



Management of Treatment-resistant of Psychotic Patients in Palestine: A Literature Review

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Abstract

Patients who do not respond adequately to pharmacological treatment existing an ongoing therapeutic challenge, and they are in need for a nonpharmacological intervention options to get treatment and rehabilitation. This study provides an overview of published studies involving nonpharmacological intervention for treatment resistant of psychiatric patients in Palestine. A computerized literature searches (Google Scholar, PubMed, Science Direct, Springer Link, Elsevier, Semantic Scholar, and HINARI) was used to collect the studies. The reviewed studies were evaluated and selected by review abstract and full article text. Nine articles were reviewed but no one of them discussed treatment-resistant management in Palestine. In contrast, articles showed the treatment adherence in mental health patients and the experience of care givers, family, mother of mental health clients and their attitudes toward mental illness patients, as well as the challenges in treatment and rehabilitation that they faced in West Bank and Gaza Strip.

Conclusion: No evidences have been existed about managing of treatment-resistant among mental health patients in Palestine, all studies discussed different diminutions such as pharmacological treatment options (monotherapy and combined therapy), treatment adherence, experience for mothers and caregivers with facing the challenges appeared while dealing with mental health patients and the causes of using opioids.

Recommendation: Studies about treatment-resistant in psychotropic patients, and about non-pharmacological intervention strategies among them should be taken in consider and have more evidence about it in Palestine.

Keywords: Treatment, treatment-resistant, Palestine, Psychotic, nonpharmacological, Schizophrenia, Depression, Anxiety

Abbreviations: APP: Antipsychotic polypharmacy; BS: Brain Stimulation; CBT: Cognitive Behavioral Therapy; CMRF: Cardiometabolic Risk Factors; ECT: Electroconvulsive Therapy; FEP: First-Episode Psychosis; MDD : Major Depressive Disorder; MoH: Palestinian Ministry of Health; MST: Magnetic Seizure Therapy; PDT: Psychodynamic Therapy; TMS: Transcranial Magnetic Stimulation; TRA: Treatment-resistant Anxiety; TRD: Treatment-resistant Depression; TRS: Treatment-resistant Schizophrenia; TRP: Treatment-resistant patients; VNS: Vagus Nerve Stimulation; WHO: World Health Organization

Background

Palestine, a country with a low income, its history marked with a long-lasting conflict which indicate to the political events surrounding it [1]. This Palestinian-Israelian conflict on the Palestinians lands, effects on the physical and mental health [2]. Historically, Palestine was divided into two areas (West Bank and Gaza Strip) [2]. Those two areas were occupied by Israel in 1948, related to that about 60 percent of the Palestinians living in villages with 27 percent of them in refugee camps [3]. Accordingly, Israel attacks the civilians in their places and they experience infringement of their human rights which impact their health [4]. Because of affection on the civilian health, especially the mental health, there

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is a need to develop mental health services [5]. Therefore, in 2004 the mental health policy officially adopted for West Bank and Gaza Strip by Palestinian Ministry of Health (MoH) and in 2002-2003 it was formulated. As a result, Palestinians need to meet their human rights and develop the mental health policies and services [1].

In summary, the history that the researchers mentioned above about Palestine's political condition, clearly showed that there are major challenges faced the civilians' mental health, as well as, their social and economic state. And the political events have made around one-third of Palestinians in need of mental health interventions, which makes mental ill-health one of the largest but least acknowledged of all health problems [6].

Introduction

Mental health illness does not exclude any individual, mental disorders affect all different ages, ethnic, racial, socioeconomic and cultural groups [7]. Many mental health patients do not response for the first line treatment by medications, and they are in need for a nonpharmacological intervention options to get treatment and rehabilitation [8]. Rehabilitation is any intervention which may help individuals with mental health disorders to be free from restrictions to practice their life in a good manner and to be able to manage their own work, homes and relationships with others [9]. However, treatment resistant among mental health patients according to its standard categorical definition means "'an inadequate response to at least two adequate (appropriate dose and lasting for at least six weeks) episodes with different drugs". Besides, response means a decrease in the symptom's severity and percentage improvement in the global score of a rating scale can obscure clinical reality. What is supposed to be an inadequate response differs from disorder to disorder and is sometimes defined differently in a first step treatment versus a treatment resistant patient.

Depending on that, mental health patients are in need for another therapeutic options to support pharmacological intervention. This options which are nonpharmacological include formal psychological therapies such as Interpersonal Psychotherapy (IPT), Cognitive Behavior Therapy (CBT) and as well as less formal supportive therapies such as mindfulness-based therapy, mediation, behavioral activation and self-help strategies, life style changes, exercise and counselling within primary care [10]. Moreover, psychiatric disorders such as schizophrenia, depression, anxiety disorders and other psychotic disorders, effectively are treated with both pharmacological and non-pharmacological therapeutic options. But the effectiveness depends on the disorder and the severity of it while applying one of the nonpharmacological interventions which are recommended by American Psychiatric Association (APA)

[11]. Although pharmacological treatment is a necessary first step in managing incompletely recovered patients, adjunctive psychosocial interventions are needed to optimize treatment success. Patients who do not respond adequately to pharmacological treatment existing an ongoing therapeutic challenge [12].

An overview of non-pharmacological intervention for treatment-resistant psychiatric patients

Treatment-resistant schizophrenia (TRS)

In general population, 20%–45% of schizophrenic patients of over two years' duration are only partially responsive to pharmacological treatment and 5%–10% of patients do not receive any improvement at all [13]. In a paper, discussed managing patients with "treatment-resistant" schizophrenia, researchers indicate that pharmacotherapy should not be given without other associated interventions which is essential. The treatment aim should be slanted towards integration for patients with an incomplete recovery, and pharmacotherapy should be seen as one of many applicable strategies to achieve the goal. There for, for many patients classified under the "truly treatment-resistant" rubric, small changes in family, occupational or social functioning may be highly significant for the patient and his or her careers.

Thus, a systematic review, in 2019, published by Tumiel [14], was carried out to provide an overview of studies and a critical analysis of pilot programs involving nonpharmacological measures aimed at prevention and treatment of Cardiometabolic Risk Factors (CMRF) in patients with schizophrenia. The results have showed nonpharmacological interventions enhance physical health and showed a notable potential for implementation in treatment programs dedicated to CMRF patients with schizophrenia [14]. However, one of the nonpharmacological interventions in treatment and rehabilitation for schizophrenic patients is exercise. A published study, in 2016, was conducted to evaluate the feasibility of an exercise intervention for early psychosis and to determine if it is associated with physical and mental health changes. This study recruited 31 patients with First-Episode Psychosis (FEP) from early intervention services to a 10-week exercise intervention. The intervention group received individualized training programmes (tailored to individual preferences and needs), which aimed to achieve ≥ 90 min of moderate-to-vigorous activity every week. A comparison FEP sample from the same services ($n = 7$) received treatment as usual. Results have showed reducing by 13.3 points after 10 weeks of exercise negative and positive syndrome scale total scores, which was significantly greater than the treatment as usual comparison group ($P = 0.010$). The markable improvement was observed in negative symptoms, which reduced by

33% in the intervention group ($P = 0.013$). Also, Significant improvements were observed in psychosocial functioning and verbal short-term memory. Increases in cardiovascular fitness and processing speed were positively associated with the amounts of exercise achieved by participants [15].

Treatment-resistant Depression (TRD)

In 2003, a published study for enhancing outcomes in the management of treatment resistant depression was indicated that over than 50% of depressed patients marked inadequate response to antidepressant treatment. study results have showed a significant improvement in TRD patients with atypical antipsychotic medications which are including; risperidone, olanzapine, ziprasidone, and quetiapine. Other nonpharmacological intervention strategies and investigational physical treatments, have demonstrated some benefits, but availability and patient preference should also be considered. With today's therapeutic alternatives, full remission of depression is an attainable goal. For some patients, combination and augmentation strategies earlier in treatment may increase the likelihood of remission [16].

However, several potential nonpharmacologic treatments for TRD patients include; psychotherapy, repetitive Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), and Magnetic Seizure Therapy (MST) [17]. Studies showed that adding Cognitive Behavior Therapy (CBT) or Interpersonal Therapy (IT) to pharmacotherapy was significantly increased rehabilitation rates in partial responders and in patients with TRD. Electroconvulsive Therapy (ECT) as a nonpharmacological intervention used in treating TRD, has shown the greatest efficacy in reducing depressive symptoms, with remission rates ranging from 50% to 89% in patients unresponsive to a prior antidepressant trial. Though ECT demonstrates superior efficacy to oral antidepressants, its use is limited by the need for patients to undergo anesthesia and neuromuscular blockade, the small number of psychiatrists able to perform the procedure, and cost [18].

A systematic review carried out to review more than 140 pharmacological and non-pharmacological therapeutic options for Major Depressive Disorder (MDD) and to evaluate their effects. This study was conducted from 2011 to 2017 among randomized controlled trials in adult patients with acute-phase MDD. Results have showed that only Cognitive Behavioral Therapy (CBT) is supported by reliable evidence (moderate strength) to produce responses to treatment similar to those of second-generation antidepressants. All evidence of non-pharmacological treatments with second-generation antidepressants either led to inconclusive results or had substantial methodological shortcomings (low or inadequate strength of evidence) [19].

Treatment-resistant Anxiety (TRA)

Up to 30% from anxiety patients are treatment-resistant [20], In a published paper, in 2010, which was carried out to review the evidence for possible pharmacological, psychotherapy, Brain Stimulation (BS), and neurosurgical approaches for managing treatment-resistant anxiety disorders. Results have recommended the following to treat TRA: 1. Switching to or augmenting with another first-line treatment 2. If a medication is effective, using good clinical judgment, taking in consider the patient preference and a both of risk and benefit assessment on a case-by base basis, is advised 3. Cognitive Behavior Therapy (CBT) as a nonpharmacological intervention for 10-20 sessions with giving the patient a daily homework. This study highlighted that there is a large gap remain clear in the way of managing TRA, but the recent advances offer promise [21].

Moreover, Prasko [22] published a cross-sectional study, aimed to explore a relationship between treatment efficacy in patients with anxiety disorder and the psychological factors. This study was among 109 patients with anxiety disorder with a high frequency of comorbidity with depression and/or personality disorder were evaluated at the start of the treatment by the following scales after revised: The Mini-International Neuropsychiatric Interview (MINIPS), the Internalized Stigma of Mental Illness scale (ISMI), the Adult Dispositional Hope Scale (ADHS), and the Temperament and Character Inventory (TCI). The participants, completed the following scales at the beginning and end of an inpatient-therapy program: Clinical Global Impression (objective and subjective) the Beck Depression Inventory (BDI) second edition, the Beck Anxiety Inventory (BAI), and the Dissociative Experiences Scale (DES). The treatment consisted of 25 group sessions and five individual sessions of nonpharmacological interventions such as, cognitive behavioral therapy (CBT) or Psychodynamic Therapy (PDT) in combination with pharmacotherapy. This study results have showed a markable improvement in psychopathology, was associated with low initial harm avoidance, dissociation level, self-stigma, higher amounts of hope and self-directedness. Also, there was a significant improvement among anxiety patients without comorbid disorders in contrast of who was with comorbid disorders [22].

Methodology

Literature search

A computerized literature searches through Google Scholar, PubMed, ScienceDirect, SpringerLink, ResearchGate, Semantic Scholar, and HINARI was used to collect studies addressing the effect of B vitamins on mental health in March 2021. The following search terms were used: "Treatment psychiatry AND Palestine," "Treatment rehabilitation psychiatry AND Palestine," "Rehabilitation schizophrenia

Palestine,” “psychiatric symptoms rehabilitation Palestine,” “rehabilitation Palestine psychiatry,” “Nonpharmacological treatment resistant.” By using this search method, the number hits of founded articles was 46751. After removing excluded, irrelevant and duplicated articles, 25 publications existed. Additional papers which did not appeared clearly in the electronic database search were obtained via an examination of references lists of publisher papers. 9 studies remained after examination of articles to meet the included criteria. Relevant empirical studies are summarized and presented hither.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they satisfied the following criteria: (1) Reviewed treatment and rehabilitation for psychiatric patients. (2) Reviewed nonpharmacological intervention for mental health patients (3) Reviewed nonpharmacological intervention for treatment resistant of psychotic patients. All articles that do not discussed treatment, rehabilitation and nonpharmacological intervention were excluded.

Quality assessment

The quality assessment of all studies was assessed according to a checklist. It was included a following criteria: clear study aims, representative sample, response rate reported with losses given, an adequate description of data, explicit inclusion and exclusion criteria, valid and reliable measure of mental health and appropriate statistical analysis. The researcher investigates assessed article quality, and inconsistencies were resolved by the principal investigator.

Results

Swelieh [23] in 2013, published a cross-sectional study which was carried out to evaluate the prescribing pattern of antipsychotic medications and its conformance to international treatment guidelines. Researchers reviewed patients' medical files to obtain clinical information, medication and demographic data. And an international guideline for schizophrenia were used to create conformance indicators. Results for 350 patients have showed that the prevalence of antipsychotic combination was 50.4%. There was no significant difference in positive, negative and psychopathology scores of schizophrenia symptoms among patients on monotherapy versus those on antipsychotic combination. From the participants only 42% were using optimum dose of (300 – 600 mg CPZeq) while the remaining were using sub or supra therapeutic doses without following the guidelines. Therefore, the prescribing for antipsychotics was not conformance with international guidelines with respect to maintenance dose and combination therapy. Type of antipsychotic treatment regimen, combination

versus monotherapy, was not associated with better clinical or economic outcome [23].

However, a cross-sectional study, in 2011, was carried out to assess adherence to medication and to investigate relationships of adherence to medication with treatment satisfaction and clinical symptoms among Palestinian patients with schizophrenia disorder. A convenience sample of 131 schizophrenic patients was studied, Morisky Medication Adherence Scale (MMAS) was used to measure medication adherence, while Treatment Satisfaction Questionnaire for Medication (TSQM) was used to measure treatment satisfaction. Psychiatric symptoms were measured using the expanded Brief Psychiatric Rating Scale (BPRS-E). Results in this study have showed low, medium and high rate of adherence for treatment based on MMAS, 33.6%, 44.3%, 22.1% respectively. Satisfaction means was 72.6 ± 20.5 for effectiveness, 67.9 ± 31.47 for side effects, 63.2 ± 14.3 for convenience and 63.1 ± 18.8 for global satisfaction. Furthermore, there was a significant difference in the mean of positive symptom score ($P < 0.01$) but negative symptom score ($P = 0.4$) among patients with different levels of adherence. Researchers conclude that non-adherence to medication was common among Palestinian patients with schizophrenia disorder and it was associated with low treatment satisfaction scores and poor symptoms scores [24]. Adherence is defined as “the extent to which the patient’s behavior matches agreed recommendations from the prescriber” [25].

Furthermore, Ihbeasheh [26] in 2014, published cross-sectional study which was carried out to study antipsychotic medication use in the outpatient psychiatry department in Palestine. The participants in this study were schizophrenic patients aged between 20 to 65 years old whose medications have not been changed in the past six months and they did not have an acute attack in the last year. Information was obtained from patients’ medical files; patients’ psychiatric symptoms were evaluated using the Expanded Brief Psychiatric Rating Scale (BPRS-E). The results in this study showed that more than half of patients (53.1%) were on Antipsychotic Polypharmacy (APP) with average daily dose of 546.9 ± 254.9 mg chlorpromazine equivalents. The average number (mean \pm SD) of medications a patient received was 1.7 ± 0.7 . One third of patients on APP regimen received atypical antipsychotic and all of them received at least one conventional antipsychotic. Factors significantly and positively associated with APP [26].

Moreover, a qualitative descriptive phenomenological study, in 2017, aimed to explore the experience of mothers of Palestinian patients with schizophrenia disorder and their management’s practices that they used which include; difficulties and barrier that face the mother, and investigate

both the positive and negative experiences of care giving, mother coping strategies, supportive factors, attitudes and perceptions. The researchers were used face to face, in-depth, semi-structured interviews with 11 mothers of client affected with schizophrenia. This study was conducted in Hebron Community Mental Health Center, in Hebron district, West Bank, Palestine. Results have emerged 4 main themes and 18 subthemes. This theme includes; 1. Coping with new situation 2. Knowledge deficit 3. Emotional and social experience and 4. Ongoing Struggle. Researchers conclude that each mother has her unique experience in caring and living journey with a schizophrenic patient in the family, each one of mothers experienced varies of difficulties and burden while caring for their client affected with schizophrenia include, psychological, Emotional, social and economic factors. Many lifestyle changes include being socially isolated due to need to be always with their client who become dependent. Also, mothers reported a need to help them handle with new situation, as they are in need for adequate information and education about the disorder, and counseling center, and center for rehabilitation and entertainments activity for their clients supported with mental health professionals. Mothers developed a coping mechanism to face challenges that they pass through by their client affected with schizophrenia. Lastly, some mothers also reported positive, character building experiences arising from their caring for their relative with schizophrenia, that they felt satisfied when their client become better, and some mothers become closer and give more love to their client [27].

Besides, in 2015, a descriptive cross-sectional study, published by El-Jedi and Shair, aimed to examine the level of emotional, economic, physical and social burden experienced by the caregivers of schizophrenic patients in Gaza strip as well as determining the association between burden and socio-demographic characteristics of both caregivers and patients. Randomly, 120 participants were selected from different governmental community mental health centers in Gaza strip. A set of questionnaires were used including: socio-demographic characteristics of patients and caregivers, and the Caregiver Burden Assessment Scale. Results have showed 68.1% from caregivers were females, 45.3% aged 40 years old and above, 47.5% low educated and 72.0% unemployed. From the participants 52.5% provide care at least for 10 years and suffer from very high level of overall burden, the physical burden was the highest (81.0%), while the social burden was the lowest (68.3%). There were significant differences in level of burden, and education, occupation and monthly income of both caregivers and patients. Whereas, no significant association was found between level of burden and caregiver's age, gender, period of care, and the relationship with the patient Collapse [28].

Accordingly, a quantitative study, in 2010, was carried out to assess the attitudes of professionals towards patients with mental disorders in the only psychiatric hospital in Palestine in Bethlehem city. In this study, an Attitudes Toward Acute Mental Health Scale (ATAMHS) was used, and it was distributed to a variety of professionals at the Bethlehem psychiatric hospital. Most of the participants were nurses, and they expressed positive and negative attitudes toward patients. Results have showed negative attitudes were more than positive particularly in relation to alcohol misuse, medication, patients' ability to control their emotions, and genetic predisposition to mental illness. Researchers conclude that education and direct contact with patients with mental disorders may not be sufficient to enhance positive attitudes towards them. This may indicate the need to modify educational curriculum at the Palestinian universities and offer more training for mental health professionals in order to change their attitudes [29].

Another qualitative study was carried out to explore the experiences of professionals working with Palestinian families and children affected by substance use and addiction in the home. Four focus groups (n=42) were conducted in West Bank and Gaza Strip. Thematic analysis was used to analyse the data. In this study results, four main themes were emerged as the following: 1. The rising and shifting problem of drug use in Palestine 2. Psychosocial causal factors of drug use in Palestine 3. The consequences for children and families living with drug use and 4. Potential solutions to the problem are complex and multifaceted. The researchers conclude a worried picture about the impact of drug abuse on Palestinian families subjected to multiple pressures, risks, stigmas and harms relating to their situation [30].

In addition, in 2020, published qualitative study in Gaza Strip in Palestine, aimed to determine the perceptions of the individual, community, and socio-political determinants of tramadol use, its effect on quality of life, and the challenges experienced in the recovery process. Interviews with psychiatrists and tramadol user were the way to collect data. After thematic analysis for 26 interviews (13 psychiatrists and 13 tramadol users), results showed three main themes emerged like the following: 1. conditions contributing to the misuse of tramadol 2. challenges in recovering from tramadol misuse and 3. consequences of misuse on individuals and social networks. Participants reported that living conditions and critical environmental, such as unemployment, poverty, stress, health, and mental health-related determinants have led to the use of the opioid. Also, disrupted and weak social services that are unprepared to manage widespread substance use cannot safeguard and assist tramadol users. Researchers conceptualize the data in terms of a socio-ecological model depending on individual,

cultural and social determinants of tramadol use [31,32].

Discussion

Patients who do not respond adequately to pharmacological treatment existing an ongoing therapeutic challenge. Therefore, a non-pharmacological intervention strategy is needed to support the first line therapeutic options. Furthermore, psychiatric disorders such as schizophrenia, depression, anxiety disorders and other psychotic disorders, effectively are treated with both pharmacological and non-pharmacological therapeutic options. But the effectiveness depends on the disorder and its severity. According to Tumiel, the non-pharmacological intervention showed a markable improvement among treatment-resistant schizophrenic patients, as it was in treatment-resistant depression and treatment-resistant anxiety.

However, nonpharmacological interventions enhance physical health and showed a notable potential for implementation in treatment programs dedicated to Cardiometabolic Risk Factors (CMRF) patients with schizophrenia. For example, exercise training could provide a feasible treatment option for improving symptomatic, neurocognitive and metabolic outcomes in First-Episode Psychosis. In contrast, one third of Palestinian patients on Antipsychotic Polypharmacy (APP) regimen received atypical antipsychotic and all of them received at least one conventional antipsychotic. Factors significantly and positively associated with APP. However, non-adherence to medication was common among Palestinian patients with schizophrenia disorder and it was associated with low treatment satisfaction scores and poor symptoms scores.

Moreover, each one of mothers experienced varies of difficulties and burden while caring for their client affected with schizophrenia include, psychological, Emotional, social and economic factors. Many lifestyle changes include being socially isolated due to need to be always with their client who become dependent. Also, mothers reported a need to help them handle with new situation, as they are in need for adequate information and education about the disorder, and counseling center, and center for rehabilitation and entertainments activity for their clients supported with mental health professionals. Mothers developed a coping mechanism to face challenges that they pass through by their client affected with schizophrenia. Lastly, some mothers also reported positive, character building experiences arising from their caring for their relative with schizophrenia, that they felt satisfied when their client become better, and some mothers become closer and give more love to their client.

According to that, there were significant differences in level of burden, and education, occupation and monthly

income of both caregivers and patients. Whereas, no significant association was found between level of burden and caregiver's age, gender, period of care, and the relationship with the patient Collapse. Also, in dealing with mental health and alcohol users, the negative attitudes were more than positive particularly in relation to alcohol misuse, medication, patients' ability to control their emotions, and genetic predisposition to mental illness. The causes were that the education and direct contact with patients with mental disorders may not be sufficient to enhance positive attitudes towards them. This may indicate the need to modify educational curriculum at the Palestinian universities and offer more training for mental health professionals in order to change their attitudes. However, that living conditions and critical environmental, such as unemployment, poverty, stress, health, and mental health-related determinants have led to the use of the opioid. Also, disrupted and weak social services that are unprepared to manage widespread substance use cannot safeguard and assist tramadol users. Researchers conceptualize the data in terms of a socio-ecological model depending on individual, cultural and social determinants of tramadol use. The researchers conclude a worried picture about the impact of drug abuse on Palestinian families subjected to multiple pressures, risks, stigmas and harms relating to their situation.

Conclusion

The researcher concludes that managing treatment-resistant patients with mental disorders can be through both pharmacological and nonpharmacological therapeutic strategies. Non-pharmacological options for treatment and rehabilitation of psychiatric patients includes; cognitive behavioural therapy, deep brain stimulation, interpersonal psychotherapy, electroconvulsion therapy, exercise and life-style changes. Although pharmacological options are the first line, but studies showed a significant improvement in patients with treatment-resistant schizophrenia, treatment-resistant depression and treatment-resistant anxiety disorders.

unfortunately, no evidences have been existed about managing of treatment-resistant among mental health patients in Palestine, all studies discussed different diminutions such as pharmacological treatment options (monotherapy and combined therapy), treatment adherence, experience for mothers and caregivers with facing the challenges appeared while dealing with mental health patients and the causes of using opioids.

Recommendation

The researcher recommends to apply studies about managing treatment-resistant patients with mental disorders by using a nonpharmacological intervention

strategy in Palestine, and take in consider the importance of this studies.

Limitation

There was a lack of studies about clear management for treatment-resistant patients with most common mental disorders (Schizophrenia, depression and anxiety). And the researcher did not find a study in Palestine related to treatment-resistant and the non-pharmacological intervention among Palestinian people with mental health illness.

Ethics approval and consent form participate

Human participants were not involved in this review.

Availability of data

This is an evidence synthesis study, all data is available from the primary research studies, or can be circulated from the corresponding author

Competing interests

There are no competing interests in this study.

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