[7]: The scale has been specifically developed to evaluate preoperative anxiety. It is a six-item questionnaire with a 5-point Likert scale for each item. It has been validated against standard measures of anxiety. It has good psychometric properties. The instrument has been translated into many languages and has been validated for use across countries. In this study, we used its English version. Patients with an anxiety score of ≥13 on the scale are considered to have clinically significant preoperative anxiety

(ii) A specially designed proforma to collect sociodemographic characteristics, clinical details, information regarding proposed surgery, and previously known factors associated with preoperative anxiety.

Since the APAIS questionnaire did not distinguish well between the fear of anesthesia and fear of surgery, a list of some selected variables from previous studies that were associated with preoperative anxiety was included in the proforma.

Procedure

Patients who presented to the ward for day care surgery were invited to take part in the study. Details of the study were explained, and written consent was obtained. The APAIS was administered on the day prior to the surgery and repeated on the morning of the surgery. Details of the time taken from admission to the day care ward to the induction of anesthesia and waiting time were also documented.

Statistics

The recommended APAIS threshold of ≥13 was used to divide the sample into cases with preoperative

anxiety; patients who scored <13 were not anxious and consequently considered controls. The mean and standard deviation were used to describe continuous variables, while frequency distributions were obtained for categorical data. The Chi-squared test and Student's *t*-test were used to assess the significance of bivariate associations for the categorical and continuous variables, respectively. Variables that were significant on bivariate statistical tests were entered into multiple logistic regression analysis. Odds ratio and 95% confidence interval were calculated. SPSS version 16 was used to analyze the data.

The sample size was calculated using the Epi Info program using the following assumptions:

(i) For the prevalence component, with a precision of 5%, confidence interval of 95%, and a 25% prevalence,[8] the sample size calculated was 323. (ii) For the factors associated with preoperative anxiety component, assuming exposure among cases being 25% and among controls being 10%, power of study 80%, and error of 5%, the sample size required was 224, with 112 cases and 112 controls.

Ethics

Approval was obtained for the research protocol from the Institutional Review Board (IRB Min. No. 10909) of Christian Medical College, Vellore, prior to the recruitment of patients.

RESULTS

A total of 399 people were recruited for the study. The sociodemographic and clinical characteristics of the total study population are documented in Tables 1 and 2, respectively. The majority were middle-aged men (72.2%), literate (86.5%), married (79.2%), with a previous history of surgery (59.4%) and without health insurance (97.2%), coming from places which are outside Tamil Nadu (65.2%), and undergoing procedures under general anesthesia (58.6%). Different types of day care surgeries were included under a broad heading of general surgery, orthopedics, ear–nose–throat, urology, and epidural steroid injections.

The majority of patients who were found to be anxious gave history of surgery in the past (56%). They were from other states outside Tamil Nadu (56.5%) and were scheduled for only general anesthesia (56%). The anxiety score taken a day before the surgery (APAIS A1) for cases and controls was 14.22 ± 2.25 and 11.23 ± 2.81, respectively, which was significant ($P < 0.001$). Similarly, the anxiety score taken on the day of surgery (APAIS A2) for cases and controls was 16.09 ± 1.89 and 10.60 ± 2.73, respectively, with $P < 0.001$.

The factors significantly associated with preoperative anxiety were patient's fear of needles/injections ($P = 0.002$), fear of waking up during the surgery ($P < 0.001$), and the need for additional information regarding anesthesia and surgery, which is generally given during the preanesthetic clearance for surgery ($P < 0.001$). Multiple logistic regression analysis showed that factors associated with preoperative anxiety remained statistically significant ($P < 0.05$) [Table 3].

DISCUSSION

This study attempted to examine the prevalence and factors associated with preoperative anxiety. Its strengths included the fact that it recruited consecutive patients, had a large sample size, used a standard instrument to evaluate anxiety, and used multivariate statistics.

The prevalence of preoperative anxiety in our study, using the APAIS, was 58.1%. Studies from different

Table 1: Sociodemographic details of cases and controls

Characteristics	Total *n*=399	Cases *n*=232	Controls *n*=167
Age (in years)[a]	38.75±11.44	37.74±11.15	40.14±11.72
BMI[a]	24.94±3.78	25.04±3.78	24.81±3.79
Marital status - married[b]	316 (79.2)	181 (78)	135 (80.8)
Gender - male[b]	288 (72.2)	165 (71.1)	123 (73.7)
Education - literate[b]	345 (86.5)	198 (85.3)	147 (88.0)
ASA class of patients - 1[b]	291 (72.9)	177 (76.3)	114 (68.3)
Previous surgical experience[b]	237 (59.4)	130 (56)	107 (64.1)
Without health insurance[b]	388 (97.2)	229 (98.7)	159 (95.2)
Type of house - thatched[b]	313 (78.4)	187 (80.6)	126 (75.4)
Monthly income[c]	5000-10000	5000-10000	8000-15000
Residence (within Tamil Nadu)[b]	139 (34.8)	81 (34.9)	58 (34.7)
Residence (outside Tamil Nadu but within India)[b]	231 (57.9)	131 (56.5)	100 (59.9)
Residence (outside India)[b]	29 (7.3)	20 (8.6)	9 (5.4)

BMI – Body mass index; ASA – American Society of Anaesthesiologists. [a]Mean±standard deviation; [b]Frequency (%); [c]Median, interquartile range

Table 2: Clinical profile of the cases and controls

Clinical variables	Total *n*=399	Cases *n*=232	Controls *n*=167
APAIS-A1 (anxiety on reporting to day care ward a day before surgery)[a]	12.9±2.90	14.22±2.25	11.23±2.81
APAIS-A2 (anxiety on the day of surgery)[a]	13.8±3.54	16.09±1.89	10.60±2.73
APAIS-N1 (needs more information on reporting a day before surgery)[a]	6.90±1.63	7.31±1.34	6.32±1.81
APAIS-N2 (needs information on day of surgery)[a]	7.17±1.72	8.16±1.02	5.79±1.55
General surgery	152 (38.1)	86 (36.1)	66 (39.5)
Orthopedic surgery	118 (29.6)	67 (28.9)	51 (30.5)
ENT surgery	37 (9.3)	22 (9.5)	15 (9)
Urological surgery	69 (17.3)	45 (19.4)	24 (14.4)
Epidural steroid injections	23 (5.8)	12 (5.2)	11 (6.6)
Fear of needles[b]	60 (15)	46 (19.8)	14 (8.4)
Fear of waking up during the surgery[b]	83 (20.8)	77 (33.2)	6 (3.6)
Fear of pain[b]	354 (88.7)	206 (88.8)	148 (88.6)
Fear of bleeding[b]	22 (5.5)	17 (7.3)	5 (3)
Fear of disability[b]	3 (0.8)	3 (1.3)	0
Fear of nil per oral status[b]	1 (0.3)	1 (0.4)	0
Duration of surgery ≤1 h[b]	265 (66.4)	145 (62.5)	120 (71.9)
Type of anesthesia[b]			
GA	234 (58.6)	130 (56)	104 (62.3)
Neuraxial block	131 (32.8)	86 (37.1)	45 (26.9)
Local anesthesia	34 (8.5)	16 (6.9)	18 (10.8)
Waiting time (h)[c]	1.35, 0.3-3	1.5, 0.45-3	1.3, 0.2-2.35
Total PACU time (from PACU time to discharge from day care), h[a]	6.04±1.85	6.01±1.79	6.09±1.94

APAIS – Amsterdam Preoperative Anxiety and Information Scale; GA – General Anesthesia; PACU – Postanesthesia care unit. [a]Mean±standard deviation; [b]Frequency (%); [c]Median, interquartile range

Table 3: Multiple logistic regression analysis showing factors associated with preoperative anxiety

Variables	Odds ratio	95% CI	*P*
Fear of needles	3.11	1.12-8.65	0.029
Fear of waking up during the surgery	6.03	2.02-18.0	<0.001
APAIS (N2)	5.89	4.13-8.38	<0.001

CI – Confidence interval; APAIS N2 – Amsterdam Preoperative Anxiety and Information Scale (need for information score). Factors such as age, gender, marital status, economic status, h/o previous surgery, health insurance, duration of surgery, fear of postop pain, disability, and NPO status were not significant

parts of the world have reported varying prevalence rates, from 23.4% to 76%. A Sri Lankan study reported a prevalence of preoperative anxiety of 23.4%,[8] whereas a Mexican study showed a much higher prevalence of 76%.[9]

A study reported 42.2% prevalence and concluded that the preoperative anxiety is a multifactorial issue which needs reduction strategies.[10] Lichtor *et al.* showed the prevalence of preoperative anxiety as 59% and stated that anxiety seen at the preoperative holding bay could be predicted from the anxiety seen in the afternoon before the surgery.[11] Our study found this similar association between the anxiety score on the day of surgery and anxiety score taken a day before the surgery, where both the values were not very different from each other. Gangadharan *et al.* reported a 60% prevalence, with the important associated factors being age, gender, marital status, previous surgical experience, and different types of surgeries.[12] Wetsch *et al.* reported 38.3% prevalence of preoperative anxiety in day care surgery patients.[3]

More than half of the patients admitted to day care surgery wards are anxious. This finding is of significance because according to standard day care anesthesia protocols, generally, premedication is usually avoided and therefore, such patients are likely to have more preoperative anxiety. The awareness about the prevalence also points out toward the scope of further research to find out the means to allay the anxiety.

Many factors associated with preoperative anxiety have been mentioned in the literature, namely, gender, marital status, fear of complications, apprehensions, previous surgical experience, socioeconomic status, postoperative pain, type of anesthesia, lack of preoperative information, cigarette and alcohol usage, education, and occupation.[10,13] We have taken selected variables to examine their association with preoperative anxiety. The majority of patients who were anxious gave a history of previous experience of surgery in our study, but this finding varied from other study.[14] This may be attributed to the previous unpleasant experience they would have had, or related to surgery or anesthesia. While some studies reported that anxiety is more common in women, we found that males had more anxiety than females.[7,14]

We found a close association between anxiety and the need for additional information. As in the APAIS study, patients who had a high anxiety score were the ones who needed additional or more information than the patients who had low anxiety score.[7,14,15] This finding may strengthen the recommendation for a good preoperative workup of patients before surgery, where additional information can be provided and problems can be addressed. Fear of complications during surgery has been reported to have an association with preoperative anxiety.[13] Out of the selected variables that were studied, the fear of needles or injections and fear of waking up during the operation were found to be significant and commonly associated with the preoperative anxiety, in our day care population.

During the preanesthetic check-up, information regarding the type of anesthesia is generally explained to all patients by the examining anesthesiologist. But, due to time constraints, complexity of the disease process, or language barrier, there might be a deficiency in the explanation of the related information of anesthetics and surgery. In some studies, it has been found that the patients who received better preanesthetic information showed low scores on the anxiety scale when compared with those who did not receive any explanation.[16] However, an association was found in our study where the anxious patient had a higher need for additional information. Our study did not show any significant association between the level of anxiety and educational status or occupational status.

Other factors such as age, sex, socioeconomic status, marital status, body mass index, previous experience of surgery, presence or absence of health insurance, duration of waiting period prior to administration of anesthesia, type of anesthesia, and residential status were not significantly associated with preoperative anxiety. In our institutional practice, the surgical waiting period ranges from 2 to 3 months; hence, patients may not mind waiting for 6 h preoperatively on the day of surgery. Therefore, this did not have an association with anxiety in our patients, unlike some study where prolonged waiting time was shown to cause distress among patients.[17] But even then, support strategies are recommended by the authors, to be implemented by the nursing staff during the waiting period in day care centres to reduce anxiety. There was no significant difference found in relation to the type of anesthesia, but patients who were planned for general anesthesia were more anxious than the ones who were planned for regional or local anesthesia, which was similar to the results of a recently published study.[18] This may point toward a limited knowledge about the types of anesthesia available, the risks associated with each, and previous surgical experience. This can also help us in planning future studies to assess the awareness about anesthesia among patients and thereby improving the quality of care. Incidentally, we also found that patients who were anxious belonged mainly from states outside Tamil Nadu, even though this did not reach statistical significance. This might imply that most of the patients who come from far off places need more flexibility in their treatment plans and facilities to reduce their anxiety.

There have been some limitations to our study. The pediatric and geriatric populations have been excluded from the study, even though they constitute a good number in the daycare surgery patient pool. Different types of surgeries were included in the study and they were not divided according to their duration and nature.

CONCLUSION

A considerable number of patients scheduled for day care surgery were found to have a significant amount of preoperative anxiety. In our study, the factors associated with preoperative anxiety that were significant were the fear of injections or needles, fear of waking up during the surgery, and the need for additional information that the patients require regarding anesthesia and surgery. Hence, a good preanesthetic workup of patients, with adequate clarification about their doubts and fears related to anesthesia and surgery, is recommended to bring down the level of anxiety.

Amsterdam preoperative anxiety and information scale (APAIS)

1. I am worried about the anesthetic
2. The anesthetic is on my mind continually
3. The procedure is on my mind continually
4. I am worried about the procedure
5. I would like to know as much as possible about the anesthetic
6. I would like to know as much as possible about the procedure.

(The measure of agreement with these statements should be graded on a 5-point Likert scale from 1 = *not at all* to 5 = *extremely*).

The anxiety scale (APAIS A) consists of four items (questions 1, 2, 3, 4), each of which could be scored from 1 to 5. The score of the anxiety scale is the sum of these four questions, with a scoring range from 4 to 20.The cut-off score is 13. Score ≥13 defines significant anxiety, whereas <13 defines mild anxiety.

The need-for-information scale (APAIS N) consists of two items (questions 5 and 6), each of which could be scored from 1 to 5. The sum of the need-for-information

scale is the sum of these two questions, with a scoring range from 2 to 10. Cut-off being 5. Score ≤5 needs no excessive information, whereas score >5 needs more information than the legal explanation about the procedure.

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Conflicts of interest

There are no conflicts of interest.

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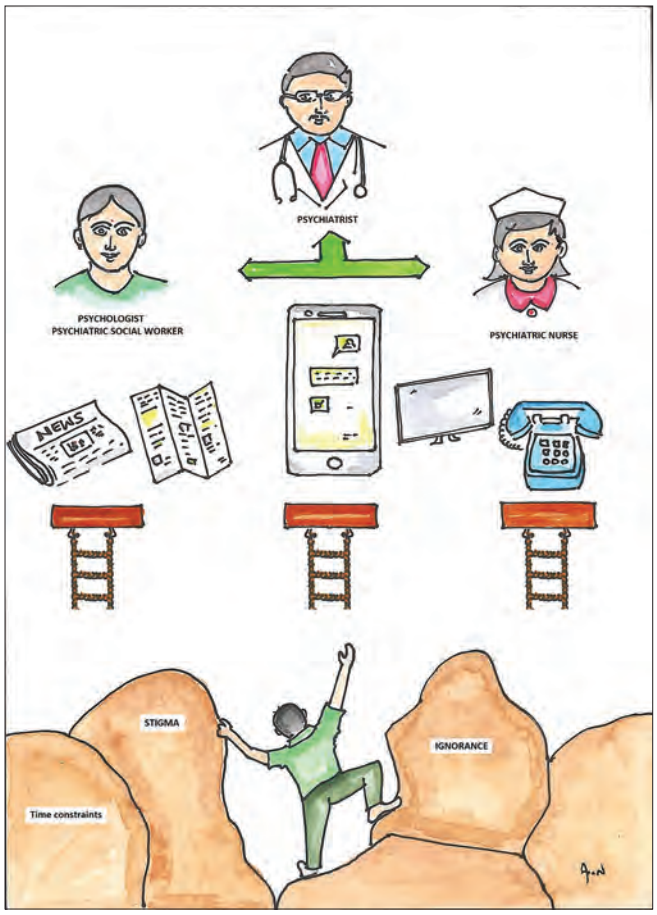
Reaching the Unreached: Insights on Psychological Interventions Beyond the Clinic–Walls

There is a strong body of evidence which points to the utility of psychological interventions in the field of mental health. Psychological interventions have been found to be efficacious in the treatment of various common mental disorders (CMDs), recommended as the first line of interventions and observed to have utility for improving adherence and lowering the rates of relapse and recurrence.[1-3] These observations broadly hold true despite some variability in the strength of evidence across type and severity of CMDs and type of psychological intervention[2] The paper aims at highlighting the need for psychological interventions beyond clinics and hospitals and provides a few illustrations from urban India. This is followed by a discussion of therapeutic elements in these interventions, challenges, limitations as well as sources of gratification for therapists engaging in such interventions.

ACCESS TO PSYCHOLOGICAL INTERVENTIONS

Notwithstanding the evidence on the effectiveness of psychological interventions, the available literature across the globe suggests that these interventions are not accessible to a large proportion of individuals who are likely to benefit from them[4,5] Need for multipronged approaches has been discussed to increase access to mental health services in general and psychological interventions in particular.[4-6] A recent review of evidence from 4 developed countries from 1990 to 2015 showed that despite a substantial increase in the provision of treatment (primarily in terms of pharmacotherapy), the prevalence of mood and anxiety disorders and symptoms had not decreased. There was limited evidence for an increase in psychological interventions during this period, and no significant masking of evidence for decreased prevalence due to increased exposure to risk factors was observed. This review highlighted the role of improving the quality of services for those in need and the necessity of enhanced and systematic focus on preventive interventions.[7]

A comprehensive approach to impacting public mental health would need to focus not merely on increasing the number of specialists and services, but making



professional services more accessible and use of strategies aimed at breaking mental and social barrier to services, increasing capacities for self-care and peer support in the communities as the first line of management for milder problems as well as enhancing focus on prevention and promotion.[8,9]

Innovations in the field of mental health directed at improving access to mental health services have tended to typically focus maximally on supply-side- barriers. These include innovative ways of improving the supply of mental health professionals offering a range of interventions, the supply of trained non-specialists offering basic psychological interventions, early identification and timely referrals in general/primary health services, and reducing structural and organisational barriers. In contrast, there has been

relatively less and inconsistent investment of resources in developing innovations for changing demand-side factors.[10] These demand-side factors that require to be addressed through access – innovations include complex factors such as meaning and interpretations of symptoms, perceived candidacy, eligibility for healthcare often jointly negotiated by initial interactions of individuals with healthcare systems as well as the dynamic process of individuals navigating their entry to health systems, circumventing ambivalences and other barriers.[10,11]

A closer examination of demand-side barriers can be a useful exercise for developing access- innovation, particularly for vulnerable sections of the population. Late adolescence and young adulthood are known to be a vulnerability period for the onset of various mental disorders, including CMDs.[12] In an ongoing Indian study on college youth, it was observed that those who were significantly distressed had higher perceived barriers to seeking professional help than their counterparts and were no more inclined than others to seek professional help (T.H. Noufal, personal communication, August 17 2018). This suggests that experience of distress in itself may not predict help-seeking inclination. Whether the experience of distress may also be linked to the perception of barriers and thus results in lower rates of actual help-seeking needs to be examined in further studies. In another study on urban Indian young adults, it was observed that only 29% of the sampled youth reported that a vignette which described moderate clinical depression in the background of a failure event was likely to be depicting a mental health problem. Moreover, about 51% of the youth were unsure if it was depicting a mental health problem and about 66% of the sample in this study indicated that they were unlikely to seek professional help if they were experiencing similar problems as depicted in the vignette.[13] Moreover, correct recognition of the vignette was not linked to higher self-efficacy for seeking professional help. In this study too, youth who had significant distress on a standardised measure were likely to report higher perceived barriers, and distress was unrelated to the inclination to seek professional help.[14]

REACHING THE UNREACHED- ILLUSTRATIONS

The above mentioned trends highlight the need for mental health professionals in general and clinical psychologists in particular to proactively reach out to people in need beyond the clinic walls and offer psychological interventions in various formats that may help in increasing the reach of such interventions, reducing access barriers, empowering communities to engage in self-help and peer support, as well as encouraging professional help-seeking, as and when appropriate. A few such initiatives and observations based on the same are now briefly discussed.

Extensive engagement with stakeholders, using surveys and focus group discussions, across 17 institutes of higher education in Bangalore, resulted in the development of a mental health promotive intervention program for youth named Feeling Good and Doing Well. This is a 20-hour, manualised, group-based universal intervention program. The results of a randomised controlled trial using this intervention indicated a beneficial impact on psychological well-being, positive affect, life satisfaction and distress, with gains being maintained at follow up.[15] Importantly, 31% of the youth who enrolled themselves in this program had significant levels of distress. There was a significant decline in distress post-program participation in the high distress group. These findings indicate the utility of a promotive intervention program of this nature to reach individuals in need and result in beneficial outcomes.

Such programs are well recognised as psychological 'interventions' and fall within the ambit of clinical psychology.[8,16] The therapeutic elements that are likely to have played a role in this intervention trial overlap to an extent with face to face psychotherapies for treatment of mental health conditions. These include a safe and non-threatening space, sense of connection to the facilitator and other participants, feeling empathised and validated through disclosure as well as discussion on common issues youth face, arousal of emotions and opportunities to reframe one's appraisals, sense of universality, vicarious learning from each other, reflection on life priorities, strengths, and weaknesses, development of individualised goal plan and education on emotion regulation strategies.

Compared to traditional face-to-face therapy, a promotive psychological intervention of this kind does have some constraints. There is little scope for individualised attention, along with limited opportunities for self-disclosure or discussion of individual-specific issues as well as dependency on the participants' ability to deduce personally relevant learning material and apply it in their day-to-day life.

Here are a few questions that emerge in hindsight that demand reflection. Is this a doorway to reach out to persons in need that we could use more frequently? Are we, as professionals, particularly in developing countries, under-utilizing such pathways rather than mainstreaming them? Do such findings reiterate the

overlapping nature of preventive and promotive efforts and efforts to reach out to distressed persons in the community? Does it have scope for scalability and potential to enhance mental health support to youth in the community? Review of relevant international and national published literature as well as field experience of the researcher suggests that perhaps all the answers to the above questions are in affirmative.[8,16-18] In addition to resource limitations in terms of trained workforce and limited public funding for programs of such nature, one of the important barriers to wider implementation has also to do with ambivalence or lack of sufficient clarity about the status of such programs as integral aspects of legitimate roles of mental health professionals.[16]

I now move on to illustrate two different kinds of digital pathways to increase access to psychological interventions for distressed non–treatment-seeking individuals. An initiative called Wellness Check (https://echargementalhealth.nimhans.ac.in/wellness-check/) comprises of a few standardised measures of distress and wellbeing that can be answered online (via a web browser or an app on the Play Store) and the respondent receives immediate, detailed online feedback, as well as suggestions to maintain/enhance wellbeing and links to mental health information and self-help resources. We began with the assumption that a broad conceptualisation of mental health (from distress to well-being) and ease of access on a digital platform can have the potential to engage distressed non-treatment-seeking adults in themes related to mental health. The findings of the pilot trial provided some support to this assumption when we examined the pilot data of individuals who accessed and used the website/app (N = 300). About 58% of the seekers of this initiative had significant distress, with 38% having scores in moderate to severe distress range. Moreover, about 70% of the users reported that they had no exposure to mental health services at any time in the past, and only about 12% were currently seeking mental health professional services. Out of the severely distressed sub-group, 76% reported that they were ambivalent or unlikely to seek professional mental health services in the subsequent three months. The resources on this site aim at enhancing self-awareness, self-help skills for enhancing well-being, as well as breaking motivational barriers to seeking help. Again, this highlights a digital approach that has the potential to reach out to the unreached.

Another digital intervention that I would like to use as an illustration is a digital self-help intervention for depression. The recently completed National Mental Health Survey reported that about 85% of individuals in India who are depressed are not receiving/seeking any professional help for the same.[19] This is despite the availability of empirically supported psychological interventions, as mentioned earlier. Empowering communities with structured self-help interventions has been discussed as an important first line strategy in addressing the treatment gap. Internet-based self-help interventions, particularly those with some level of human contact (guided self-help), have been found to be effective in several research trials across the globe.[20-22] However, there is a dearth of such studies from limited resource settings, including in India. A review of free apps on depression available for android phones for Indian users highlighted that most were limited to psychoeducation or self-monitoring tools. 33 interactive apps were identified in the review. Findings indicated that several did not clearly delineate the scope of the app/offered screening or provided any component aimed at breaking motivational barriers to professional help-seeking.[23]

An app named PUSH-D (Practice and Use Self-Help for Depression, https://echargementalhealth.nimhans.ac.in/pushd/) was developed to address some of the limitations of the reviewed apps in the Indian provides context. This is an interactive app which provide structured self-help modules and basic periodic telephonic-guidance for dealing with depressive symptoms. During the research trial, the typical seeker of PUSH-D was a young adult with an undergraduate level of education, mild to moderate severity of depressive symptoms amounting to major depression or dysthymia, and significantly impaired functioning. Most importantly, it was noted that 2/3rd were those who had never sought mental health professional help any time in the past, and 82% had not sought professional help for the current issues. Insufficient self-awareness, limited information on professional services, time constraints, stigma, and prior unsatisfying experiences with services emerged as some of the self-reported barriers to seeking professional help.[24]

On the other hand, ease of access, perception of problems as less severe, need for self-reliance, flexibility, and desire for self-empowerment to prevent further problems were reported as some of the factors that resulted in the appeal of PUSH-D.[25] The trial indicated statistically and clinically significant changes in depressive symptoms, functioning, well-being, and self-esteem in full as well as partial completers of PUSH-D modules. Qualitative feedback from users lent further support for its utility (e.g., 'availability of PUSH-D itself made me feel that there is something to help me,' 'it helped me to understand ways of fighting depression').[26]

Again, it is worth examining the potential therapeutic qualities in this digital self-help intervention. These include the provision of a structured framework to deal with depressive symptoms, education, motivation-enhancement, tools for self-learning and application, cultivation of hope and sense of self efficacy as well as awareness of therapeutic support in the background. These factors partially overlap with the therapeutic mechanisms in face to face psychotherapies. The app incorporated empirically supported therapeutic strategies such as behavioural activation, cognitive restructuring, self-soothing, decreasing self-criticality and increasing self-compassion, enhancing a sense of mastery and mobilising support in a self-help format, in addition to improving awareness on when to step up to higher intensity intervention. Unlike face-to-face psychotherapies, some of the limitations of PUSH-D include insufficient scope for consistently working through the medium of a therapeutic relationship in a narrative/conversational format, focusing on past issues, processing of difficult emotions in safe space and 'real' therapist presence, or corrective emotional experiences. Despite these limitations, the study findings on the whole indicated openness of urban Indian adults to use psychological intervention strategies in a digital format for self- help and potential to reach out to depressed individuals in the community who are otherwise not availing any professional help.

Our recent review of studies on smartphone-based psychological interventions highlighted that though such interventions are found to be efficacious, there is a dearth of implementation studies, field reports of deployment, and studies on factors related to user uptake and engagement in diverse cultures and low resource settings.[25] This reiterates the viewpoint that digital pathways have significant potential to reach out to the unreached. Unfortunately, most of the researched apps are not freely accessible to the public, and the reverse is also true that most of the apps freely available in the public domain have not gone through empirical testing.[27]

REACHING THE UNREACHED: CHALLENGES AND SOURCES OF GRATIFICATION IN TAKING PSYCHOLOGICAL INTERVENTIONS BEYOND THE CLINIC-WALLS

There are several challenges that therapists may need to negotiate when they intend/attempt to reach out to those in distress by going beyond the clinic walls. Inadequacy of apps in handling complex issues and non-contextualised, non-individualised solutions that are typical of most parts of unguided/guided self-help interventions can be sources of dissatisfaction in clinicians.[21] Not having sufficient information on how the app-content is being assimilated could emerge as another cause of concern for professionals. Offering app-based interventions could also give rise to apprehensions that clients may become complacent and not step up to higher intensity interventions when that is required. Some of these challenges could be at least partially addressed by providing some scope for customisation built into the apps and supplementary telephonic contact and/or online communication or the use of a blended approach that combines face to face and digital interventions as per need. Above all these aspects, clinicians may experience a sense of not offering the 'best of themselves as therapists' to their clients when they deploy self-help/guided self-help or blended interventions that combine face-to-face and Internet-based interventions.

Notwithstanding the challenges, reaching beyond clinic walls and offering psychological interventions can be gratifying in several ways. First of all, psychological interventions offered in varied formats, though typically low in intensity, can increase access to the same to those who otherwise may not be seeking any form of routine mental health care. The possibility that such access innovations can trigger a therapeutic change process and also provide an opportunity to decrease motivational barriers to seeking face to face professional help can serve as a major source of gratification for therapists.

On the whole, there are several factors that can help the 'therapist-self' in a clinician to invest efforts in innovative approaches to reaching out to distressed persons and increasing access to psychological interventions, though these may not always be seen by the professional community as one's core clinical responsibility. This stance requires courage to deviate from the routine and bear with the question on the legitimacy of such interventions. Integrating components in such interventions that encourage and facilitate face-to-face professional help-seeking as well as strengthening evidence-base for the same, particularly in developing nations, require attention.

To sum up, these reflections raise the following distinct possibilities: a) Interventions aimed at enhancing one or more components of well-being (i.e., promotive interventions) may also be of relevance to non-treatment seeking distressed individuals b) Openness in mental health practitioners to judiciously explore novel pathways, including digital tools, can improve the practice-research feedback loops, c) Psychological interventions delivered beyond the traditional clinical settings may serve not just as useful low-intensity

interventions but also as gateways to seek mainstream mental health services. All these possibilities merit attention and examination in view of the fact that a broadened attention to the entire continuum of mental healthcare has been recognised as important for reducing the treatment gap. Stepping out beyond the clinic walls more often than what we do, with more conviction, more consistency and in a systematic manner, by a larger number of mental health professionals in India, including therapists, is likely to be an exercise worth undertaking.

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Seema Mehrotra

Department of Clinical Psychology, NIMHANS, Bengaluru, Karnataka, India

Address for correspondence: Dr. Seema Mehrotra
Department of Clinical Psychology, NIMHANS, Bengaluru - 560 029, Karnataka, India.
E-mail: drmehrotra_seema@yahoo.com

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Letter to Editor

Chlorpromazine-induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare condition affecting between 1 in 1,000 to 1 in 10,000 patients after exposure to associated drugs.[1] It is a life-threatening condition with a mortality rate of about 10%, which necessitates early identification and treatment.[2] We describe a case of DRESS syndrome secondary to the use of chlorpromazine in a female with paranoid schizophrenia, the diagnostic challenge encountered, and the successful treatment of the condition with corticosteroids.

CASE REPORT

Ms. Y, a 30-year-old female, was a known case of schizophrenia for 3 years. In view of significant aggression, the patient was admitted for inpatient care. Baseline physical examination and biochemical investigations were normal except for features suggestive of iron deficiency anemia, for which she was started on oral iron supplements. The patient had no history of any medical illness, and she was not on any medication apart from olanzapine (she was on olanzapine 20 mg for more than three months) at the time of presentation. She had not responded to a trial with olanzapine and had amenorrhea with the same. She was initiated on T. chlorpromazine at the dose of 50 mg/d. T. olanzapine was tapered and stopped over the period of 1 week, and the dose of chlorpromazine was gradually increased up to 600 mg/d over a period of 2 weeks. On the 21st day after initiating chlorpromazine, she developed itching all over the body along with easy fatigability, which progressed within the next 2–3 days to erythematous maculopapular rashes all over the body, tiny pustules over the face, xerosis over the legs, along with puffiness of face, periorbital swelling [Figures 1 and 2], and dizziness. T. cetirizine 10 mg three times daily and calamine lotion were started, and the dose of chlorpromazine was decreased to 100 mg/d. On the fourth day after the onset, the above symptoms exacerbated within 30 min of receiving T. chlorpromazine 100 mg. On systemic examination, she had persistent tachycardia of 150 beats per minute (bpm), blood pressure (BP) of 90/60 mmHg, and body temperature as measured in the axilla of 101°F. Chlorpromazine was immediately stopped. The vitals were monitored once every 4 h and hydration was adequately maintained.

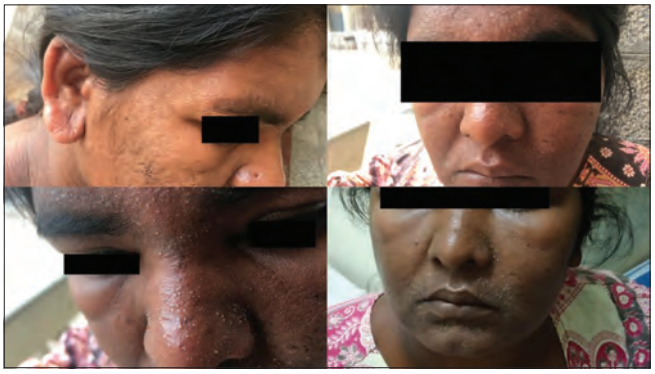

Figure 1: Facial puffiness, periorbital swelling, and a pustular rash over the face

Antipyretics were administered for fever. Hematological investigations revealed erythrocyte sedimentation rate (ESR) 30 mm/h (normal range 0–12 mm/h), eosinophilia (16.3%, normal range 0-6%), increased absolute eosinophilic count (1173.6 cells/μL, normal range 450–550 cells/μL), lymphocytopenia (15.4%, normal range 20–40%), and mildly raised alkaline phosphatase (152 U/L, normal range 30-120 U/L).

Initially, the possibility of chlorpromazine-induced photosensitive rash only was considered. Later, the patient was suspected of having DRESS syndrome, given the systemic involvement and rashes involving the nonsun-exposed areas of the body. Dermatologist consultation was sought, and a clinical diagnosis of DRESS syndrome was made. We liaised with a cardiologist to rule out myocarditis, in view of persistent tachycardia. On evaluation, there were no features suggestive of myocarditis—2D echocardiography, electrocardiogram, and cardiac enzyme profile (creatine kinase = 67 U/L, creatine kinase MB = 13 U/, troponin T = 0.004 ng/ml) were within normal limits. The patient scored nine on the Naranjo adverse drug reaction probability scale, which suggested the definitive role of chlorpromazine in the occurrence of DRESS.

For the treatment of DRESS syndrome, the patient was started on T. prednisolone 40 mg/day (tapered off over 10 days), T. cetirizine 10 mg twice daily, and calamine lotion local application over the skin lesions, with adequate hydration. Exogenous corticosteroid administration is known to induce or exacerbate

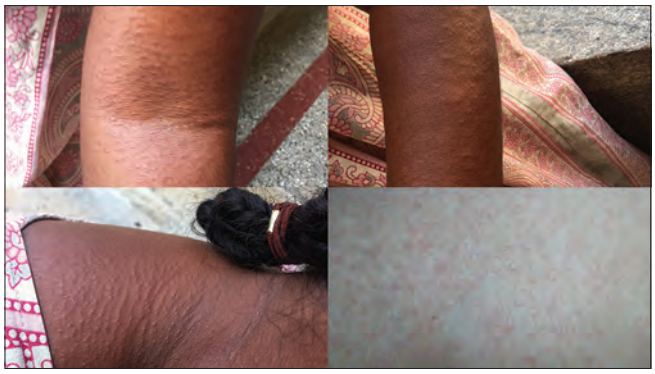

Figure 2: Maculopapular rashes over the upper limb, abdomen, neck, and shoulder region

psychosis.[3] Hence, close monitoring was done for psychotic symptoms as the patient was temporarily off antipsychotic medications while on oral prednisolone. However, we did not notice any new or worsening of pre-existing psychotic symptoms. Over a period of seven days, the patient's dermatological lesions and systemic manifestations gradually disappeared. The management of DRESS syndrome, in this case, was in line with the recommendation.[4]

After the resolution of DRESS syndrome, the patient was started on T. risperidone 2 mg/d for her psychotic symptoms. There was no cross-reaction or reappearance of dermatological symptoms after starting risperidone. The dose of risperidone was gradually increased up to 6 mg/d. The patient maintained improvement in her psychotic symptoms and was subsequently discharged from the hospital. The patient has been in follow-up for four months, and she is doing well with respect to her psychotic symptoms and there has not been any reappearance of DRESS symptoms.

DISCUSSION

DRESS syndrome usually manifests after a prodromal latency period of about 2-8 weeks.[5] The clinical feature consists of fever, rash, lymphadenopathy, hematological findings (eosinophilia, leukocytosis, thrombocytopenia, and anemia), and multisystem involvement (hepatic and renal systems are commonly involved).[6] The cutaneous manifestations typically consist of an urticarial maculopapular eruption and, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma. Due to the wide variety of clinical manifestations mimicking various medical conditions, it poses a challenge for an appropriate, timely diagnosis. Currently, the DRESS syndrome is diagnosed primarily based on the clinical and laboratory abnormalities, and many diagnostic criteria are available. Our patient met the RegiSCAR criteria[2] (scored 4 out of 7) suggestive of a diagnosis of DRESS syndrome. However, compared to other commonly used diagnostic criteria for the diagnosis of DRESS, such as Bocquet's criteria,[7] in this case, only cutaneous manifestation and blood counts abnormality were predominantly present, but the systemic involvement was not prominent.

Among the psychotropic medications, the antiepileptic-mood stabilizers—carbamazepine, oxcarbazepine, valproate, and lamotrigine—have been reported to induce DRESS syndrome.[4] There is a case report of DRESS syndrome with a combination of olanzapine and sodium valproate,[8] and the same patient had earlier received chlorpromazine. However, it is unclear whether chlorpromazine had led to the sensitization for the development of DRESS syndrome. To our knowledge, this is the first report of chlorpromazine-induced DRESS syndrome. Cutaneous adverse effects of chlorpromazine are widely reported and include photo-sensitive reactions such as maculopapular rash, urticaria, pigmentation, subacute lupus erythematosus, lichenoid eruptions, severe exfoliative reactions, and toxic epidermal necrolysis.[9] Life-threatening side effects of chlorpromazine are reported in about 0.6% of the subjects who receive the drug.[10] Chronic administration of chlorpromazine is associated with the development of a lupus-like circulating anticoagulant and a variety of immunological abnormalities.[11] One of the well-studied mechanisms for the photosensitive reactions to chlorpromazine is a delayed hypersensitivity immune reaction.[9] Although the precise pathogenesis of DRESS remains elusive, hypothesized mechanisms include deficient drug metabolism and reactive metabolites, delayed cell-mediated immune response, genetic predisposition with specific human leukocyte antigen (HLA) haplotypes, and viral reactivation.[6,12] Hence, the appearance of DRESS syndrome in our patient might be due to a delayed hypersensitivity immune reaction. Although steroid administration is very well known to induce new or worsen pre-existing psychotic symptoms, psychiatrists should be aware that not all patients on steroids may experience psychosis, and life-threatening conditions such as DRESS syndrome take the precedence in management as demonstrated in this case. However, one should be cautious about the worsening of psychotic symptoms in already diagnosed patients with psychosis. In such instances, it might be beneficial to switch over to antipsychotic medications that are least likely to cause DRESS syndrome or to use alternative psychotropic medications, which include benzodiazepines for the temporary management of aggressive behavior.

An important limitation of our report is that we did not get the skin biopsy of the lesions, due to pragmatic constraints. Still, this report suggests that

DRESS syndrome can be one of the serious adverse effects of chlorpromazine. Patients on chlorpromazine developing serious dermatological adverse effects should be assessed to rule out DRESS syndrome, in view of the high mortality rate in patients with DRESS syndrome.[2,13] Further systematic clinical and genetic studies are needed to evaluate the association of DRESS syndrome and chlorpromazine.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Shayanth Manche Gowda, K. G. Vijay Kumar, K. Shilpa[1]

Department of Psychiatry, National Institute of Mental Health and Neurosciences, [1]Department of Dermatology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Address for correspondence: Dr. Shayanth Manche Gowda
Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India.
E-mail: rushtoshayanth@gmail.com

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Sample Size and its Importance in Research

Chittaranjan Andrade

ABSTRACT

The sample size for a study needs to be estimated at the time the study is proposed; too large a sample is unnecessary and unethical, and too small a sample is unscientific and also unethical. The necessary sample size can be calculated, using statistical software, based on certain assumptions. If no assumptions can be made, then an arbitrary sample size is set for a pilot study. This article discusses sample size and how it relates to matters such as ethics, statistical power, the primary and secondary hypotheses in a study, and findings from larger vs. smaller samples.

Key words: *Ethics, primary hypothesis, research methodology, sample size, secondary hypothesisize, statistical power*

Studies are conducted on samples because it is usually impossible to study the entire population. Conclusions drawn from samples are intended to be generalized to the population, and sometimes to the future as well. The sample must therefore be representative of the population. This is best ensured by the use of proper methods of sampling. The sample must also be adequate in size – in fact, no more and no less.

SAMPLE SIZE AND ETHICS

A sample that is larger than necessary will be better representative of the population and will hence provide more accurate results. However, beyond a certain point, the increase in accuracy will be small and hence not worth the effort and expense involved in recruiting the extra patients. Furthermore, an overly large sample would inconvenience more patients than might be necessary for the study objectives; this is unethical. In contrast, a sample that is smaller than necessary would have insufficient statistical power to answer the primary research question, and a statistically nonsignificant result could merely be because of inadequate sample size (Type 2 or false negative error). Thus, a small sample could result in the patients in the study being inconvenienced with no benefit to future patients or to science. This is also unethical.

In this regard, inconvenience to patients refers to the time that they spend in clinical assessments and to the psychological and physical discomfort that they experience in assessments such as interviews, blood sampling, and other procedures.

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Clinical Psychopharmacology Unit, Department of Clinical Psychopharmacology and Neurotoxicology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence: Dr. Chittaranjan Andrade
Clinical Psychopharmacology Unit, Department of Clinical Psychopharmacology and Neurotoxicology, National Institute of Mental Health and Neurosciences, Bengaluru - 560 029, Karnataka, India. E-mail: andradec@gmail.com
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ESTIMATING SAMPLE SIZE

So how large should a sample be? In hypothesis testing studies, this is mathematically calculated, conventionally, as the sample size necessary to be 80% certain of identifying a statistically significant outcome should the hypothesis be true for the population, with *P* for statistical significance set at 0.05. Some investigators power their studies for 90% instead of 80%, and some set the threshold for significance at 0.01 rather than 0.05. Both choices are uncommon because the necessary sample size becomes large, and the study becomes more expensive and more difficult to conduct. Many investigators increase the sample size by 10%, or by whatever proportion they can justify, to compensate for expected dropout, incomplete records, biological specimens that do not meet laboratory requirements for testing, and other study-related problems.

Sample size calculations require assumptions about expected means and standard deviations, or event risks, in different groups; or, upon expected effect sizes. For example, a study may be powered to detect an effect size of 0.5; or a response rate of 60% with drug vs. 40% with placebo.[1] When no guesstimates or expectations are possible, pilot studies are conducted on a sample that is arbitrary in size but what might be considered reasonable for the field.

The sample size may need to be larger in multicenter studies because of statistical noise (due to variations in patient characteristics, nonspecific treatment characteristics, rating practices, environments, etc. between study centers).[2] Sample size calculations can be performed manually or using statistical software; online calculators that provide free service can easily be identified by search engines. G*Power is an example of a free, downloadable program for sample size estimation. The manual and tutorial for G*Power can also be downloaded.

PRIMARY AND SECONDARY ANALYSES

The sample size is calculated for the primary hypothesis of the study. What is the difference between the primary hypothesis, primary outcome and primary outcome measure? As an example, the primary outcome may be a reduction in the severity of depression, the primary outcome measure may be the Montgomery-Asberg Depression Rating Scale (MADRS) and the primary hypothesis may be that reduction in MADRS scores is greater with the drug than with placebo. The primary hypothesis is tested in the primary analysis.

Studies almost always have many hypotheses; for example, that the study drug will outperform placebo on measures of depression, suicidality, anxiety, disability and quality of life. The sample size necessary for adequate statistical power to test each of these hypotheses will be different. Because a study can have only one sample size, it can be powered for only one outcome, the primary outcome. Therefore, the study would be either overpowered or underpowered for the other outcomes. These outcomes are therefore called secondary outcomes, and are associated with secondary hypotheses, and are tested in secondary analyses. Secondary analyses are generally considered exploratory because when many hypotheses in a study are each tested at a $P < 0.05$ level for significance, some may emerge statistically significant by chance (Type 1 or false positive errors).[3]

INTERPRETING RESULTS

Here is an interesting question. A test of the primary hypothesis yielded a *P* value of 0.07. Might we conclude that our sample was underpowered for the study and that, had our sample been larger, we would have identified a significant result? No! The reason is that larger samples will more accurately represent the population value, whereas smaller samples could be off the mark *in either direction* – towards or away from the population value. In this context, readers should also note that no matter how small the *P* value for an estimate is, the population value of that estimate remains the same.[4]

On a parting note, it is unlikely that population values will be null. That is, for example, that the response rate to the drug will be exactly the same as that to placebo, or that the correlation between height and age at onset of schizophrenia will be zero. If the sample size is large enough, even such small differences between groups, or trivial correlations, would be detected as being statistically significant. This does not mean that the findings are clinically significant.

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Conflicts of interest
There are no conflicts of interest.

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