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Letter from the Editor

November 2021



Dear Colleagues,

Welcome to another edition of the *Arab Journal of Psychiatry*. The long-established process of carrying out research to better understand how to support people with severe and enduring mental health difficulties is a key theme in the current volume. We are also reminded of the importance of keeping you up to date through reviews, such as those on recall bias in trauma recollection and the mental health of the Syrian people following 11 years of armed conflict. Such reviews have a place in shaping policy and practice.

As Editor-in-Chief, I continue to welcome manuscripts on any subject within the broad definition of mental health, especially articles that announce discoveries, present new information, or break new theoretical ground, as well as those that address methodological issues, explore the symbiosis between field methodology and the analysis of clinic-based knowledge, or illuminate in novel ways how to extend our traditional understanding of mental health.

I thus invite readers who are interested in writing such pieces to send me their manuscripts so that we can continue to offer you a lively and up to date journal.

Sincerely,

Walid Sarhan

Editor-in-Chief

Amman, Jordan

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Improving Treatment Response in Psychiatric Practice

Abdil-Monaf Al-Jadiry

تحسين الاستجابة العلاجية في الطب النفسي

عبد المناف الجادري

Abstract

In clinical practice, psychiatrists and other physicians are often challenged by treatment non-response, which they often attribute to inherent factors in the disorder. While, to some extent, this is true with some disorders, the case cannot be generalized. The majority of mental disorders, which are viewed as treatment-resistant, require comprehensive reviewing to identify underlying factors making them resistant to treatment. Psychotropic medicines are considered effective treatments for mental disorders when their administration follows evidence-based guidance. Optimal response to treatment requires accuracy of diagnosis and thoroughness of mental health assessment, exclusion of comorbidities, appropriate communication tools and doctor-patient relationship to ensure patient's compliance and adherence, search for stressors, and an evidence-based drug selection and knowledge of their pharmacological properties. Moreover, in many conditions, the addition of non-pharmacological therapies is required to augment response. In recent decades, understanding pharmacogenomics of administered medications has evolved to be significant in drug selection and response prediction. This is an overview that aims, in addition to discussing important clinical and psychosocial determinants of good response to treatment, to highlight the current knowledge and understanding of the role of psycho-pharmacogenomics as a treatment-response predictor, a means to improve treatment outcome, and promote better selection and use of psychiatric medications.

Keywords: psychiatry, psychiatric treatment; treatment-response

Declaration of interest: None

Introduction

The importance of treating mental disorders successfully arises from the fact that mental illness is a leading cause of disease burden. For instance, common disorders like depression are a risk factor for many serious and chronic physical diseases such as cardiac disease and hypertension, diabetes, asthma, chronic bronchitis, arthritis and back pain, and migraine.¹⁻³ In addition to their physical impact upon health, depressive disorders, and anxiety disorders result in a significant burden on the economy at both individual and national levels.^{4,5}

Instead of making efforts to screen for actual underlying factors for no response, clinicians often tend to blame factors inherent in the disorder, which can be true with some disorders but cannot be generalized. In this regard and to distinguish treatment responsive mental disorders from non-responsive ones, Schulz and Patricia (2004), classified mental disorders according to their course and treatment outcome into three groups: a group, which is chronic and often run a downhill course such as "schizophrenia and Alzheimer disease and other dementias". Except for some of the associated symptoms and comorbid conditions that may respond to treatment

and hence good prediction may be made, a poor response is likely to be related to inherent issues in these disorders. The second group includes disorders such as "acute stress disorders". This group usually runs a favorable course, and satisfactory response to treatment is frequently predicted. The last group includes categories of some "depressive and anxiety disorders" whose evolution is variable in different individuals and accordingly the range of response would also be widely variable ranging from complete or spontaneous response to no response and even death.⁶ This grouping supports the fact that failure of response to treatment should not be always attributed to inherent factors, and the clinician is required to screen for other manageable factors.

The traditional approach of prescribing medications through trial and error often leads to non-response, low remission rates, and adverse effects, with more than half of patients with depression who receive antidepressant therapy not responding to their first line of treatment.⁷ As the number of failed medication trials increases, the probability of a patient achieving response or remission decreases, highlighting the clinical importance of better

treatment selection early in the patient's treatment process.^{8,9} Referral to the concept of "personalized medicine", which will be discussed later in this paper, may be a convenient treatment approach for achieving better treatment outcome

The negative impact of mental disorders on physical health and their burden on the economy inspired a search for approaches to improve drug response. Such approaches emphasize the importance of reviewing clinical diagnosis and mental assessment, using better communication skills to ensure patient's drug acceptability, compliance and adherence to treatment, proper drug selection and promotion, and the addition of non-pharmacological therapies. When used in conjunction with psychosocial interventions, psychotropic medications are proved to be effective therapeutic agents in most accurately diagnosed mental disorders.¹⁰

McMahon (2014) considered the issue of the prediction of drug effect as one of considerable practical and theoretical importance. He stated that it is difficult to arrive at generally valid conclusions predictive of drug effect from clinical empiricism because of spontaneous remissions, uncontrolled fluctuations of life circumstance, and the meager abilities of many psychiatric patients to describe objectively their level of cognitive, affective, and social functioning.¹¹

As mentioned earlier, better treatment outcomes are often predicted when combinations of pharmacologic and non-pharmacologic treatment are offered. However, some patients may develop chronic disabilities, and others may be overwhelmed by side effects. These often occur as consequences of trial and error in drug selection. This necessitates a search for a tool that provides more effective and safer means of drug selection to protect against negative consequences of non-evidence-based treatment approaches.

Although most currently used psychopharmaceutical agents are safe and well-tolerated, side effects can be problematic even with acute use, leading to treatment non-adherence and poorer outcomes.¹² Moreover, response rates for most psychopharmaceutical agents are not optimal, and it can take months for clinicians to find the best medication or combination treatment for individual patients.¹³ However, treatment outcome prediction is a challenging endeavor, since many different variables can play a role. Among these: diagnosis accuracy, presence of comorbidities, and treatment adherence are tremendously significant.

In recent years, considerable effort has gone into developing biomarkers of treatment response. Genetic markers have received the most attention.¹⁴ Pharmacogenomics has evolved to reduce acute and long-term adverse events and optimize response rates by using genetic information to match medications to individual disorders.¹⁵ Other biomarkers are being sought by a variety of methods, including neuroimaging, proteomics, and metabolomics. These areas have been well searched for intractable diseases like cancer. However, in recent years, the search for biomarkers as a source of prediction of treatment outcome in psychiatry, though yet not well explored, has been receiving increasing attention. Such discovery is expected to revolutionize better prediction of treatment response through accurately matching the right drug with the specific disorder. Achieving this would significantly minimize the negative impact of mental disorders on health and the economy.

This overview aims to highlight some of the clinical, psychosocial, pharmacological, and pharmacogenomic perspectives relevant to improving treatment response in psychiatry.

Determinants of response to treatment in psychiatry

Improving response to psychiatric medications requires consideration of the relevant factors that bear heavy interventional influence upon the course and outcome of the mental disorder and subsequently, and hopefully, would determine better treatment response. Generally, these determinants, for the sake of the discussion, can be grouped into clinical, pharmacological, pharmacogenomic factors. Further, "Personalized Medicine" has recently emerged as a successful means in matching the right drug with the specific mental disorder.

Clinical determinants

The first brick in building a good response to treatment is the accuracy of the clinical assessment of the case and the attached diagnostic label. In the past seven decades, treatment in psychiatry has been revolutionized by the development of generations of effective psychotropic medicines and psychosocial interventions that have led to an enormous reduction in the gloomy attitude towards future outcomes for people with mental health difficulties, created hope that mental illness has become treatable as any other medical illness, and reflected in the better services offered and prompted respect for the rights of

people with such difficulties to live a normal life. These generations of medicines act specifically upon different mental disorders. Hence, accurate clinical diagnosis is fundamental for the selection of the appropriate drug.

A related issue, which complicates the diagnostic operation, is that mental disorders frequently share symptoms that complicate the diagnostic process. To facilitate the differential exercise a detailed clinical history with a thorough psychosocial evaluation, mental status assessment and physical examination should be performed. Also, referral to diagnostic criteria, introduced by ICD-11 or DSM-5, can help the diagnostic process. An example of shared symptoms is the complaint of low mood and anxiety. Both symptoms occur in multiple mental disorders with different psychopathologies requiring different treatment approaches.

Another related issue is a missed underlying organic disorder that often fails in response to treatment. Many psychiatric symptoms can be the only or the predominant manifestation for organic conditions, which are overlooked. For instance, endocrine disorders, brain tumors, and other brain diseases, and autoimmune disorders are examples of organic disorders that do not uncommonly manifest with mental symptoms. To avoid pitfalls in clinical practice and to obtain better treatment responses, precision in clinical evaluation is essential.

Comorbidity in psychiatry is not uncommon. Two psychiatric disorders may occur simultaneously, for instance, anxiety and depression or anxiety disorder with substance use disorder. Missing such comorbidities can be an underlying factor for treatment non-response.¹⁶⁻¹⁸ Comorbid anxiety disorders and comorbid substance use disorder, for instance, are well-known risk factors for poor treatment outcomes in major depression. Substance use interferes with treatment response to antidepressants and anti-anxiety agents, associated with poorer treatment adherence, greater complaints of treatment-emergent adverse events, and more medical complications, all of which correlate with poorer outcomes.¹⁹⁻²¹

The major limitation of predictors based on diagnosis and clinical features is dependence on clinical assessments that may be inaccurate, imprecise, or unstable over time. Diagnosis may also be too distal from underlying biological processes that presumably underlie various outcomes. New diagnostic systems such as the research domain criteria (RDoC) seek to address this problem by focusing on dimensions of observable behavior and neurobiological measures.²² Based on this idea, much recent research has focused on cognitive symptoms in schizophrenia as prognostic indicators and as treatment targets in themselves.²³⁻²⁵ Widely used antipsychotics that control positive symptoms such as hallucinations do not treat and may exacerbate, many of the deficits in working

memory, social cognition, and executive functioning that contribute to the disability associated with schizophrenia.²⁶ Psychotherapeutic and pharmacologic interventions that effectively target these cognitive symptoms could thus contribute to better functional outcomes in patients suffering from other psychotic disorders.

Physical and psychosocial stressors and trauma are frequently encountered in practice as precipitating and perpetuating factors that herald or aggravate patients' suffering. Because of embarrassment and fear of stigmatization, some patients conceal declaring exposure to stressors, or minimize their impact despite their actual significant negative impact. Identification of stress sources requires in-depth inquiry during a psychiatric interview. Response to treatment in such cases will be poor if only drugs are used. Drugs in such instances may temporarily ameliorate symptoms without healing the damage induced by the stressor. In such instances, to ensure a better outcome, psychosocial approaches with/without medications are required.

Other relevant factors that have been reported to be influential in treatment outcomes include socioeconomic status, race, and adverse life events. Since these variables tend to be correlated in many populations, it is difficult to disentangle causes from consequences. Socioeconomic factors had greater predictive power than symptoms or other clinical factors, and profiles combining multiple factors were stronger predictors than individual factors alone.²⁷ Severe events reported during or immediately before treatment predicted poor response in the antidepressant medications condition but not in the psychotherapy conditions. In contrast, non-severe life events experienced before onset predicted superior response to treatment.²⁸ African studies considered a role for race in predicting poor treatment outcome, however, Murphy *et al.* (2013) found a significant portion of the residual disparity is explained by genetic ancestry rather than race.²⁹ One big disadvantage of these kinds of variables is that they are often not considered modifiable risk factors for poor treatment outcomes, so will always have limited clinical utility.

Recent literature on response to a variety of psychotropic treatments has highlighted the importance of "early symptomatic improvement". While the published studies vary in their definition of early response, several have suggested that a reduction in symptoms within the first week of drug exposure strongly predicts response after many weeks of therapy. In patients with unipolar major depression, sensitivities and specificities in the range of 80% have been reported.²⁹ For patients with bipolar depression, specificity is low, i.e., lack of early improvement predicts poor response, but the presence of early improvement is unreliable.³⁰ This finding seems to

hold both for pharmacological and psychotherapeutic (cognitive-behavioral) modalities and has been linked to changes in brain-derived neurotrophic factor (BDNF) in one study.^{31,32} Similar results have been reported for mania, schizophrenia, and ADHD.³³⁻³⁶ These findings may contradict the established view that response to psychiatric treatments cannot be accurately gauged before several weeks. If supported in future studies, this observation could prove to be a valuable clinical predictor of response; patients who fail to show any response within the first week of treatment may benefit from a change.

Poor compliance and imperfect adherence to medications are often overlooked as significant reasons for non-response to treatment and poor outcomes. Although insight of the patient and awareness of his/her mental condition cannot be underestimated, however, the role of the doctor should be emphasized in achieving patients' cooperation and willingness to comply with treatment. One consistent predictor of good treatment compliance is a subjective sense of positive regard for the treating clinician, which emphasizes the importance of the doctor-patient relationship for predicting treatment outcomes.^{37,38} Communication skill plays a major role in supporting the patient to gain greater self-awareness raising awareness, promotion of motivation to treatment, and regard to his/her doctor and appreciation to his/her instruction. Moreover, two studies reported that poor treatment adherence was related to adverse drug events. STAR*D study of outpatients with major depression reported adherence was lowest in those with the highest perceived side-effect burden.³⁹ A similar phenomenon was observed in the CATIE study of outpatients with schizophrenia.⁴⁰ Thus special attention ought to be paid to this issue when drug selection is considered.

Pharmacological determinants

It is noteworthy that in clinical practice prescriptions are often offered without sufficient attention to the pharmacological characteristics of the prescribed drugs. This may result in adverse drug reactions and drug interactions or interactions with certain foods that lead to poor patient compliance and non-adherence to treatment. To ensure better treatment outcomes, more attention needs to be paid to the relevant principles of pharmacokinetics and pharmacodynamics of psychotropic medications.

Pharmacokinetics means what the body does to a drug. It refers to the movement of drugs into, through, and out of the body. It is concerned with the time course of its absorption, bioavailability, distribution, metabolism, and excretion. Drug pharmacokinetics determines the onset, duration, and intensity of a drug's effect. The

pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Some patient-related factors (eg, renal function, genetic makeup, gender, age) can be used to predict the pharmacokinetic parameters in populations. For example, the half-life of some drugs, especially those that require both metabolism and excretion, may be remarkably long in older people.

On the other hand, pharmacodynamics describes what a drug does to the body; it involves receptor binding, post-receptor effects, and chemical interactions. This includes an understanding of drug-protein binding, drug half-life, polymorphic genes, and drug interactions. Also, other factors are important including gender, body size, type and dose of the drug, administration route, other administered drugs, use of psychoactive substances. Moreover, the placebo effect can have a powerful influence. In other words, pharmacodynamics is the study of the biochemical, physiologic, and molecular effects of drugs on the body and involves receptor binding (including receptor sensitivity), post-receptor effects, and chemical reactions.

Pharmacodynamics, with pharmacokinetics, helps explain the relationship between the dose and response, i.e., the drug's effects. The pharmacologic response depends on the drug binding to its target. The concentration of the drug at the receptor site influences the drug's effect. A drug's pharmacodynamics can be affected by physiologic changes due to a disorder or disease, the aging process, and other drugs. Disorders that affect pharmacodynamic responses include genetic mutations, thyrotoxicosis, malnutrition, myasthenia gravis, Parkinson's disease, and some forms of insulin-resistant diabetes mellitus. These disorders can change receptor binding, alter the level of binding proteins, or decrease receptor sensitivity. Aging tends to affect pharmacodynamic responses through alterations in receptor binding or post-receptor response sensitivity). Pharmacodynamic drug-drug interactions result in competition for receptor binding sites or alter the post-receptor response. Understanding these pharmacological characteristics is significant for drug selection and dose determination tailored to the patient need, prescription safety, and improvement in response

Personalized medicine approach

In recent years, a new approach to treatment in medicine in general called “personalized medicine” is rapidly developing and becoming relevant to many medical fields including psychiatry. It refers to the tailoring of medical treatment to the individual characteristics of each patient and the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. It is based on the genetic profile of individual patients. The development of personalized medicine is coupled with the identification of biomarkers and classification algorithms that help predict the responses of different patients to different drugs.⁴¹ The diversity of available drugs today for psychiatric disorders alone shows the difficulty of finding the right treatment for the right patient. The mechanism by which these drugs act is usually not well understood. Each drug carries a long list of side effects, so when an ineffective drug is prescribed, not only is it a waste of time for the patient whose symptoms do not improve but there are also the side effects that act on other systems, sometimes causing long-lasting and irreversible damage. For schizophrenia, for example, there are over 30 suggested drugs, including antipsychotics.^{42,43} While 30% of patients will not respond to the drugs at all, about 30-40% will have a partial response and approximately 30% of the responders will relapse.⁴⁴ For bipolar disorder, lithium is currently considered the first-line treatment, but only 30% of bipolar disorder patients will fully respond to it.^{45,46} For major depression, around 30-50% of patients have a full remission of symptoms with treatment.⁴⁷⁻⁴⁹ The treatments include selective serotonin reuptake inhibitors (SSRIs), which are prescribed first (e.g. Prozac, Sertraline), norepinephrine-dopamine reuptake inhibitors, such as bupropion, and older classes of antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors.⁵⁰ These antidepressants are sometimes combined with mood stabilizers such as lithium and valproic acid.⁵¹ For autism spectrum disorder, drug treatment is used to reduce irritability and aggression. Two drugs have been approved for treatment in children: risperidone and aripiprazole; other drugs include clozapine, haloperidol, and sertraline.⁵² Yet other drugs are used to treat attention deficit hyperactivity disorder (ADHD). In schizophrenia, a large meta-analysis with 65 trials involving 6493 patients showed the superiority of treatment with antipsychotics compared with placebo, and the antipsychotics reduced the relapse rate to less than half and readmission rates to less than half.⁵³

Pharmacogenomic determinants

Pharmacogenomics has evolved from “pharmacogenetics”. Pharmacogenetics refers to the study of how people respond differently to drug therapy based upon their genetic makeup. It refers to how variation in one single gene influences the response to a single drug, while “pharmacogenomics” is a broader term that refers to how all of the genes, “the genome”, can influence response to drugs. Genomics helps to choose the right medication at the right dose for each patient. The sequence of the individuals’ genome can determine how he or she responds to certain medications. Understanding pharmacogenomics, or tailoring a persons’ medications based on their genome, would not be possible without sequencing the genomes of many people and comparing their responses to medicines. The long-term goal of pharmacogenomics is to help doctors select the drug best suited for each person.

Reference to the beginning of the role played by gene variation upon drug response may be found in the writings of the ancient Greek philosopher Pythagoras (510 BC) who noted that ingestion of fava beans resulted in a potentially fatal reaction in some individuals. This was later characterized to be due to deficiency of glucose-6-phosphate dehydrogenase (G6PD).⁵⁴ In 1906, English physiologist Archibald Garrod, author of the publication “Inborn Errors of Metabolism”, was the first to propose that genetic variants might account for varying drug responses.⁵⁵ The first pharmacogenomics study was reported by Snyder in 1932 on phenylthiocarbamide (phenylthiourea), which confirmed that chemicals react differently according to the genetic makeup of an individual.⁵⁶ Carson, *et al.* in 1956 discovered that several soldiers of WW2, who were given the anti-malarial drug “premaquine” developed anemia because they lacked the enzyme (G6PD).⁵⁷ In 1959, Friedrich Vogel coined the term “pharmacogenetics” to describe the genetic-based differences in drug response, and in 1962, Werner Kalow published the first textbook on pharmacogenetics named “Pharmacogenetics - Heredity and the Response to Drugs”.^{58,59} Vesell's twin studies (1968) supported the inference of genetic involvement in drug metabolism, with identical twins sharing remarkable similarities to drug response as compared to fraternal twins.⁶⁰ Authors, Smith of Britain (1975) and Eichelbaum of Germany (1979) and their co-workers, independently discovered that debrisoquine/sparteine polymorphism of drug oxidation.^{61,62} The enzyme involved was named “sparteine/debrisoquine hydroxylase”, now known as “CYP2D6”. On 26th June 2000, the “International Human Genome Sequencing Consortium” announced that it had completed a working draft of the sequence of the human

genome - the genetic blueprint for a human being. In 2003, an accurate and complete human genome sequence was finished two years ahead of schedule and at a cost less than the original estimated budget, and two years later, in 2005, the first FDA approval of a pharmacogenetic test (for alleles in CYP2D6 and CYP2C1) was passed.⁶³

From early findings, the 1950s, uncovering inherited deficiencies in drug metabolism, that explained drug-related adverse events, to nowadays genome-wide approaches assessing genetic variation in multiple genes, pharmacogenomics has come a long way. Despite these advances, the implementation of pharmacogenomics in clinical practice has yet been limited.⁶⁴

Pharmacogenomic testing is a new approach to improving the treatment of mental illness. Pharmacogenomics plays two major roles in medicine. First, it guides pharmaceutical companies in drug discovery and development. Second, it guides physicians in selecting the right drug for patients based on their genetic make-up, in avoiding adverse drug reactions, and in maximizing drug efficacy by prescribing the right dose. Several “pharmacogenomic tests” have been developed in which pharmacokinetic and/or pharmacodynamics genes are evaluated. The field of pharmacogenomic testing has evolved from first-generation testing of single cytochrome P450 genes to second-generation tests of multiple gene-drug interactions, and third-generation combinatorial tests weighting and counterbalancing the gene-drug interactions for multiple genetic variants. In the United States, “combinatorial pharmacogenomic testing to guide depression treatment has been associated with reimbursement savings, reduced polypharmacy and health care utilization, and it is cost-effective in patients with treatment-resistant depression.⁶⁵⁻⁷⁰ The American Psychiatric Association (APA) guidelines for the treatment of major depressive disorder acknowledge individual pharmacodynamic and pharmacodynamic differences among individuals that may necessitate doses higher than those approved by the FDA to achieve therapeutic benefit.⁷¹ Additionally, FDA guidance for new drug approvals further supports the importance of pharmacogenetic testing to reduce adverse drug events and personalize dosing.⁷²

Tanner *et al.* (2019) found that patients who followed the guidance of combinatorial pharmacogenomic testing in taking antidepressants or antipsychotics saved \$1061 Canadian dollars per member per year on total prescription medication costs compared with patients whose medications were not congruent with the test guidance. The same researchers commented that their findings provide indirect evidence of the economic utility of combinatorial pharmacogenomic testing to guide the pharmacological treatment of psychiatric disorders in the

Canadian healthcare system.⁷³ Moreover, two other meta-analyses concluded that evidence supports improved response and remission rates when depression treatment is guided by pharmacogenomic testing compared with treatment as usual.^{74,75}

While an individual/s genetic makeup is important in determining the best treatment for many drugs, it does not explain how all drugs are broken down. There are still medications for which there are no drug-gene tests; the tests only involve some of the many genes in the body. To evaluate the effect of pharmacogenetics-guided treatment on patients diagnosed with depression and/or anxiety in a diverse set of clinical settings, as compared to the standard of care, Bradely *et al.* (2018), implemented the NeuroIDgenetix® test on 685 patients from clinical providers specializing in psychiatry, internal medicine, obstetrics and gynecology, and family medicine. The trial design followed a prospective, randomized, subject- and rater-blinded approach. They used a genetic variant panel of ten genes for over 40 medications used in the treatment of depression and anxiety. In patients diagnosed with depression, response rates and remission rates were significantly higher in the pharmacogenetics-guided group as compared to the control group at 12 weeks. Besides, patients in the experimental group diagnosed with anxiety showed a meaningful improvement in the Hamilton Anxiety Rating Scale (HAM-A\) scores at both 8 and 12 weeks, along with higher response rates. They concluded that pharmacogenetic-guided medication selection significantly improves outcomes for patients diagnosed with depression or anxiety, in a variety of healthcare settings.⁷⁶

Pharmacogenomic testing in psychiatric practice initially focused on identifying pharmacokinetic variability that would influence the responses of patients who had atypical genotypes. This variability reflects the capacity of the individual patient to respond to adequate exposure to the drug. Prediction of response is estimated based on the documentation of variations in “target genes” that code for receptors and transporters that influence the response of the patient to a particular medication.⁷⁷ Many genes code for enzymes that influence drug response. CYP2D6 was the first drug-metabolizing enzyme gene that was genotyped to identify psychiatric patients with increased or decreased metabolic capacity. It is located on chromosome 22 and consists of 4382 nucleotides. Patients who are poor metabolizers are at increased risk for adverse events when they are prescribed, because of their low metabolic capacity. Individuals are considered poor metabolizers if they have two inactive alleles, or one inactive allele and one deficient allele. They are at increased risk of adverse drug effects when prescribed 2D6 substrate medications. The second group of individuals is the ultrarapid metabolizers; they have either

three or more active copies of CYP2D6 or two or more enhanced copies of CYP2D6. This group is unlikely to respond to 2D6 substrate medications at standard doses. A third group is the intermediate metabolizers who have one normal copy of CYP2D6, and one copy that is either deficient or inactive. They benefit from 2D6 substrate medications at low-to-moderate doses, but they are at increased risk for the development of side effects at higher doses. When intermediate metabolizers are exposed to powerful 2D6 inhibitors such as paroxetine or fluoxetine, their metabolic capacity can be further decreased to the level of a poor metabolizer.⁷⁷ The 2D6 enzyme: primarily metabolizes five antidepressants (fluoxetine, paroxetine, venlafaxine, desipramine, and nortriptyline), substantially metabolizes amitriptyline, imipramine, doxepin, duloxetine, trazodone, and mirtazapine, primarily metabolizes risperidone and four of the typical antipsychotic medications (chlorpromazine, thioridazine, perphenazine, and haloperidol), has substantial involvement in the metabolism of aripiprazole and olanzapine, and primarily metabolizes atomoxetine and dextroamphetamine.⁷⁷

An example of the psychotropic genomic tests is the “GeneSight Psychotropic Test”. GeneSight Psychotropic is a multi-gene, multivariant genetic test that combines genotype (a person's genetic profile), phenotype (a person's physical characteristics), and drug metabolism information in an algorithm to categorize included medications for each patient using a system of green, yellow, and red bins.^{78,79} “Green” medications are supported for use as usual, “yellow” for use with caution, and “red” for use with increased caution and more frequent monitoring by the prescribing clinician. Eight genes were included in the version of the GeneSight Psychotropic test. Of these, six were pharmacokinetic - members of the cytochrome P450 family of liver enzymes,

which play an important role in overall drug metabolism. The other two were pharmacodynamic - associated with the serotonergic transporter and receptor genes, where variations can affect the mechanism of action of SSRIs.^{78,79} The test is noninvasive and easy to administer; it requires only a cheek swab to collect a sample of a person's DNA and the results can be obtained within 36 hours.

Besides the pharmacogenomic testing that has already been described, currently, other approaches to improve response prediction are being researched. Of these, measures of gene expression, neuroimaging measures, circulating inflammatory factors, electroencephalographic measures, and metabolomics and proteomics.⁸⁰⁻⁸⁷ Proteomics goes beyond measures of individual proteins to assess widespread patterns of protein expression.^{88,89} A new technology called the “induced pluripotent stem cells (iPSc)” methodology has been developed that is hoped to build cellular models of mental illness that exhibit defects in neuronal development and brain in living patients.⁹⁰ Most of these approaches are severely limited by the inaccessibility of the living brain.

Last, but not least, in connection with the role of pharmacogenomics in response prediction, it might be interesting to mention the role of family history. The Family gives a practical example of the interaction between environmental and genetic factors.^{91,92} While everyone in a family is genetically distinct, relatives share substantial fractions of rare and common genetic variation in the context of shared environment and life experiences. Do *et al.* (2012) and Wilson *et al.* (2009) considered family history as a much better predictor of common health and treatment outcomes than any available genetic tests.^{93,94} Family history, for instance, was found to be the best predictor of response to lithium in bipolar disorder.⁹⁵

Conclusion

The negative impact of mental disorders on health and the economy calls for effective therapeutic measures. During the last seven decades, a large number of pharmacological agents and non-pharmacological approaches have been introduced as treatment measures in psychiatry, but in many disorders, and the best situations, the response rates are unsatisfactory, or adverse drug effects resulted in poor

compliance and adherence to treatment. Thus, to improve treatment response, plans for treatment ought to be based upon clinical, psychosocial, pharmacological, and pharmacogenomic treatment response predictors. Moreover, personalized medicine is a new convenient approach to achieve the objective of optimal treatment response.

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المخلص

في الممارسة السريرية غالباً ما يواجه الأطباء النفسيون والأطباء الآخرون تحدي عدم استجابة الاضطراب النفسي للعلاج. ويعززون ذلك الى سمة متأصلة في المرض. وقد يكون ذلك في بعض الحالات صحيحاً الى حد ما ولكن لا يمكن تعميمه. أن معظم الاضطرابات النفسية غير المستجيبة للعلاج تستوجب اعادة تقييم شامل لمعرفة مبررات عدم الاستجابة للعلاج. ينظر الى العقاقير النفسية على انها مؤثرة علاجياً إذا ما تم استخدامها بالاستناد الى الدليل العلمي. وتستوجب الاستجابة العلاجية الفضلى الى تشخيص صحيح وتقييم سريري شامل واستبعاد لوجود اضطراب اخر مواكب والى استخدام وسائل الاتصال الملائمة وبناء علاقة علاجية مع المريض تؤمن تعاون المريض والتزامه بتناول العقار وتحري الضغوط التي يتعرض لها والاختيار السليم للعقار ومعرفة خصائصه الدوائية. وفي حالات عديدة توجد حاجة لدعم الدواء بوسائل علاجية غير دوائية. وشهدت العقود الأخيرة نماء المعرفة بعلم العقاقير الجيني (الفارماكوجينوميك) للتمييز بالاستجابة العلاجية وكوسيلة لتحسين مخرجات العلاج الدوائي والارتقاء باختيار العقار الأفضل.

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Recall Bias in Trauma Recollection

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تحيز استرجاع ذكري الصدمات

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Abstract

Introduction: Published studies assessing recall of traumatic memories were reviewed to understand the changes and the factors affecting recall. **Objectives:** The current review examined the nature, evolution, causes, and factors that contribute to traumatic memory inconsistencies, also referred to as traumatic recall bias, in survivors of natural and man-made disasters. **Methods:** Articles were identified using ScienceDirect, PubMed, Research Gate, Springer Link, and Google Scholar. These were assessed for eligibility, filtered, and presented in a table. **Results:** In total, 19 out of 109 studies were selected. The studies assessed veterans, witnesses of the World Trade Center attack, witnesses of natural disaster, witnesses of a school shooting, motor accident survivors, and participants in an experimental study. Prominent findings associated with traumatic recall bias were media coverage, psychopathology, increase in PTSD symptoms, and possible cognitive distortions (memory deletion, memory creation) as a result of trauma. **Conclusions:** Multiple common factors may affect trauma recollection. Further research is needed to uncover other factors associated with memory deletion, false memories, and memory inconsistencies. A prospective longitudinal study, designed specifically for that purpose, may better follow the evolution of traumatic memory recollection in survivors immediately after an event and in the years following. This may include tools to assess participants' changes in recall by inquiring about the reasons for their altered responses.

Keywords: Traumatic memory, test-retest, disaster, recall bias; trauma exposure “false memories and trauma”, “changes in trauma memory”, “flashbulb memory/event memory”, “memory and trauma narrative”, “nature of traumatic memory”, “traumatic memories”, “traumatic memory inconsistencies”, “trauma recollection”

Declaration of interest: None

Introduction

Researchers have been studying the inconsistencies in traumatic memory recollection for decades, in the most exposed populations like veterans, restoration workers, and witnesses to traumatic events.¹⁻⁶ In the current review we examined an emerging area of research around inconsistencies in memories of trauma.

We examined published studies to learn more about the methods used to assess traumatic memories, which also shed light on reasons for inconsistencies in memory recollection. Most importantly, we aimed at understanding the changes in recollection, factors affecting recall bias, and the nature of traumatic memories.

Methods

Protocol for present review: First, we identified the research question “What are the factors associated with inconsistent recollection of trauma?”. Second, we identified and selected the relevant studies. Third, we summarized the results and methods. Finally, we discussed the findings, the limitations, and suggestions for future research.

Study selection: ScienceDirect, PubMed, Research Gate, Springer Link, and Google Scholar were used to gather the

English language articles published between 1993 and 2020 which fit the objective of this review. The keywords used for recall of exposure were “false memories and trauma”, “changes in trauma memory”, “flashbulb memory/event memory”, “memory and trauma narrative”, “nature of traumatic memory”, “traumatic memories”, “traumatic memory inconsistencies”, “trauma recollection”, and “trauma recall bias”. The collected studies took place in the USA, the Netherlands, Australia, the UK, Germany, Canada, and Norway.

Table 1.

Authors (Year), Location	Title	Methods	Results
Schwarz <i>et al.</i> (1993), USA	Malignant memories: post-traumatic changes in memory in adults after a school shooting.	Self-reported proximity to the site, perceived life threat, and sensations during the traumatic event, at 6 months (Time 1) and 18 months (Time 2) after the shooting.	At 18 months, increase in perceived proximity to the event and life threat were associated with the presence of PTSD, while decrease in perceived proximity and life threat were correlated with an improvement in anxiety and depressive symptoms.
Southwick <i>et al.</i> (1997), USA	Consistency of memory for combat-related traumatic events in veterans of Operation Desert Storm.	19-item trauma questionnaire at stage 1, a month after their return from the war, and at stage two, after 2 years.	Amplification of trauma recollection increases with the worsening of PTSD symptoms.
Roemer <i>et al.</i> (1998), USA	Increases in retrospective accounts of war-zone exposure over time: The role of PTSD symptom severity	7-item subscale (extracted from the Combat Exposure Scale) measuring exposure and PTSD first-year post-deployment (Time 1), and again after 1 to 3 years (Time 2).	Higher frequency of report of exposure at follow-up than at post-deployment assessment.
Harvey and Bryant (2001), Australia	Reconstructing trauma memories: A prospective study of “Amnesic” trauma survivors.	Time 1: Acute Stress Disorder Interview, Injury Severity Score, and questions about the accident. Time 2: same questions to assess the memory of the accident and a PTSD severity measure.	20 of the 50 participants recalled the accident at Time 2, even after displaying traumatic amnesia at Time 1.
Bramsen <i>et al.</i> (2001), The Netherlands	Consistency of self-reports of traumatic events in a population of Dutch peacekeepers: Reason for optimism?	16-item checklist examining exposure to stressful events, 3 years (Time 1) and 4 years (Time 2) post-deployment.	No changes were seen in the number of reported events.
Krinsley <i>et al.</i> (2003), USA	Consistency of retrospective reporting about exposure to traumatic events.	ELS-Q and ELS-I with a 2 to 7 days test-retest interval.	Adults recall recent personal experiences (events experienced by the participants themselves) more accurately than recent events that they witnessed, but recalled witnessed events during childhood more accurately than personal experiences
Wessely <i>et al.</i> (2003), UK	Stability of recall of military hazards over time.	A questionnaire that measured medical health, exposure to military hazards, and post-traumatic stress reaction.	More exposures were reported at follow-up.
Hardt and Rutter (2004), Germany	Validity of adult retrospective reports of adverse childhood experiences: review of the evidence.	Internet and hand search (1980 to 2001).	People with good functioning in adult life tend to forget early parental negativity.
Schmier <i>et al.</i> (2004), USA	Patient recall and recall bias of health status.	MEDLINE search.	Past health status may be recalled as worse or better than it really was.

Kenny and Bryant (2007), Australia	Keeping memories at an arm's length: Vantage point of trauma memories.	IES-Avoidance subscale, interview about traumatic, positive, and neutral memories.	Subjects with a high level of avoidance remembered the event from an observer's viewpoint, as opposed to subjects who scored lower on the avoidance subscale.
Giosan et al. (2009), USA	Relation between memory inconsistency for traumatic events following 9/11 and PTSD in disaster restoration workers.	Clinician-Administered PTSD scale and WTC Exposure Questionnaire, Time 1 and a year later at Time 2.	Traumatic memory recollection was amplified with the passage of time and increase in PTSD severity.
Heir et al. (2009), Norway	Longitudinal changes in recalled perceived life threat after a natural disaster.	Questionnaire that examined perceived life-threat severity, exposure, acute stress response, psychopathology, personality dimensions, self-efficacy, and social support.	Passage of time may cause amplification of trauma memories.
Kenny et al. (2009), Australia	Distant Memories: A Prospective Study of Vantage Point of Trauma Memories	Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995), and the Vantage-Point Measure one month (Time 1) and one year (Time 2) after the traumatic event.	Remembering the event from an observer's perspective was linked to more serious PTSD symptoms at Time 1 and Time 2. Patients who changed their vantage point from a field to an observer's viewpoint showed worse PTSD symptoms at Time 2.
Hirst et al. (2009), USA	Long-term memory for the terrorist attack of September 11: Flashbulb memories, event memories, and the factors that influence their retention.	They tested the flashbulb memories of the WTC disaster of 3000 subjects residing in the US, 1 week, 11 months, and 35 months after the attack.	After a year has elapsed, the forgetfulness rate of flashbulb memories and detailed memories of the event decreases
Strange and Takarangi (2012), USA	False memories for missing aspects of traumatic events.	Participants were instructed to evaluate a clip of traumatic events twice, each time focusing on different events.	The most traumatic events were remembered more inconsistently than the non-traumatic events
Hirst et al. (2015), USA	A ten-year follow-up of a study of memory for the attack of September 11, 2001: Flashbulb memories and memories for flashbulb events.	Same measures as Hirst et al. (2009) ten years after the 9/11 attack.	These results show that traumatic memories can stay inconsistent long-term.
Wilker et al. (2015), Germany	How to quantify exposure to traumatic stress? Reliability and predictive validity of measures for cumulative trauma exposure in a post-conflict population.	Multiple trauma measures were examined in a sample of 227 Ugandan rebel war survivors.	Traumatic events that occurred between the ages of 6 y and 13 y were recalled correctly as opposed to events that occurred before the age of 6 y.
Bryant et al. (2016), Australia	Activating attachments reduces memories of traumatic images.	Exposed 67 college students to attachment-related vs non-attachment related images, followed by traumatic and non-traumatic images, and assessed them two days later for intrusive memories.	Attachment representations help regulate the consolidation of emotionally charged memories.

Recall Bias in Trauma Recollection

Silverberg <i>et al.</i> (2016), Canada	The nature and clinical significance of preinjury recall bias following mild traumatic brain Injury.	British Columbia Post-concussion Symptom Inventory. Time 1: 6 weeks Time 2: 12 months	Recall bias was stronger in patients with more symptoms.
Sachscha <i>et al.</i> (2019), UK	Differential effects of poor recall and memory disjointedness on trauma Symptoms.	60 participants were exposed to a 10-minute-long trauma-film, and 30 saw a neutral film, and were assessed the day of the exposure and 7 days later.	All participants experienced an increase in poor memory recall over time.

Data collection and results

1. **Literature search:** Nineteen studies were selected out of the 109 initially identified and will be discussed in this review.
2. **Study characteristics:** The studied populations were veterans, witnesses of the World Trade Center attack, witnesses of natural disaster, witnesses of a school shooting, motor accident survivors, and participants in an experimental study that lasted seven days, with the first assessment immediately after exposure, and the second assessment one week later.
3. **Results:**

3.3.1. Studies examining the World Trade Center attack (9/11):

a. In Giosan *et al.* “participants were evaluated as a part of an annual screening program for WTC disaster restoration workers”. In addition to social desirability bias, the sample was assessed several months after the event, equally affecting the participants’ recollection. Additionally, the WTC exposure questionnaire was not validated at the time and was only designed for the study.³

The authors assessed 2641 World Trade Center attack restoration workers at Time 1 and a year later at Time 2. They used the Clinician-Administered PTSD scale⁷ and the WTC Exposure Questionnaire, which was designed specifically for the study by Giosan *et al.*

Results: The authors found that with time, traumatic event recollection (perceived life threat, seeing human remains, etc.) was amplified. In addition, they found a correlation between endorsement of traumas in the second assessment one year later and increasing severity of post-traumatic stress disorder.

b. Hirst *et al.* collected postal and web-based responses from participants that they recruited using snowball sampling. Hirst and his colleagues sent out surveys that were designed specifically for the study. The surveys took 45 minutes to complete, and only 18% of their sample participated at Time 1, 2 and 3. Considering the time-consuming and self-report nature of the survey, it is only natural that the minority of the sample participate in the follow-up self-assessments. Naturally, this approach affected the sample size, which was also subject to self-reporting bias. Additionally, only 10% of participants had taken part in every assessment at Hirst *et al.* (2015)’s 10-year follow-up.^{8,9}

Results: In 2015, inconsistent flashbulb memories tended to re-occur, while incorrect event memories tended to be corrected.

3.3.2. Studies Examining War

a. Roemer *et al.* studied the frequency of exposure to stressful experiences of 460 US veterans who served in a peacekeeping mission in Somalia. The subjects were assessed for recalled exposure and PTSD in the first-year post-deployment (Time 1) and re-assessed after 1 to 3 years (Time 2).¹⁰ They used the same 7-item subscale which was extracted from the Combat Exposure Scale,¹¹ The Brief Symptom Inventory (BSI; Derogatis, 1993), the Mississippi Scale for Combat-Related PTSD (M-PTSD)¹² and the PTSD Checklist (PCL).^{13,14}

Results: The authors concluded that the subjects reported a higher frequency of exposure at follow-up than at initial post-deployment assessment.

b. Southwick *et al.* recruited 59 US veterans of the Gulf war (Aug 1990 - Feb 1991), of which 51% were from a medical unit. Participants completed a 19-item trauma questionnaire at stage 1, a month after their return from the war, and at stage two, after 2 years. They also used self-report scale, the Desert Storm Questionnaire, which was not validated at the time.¹⁵

Results: The authors concluded that amplification of trauma recollection increases with the aggravation of PTSD symptoms.

c. Bramsen *et al.* studied 137 Dutch United Nations veterans who served in Cambodia (1992-1993) to investigate the generalizability of past research findings. Bramsen *et al.* self-report questionnaires to assess PTSD, anxiety, and depression. The participants completed a 16-item checklist examining exposure to stressful events, 3 years (Time 1) and 4 years (Time 2) post-deployment.¹

Results: Results did not reveal any changes in the number of reported events.

d. Wessely *et al.* conducted a three-year, follow-up study on a sample of 2370 UK military personnel, examining their exposure to military hazards. Initially, the first study was conducted six years after the end of the Gulf war, and five years after the Bosnia deployment. The follow up study was done approximately three years later. The authors used a questionnaire that measured medical health, exposure to military hazards, and posttraumatic stress reaction.¹⁶

Results: The authors found that more exposures were reported at follow-up, and the increase in the number of exposures recalled could point to contemporary distress.

e. Wilker *et al.* studied survivors of the Uganda rebel war, where they experienced sexual violence, kidnappings, forced recruitment of minors, murder, and mutilation. The assessment tools were translated to the local language, noting that access to education in this population was limited. Interviews were done in a one-week test-retest interval, and the study was conducted eight years after the end of the war.¹⁷

Results: Participants' reports of trauma that occurred between the ages of 6 to 13 years were reliable, while recalled exposure before the age of 6 years was "impossible" to assess.

In addition, Wilker *et al.*, suggest that, even in a heavily traumatized community with limited literacy, a complex trauma assessment is possible and produces accurate assessments.¹⁷

3.3.3. Natural disasters

a. Heir *et al.* recruited 532 Norwegian people who witnessed the 2004 South-East Asia tsunami and assessed them six (Time 1) and 24 months (Time 2) after the tragedy. Perceived life-threat severity, exposure, acute stress response, psychopathology, personality dimensions, self-efficacy, and social support were all assessed using the questionnaire. The intensity of perceived life threat reported at Time 2 was found to be higher than it was at Time 1.⁴

Results: The authors suggest that the passage of time may cause amplification of trauma memories. This type of recall bias can put into question the reliability of PTSD diagnosis and could obstruct PTSD treatment. If an individual recalls one aspect of the event or its aftermath in an exaggerated manner, the experience could be falsely labeled as traumatic and easily create a false PTSD diagnosis. Moreover, a minimized recollection of the emotions experienced during or after the event could leave out important PTSD symptoms, and PTSD scales can easily miss those that go unmentioned.

3.3.4. Other man-made disasters

After a school shooting that took place in Chicago Tribune on May 21, 1988,¹⁸ tested 12 school staff for proximity to the site, perceived life threat, and sensations during the traumatic event, at six months (Time 1) and 18 months (Time 2) after the shooting.

Results: At 18 months, increase in perceived proximity to the event and life threat was associated with the presence of PTSD, while decrease in perceived proximity and life

threat was correlated with an improvement in anxiety and depressive symptoms.

3.3.5. Experimental

a. Strange and Takarangi exposed 84 undergraduates to a three-minute clip twice while focusing on the general events the first time and the less obvious events the second time.¹⁹ Then they self-administered the Impact of Event Scale (IES)²⁰ 24 hours later, participants were shown 18 clips of the video along with new clips and asked to identify the new and the old clips.

Results: The participants were more likely to falsely remember the most traumatic clips.

b. Bryant *et al.* exposed 67 college students to attachment-related vs non-attachment related images, followed by traumatic and non-traumatic images, and assessed them two days later for intrusive memories.²

Results: Findings suggest that activating attachment representations helps regulate the consolidation of emotionally charged memories.²

c. Sachschal *et al.* measured the difficulty in memory recollection for 90 participants, of whom 60 were exposed to a 10-minute trauma-film, and 30 saw a neutral film. Participants were assessed the day of the exposure and seven days later.²¹

Results: Both groups experienced an increase in poor memory recall over time.

3.3.6. Individual trauma

a. Harvey and Bryant studied the trauma recollection of 50 motor vehicle accident survivors who were amnesic immediately after the accident, one month and two years after the accident. To assess participants at Time 1, they used the Acute Stress Disorder Interview, Injury Severity Score, and questions about the accident. At Time 2, they used the same questions to assess the memory of the accident, along with a PTSD severity measure. They interviewed their participants at every stage of the study, and no self-report measures were used. Respondent and social desirability bias could have occurred. Additionally, the authors considered the possibility of misdiagnosis of mild traumatic brain injury.²²

Results: The results indicated that 20 of the 50 participants seemed to have recalled the accident at Time 2, although having had traumatic amnesia at Time 1. They wondered whether these patients' recollection of the trauma could have been encouraged by frequent discussions about the accident, photos, and police reports.

b. In another study, Kenny and Bryant used self-report measures and interviewed their participants to assess exposure, depression, anxiety, memories of the event, and vantage point.²³ Kenny, Bryant *et al.*, interviewed 60 patients with posttraumatic stress disorder about their traumatic memories along with positive and neutral memories. Next, the participants were asked to determine the vantage point from which they experienced the trauma, and the vantage point from which they remember their trauma. One of the scales used was the Impact of Events Scale (IES),²⁰ focusing on the IES-Avoidance subscale.

Results: The results showed that participants with a high level of avoidance generally remembered the trauma from an observer's viewpoint, as opposed to participants who scored lower on the avoidance subscale.²³

c. Kenny *et al.* assessed 730 subjects at one month (Time 1) and one year (Time 2) after their traumatic physical injury.²⁴ They used the Clinician-Administered PTSD Scale (CAPS),⁷ and the Vantage-Point Measure which consists of the question "When you think back to what happened to you, do you see the event through your own eyes, or do you see it from an observer's or an onlooker's point of view?".

Results: Remembering the event from an observer's perspective was linked to more serious PTSD symptoms at Time 1 and Time 2. Additionally, participants who changed their vantage point from a field to an observer's viewpoint also showed a worsening of their PTSD at Time 2.

3.3.7. Childhood trauma: According to Krinsley *et al.*, adults recall recent personal experiences more accurately than recent events that they witnessed.²⁵ On the other hand, recollection of witnessed traumatic events during childhood was more consistent than memories of personal experiences of the same nature.

3.3.8. Review: Hardt and Rutter looked for the validity of retrospective recollection of child physical, sexual abuse or neglect in adults. Hardt and Rutter concluded, based on a review of 14 studies, that recall bias could often reflect "a tendency for people with good functioning in adult life to forget early parental negativity".²⁶

3.4 Duration of assessment of memory inconsistencies

In all the reviewed studies, participants were assessed at least twice: one time up to a year after the traumatic event, and a second time after some time has passed, and some studies assessed participants more than twice. Test-retest intervals varied from days, months, to years after the event. However not all participants recruited at Time 1 were assessed again in the later evaluations, which meant that the results were limited to the participants that responded to both Time 2 (and in some cases at Time 3). The assessment tools were diverse, some were administered by interviewers, and some were self-reports. Many of the instruments were standardized, others were designed specifically for the studies in which they were used. It is to be noted here that some measures tested the ability of participants to recall their perceived life threat at the time of the incident, along with what they recalled was their acute emotional reaction, in addition to proximity to the location of the event and while others did not (Table 1).

3.5 Items of assessed exposure

Researchers used Early Life Stress Questionnaire (ELS-Q), Early Life Stress Inventory (ELS-I), World Trade Center Exposure Questionnaire, Acute Stress Disorder Interview, Injury Severity Score, IES-Avoidance subscale, and questionnaires designed by the authors to measure the extent of exposure to traumatic events and the repercussions. The ELS-Q measures the presence and the nature of any traumatic event that the respondent has survived. Whereas the ELS-I examines specific elements of the traumatic events, as well as emotions associated with it such as fear, and defenselessness.²⁵ The WTC questionnaire included questions about "witnessing people jumping from the towers; saw human remains ("bodies, body bags, or body parts"); concerned (during the attacks) about someone who was at the WTC; knew someone injured in the attack; knew someone killed in the attack; attended funerals or memorial services; assisted people affected by the attack, displaced from residence, had to be evacuated for safety while working at the site; perceived life danger while working at the site; and being disturbed by the smell while working at the site".³

Limitations

This review has multiple limitations, including the relatively uncommon research on traumatic memory recollection, and some methodological limitations in some but not all studies we recovered such as: small sample size,¹⁸ non-validated assessment tools, short test-retest

intervals,²¹ social-desirability bias, and the potential issues with self-report questionnaires and scales.

For instance, Giosan *et al.* had a study that was mainly correlational, so a clear direction of causality could not be pinpointed. Second, because of the unprecedented nature

of the index trauma (WTC attack), exposure to potentially traumatizing events was assessed with an instrument created for the study rather than an existing instrument with known psychometric properties.³ Third, the sample was assessed several months to one year after initial exposure for Time 1, and a year later at Time 2, which could have been too late to draw any conclusions.

In the study by Roemer *et al.*, participants self-reported at Time 1 but were interviewed by phone at follow-up. This inconsistency might have affected the estimations of the participants in the different assessments.¹⁰ For instance, self-report bias and respondent bias manifest differently from face-to-face interviews, which can result in social desirability bias where participants answer in ways that either accentuate or undermine their true recalled experience. Also, participants could have understood the same question in the self-report questionnaire and during direct interview differently, making it harder to compare answers between the first and the second assessments.

Wilker *et al.*, who studied the validity of trauma assessment measures on a highly traumatized population, conducted the second assessment on their participants only one week after the initial assessment, which is a relatively short interval and thus makes it difficult to generalize to longer inter assessment studies.¹⁷

Some limitations to Heir *et al.* reside in the composition of their sample: the low response rate in the study was explained by the fact that a lot of participants were not directly exposed to the tsunami.⁴ Furthermore, their conclusions are not inclusive of people with chronic stressors, and the assessment method for the perceived life threat was minimal with only one item. Also, disaster exposures as well as immediate stress response data were ascertained retrospectively six months post-disaster.

Discussion

In the current review, common themes in the relevant articles for changes in recall included: media coverage, psychopathology, memory amplification due to increase in PTSD symptoms, and possible cognitive distortions because of trauma. We found that some studies had more robust findings. Hence, in this discussion we expand on the most intriguing/unusual findings and elaborate on the implications for future research.

Hirst *et al.* examined memories for the events of the 9/11 attack in New York and demonstrated initial forgetting, especially of non-critical details in the first year.⁹ However, external influences, such as the films *Fahrenheit 9/11* and *United 93*, might have led to corrections.

Schwarz *et al.* identified many limitations that influenced their results. Their sample was small and consisted of women instructors only, in their study about the school shooting. The first assessment was done six months after the event.¹⁸

Findings from Sachschal *et al.* may be interpreted with caution since participants were exposed to traumatic and neutral films. Similarities between film-based disaster and real-life disaster are unclear. Also, the trauma films were relatively mediocre and without context or complex elements.²¹

Strange and Takarangi attributed their results to a variety of biases, most importantly people's general tendency to report remembering very graphic, dramatic events.¹⁹ Additionally, it could be participants rehearsed the clips during the test-retest interval which was 24 hours. Either way, the results of the study could be either due to multiple factors, or impossible to attribute to valid and certain factors. This highlights the importance of control for confounding variables in future studies. Moreover, Harvey and Bryant disclosed the presence of social desirability bias due to the nature of the data collection method and interviewing.²²

Finally, Hardt and Rutter found that false negative experiences were reported more often than false positive memories. However, inconsistent recollection of major traumatic experiences cannot be explained solely by recall bias. For instance, suggestion, reconstruction, cognitive bias and the presence or history of depression can either exaggerate or undermine the reports given by participants.²⁶

The researchers highlighted the rapid forgetting of both flashbulb and event memories within the first year, but the forgetting curves leveled off after that, not significantly changing even after a 10-year delay. Five putative factors affecting flashbulb memory consistency and event memory accuracy were examined: (a) attention to media, (b) the amount of discussion, (c) residency, (d) personal loss and/or inconvenience, and (e) emotional intensity. After 10 years, none of these factors predicted flashbulb memory consistency. However, media attention and ensuing conversation predicted event memory accuracy. Of course, external influences can do more than correct erroneous memories. They can also do the reverse: create erroneous memories. The researchers emphasized the

need to look at the interaction between cognitive processes and social influences in future studies.

Heir *et al.* examined the aftermath of the 2004 tsunami in southeast Asia.⁴ Their study looked at recall amplification to examine whether recalled threat intensity changes over time during the aftermath of a large disaster in a novel community sample that was exposed to a single, well-defined stressor. Compared with a baseline six-month assessment, they found a greater intensity of recalled perceived life threat at two-year follow-up, which suggests that memories for stressful events are amplified as time passes. Their findings support other notions about the inaccuracy of recall for stressful events. To understand why the recall of threat intensity increased over time in their sample, they examined the possible influence of disaster-related variables such as magnitude of exposure, immediate stress response and PTSD symptoms, as well as the possible influence of intra-individual variables such as age, gender, socioeconomic status, depression and other psychopathology, personality dimensions, self-efficacy and social support.

In conclusion, their findings suggest that recall amplification of perceived life threat occurs in the general population when exposed to a distinct stressful event. This phenomenon raises potentially critical questions about the diagnostic validity of PTSD as currently defined by the ICD-10 and the DSM-5. Furthermore, recall amplification of perceived life threat appears to correlate with the PTSD healing process in important, possibly harmful ways (PTSD symptoms developing over time). Additional stressful event recall research should widen the time horizon and frequency of assessments and examine the influence of other types of stress exposure as well as moderators and mediators of recall amplification.⁴

Also, it is possible that recall amplification resulted from distorted cognitive processing because of the presence of other psychopathology. However, dimensions of psychological functioning such as anxiety, depression, and personality traits (e.g. neuroticism) were not related to changes in recalled threat. This is especially noteworthy with depression, where recall is said to usually emphasize negative events.

In another approach Southwick *et al.* concluded that possible reasons for change in recall involved several possible explanations for changes from “no” to “yes” responses.¹⁵

1. First, material that had been forgotten, denied, suppressed, or repressed at one month may have become conscious by two years.
2. Second, memories may have become exaggerated after exposure to media coverage, after conversations with other traumatized

reservists, or after multiple narrations of the same events.

3. Third, it is possible that individuals with intrusive memories, nightmares, and flashbacks gradually recalled traumatic memories as a result of their involuntary re-experiencing of symptoms.
4. Fourth, it may be that individuals who became increasingly symptomatic over time unknowingly exaggerated their memory for traumatic events as a way to comprehend or make sense of their emerging psychopathology.

As a result, the study raised questions about the accuracy of recall for traumatic events, as well as about the well-established but retrospectively determined relationship between level of exposure to trauma and degree of PTSD symptoms.

Interestingly, Giosan *et al.* studied the relationships between memory inconsistency for traumatic events following 9/11 and PTSD in disaster restoration workers.³

The results of the study suggest that a memory amplification effect occurs in civilian as well as veteran samples, and that it can be associated with single incident trauma as well as combat exposure. Moreover, the collected findings suggested that reports of trauma exposure appear to be most consistently related to concurrent re-experiencing symptoms, which calls into question the directionality of the association between PTSD symptoms and the intensity of exposure and emotional responses.

Furthermore, the effects of ongoing media coverage on the sample’s change in endorsements was unknown and would have required ideally more experimental control of exposure to reminders of the traumatic event to be fully understood.

The study creatively envisioned a new way of elucidating the reasons for the discrepancies over time, which may support future research e.g., it could examine data from the different time points and to ask participants their opinions on why the reports changed; for example, forgetting, changing personal criteria/definitions of what counts as being disturbed by the smell.

Strange and Takarangi examined the way people fill in memory lapses. Participants were most likely to falsely remember the most salient (most important clips), the parts of the film that also happen to be reliably more traumatic than the non-cruxes.¹⁹ The study did not include a non-emotional comparison event, which meant direct comparisons were not possible; however, the study questioned why the pattern of errors differed for an emotionally negative event. One explanation suggests that

participants concentrated on the more negative material because they were more likely to rehearse such material - whether intentionally or unintentionally - during the delay period; that is, those negative details persist or intrude in memory.

Hence, delay seemed to be impactful. Perhaps, if the delay period were longer, intrusions would have more opportunity to become familiar leading to more source monitoring errors and greater memory distortion. This calls for further examination of this phenomenon in the future. At present, however, the exact mechanism underlying people's errors is unclear. There are at least two possibilities, both of which draw on aspects of the Source Monitoring Framework.²⁷ While the result (memory distortion) is the same in each case, one possibility begins with unintentional recall (intrusions), the other with intentional recall.¹⁹

Both intentional and unintentional recall can be compromised in people suffering from PTSD.²⁸ The first possibility is that participants mistook the intrusive thoughts they experienced, for genuine memory traces. While their data offer some preliminary evidence that intrusive thoughts might be important, they couldn't find out whether the content of those thoughts were experienced by participants as genuine memory traces.

Asking participants to keep a diary of their intrusive thoughts during the delay period could help to uncover whether there is a relationship between the intrusive thoughts people experience and their later memory distortion. On the other hand, it may be that participants engaged in a more intentional rehearsal process during the delay period. For example, perhaps participants recognized that there were gaps in the film and generated content to fill those gaps. This study is particularly important because it lays the groundwork for future studies that can examine the nature of recall.

Suggestions for Future Research

Future research could address the issue of conflating alteration in features of a single traumatic event versus endorsing (or failing to endorse) exposure to an entirely new event. These might be different kinds of memory problems, in that getting a detail wrong about a single event may differ from creating a false memory of the entire event.¹⁹

Future prospective longitudinal studies that can assess trauma survivors more immediately after exposure, as well as the development of externally valid laboratory analogues to study trauma memories could help to increase our understanding of the relationship between trauma exposure, recollections of trauma memories, and PTSD.³

In addition, more longitudinal studies can help us uncover these questions of interest by examining subjects over several years and using mental health professionals to assess them with validated assessment tools and interview methods. Longitudinal studies might make possible to predict risk factors, personality traits, and environments that reinforce recall bias and memory inconsistencies in traumatized populations. Both collective and individual

trauma survivors must be studied together but also separately because results concerning different types of trauma in different age ranges and nationalities might not be generalizable.

Future studies could focus on looking at factors which create new memories, factors which delete memories and factors which seem to maintain original memory. This approach will aid in uncovering more knowledge around the nature of recall and memories and its unique interactions with external factors, such as trauma, psychopathology, injuries, and other confounding variables.

Finally, future researchers might want to refine their sampling techniques to maximize sample size and representativeness, use standardized assessment tools, and control for respondent bias, to identify more clearly the factors that may influence traumatic recall bias. One example is creating standardized tools to examine changes in recall by asking participants about their altered responses.

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المخلص

مقدمة: لقد تمت مراجعة الدراسات المنشورة لتقييم الذكريات الصادمة لفهم التغييرات والعوامل التي تؤثر عليها بشكل أفضل. **الأهداف:** تهدف هذه المقالة إلى دراسة الطبيعة والتطور والأسباب والعوامل التي تساهم في تناقضات الذاكرة الصدمة والتي يشار إليها أيضًا باسم تحيز الاسترجاع الصادم لدى الناجين من الكوارث الطبيعية والكوارث التي هي من صنع الإنسان. **الطريقة:** تم جمع المقالات باستخدام ScienceDirect و PubMed و Research Gate و Springer Link و Google Scholar، وتم تقييمها من حيث الأهلية وتصفيحتها وتقديمها في جدول. **النتائج:** تم اختبار تسعة عشر دراسة من أصل مائة وتسعة دراسات، هذه المنشورات درست قدامى المحاربين، وشهود على هجوم مركز التجارة العالمي، وشهود الكوارث الطبيعية، وشهود إطلاق النار على مدرسة، والناجين من حوادث السيارات، والمشاركين في دراسة تجريبية. كانت المفاهيم البارزة المرتبطة بتحيز استدعاء الصدمة هي التغطية الإعلامية، وعلم الأمراض النفسية، وزيادة أعراض اضطراب ما بعد الصدمة، والتشوهات المعرفية المحتملة (حذف الذاكرة، إنشاء الذاكرة) نتيجة للصدمة. **الاستنتاجات:** تم العثور على العديد من العوامل المشتركة التي قد تؤثر على تذكر الصدمة. هناك حاجة إلى مزيد من البحث للكشف عن العوامل الأخرى المرتبطة بحذف الذاكرة والذكريات الخاطئة وعدم تناسق الذاكرة. بالإضافة إلى ذلك، يمكن دراسة طويلة مستقبلية مصممة خصيصًا لهذا الغرض، أن تتابع بشكل أفضل تطور تذكر الذاكرة الصادمة لدى الناجين فور وقوع الحدث وخلال السنوات التالية. قد يشمل ذلك الأدوات التي تتضمن فحص تغييرات المشاركين في الاستدعاء من خلال الاستفسار عن أسباب استجاباتهم المعدلة.

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Making Sense of Adult Attention Deficit Hyperactivity Disorder (A-ADHD)

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مراجعة منطقية لاضطراب عجز الانتباه فرط الحركة في البالغين

سداد جواد التميمي ونهلة فوزي جميل

Abstract

Adult ADHD (A-ADHD) is a relatively new diagnostic category in general adult psychiatry. Many psychiatrists do not accept the diagnosis and its treatment, which is primarily with psychostimulant medication. Assessment, diagnosis, and treatment of A-ADHD need a specialized service for a proper delivery by an experienced team. There are comorbid psychiatric disorders associated with A-ADHD that may influence its course and management. The disorder could be modelled as a neuropsychological or a neurobiological disorder. Psychostimulant medications are the first line treatment and require careful monitoring.

Keywords: Adult-ADHD, psychostimulants.

Declaration of interest: None

Introduction

Adult Attention Deficit and Hyperactivity Disorder (A-ADHD) is a relatively new diagnostic category in general adult psychiatry introduced with the publication of The Diagnostic and Statistical Manual Fifth Edition (DSM-5).¹ Prior to the publication of DSM-5, ADHD was considered a childhood psychiatric disorder that was not relevant to adults. ICD-10 does not formally recognize A-ADHD, but it is expected that ICD-11 will include it as a formal diagnostic category when it is published in 2022. Despite the introduction of A-ADHD, many psychiatrists and workers in adult mental health remain cautious as to its relevance to adult psychiatry and are of the opinion that it is another download diagnosis through which individuals seek to obtain psychostimulant medication to enhance their performance in school and work. The fact that psychostimulant medications are the mainstay of treatment deters many psychiatrists from getting involved in its diagnosis and treatment. Added to the latter dilemma is the high frequency of co-morbid psychiatric disorders that may well explain the patient's clinical presentation rather than A-ADHD. This review attempts to discuss controversial issues related to this new, but not a universally accepted or welcome addition to the list of mental disorders. The debate about the validity of the concept was widely publicized in the British Medical Journal in 2010 and

reflected considerable anxiety that still exists about the concept in adults, and the role of the pharmaceutical industry in promoting it.²

The first reference to symptoms of ADHD was presented by George Still (1902)³ to the Royal College of Physicians when he described 43 children suffering from attention difficulties and dyscontrol of their moral behavior. His clients were also hyperactive, defiant, and showing little inhibitory control of their behavior. He also mentioned the chronicity of the disorder and concluded that their problem was the result of a defect in moral control. The equivalent concept in children and adults was well known in late 1960s as minimal brain damage or dysfunction (MBD)⁴ believed to be caused by organic factors or brain damage. An influential paper in 1973 by Anneliese Pontius⁵ proposed that many adults with hyperactive and impulsive behavior suffer from frontal lobe and caudate dysfunction. Another study in 1975 suggested that a disorder referred to as Episodic Dyscontrol Syndrome⁶ might well represent the adult outcome of the hyperactive child syndrome. However, the first clear reference to the possibility of ADHD in adults is credited to Wender,⁷ who developed an approach for the diagnosis of the disorder in adults and the Wender Uta Rating Scale (WURS) in 1990s. It was with publication of the DSM-5 that the concept of A-ADHD became a recognized clinical entity.

The three arms for the diagnosis of ADHD are attention deficit, hyperactivity, and impulsivity. Traditionally it was assumed to be a childhood mental disorder with gradual improvement of the first two arms with maturity, but it was also generally accepted that impulsivity might persist into adulthood, and the individual might simply be considered more impulsive or impatient, but not necessarily suffering from a

mental disorder requiring professional mental health input. The issue of impatience of human beings is well illustrated by Tokugawa Ieyasu (1543-1616)⁸ who stated that there are seven emotions: joy, anger, love, grief, anxiety, fear and hate; and if a man does not give way to these, he can be called patient, and he practiced patience all his life.

Adult ADHD in general adult psychiatry

There are three groups of patients in clinical practice, and more specifically in specialized clinics established to deal with assessment and management of A-ADHD. The first group are adults diagnosed by Child Adolescent Mental Health Services (CAMHS), and their care transferred to Adult Services at the age of 18 years. Most if not all the members of the group are treated with psychostimulant medication. The second group are the Self- Referred Group who suspect that they suffer from ADHD because of poor concentration which led to poor academic or occupational achievement. The latter group are self-diagnosed through internet consultation, with some demanding to obtain psychostimulant medication, would refuse alternative diagnosis, and migrating from one psychiatrist to another until their demands are met. The third group of patients referred to as the Suspected Adult, who are a minority, often suspected of the diagnosis by a clinician or a mental health worker because of behavioral difficulties and mental health problems that are challenging and relatively resistant to interventions.

ADHD in adults and in children refers primarily to impairment of functioning,¹ which could be educational, social, or occupational. As a result, the presence of symptoms per se without significant impairment in functioning does not lead to its diagnosis. Furthermore, the impairment in functioning might well be the result of another disorder such as traumatic brain injury, attachment disorder or substance use disorder, rather than symptoms of ADHD.

The diagnosis of ADHD, according to the DSM-5, is based on the presence of at least six inattentive or hyperactive-impulsive symptoms before the age of 12 years, and for a period of at least six months in two or more settings. For older adults it requires at least five

symptoms and evidence that symptoms interfere with or reduce the quality of social, academic, or occupational functioning.¹ These requirements are not easily met in clinical setting, and the account obtained from the patient is often subjective and cognitively biased. The difficulties in history taking, and the demands for psychostimulant medication might explain why some psychiatrists decline referrals for Adult ADHD and dismiss the concept.

The prevalence⁹ of ADHD in children is estimated to be 6-8%, but there is a wide variation in the prevalence across the globe with the highest reported in the United States, which in turn reflects the heterogeneity of the concept and threshold for clinical diagnosis.¹⁰ It is generally accepted that the disorder in adults could not be made without a history of onset in childhood. It is often associated with being male, white, unemployed, and previously married.⁹ ADHD is a neurodevelopmental disorder which is likely to persist into adulthood with variable severity, but the diagnosis could only be made if there is a significant impairment of functioning. The generally accepted opinion now is that ADHD symptoms might persist into adulthood with or without impairment of functioning, and as a result its prevalence rate in adults is lower - estimated to be 4%.

Adult-onset ADHD¹¹ has been described in some studies with no prior history of onset in childhood. The latter view is not universally accepted, and onset in childhood could have been missed due to mild symptoms, or the ADHD symptoms are the result of a sleep disorder or other chronic health condition. It is not unusual in ADHD clinics for patients in their fifth- and sixth decade demanding assessment and diagnosis of ADHD which in their opinion might explain their past difficulties and poor functional performance.

Diagnosis of A-ADHD

The diagnosis of ADHD in children and adolescents is far less problematic than the diagnosis in adults. A-ADHD requires the presence of five or more symptoms of inattentiveness, or five or more symptoms of hyperactivity and impulsiveness, but the onset of symptoms must be present from childhood. The verification of onset of symptoms in childhood is difficult and might require interviewing the parents and/or reviewing school records. However, the third group of patients (suspected adults) who might well suffer from A-ADHD but do not seek the psychiatric help for the disorder, their diagnosis is even more challenging than other groups, because they have difficulties with self-reflection and recall of symptoms and may not readily accept the diagnosis and treatment.

The core symptoms¹² observed in people referred for ADHD assessment are:

- 1 Inattentiveness
- 2 Hyperactivity
- 3 Labile mood
- 4 Irritability
- 5 Hot temper
- 6 Impaired stress intolerance
- 7 Disorganization
- 8 Impulsiveness

The list of symptoms above requires careful history and mental state examination and could well be explained by other psychiatric disorders, including

bipolar disorder, personality disorder, and obsessive-compulsive disorder. The most contentious issue facing the assessing team is substance use disorder. It is often the opinion of some patients that their ADHD is the cause of their substance use while the treating psychiatrist may be cautious in prescribing psychostimulant medication that might exacerbate their symptoms and is potentially contraindicated.

The assessment of ADHD in a specialist clinic should include a proper structured interview which assesses the presence of symptoms, determine their chronicity, and the resulting functional impairment. The diagnostic interview for ADHD in adults¹³ covers DSM-5 criteria and referred to as DIVA-5.

Rating scales are often used in ADHD assessment, but are neither a substitute for careful clinical assessment nor diagnostic per se. In most cases they are designed to assess the severity and frequency of symptoms and their impact on social, academic, and occupational functioning. Most commonly used rating scale¹⁴ is Conners' Adult ADHD Rating Scales (CAARS) which exists in short and long forms for self-report and observer's report. The CAARS factor-derived subscales cover inattention/memory problems, hyperactivity/restlessness, impulsivity, emotional lability, and problems with self-concept. It provides an ADHD index and inconsistency index and can be easily administered.

Depression, anxiety, and substance use disorders are more likely to be detected in people suffering from A-ADHD. However, there is no evidence to support any association with bipolar disorder or obsessive-compulsive disorder.¹⁵

The psychobiological model of ADHD

It is essential to have a clear concept of ADHD as a clinical entity that could be communicated to the patients who often ask about the cause of their disorder. Family history of ADHD is not difficult to obtain, and twin studies suggest a heritability of about 70%.¹⁶

A-ADHD could be conceptualized¹⁷ as a neuropsychological disorder characterized by symptoms of inattention, hyperactivity, and/or impulsivity. Symptoms of impulsivity commonly observed as behaviors such as blurting out answers to

question, interrupting others, difficulty waiting their turn, road traffic offences and gossiping in social gatherings. The dominance of the impulsivity trait is not unique to ADHD and could be observed in Impulse - Control Disorder, Substance Use Disorder, and Bipolar Mood Disorder. Impulsivity¹⁷ is viewed as a deficit in frontal executive function and/or inhibitory control, resulting in slower inhibitory response rather than a faster prepotent response or an adaptable response. People with ADHD tend to have difficulty stopping a behavior once it has started than preventing

the behavior from the beginning. As a result of their impulsivity, they tend to have lower level of self-control resulting in psychosocial impairment, interpersonal difficulties, conflicted relationship, poor occupational performance, and lower academic achievement.

There have been numerous studies of ADHD focusing on the neurobiological concept of the disorder. Neuroimaging studies have yet to establish the precise neurobiological basis of the disorder, and the diagnosis remains purely clinical, but they provide some insight about possible mechanism of the disorder.¹⁸ The frontostriatal pathway controls decision making, memory, and attention, and it is assumed to be impaired in patients with ADHD. Positron Emission Tomography (PET)¹⁹ suggests reduced activity in the premotor cortex which influence motor activity and control of attention. Other areas implicated in the symptomatology of ADHD suggested by imaging studies include dorsal anterior midcingulate gyrus, dorsolateral prefrontal cortex,

ventrolateral prefrontal cortex, parietal cortex, and cerebellum.²⁰ It is believed that abnormalities in the dorsal anterior midcingulate gyrus are linked to impulsivity, while hyperactivity in people with ADHD has been linked to abnormalities in basal nuclei that control voluntary motor activities.¹⁹ Dopamine²¹ is linked to the activity of the prefrontal cortex and basal nuclei, and reduced amount of the neurotransmitter in this area is linked to the three arms of ADHD namely attentional deficit, hyperactivity, and impulsivity.

It is important to emphasize the issue of impairment in diagnosing A-ADHD, because having the symptoms of the disorder is not enough to reach a diagnosis. People who suffer from symptoms of ADHD are characterized by heightened energy, drive, and goal-pursuit which could be important factors in many industries such as entertainment and sales. Those individuals are not impaired, and their personality traits that are linked to the concept of ADHD can be advantageous.

Management of A-ADHD

A-ADHD should be carefully managed by team members who have training and expertise in the diagnosis and management of patients suffering from A-ADHD. All three groups of patients identified above are challenging and could be expecting an instant solution to have a diagnosis and pharmacological treatment. The psychiatrist should be aware of his own cognitive bias especially about the self-referred group who may be resistant to accept an alternative diagnosis.

People with A-ADHD^{22,23} might have suffered from inability to perceive social signals because of the nature of their disorder. They often use maladaptive immature defense styles,²⁴ and as a result may act out leading to conflicted relationships, particularly with people in management positions above them.

Diagnosing A-ADHD is complex, and its treatment is made more challenging because it involves potentially prescribing psychostimulant medication²⁵ namely amphetamines (lisdexamphetamine) and methylphenidate. While methylphenidate is the first medication to try in children with ADHD, amphetamines are often the first and more favored drug to use in patients with A-ADHD. Both medications are available in instant and slow-release preparations. At no point should the two medications

be combined, and non-response to one stimulant results in switching to the other.

Psychostimulant medication is classified as a Controlled Drug and needs to be prescribed carefully and monitored regularly.²⁶ It is worthwhile remembering that patients with A-ADHD may also experience co-existing psychiatric disorders, and the effects of medication might influence their behavior and physical health. Prior to initiating treatment, the patient must be medically screened carefully, and their medical history, blood pressure, pulse rate, weight, and electrocardiography are clearly recorded. The patient should be monitored on a regular basis, and the duration of prescriptions should be limited to the interval between visits. Every clinic should have a well-documented protocol to adhere to and shared between the members of the team and other professionals.

An important observation about psychostimulants is the dose-response relationship which is an inverted U meaning gradual increments lead to increased response, but at certain points increasing the dose might lead to worse response. This fact must be explained to the patient, who must be provided with full information about the drug prescribed. Many clinics run a strict protocol of illicit drug screening,

and if positive withhold treatment until a negative drug screen is returned.

Non-stimulant medication²⁶ for A-ADHD namely atomoxetine is only offered if the patient is either intolerant or a non-responder to stimulant preparation. Other drugs such as clonidine, bupropion, and guanfacine are probably superior to placebo but less effective than stimulant medication and may be prescribed if the patient suffers from comorbid anxiety and depression or substance use disorder.

Modafinil²⁷ is probably the most controversial preparation that has been used for more than a decade to treat A-ADHD, but not included in official treatment guidelines. It is also a commonly used psychostimulant by students, and often requested by self-referred clients prior to final examinations. It has a different mechanism of action compared with other psychostimulant primarily acting through ascending

arousal and attention system increasing frontal cortical activity. It is often used as third- or fourth-line treatment and is probably less effective than amphetamines and methylphenidate. Further studies are needed to establish its efficacy in treating A-ADHD rather than enhancing performance of university students.

Many patients would benefit from counselling and Cognitive Behavioral Therapy (CBT) to help them to better self-organize and maintain a healthy daily rhythm.²⁵ Some patients might decide to discontinue treatment especially the group diagnosed in childhood. Drug holidays are advised, and many advocate having one to two days per week without treatment. It is hoped that eventually the patient would be able to gain greater self-control and learn how best to overcome their difficulties without the need for medication, and this is ideally the most favorable outcome.

Conclusion

A-ADHD is a valid diagnosis and should not be dismissed readily by psychiatrists. Its diagnosis and management could be problematic, and better be managed by an experienced team who are able to

monitor the patient regularly. It is essential to follow strict guidelines when prescribing psychostimulant medication to ensure safety and proper adherence on behalf of the patient.

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الملخص

اضطراب عجز الانتباه فرط الحركة في البالغين فئة تشخيصية جديدة نسبياً في الطب النفسي للبالغين. لا يزال بعض الأطباء العاملين في الطب النفسي يتجنب تشخيصه وعلاجه ربما بسبب استعمال العقاقير المنشطة. علاج الاضطراب يحتاج الى خدمات متخصصة من قبل فريق متمرس من اجل تقديم خدمات سليمة. هناك العديد من الاضطرابات النفسية التي تصاحب الاضطراب وبدورها قد تؤثر على مساره ومعالجته. يمكن صياغة الاضطراب في نموذج نفسي عصبي او بيولوجي عصبي. العقاقير النفسية المنبهة هي الخط الأول للعلاج وتحتاج الى مراقبة دقيقة.

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Microbiome-Gut-Brain Axis

Nazar MM Amin

محور الدماغ – جهاز الهضم ومكروبياته

نزار م. م. أمين

Abstract

The structure of the human body is rather complex and the relation between various parts is intriguing. There are certain processes in the body that are the result of the interaction between various parts and organs. The relation between the gut and the brain is relatively new and the bidirectional relations between them, entitled Microbiome-Gut-brain axis (MBG), have received much attention. The current review discusses some of the literature on this subject that are the result of research conducted on animals and human beings. Future modern treatments for psychological and neurological disorders suggested by the findings will be discussed for further action.

Keywords: Microbiome, brain, gut, bidirectional, vagus nerve, stress

Declaration of interest: None

Introduction

Microbiomes are a collection of microbes and their genetic material in certain places in the human body. Probiotics are microorganisms that are administered as food supplements. There are about 100 trillion microbes in the human intestine. There is a continuous commensal relation between the microbes and their host. This symbiotic relation is essential for the health of the

individual. The gut with its enteric nervous system is in continuous interaction with the nervous system and this was described as a bidirectional relation between them resulting in the concept of Microbiome-Gut-Brain axis. The mechanisms and details of the interaction will be discussed further by reviewing the literature on the subject.

Adult microbiome stability

It is obvious that infants get their microbiome from their mothers depending on the method of birth and the number is different in various infants depending on their contact with the mother. Newborn babies get their microbiome by passing through birth canal during vaginal delivery while those who are born by caesarian section get their microbiome by contact with mother's skin. The number

increases with the passage of time until the child reaches the age of three years when most of the children have almost the same number of microbiomes in various parts of the body. This number will remain stable throughout life provided it is not affected by external factors that will be mentioned later in this review.

Microbiome and psychiatry

The interest in microbiome and its link with the gut stimulated a number of researchers in different specialties to work on the effect of gut and its microbes on the brain. The effect of the brain on the function of the gastrointestinal system was studied simultaneously. The

mechanisms for this bidirectional relationship were proposed by researchers and the vagus nerve was found to be the main channel of this communication. The effect of this relationship was obvious in the large number of

publications on this subject and the current review considers some of those publications.

The commensal gut microorganisms that produce biogenic amines (dopamine, norepinephrine, serotonin, and histamine) are discussed in a study by Sudo¹. These microorganisms are important players of the “microbiota-gut-brain” (MGB) axis. Their production in the gut was proposed to play possible role in the etiology of anxiety, depression, and psychosis. The concept of auto-intoxication was introduced referring to generating toxins in the gut mediated by biogenic amines. Regulating the balance between those resident bacteria might help in the development of new therapies for psychiatric disorders.

Another article by Sudo² referred to the relation between brain and gut. The concept of stress immunization happens when the animal is exposed to manageable stresses early in life leading to stress resilience later in life. Gut bacteria send signals activating brain areas that regulate stress and are useful for survival. A study by Liu³, in the United States, referred to the effect of enteric dysfunction induced by stress and through a combination of immunoregulatory, endocrinal, and neural mechanisms leading to psychiatric disorders. Much of the work on this subject was conducted on animals and a few on humans. Further research might lead the way to the development of novel treatments for mental disorders. In an excellent review by Mohajeri, the bidirectional relations between the gut and the brain via the vagus nerve was discussed in detail. Mohajeri referred to a World Health Organization (WHO) statement indicating that probiotics are beneficial to the human body leading to reduction of pathogenic microorganisms and protection of macromolecules (DNA, proteins, and lipids) from oxidative damage. “The colon harbors the highest density of human microbiome and they consist of bacteria, bacteriophages, viruses, fungi, protozoa, and archaea. The composition is affected by many factors including stress, diet and infection. Microbiota send signals to the brain by the sensory part of the vagus nerve via neuro-endocrine and neuro-immune pathways while the central nervous system regulates the secretory, sensory functions and mobility of the gastrointestinal tract. The central nervous system, the enteric nervous system (neurons in the gut), the sympathetic and parasympathetic branches of the autonomic nervous system are the main pathways for the bidirectional communication between the gut and the brain. Host bacteria are crucial for regulating microglial maturation and function and that microglial impairment

can be ameliorated to some extent by the microbiota. The gut microbes are implicated in the pathophysiology of depression and anxiety and that some strains confer a certain degree of resilience against these conditions. Mohajeri concludes that the communication between the two sides involves epithelial receptor-mediated signaling, immune modulation, and stimulation of enteric neurons by bacterial metabolites. Diet helps in modification of gut microbiome which in turn help in preventing and treating brain-related disorders”.⁴

Wang and Wang suggested the routes of communication between the gut microbiota and the brain to include gut immune system, hypothalamic pituitary adrenal axis and neurotransmitters synthesized by gut bacteria.⁵ Huang *et al.*, referred to the bidirectional communication system between the gut and brain and mentioned that the change in microbiota has a direct effect on the immune system and affects the brain via the disrupted balance between pro-inflammatory and anti-inflammatory cytokines. They also suggested that the future use of more advanced techniques such as proteomics, metabolomics and metagenomics might help further studies in the future.⁶ In an article by Scriven *et al.*, the bidirectional modes of communication between the brain and the gut are both direct and indirect and includes the effect of gut microbiota on the immune system which by itself affects the hypothalamic pituitary adrenal axis and the circulating levels of cytokines. The latter send signals via the vagus nerve to the brain and act directly on the blood brain barrier. They suggest probiotics to be used in the future as psychobiotics for treatment of psychiatric disorders.⁷ Foster *et al.*, some time ago suggested that stress affects the composition of gut microbiota and affects stress reactivity through the communication between the gut and central nervous system and influences reactivity to stress. Alteration of microbiota modulate plasticity-related, serotonergic, and GABAergic signaling systems in the central nervous system.⁸ Lozupone, (indicated that altering the symbiosis between the host and gut microbiota might lead to inflammatory bowel disease and cancer.⁹ Zyoud *et al.*, referred to increased interest in the concept of MGB Axis between 2009-2018 and around 51,000 articles were published on Microbiome from US, Ireland, China and Canada; the articles were mainly about animal models of the Axis, the relation between the gut microbiome and immune system as well as irritable bowel disease (IBD) and the link with neurodegenerative diseases.¹⁰ Levin highlighted a debate on the relation between the digestive and nervous system. Using genetic microbial signature has stimulated research on the interdependence of the

microbiota and the host in neurodevelopment, inflammation, stress response, and more.¹¹ Ma *et al.*, highlighted the biological link between microbiota, central nervous system and immune signaling. The signaling is an indirect way of communication while microbial metabolite act directly on the link. The specific mechanism for this link is not clear yet.¹² Cerdó *et al.*, suggested that prenatal and postnatal diet influence fetal microbial population and the gut microbiota in postnatal life, after being affected by the microbiota of the mother, affects brain development from early life. Therefore, identifying dysfunctions of the MGB axis in early life might help the identification of novel specific and personalized therapeutic interventions to prevent mental diseases and behavioral problems later in life.¹³ Kim *et al.*, believed that imbalance of gut microbiota is associated with abnormalities in stress response and neurological disorders and correcting the imbalance by administration of probiotics can relieve a lot of neurological disease symptoms.¹⁴ Kim and Shin highlighted the clinical trials using probiotics in animals to improve psychological symptoms. There are a few promising trials for the use of prebiotics and fecal microbiota transplantation, but it is too soon to decide on their results.¹⁵ This interaction between the gut and the nervous system could be invested in the treatment of many disorders depending on the various mechanisms of interaction. Raka *et al.*, referred to the potential for treating obesity and other metabolic disorders.¹⁶ Neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease are conditions in which the MGB axis has been implicated in the pathology.¹⁷ Probiotic administration resulted in significant improvement in Alzheimer's disease symptoms.⁷ It has been suggested that diversity in gut

microbiome might lead to inflammation and increases the risk of Alzheimer's disease,¹⁸ therefore inflammatory markers are important to consider in the early diagnosis and the role of probiotics in preventing dementia seems promising.¹⁹ A research done on War Veterans with cirrhosis revealed that combat-related posttraumatic stress disorder (PTSD) is associated with cognitive impairment and lower microbial diversity the correction of which might represent a new therapeutic target.²⁰ Microbiome is implicated in neurodevelopmental disorders, such as Autism Spectrum Disorders (ASD);¹⁷ antibiotics and infections of the gastrointestinal tract might affect brain development and the gut microbiome contributing in the etiology of ASD.²¹ Research revealed that selective food intake by children affects composition of gut microbiota, which might have a role in ASD and treatment that regulate the microbiota of the gut, might improve symptoms of ASD.²² Microbiome-Gut-Brain axis implicated in psychiatric disorders such as schizophrenia, anxiety and mood disorders¹⁷ and studies showed that diet that could serve as substrates for bacterial fermentation might help in lowering the risk of depression.²⁴ Research findings on human subjects revealed that proinflammatory genera of gut microbiota and those involved in lipid metabolism were increased in patients with depressive episodes.⁶ Mohajeri, in his extensive review, referred to animal studies showing that some gut microbes are implicated in the pathophysiology of depression while other strains and some healthy diet offer immunity against those disorders.⁴ Probiotics were found to improve symptoms of depression⁷ and research revealed that the constitution of intestinal microbiota can change symptoms of mood disorders and the latter can change their constitution.²⁴

The role of microbiome in treatment

The studies mentioned indicated a strong effect of the gut on the brain function and pathology which was obvious in various neurologic and psychiatric disorders. The effect was of the microbes in the gastrointestinal tract or diet taken orally including how probiotics might play a role in the treatment of diseases of the brain and psychiatric disorders. There are some modern techniques through

which the effect of diet and the microbes in the gut could be used in the treatment of some mental disorders. An example is the fecal transfer for treatment of ASD. These treatments are still experimental but rather promising

Conclusion

There is a bidirectional relationship between the gut through its enteric nervous system and its residing microbiota and the brain, which is conveyed via the vagus nerve. The communication is through neuroimmune and neuroendocrine mechanisms as well as the autonomic and central nervous system. Both sides affect each other and a lot of research on animals and some research on humans revealed very important results that explain the nature of

the link between the two sides. The findings explained the pathology of many psychiatric and neurological conditions in general and the author concentrated on literature specifically on certain disorders, such as ASD, Alzheimer's disease and mood disorders. The results of these findings open the avenue for modern therapies for these disorders in the near future.

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المخلص

توجد علاقة متبادلة بين الدماغ والجهاز الهضمي مع ما يحتويه هذا الجهاز من ميكروبات. ويتم التواصل بينهم عن طريق العصب التائه. يؤثر الدماغ عن هذا الطريق على وظائف الجهاز الهضمي ومحتوياته من البكتيريا وغيرها ويؤثر الجهاز الهضمي بدوره على الدماغ والجهاز العصبي المركزي ويقوم بهذه المهمة عن طريق جهاز المناعة العصبي والغدد الصماء العصبية مع الجهاز العصبي السمبثاوي. لقد تطرق الكاتب الى العديد من المقالات التي نشرت بحوثا اجريت على الحيوانات وبعضها على البشر. كما تطرق الى المقالات التي تدرس تأثير هذه العلاقة على بعض الامراض مثل طيف التوحد والخرف مع اضطرابات المزاج والمقترحات حول توظيف هذه العلاقة لاستحداث علاجات حديثة لهذه الحالات.

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Current Topics in the Evaluation and Treatment of Negative Symptoms in Schizophrenia

Istvan Bitter

المواضيع المعاصرة في تقييم وعلاج الاعراض السلبية للفصام

استيفان بيتر

Abstract

Negative symptoms have been considered the core features of schizophrenia, however they still represent a neglected area of research and their treatment represents a largely unmet need. This Editorial summarizes some of the current major milestones in the development of the concept of negative symptoms in schizophrenia and the current challenges and questions in their evaluation and treatment.

The concept of negative symptoms has been redefined in the last 15 years as five symptom domains and as having a 5-factor structure. Based on the revised concept, new second generation negative symptom rating scales have been developed, including the Brief Negative Symptom Scale (BNSS). Negative symptoms have been recognized as treatment targets by the European Medicines Agency and by the US Food and Drug Administration. Further research is needed to answer important clinical questions e.g., the relationship of primary and persistent negative symptoms, the importance of individual negative symptoms in the long-term course and outcome of schizophrenia and the response of individual negative symptoms to treatment. Cultural differences may be important in the definition and evaluation of negative symptoms. There are only a few effective pharmacological and non-pharmacological interventions available for their treatment. Current treatment research is focusing on non-dopaminergic compounds.

Keywords: Negative symptoms, schizophrenia, evaluation, treatment

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Introduction

The first description of “schizophrenias” by Eugen Bleuler and the description of dementia praecox earlier by Emil Kraepelin were based on negative and cognitive symptoms, while positive symptoms were considered accessory.¹ However, the focus of research and clinical thinking about schizophrenia shifted to positive symptoms reaching almost exclusivity in the diagnosis of schizophrenia in the middle of the 20th century. Kurt Schneider described a group of “first-rank” symptoms as highly typical for schizophrenia and a group of “second-rank” symptoms, which were considered less important for its diagnosis and were also present in other mental disorders.² It is important to note, that both the first- and second-rank symptoms are positive symptoms. Today only one out of five symptom criteria for schizophrenia listed in the influential DSM-5 includes negative symptoms.³ The proven efficacy of antipsychotic drugs in the treatment of positive symptoms maintained or even increased the interest of clinicians and researchers in positive symptoms. The vast majority of antipsychotics - especially those having non-partial dopamine D2 receptor

antagonist properties - have little or no effect against negative symptoms.

In the 1980's the interest in negative symptoms reemerged, and various concepts, symptom definitions and measurement tools were published, which are summarized in the above cited book chapter.¹ Based on the available research data in schizophrenia the need for the reconceptualization of the negative and cognitive symptoms domains became evident by 2005. Our US colleagues organized the NIMH-MATRICES consensus conference, which resulted in a consensus statement about negative symptoms in schizophrenia⁴ and in the development of new scales for both research and clinical use.

In this Editorial, we shortly summarize some of the major milestones and current clinical research questions in the field of negative symptoms in schizophrenia. While there have been advances in the biological research of negative symptoms, their results have not been translated in the

clinical practice yet and they will not be addressed in this paper.

Which symptoms are negative symptoms? The development of new (“next generation” or “second generation”) rating scales for negative symptoms in schizophrenia

One of the major outcomes of the NIMH-MATRICES consensus conference⁴ has been the development of the Brief Negative Symptoms Scale (BNSS), a prototype of second-generation negative symptom rating scales. The BNSS covers five symptom factors as suggested by the NIMH-MATRICES consensus conference: anhedonia, asociality, avolition, alogia, and blunted affect. It has been supported by data, that negative symptoms are best conceptualized by these five factors and they “cross rating scales and cultures”.⁶

The contribution of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to the definition of negative symptoms

The EMA guideline on “clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia”⁷ requires the following inclusion and exclusion criteria for the study of “true” negative symptoms in schizophrenia:

“inclusion criteria should encompass:

- a) Predominant and persistent negative symptoms.
- b) Flat affect, poverty of speech, and avolition being present as representative of core negative symptoms.
- c) Stable condition of schizophrenic illness for longer than 6 months, especially of the negative symptoms.

Exclusion criteria should include:

d) Major depression; low depression scores are preferable.

e) Subjects with substantially confounding extrapyramidal symptoms.

f) Substantial non-compliance or substance abuse.”

The FDA commented on methodological issues related to negative symptom trials and acknowledged, that negative symptoms in schizophrenia can be legitimate targets for drug development. The FDA required evidence, that negative symptoms represent a specific feature of schizophrenia and are distinct from such symptom domains as depressive or extrapyramidal symptoms.⁸

Thus, both regulatory agencies have required the separation of primary and secondary negative symptoms (e.g., negative symptoms secondary to depressive or extrapyramidal symptoms). However, rating scales cannot differentiate between primary and secondary negative symptoms. Many causes associated with secondary negative symptoms have to be excluded and an analysis of the medium- and long-term course of schizophrenia - including negative symptoms - is also required for the definition of “persistent” negative symptoms. The definition of “predominant” negative symptoms is based on a cross-sectional evaluation. The relationship between “primary” and “persistent” negative symptoms needs further studies. Due to the variability in the validity and reliability of rating scales Kirkpatrick *et al.* recently suggested the use of digitalized measures (“digital phenotyping”).⁹

What is/are the treatment target/s? Primary and/or persistent and/or predominant negative symptoms?

Negative symptoms and syndromes have been characterized based on different criteria e.g., prominent, persistent, and predominant negative symptoms, Type I. (associated with positive symptoms) and Type II. (Associated with negative symptoms) schizophrenia, deficit schizophrenia or deficit syndrome in schizophrenia.¹ The usefulness of the requirement of “predominant” negative symptoms for the identification of patients suffering from negative symptoms has been challenged^{1,10} since “predominant negative symptoms”

may not represent a stable phenotype. The relationship between positive and negative symptoms changes during the course of schizophrenia, which may result in a pattern of changes of time periods (episodes) with either predominant negative symptoms or predominant positive symptoms.

Primary negative symptoms remain conceptually in the focus of research; however, our research questions need to be refined.⁹

What is the level of correlation between negative symptoms?

When addressing these questions, we should consider that using a single score of a scale, subscale, or factor for the measurement of the severity or of the treatment response of negative symptoms is associated with a loss of

information about the individual items, while the simultaneous use of two scales is associated with various levels of redundancy.¹¹

Do negative symptoms respond to treatment?

Once we apply the criteria suggested by EMA (see above) and search only for treatment studies, including patients with predominant and persistent negative symptoms, then we can conclude, that only very few pharmacological and nonpharmacological interventions have any evidence of efficacy.

A current review of the literature found that only some second-generation antipsychotics and some antidepressants have evidence supporting their use in the pharmacological treatment of predominant and/or persistent negative symptoms:¹² Amisulpride was found to be better than placebo and cariprazine was superior to risperidone in a large study well controlled for secondary negative symptoms. “Direct comparisons of antipsychotics in patients with predominant negative symptoms indicated no significant difference between amisulpride and olanzapine and between asenapine and olanzapine in the improvement on negative symptoms.”¹² Both amisulpride and cariprazine bind with higher affinity to D3 receptors than to D2 receptors, which might be an explanation for their efficacy in the treatment of depressive and negative symptoms.¹³ Antidepressants have low level and controversial evidence for their efficacy in the treatment of primary negative symptoms of schizophrenia.¹⁴

Current drug research for the treatment of negative symptoms in schizophrenia is focusing on nondopaminergic compounds e.g., pimavanserin, which is an inverse agonist and antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors and also binds to sigma-1 receptors; roluperidone (former code names: MIN-101, CYR-101, MT-210), which is a serotonin 5-HT_{2A} and sigma-2 receptor antagonist; SEP-363856, an agonist of the TAAR1 (trace amine-associated receptor 1) and serotonin 5-HT_{1A} receptor; xanomelin (a muscarinic receptor agonist in combination with trospium, which is a

muscarinic receptor antagonist for the reduction of cholinergic side effects).¹⁵

Another review of the literature investigating nonpharmacological interventions for negative symptoms of schizophrenia found that few studies applied the criteria of “predominant” and/or “persistent” negative symptoms i.e., many studies measure global negative symptoms (the mixture of primary and secondary negative symptoms). The main conclusions of the review include: “In a series of meta-analyses social skills training, music therapy, non-invasive brain stimulation, mindfulness, and exercise-based interventions have all been found to improve negative symptoms in randomized controlled trials, relative to treatment as usual.”¹⁶

Current recommendations for the conduct of negative symptom studies, such as the inclusion of patients with well-defined negative symptoms (e.g., primary, persistent), the exclusion of subjects with secondary negative symptoms or the proper control of secondary negative symptoms and the use of second-generation negative symptom rating scales (e.g., BNSS) may improve signal detection in these studies. The exclusion of subjects with secondary negative symptoms is a complex task, since these symptoms have been associated with a large number of causes, such as psychiatric (e.g., depression, substance use) and medical (e.g., endocrinological diseases, traumatic brain injury) comorbidities, treatment adverse effects (e.g., extrapyramidal symptoms caused by antipsychotics), or environmental factors (e.g., social deprivation, under stimulation).¹⁷ It is important to clarify the potential causes of secondary negative symptoms, including the lack of opportunities for social and leisure activities due to poverty, stigma and discrimination.

What is the relationship between the treatment response of primary and secondary negative symptoms?

Many treatment studies do not appropriately control for secondary negative symptoms, thus the treatment

response in such studies can be considered as a sum of changes in primary and secondary negative symptoms.

Unfortunately, there are only a few studies about secondary negative symptoms and about their treatment response.

Transcultural aspects of negative symptoms

A current cross-cultural validation of the 5-factor structure of negative symptoms in schizophrenia challenged the “classical” 2-factor model of negative symptoms (diminished expression and avolition/apathy) and

highlighted the importance of considering the cultural aspects in the evaluation of negative symptoms – and in fact their importance in psychiatry in general.¹⁸

Acknowledgement

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المخلص

لقد اعتبرت الأعراض السلبية من المظاهر الأساسية للفصام، ومع ذلك لا زالت تمثل جزء مهم من البحث العلمي، وعلاجها يمثل حاصل لم تلبى بشكل كبير. هذه المقالة وتلخص بعض الخطوات الكبيرة المعاصرة في تطوير مفهوم الأعراض السلبية في الفصام والتحديات والأسئلة الحالية في تقييمها وعلاجها.

لقد تم إعادة تعريف مفهوم الأعراض السلبية في الخمسة عشر عام الماضية، في خمسة مجالات لأعراض وأن لها تركيب من عدة عوامل. بناءً على المفهوم الذي تمت مراجعته، فإن مقاييس جديدة من الجيل الثاني للأعراض السلبية قد تم تطويرها، وتشمل مقياس العرض السلبي المختصر (BNSS)، وقد تم تمييز الأعراض السلبية كأهداف للعلاج من قبل جمعية الدواء الأوروبية وإدارة الدواء والغذاء الأمريكية، المزيد من البحث مطلوب للإجابة على أسئلة سريرية هامة، مثل العلاقة بين الأعراض السلبية الأولية والمستمرة، أهمية الأعراض السلبية المنفردة في المسار طويل الأمد والخرجات للفصام واستجابة الأعراض السلبية المنفردة للعلاج. الاختلافات الثقافية قد تكون هامة في تعريف وتقييم الأعراض السلبية، هناك القليل من المداخلات الدوائية وغير الدوائية الفعالة المتوفرة لعلاجها. والبحث الحالي في العلاج يركز على المركبات غير الدوبامينية.

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Adherence to Medication for Schizophrenia in a Psychiatric Outpatient Clinic in Sulaimani

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الالتزام بالادوية لدى مرضى الفصام في العيادة الاستشارية النفسية في مدينة السليمانية: دراسة مقطعية لمدة شهرين

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Abstract

Objectives: The rate of adherence to medications among patients with schizophrenia was investigated and reasons for non-adherence explored. **Methods:** A cross sectional study was conducted across a two month period at the Ali Kamal Psychiatric Outpatient Clinic in Sulaimani. In total, 100 patients were selected on the basis of DSM 5 criteria for schizophrenia using a convenience sampling technique. Outcome measures were the Drug Attitude Inventory (DAI-10) and the Medication Adherence Rating Scale (MARS) along with socio-demographic and clinical variables. **Results:** Seventy three percent of the patients studied reported being adherent to medication. A significant association was found between non-adherence and younger age group, living in rural areas, short duration of illness, being unaware of the disorder and positive family history of mental disorders. Other predictors of non-adherence were forgetfulness, carelessness, feeling (tired, sluggish, strange, or 'zombie-like') on medication, taking drugs only when feeling ill, stopping them when feel better or worse, denying feeling more relaxed or more normal or their thoughts being clearer on drugs, taking medication against one's will, believing that it is not natural for mind/body to be controlled by drugs, disadvantages of drugs are more than advantages, and drugs cannot prevent experiencing mental breakdown. **Conclusion:** Medication non-adherence among patients with a diagnosis schizophrenic is common in outpatient settings although expected to be higher among inpatients. Main factors associated with non-adherence are younger age, living in rural areas, short duration of illness, being unaware of the illness and positive family history of mental disorders.

Keywords: Adherence, schizophrenia

Declaration of Interest: None

Introduction

Adherence to medication is defined as the extent to which an individual's behavior corresponds with the prescribed medication dosing regimen, timing, dosage and medication intake intervals.¹ The estimated rates of non-adherence in patients with schizophrenia are 50%, broadly ranging from 4% to 72%.²

Medication non-adherence among people with schizophrenic has serious consequences for individuals as well for public health generally. Non-adherence can more frequently lead to higher rates of relapse and exacerbation of psychotic symptoms, frequent hospital admissions, repeated emergency visits,³ increased aggressive and violent behaviors, and worse outcome.⁴

There are multiple factors that can influence adherence. These factors can be divided into five major groups: medication-related, patient-related, illness-related,

sociocultural-related, and mental health service providers related⁵ that can also be titled as clinician-related factors.⁶

Many methods of medication adherence monitoring are available. The most commonly used method is self-report although this approach is more likely to overestimate adherence.⁷

Exploring the attitudes and reasons for poor drug adherence with appropriate management strategies planned is one way to improve adherence to medication.⁸ Accumulated research data concluded that individually tailored multi-component interventions have the best chance to improve adherence.⁹

Aims of this study are to identify the rate of adherence to medications among patients with schizophrenia and explore the reasons of non-adherence.

Methodology

This study was conducted at Ali Kamal outpatient clinic in Sulaimani city, which is situated Northern Iraq. The clinic includes almost all specialties in addition to psychiatry, which is the only public psychiatric outpatient clinic in a city with a population of approximately 2.6 million.

In this cross sectional study, the researcher selected 100 patients diagnosed with schizophrenia, according to DSM-5 criteria using a convenience sampling technique. The duration of the study was two months, from July 26th to September 26th, 2020.

Direct interviews were conducted with each using a standardized questionnaire, which consisted of three parts: part one included socio-demographic information including clinical characteristics of the patient. Parts two and three were comprised of the Drug Attitude Inventory or DAI-10 (Awad, 1993), and Medication Adherence Rating Scale or MARS (Thompson, 2000).

Both scales were translated into Arabic and Kurdish following an internationally accepted translated and back translated methodology and debriefing for participants (to determine if respondents understood the questionnaire based on its original meaning).

Socio-demographic data included gender, age, occupation, marital status, number of children, years of formal education, residence, social support, duration of schizophrenic illness, age of onset, chronic physical illness, type of antipsychotic currently receiving, route of antipsychotic use, other medicines (including psychotropic) receiving at the same time, complex drug regimen, experience of any adverse effect, substance abuse, awareness of illness, previous psychiatric hospital admission and family history of psychiatric illness.

The DAI-10 is the shortened version of the original Drug Attitude Inventory or DAI-30 (Hogan, 1983) which is regarded as the gold standard scale designed to assess attitudes to antipsychotic agents and adherence in schizophrenia.^{9,10} The DAI-10 is a brief, self-report scale that assesses patients' attitude, experience, and beliefs about antipsychotic drugs and regarded as a good predictor of adherence to medication in schizophrenia.¹¹ It consists of 10 true/false questions. An incorrect reply is scored as -1 whereas a correct reply is scored as +1. The final score is the summation of the pluses and minuses.⁴ Thus, scores range from -10 to +10.⁹ A negative total score indicates a negative attitude toward medication (non-adherent) while a positive total score is regarded as a positive attitude (adherent).⁴

The DAI-10 has good psychometric properties with inter-rater reliability index of 0.61 (p , 0.001) and internal

consistency coefficient of 0.57. It shows convergent validity and moderate reliability.¹¹ The correlation coefficient using Pearson's r test were 0.72 with good test-retest reliability (0.79).¹² Reliability reaches a Cronbach's Alpha of 0.77.⁹

MARS is a commonly used self-reported scale to measure adherence in patients with schizophrenia and was validated in patients with psychosis. It is a combination of the Drug Attitude Inventory and Medication Adherence Questionnaire¹³ and was developed by Thompson, Sergejew and Kulkarni.¹⁴ MARS consists of 10 Yes or No questions that assess behaviors and attitudes of the patients toward medication in the last week.¹⁵ Patients are adherent if they reply "No" to questions 1 to 6 and 9 to 10 and "Yes" to questions 7 to 8.¹⁶ A response consistent with adherence is coded as 1 whereas a response consistent with non-adherence is coded as zero.¹⁷ Thus, scores range from 0 to 10. Any score below 6 indicates non-adherence whereas a score equal to 6 or above is considered adherent.²

MARS is reported as a reliable and valid tool for estimating adherence to medication. Reliability using Cronbach's alpha measure of internal consistency is high (0.75), whereas test-retest reliability after two weeks using parallel-forms Chi-square is comparable at 0.72¹⁸ with correlation coefficient of 0.8222 using Pearson's r test which indicates good reliability.¹⁴ MARS has good internal validity with high validity compared to other self-report measures.¹⁸

A positive score on DAI-10 and a score above 5 on MARS are considered as adherent. A negative score on DAI-10 or a score less than 6 on MARS are considered as non-adherent regardless of the scoring in other scale.

Inclusion criteria: Patients aged 17 years or older, both genders and those who were able to give consent were included.

Exclusion criteria: Patients who were uncooperative or declined to participate or unable to give consent; patients with communication difficulties or barriers, those with severe agitation or behavioral disturbance, and patients with significant cognitive impairment that may interfere with their responses to checklist questionnaires were excluded from the study.

Ethical considerations: The research proposal was reviewed and approved by the scientific and the ethical committee of the Arab Board of Psychiatry in Iraq. The research project was approved by the Ethics Committee of the College of Medicine at University of Sulaimani. Patients were contacted via the general directory of Ali Kamal outpatient clinic. Following an explanation of the

study and its purpose, each patient was asked to provide oral consent to participate. Patient confidentiality and anonymity was assured. All were informed that the data would be used for research purposes only.

Statistical analysis: The collected data were entered into Microsoft Excel and loaded into IBM-SPSS version 26 for statistical analysis.

Descriptive statistics including frequencies and percentages were presented in tables and graphs.

Statistical analysis was performed using Pearson correlation coefficient to find out significant associations between adherence and other variables.

P-value less than 0.05 were regarded as discrimination point of statistical significance.

The variables that have significant associations (*p*-value less than 0.05) with adherence, were further analyzed for odds ratio and confidence interval using descriptive statistics cross tabulation.

Results

Socio-demographic characteristics

A total of 100 patients diagnosed with schizophrenia were involved in this study: 58% were men with approximately 36% were 45 years or above and 32% ranging from 36 to 45 years. Nearly two thirds (63%) were unemployed, 60% were single 65% did not have children. Regarding years of formal education, 50% studied 7-12 years and 31% studied 1-6 years.

In total, 67% lived in urban regions with 95% having some kind of social support (anyone who reminds them to take their medication or anyone who listens to their feelings or anyone who supports them financially/non-financially). Socio-demographic characteristics are summarized in Table 1.

Table 1. Sample distribution according to socio-demographic characteristics

Variable		Frequency	%
Gender	Male	58	58
	Female	42	42
Age in years	>25	14	14
	25-35	18	18
	36-45	32	32
	<45	36	36
Occupation	Employed	21	21
	Unemployed	63	63
	Student	7	7
	Retired	9	9
Marital status	Single	60	60
	Married	28	28
	Divorced	11	11
	Widowed	1	1
Children	No	65	65
	Yes	35	35
Years of formal education	None	4	4
	1-6	31	31
	7-12	50	50
	More than 12	15	15
Residence	Urban	67	67
	Rural	33	33
Social support	Yes	95	95
	No	5	5

Clinical characteristics

Among these 100 cases, 54% were diagnosed as having had schizophrenia for more than 10 years; 44% had age onset of schizophrenia from 21-30 years while 93% did not have any diagnosed chronic medical disease like hypertension or diabetes mellitus.

Furthermore, 53% were currently receiving one second generation antipsychotic; 63% were taking oral antipsychotic drug, while 32% were currently receiving both anticholinergic and mood stabilizer drugs at the same time.

In total, 76% had complex drug regimen which is defined as taking of at least three different drugs in once daily dose or taking at least two different drugs in twice daily doses¹⁹ and nearly the same number of cases (78%) reported experience of at least one adverse effect.

In addition, 58% were not abusing any substance, such as tobacco smoking or alcohol, and the majority of (76%) were aware of their illness e.g., having insight. More than half of cases (59%) had at least two previous admissions into psychiatric hospital and almost a similar number of patients (57%) reported presence of diagnosed psychiatric illness in their families.

Clinical characteristics are summarized in Table 2.

Table 2. Sample distribution according to clinical characteristics

Variable		Frequency	%
Duration of illness in years	Less than 6	16	16
	6-10	30	30
	More than 10	54	54
Age of onset in years	Less than 21	27	27
	21-30	44	44
	31-40	20	20
	More than 40	9	9
Chronic physical illness	No	93	93
	Yes	7	7
Current anti-psychotic use	FGA	14	14
	SGA	53	53
	SGA + FGA	33	33
Route of anti-psychotic use	LAI	10	10
	Oral	63	63
	Combined	27	27
Current other medicines use	No	8	8
	Yes	92	92
Complex drug regimen	Yes	76	76
	No	24	24
Experience of any adverse effect	No	22	22
	Yes	78	78
Substance abuse	No	58	58
	Yes	42	42
Awareness of illness	Yes	76	76
	No	24	24
Previous psychiatric hospital admission	No	17	17
	One	24	24
	Two or more	59	59
Family history of psychiatric illness	Yes	57	57
	No	43	43

FGA, first generation antipsychotic; SGA, second generation antipsychotic; LAI, long acting injection

Prevalence of adherence

Prevalence of medication adherence is 73%.

Association between socio-demographic variables and adherence

Age (p value=0.002) and residence (p value=0.001) were significantly related to adherence in bivariate correlation

analysis using Pearson correlation coefficient, whereas other socio-demographic variables (gender, occupation, marital status, number of children, years of formal education and social support) were not significantly associated.

Table 3 summarizes the association between socio-demographic characteristics and adherence.

Table 3. Association between socio-demographic variables and adherence

Variable		Adherent, n (%)	Non-adherent, n (%)	p -value
Gender	Male	43 (74.1)	15 (25.9)	0.766
	Female	30 (71.4)	12 (28.6)	
Age in years	Less than 25	7 (50.0)	7 (50.0)	0.002**
	25-35	10 (55.6)	8 (44.4)	
	36-45	25 (78.1)	7 (21.9)	
	More than 45	31 (86.1)	5 (13.9)	
Occupation	Employed	14 (66.7)	7 (33.3)	0.155
	Unemployed	46 (73.0)	17 (27.0)	
	Student	4 (57.1)	3 (42.9)	
	Retired	9 (100.0)	0 (0.0)	
Marital status	Single	43 (71.7)	17 (28.3)	0.833
	Married	22 (78.6)	6 (21.4)	
	Divorced	8 (72.7)	3 (27.3)	
	Widowed	0 (0.0)	1 (100.0)	
Have children	No	47 (72.3)	18 (27.7)	0.834
	Yes	26 (74.3)	9 (25.7)	
Years of formal education	None	2 (50.0)	2 (50.0)	0.454
	1-6	23 (74.2)	8 (25.8)	
	7-12	36 (72.0)	14 (28.0)	
	More than 12	12 (80.0)	3 (20.0)	
Residence	Urban	56 (83.6)	11 (16.4)	0.001**
	Rural	17 (51.5)	16 (48.5)	
Social support	Yes	68 (71.6)	27 (28.4)	0.166
	No	5 (100.0)	0 (0.0)	

** Statistically significant at p -value <0.05

Association between clinical variables and adherence

Duration of schizophrenia (p value=0.001), awareness of illness (p value=0.000) and family history of mental disorders (p value=0.036) were significantly related to adherence in bivariate correlation analysis using Pearson correlation coefficient, whereas other clinical variables (age of onset, chronic physical illness, type and route of

current anti-psychotic use, current other medicines use, complex drug regimen, experience of any side effect, substance abuse and previous psychiatric hospital admission) were not significantly associated.

Table 4 summarizes the association between clinical characteristics variables and adherence.

Table 4. Association between clinical variables and adherence

Variable		Adherent, n %	Non- adherent, n %	p-value
Duration of illness in years	Less than 6	6 (37.5)	10 (62.5)	0.001**
	6-10	22 (73.3)	8 (26.7)	
	More than 10	45 (83.3)	9 (16.7)	
Age of onset in years	Less than 21	19 (70.4)	8 (29.6)	0.328
	21-30	30 (68.2)	14 (31.8)	
	31-40	17 (85.0)	3 (15.0)	
	More than 40	7 (77.8)	2 (22.2)	
Chronic physical illness	No	67 (72.0)	26 (28.0)	0.437
	Yes	6 (85.7)	1 (14.3)	
Current anti-psychotic use	FGA	8 (57.1)	6 (42.9)	0.703
	SGA	42 (79.2)	11 (20.8)	
	SGA + FGA	23 (69.7)	10 (30.3)	
Route of anti-psychotic use	LAI	7 (70.0)	3 (30.0)	0.876
	Oral	47 (74.6)	16 (25.4)	
	Combined	19 (70.4)	8 (29.6)	
Current other medicines use	No	5 (62.5)	3 (37.5)	0.491
	Yes	68 (73.9)	24 (26.1)	
Complex drug regimen	Yes	55 (75.0)	21 (25.0)	0.803
	No	18 (72.4)	6 (27.6)	
Experience of any adverse effect	No	18 (81.8)	4 (18.2)	0.296
	Yes	55 (70.5)	23 (29.5)	
Substance abuse	No	44 (75.9)	14 (24.1)	0.454
	Yes	29 (69.0)	13 (31.0)	
Awareness of illness	Yes	66 (86.8)	10 (13.2)	0.000**
	No	7 (29.2)	17 (70.8)	
Previous psychiatric hospital Admission	No	12 (70.6)	5 (29.4)	0.495
	One	16 (66.7)	8 (33.3)	
	Two or more	45 (76.3)	14 (23.7)	
Family history of psychiatric illness	Yes	37 (64.9)	20 (35.1)	0.036**
	No	36 (83.7)	7 (16.3)	

** Statistically significant at p -value <0.05

Factors associated with non-adherence

Age, residence, duration of schizophrenia, awareness of illness and family history of mental disorders were significantly associated with non-adherence (p value less than 0.05) thus they were further analyzed for odds ratio and confidence interval using cross tabulation.

Accordingly, patients aged less than 25 years were nearly three and half times as likely to be non-adherent to antipsychotic medication as compared to those aged 25 years or more (OR=3.30; 95% CI: 1.03, 10.53).

The odds of developing medication non-adherence among participants who were living in rural areas were almost five times higher as compared to those who were living in urban regions (OR=4.79; 95% CI: 1.87, 12.26).

The likelihood of having medication non-adherence among patients diagnosed as having schizophrenia for less than six years was six and half times higher as compared to those who have the disorder for six years or more (OR=6.56 (95% CI 2.09, 20.61)).

Regarding awareness of illness, patients who were not aware of their disorder e.g., lack of insight, were 16 times as likely to be non-adherent compared to those who were aware (OR=16.02, 95% CI: 5.31, 48.30).

Moreover, participants who reported presence of family history of mental disorders were about three times as likely to be non-adherent as compared to those who denied it (OR=2.78, 95% CI: 1.04, 7.37).

Table 5 shows socio-demographic and clinical factors that are associated with medication non-adherence.

Among these 100 participants who replied to the questions on DAI-10 and MARS, two thirds of cases reported feeling tired and sluggish on medication whereas more than half (53%) reported forgetting to take them and approximately 41% believed that it's not natural for mind and body to be controlled by drugs.

Moreover, around one third of patients mentioned feeling strange (weird, 'zombie-like') on medication; taking drugs only when feeling ill and sometimes stopping medication when feel better.

Furthermore, around a quarter of patients denied their thoughts being clearer on medication and a similar number of cases reported being careless regarding taking drugs and even stopping them when sometimes feel worse.

In addition, approximately 21% believed that the disadvantages of taking medication were greater than the advantages.

Around 11-14% denied feeling more normal or more relaxed on medication and nearly a similar number of patients mentioned taking drugs against their will and did not believe that drugs can prevent them having breakdown or getting sick.

Table 5. Socio-demographic and clinical factors associated with medication non-adherence

Variable	Adherent, n (%)	Non-adherent, n (%)	p-value	OR (95% CI)
Age in years				
Less than 25	7 (50.0)	7 (50.0)	0.002**	3.30 (1.03, 10.53)
25 and more	66 (76.7)	20 (23.3)		
Residence				
Rural	17 (51.5)	16 (48.5)	0.001**	4.79 (1.87, 12.26)
Urban	56 (83.6)	11 (16.4)		
Duration of illness				
Less than 6 years	6 (37.5)	10 (62.5)	0.001**	6.56 (2.09, 20.61)
6 years and more	67 (79.8)	17 (20.2)		
Awareness of illness				
No	7 (29.2)	17 (70.8)	0.000**	16.02 (5.31, 48.30)
Yes	66 (86.8)	10 (13.2)		
Family history of mental illness				
Yes	37 (64.9)	20 (35.1)	0.036**	2.78 (1.04, 7.37)
No	36 (83.7)	7 (16.3)		

** Statistically significant at p-value <0.05

Discussion

In the current study, 73% of participants (n=100) were adherent to anti-psychotic treatment, which is in line with studies conducted in Northern Ethiopia (72.5%),²⁰ Europe (71.2%)²¹ and Peru (75%),¹¹ respectively. On the other hand, this finding is lower than rate of adherence that was reported in Chile (88.2%),¹¹ and higher than studies demonstrated in USA (42.5%),²² India (65.9%),¹⁶ and several papers in Ethiopia (56%,²³ 51.6%,²⁴ 59%²⁵) and 60.4%²⁶ respectively. This remarkable difference of adherence prevalence in this study compared to other papers can be explained by differences in assessing medication adherence scales, sampling techniques, sample size, inclusion criteria and the study setting whether were conducted in outpatient clinics or inpatient

psychiatric units. Logically patients who attend outpatient clinics of their own accord are more likely to be adherent to their prescribed medications compared to their inpatients counterparts who may deny their psychopathology and might even be admitted to psychiatric units coercively.

Two socio-demographic factors were significantly associated with non-adherence to medication. Age (p value=0.002) and residence (p value = 0.001) were significantly related to non-adherence in bivariate correlation analysis using Pearson correlation coefficient.

Accordingly, younger patients, e.g. under 25 years, were more likely to be non-adherent which is in line with papers

from India,¹⁶ USA^{22,27,28} and three Latin American countries (Bolivia, Peru, and Chile).¹¹ Many studies showed no significant association between age and adherence,^{26, 25, 29, 30, 24} yet older patients were found to be more non-adherent in another paper.²⁰ Younger patients may be less adherent to medication because they might be unaware of their illness severity or the need to take medications regularly¹¹ and may be more likely to deny their mental health difficulties compared to older ones.

Moreover, participants who were living in rural areas were found to be more non-adherent to treatment, which is also in line with two Ethiopian studies,^{26, 25} but the reverse was found in another study.²⁰ This might be explained by several factors including long distance to health facilities, financial issues, lack of mental health services, cultural beliefs of those areas and poor awareness regarding mental disorders in rural regions.²⁵

Whereas other socio-demographic variables (gender, occupation, marital status, have children, years of formal education and social support) were not significantly associated with non-adherence.

In addition, no significant association was detected between gender and non-adherence in the current study, which is consistent with many studies^{25, 16, 29, 30, 24, 20, 23, 22,8} and inconsistent with another study conducted in Latin America which demonstrated that women are more likely to be non-adherent.¹¹

Also, no significant association was found between occupation and non-adherence in this study, which is in line with many articles^{26,25,16,30,24,23,11} but in contrast to other studies that show unemployment as a significant risk factor associated with medication non-adherence.^{22,8}

Furthermore, no important link was estimated between marital status and non-adherence in present research, which is also a similar result in other studies.^{26,25,16,29,30,24,23,22,8,11}

Finally, significant association between education and non-adherence were not present in this research which is consistent with other papers,^{26,25,16,29,30,24,23,8,11} but in contrast with two other studies that found that being illiterate²⁰ and higher education²² is associated with less adherence to medications, respectively.

Among clinical factors that were significantly associated with medication non-adherence; schizophrenia duration (p value=0.001), awareness of illness (p value=0.000) and family history of mental disorders (p value=0.036) were significantly related to non-adherence in bivariate correlation analysis using Pearson correlation coefficient.

Individuals who were diagnosed as having schizophrenia for short duration of time e.g., less than six years, were

more likely to be regarded as non-adherent to drugs which is a similar finding in other studies^{29,31} Whereas no association was found between duration of illness and adherence in other papers.^{25,16} The possible explanation might be that such patients might have poor insight about their condition and subsequently they may not be aware of the necessity to take pharmacological treatment.

Furthermore, patients who were not aware of their illness e.g., lack of insight, were much more likely to be non-adherent to drugs, a finding which is consistent with many other studies.^{32, 30, 20, 29, 11, 33} Being unaware of the illness is the most important factor associated with non-adherence in this study. The association between lack of insight and non-adherence had been confirmed extensively in many studies.^{34,35,36,37,38} This finding suggests that mental health professionals should grasp this issue and try to modify beliefs and attitudes toward medication among patients with schizophrenia, and explore concerns of distrust toward pharmacological therapy.¹¹

In addition, patients with positive family history of diagnosed mental disorders were more likely to be non-adherent to medicines in the present study, whereas no association was found in another paper.¹⁶ A possible explanation might be that people with schizophrenia might consider their poor functioning as normal when they compare themselves to mentally disordered individuals in their family, without having the intention to change toward better, thus they might be careless about taking medication.

While other clinical variables (age of onset, chronic physical illness, type and route of current anti-psychotic use, current other medicines use, complex drug regimen, experience of any side effect, substance abuse and previous psychiatric hospital admission) were not significantly associated with non-adherence.

Accordingly, significant association between age of schizophrenia onset and non-adherence was not present in the current paper, whereas early age of onset was associated with non-adherence in other researches.^{8,11}

In addition, important association between type of anti-psychotic use and non-adherence was absent in this study, which is consistent with other papers.^{25,16,24}

Furthermore, an important correlation between route of anti-psychotic use and non-adherence was not detected in the present paper, which is also the same result in other research^{25,16,29} whereas recipients of long acting typical anti-psychotics were less adherent in another study.²⁷ It is notable that fluphenazine decanoate and flupentixol decanoate are the only available long acting injections in the region.

Moreover, a significant correlation between current other medication use and non-adherence was not demonstrated which is a comparable finding in another research²¹ but it contradicts another study²⁷ which found that concomitant medication use is risk factor for non-adherence.

Experience of side effect and non-adherence was not significantly associated in the current study which corroborates another study³⁰ whereas other studies found that participants who suffer from medication side effects, are more likely to be non-adherent to pharmacological treatment.^{8,23,22} Another study found that patients who experience extrapyramidal side effects are three times more likely to be non-adherent.²⁴

Surprisingly, substance use and non-adherence was not correlated in statistically significant analysis, which is also consistent with another article¹⁶ but in contrast to other research^{8,30,25,23,21,27,29,32} that considered psychoactive substance use as a significant risk factor for medication non-adherence.

Lastly, insignificant association was found between previous psychiatric hospital admission and non-adherence, which is similar to another study.²⁵

Other predictors of non-adherence are feeling tired and sluggish when taking psychotropic medication which was reported by two thirds of patients, almost a similar percentage (67.5%) was demonstrated in a relevant study.²⁶

Accordingly, 53% of participants in present research mentioned forgetting to take drugs, such a factor is considered to be one of most common causes of non-adherence in three studies; 50.6%,²⁶ 48.4%²² and 43.5%²³ respectively. Forgetting to take medications may be explained by cognitive impairment, which one studies identified as an apparent norm that pre-dates schizophrenia since up to 98% of studied patients performed poorly on cognitive tests.³⁹

Another study,²⁶ suggested 41% of patients expressed it not seeming natural for mind and body to be controlled by medications.

Furthermore, around one third of patients mentioned taking drugs only when feeling ill and sometimes stopping medication when feeling better. An Ethiopian research showed quite similar findings.²⁶

In addition, a third of patients mentioned feeling strange (weird, 'zombie-like'), such rate is lower than another article.²⁶ In northern Iraq, anti-psychotics available are those with the most adverse effects compared to the newer ones which are not yet available.

In the present study, a quarter of patients denied their thoughts being clearer on medication and even stopping them when sometimes feeling worse, a similar percent was estimated in two relevant studies.^{26,22}

Being careless when taking drugs was reported by 27% of participants in the current, which is supported in another study²² although much lower than a study from Ethiopia, which in which 46.1% participants reported this as a reason.²⁶

Only 12% of participants in the present study did not believe that medication can prevent psychological breakdown or stop a person from becoming mentally unwell; a much higher finding was shown in another research, 28.5%.²⁶

Psychiatrists and mental health professionals in outpatient clinics should pay more attention to patients with a diagnosis of schizophrenia of less than six years, who are younger than 25 years of age and live in rural regions, who lack insight and have family history of diagnosed mental disorders. Ensuring more time when providing an explanation and education for patients about their diagnosis may increase their adherence to the medications prescribed. More time should also be given to their follow up appointments.

In addition, it is essential to provide mental health services in rural regions, including for psychotropic agents, blood tests and psychiatric wards and improve transportation facilities for such patients as a further way to enhance adherence.

Challenges and limitations

Some challenges and limitations were faced during the course of data collection.

Data collection was obtained in the time where the Coronavirus pandemic was at its height. Understandably, many participants were concerned about the risk of becoming infected and, therefore, we endeavored to complete the interviews as soon as possible.

Further, the room where all interviews took place was neither comfortable nor private. Social desirability bias may also have had an effect on the findings.

The study findings are not necessarily generalizable to all cities in Iraq given that it was conducted in one city.

DAI-10 and MARS are subjective (self-report) methods that mainly depend on patients' recall, which may result in

overestimation or underestimation of medication adherence. And further, previous history of medication adherence was not assessed.

This study design is a cross sectional one which is less robust when establishing relationships between cause and effect.

And finally, in 9% of the patients interviewed, the average age of onset was 40 years, which means caution is needed when considering the diagnosis.

Conclusion

In the current study, non-adherence to medication was reported by 27% of outpatients with a diagnosis of schizophrenia, which reflects a challenging problem. The figure may be higher among inpatients. Contributing factors include being under 25 years of age, living in rural areas, short duration of illness, being unaware of the illness and positive family history of mental disorders.

Furthermore, predictors of non-adherence include feeling tired and sluggish on medication, forgetfulness, believing that it is not natural for mind and body to be controlled by

drugs, feeling strange (weird, zombie-like) when on medication, taking drugs only when feeling ill, stopping medication when feeling better, denying thoughts being clearer on medication, carelessness regarding taking drugs, stopping them when feeling worse, believing that disadvantages of medication are greater than advantages, denying feeling more normal or more relaxed on medication, taking drugs against one's will and not believing that drugs can prevent having breakdown or getting sick.

Recommendations

Increasing patient adherence to medication may be possible by improving the psychoeducation about schizophrenia, including etiology, course of illness, anti-psychotic agents and functional outcome, which might raise greater awareness about schizophrenia.

Psychological therapy or counselling provision may help patients to better understand their own barriers for adhering to medication and support them to develop strategies for improving adherence, including through use of written or electronic aide memoire or through visual cues. Linking daily activities with regular times for taking medication may also help patients develop a better pattern

as would involving family members or caregivers in encouraging or reminding the patient to take medication.

More broadly, health authorities should be advised to provide medications with the least adverse effects in the future.

In terms of future research, similar investigation on a larger population and in other cities of Iraq may be of interest, but could include inpatients and those experiencing other mental health difficulties. Longitudinal studies could be used to establish any significant relationships between cause and effect..

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المخلص

الاهداف: تحديد معدل الالتزام باستخدام الأدوية لدى مرضى الفصام واستكشاف أسباب عدم الالتزام. **طريقة البحث:** أجريت هذه الدراسة المقطعية في عيادة علي كمال الاستشارية للأمراض النفسية في مدينة السليمانية. تم اختيار 100 مريض تم تشخيص إصابتهم بالفصام وفقاً لمعايير DSM 5 باستخدام تقنية أخذ العينات الملائمة. كانت مدة الدراسة شهرين، من 26 تموز إلى 26 ايلول 2020. تضمنت البيانات التي تم جمعها جرد الموقف تجاه الادوية؛ DAI-10 ومقياس تقدير الالتزام بتناول الأدوية؛ MARS جنباً إلى جنب المتغيرات الاجتماعية والسريرية. **النتائج:** 73% من عينة الدراسة التي أجريناها كانوا ملتزمين بتناول الأدوية. تم العثور على ارتباط هام بين عدم الالتزام بالأدوية والفئة العمرية الأصغر، العيش في المناطق الريفية، قصر مدة المرض، عدم الوعي بالمرض والتاريخ العائلي الإيجابي للأضطرابات النفسية. **النتائج:** متنبات أخرى بعدم الالتزام بتناول الأدوية هي النسيان، الإهمال، الشعور (بالتعب، بالبطء، بالغرابة، مثل "زومبي - حي ميت") عند تناول الأدوية، تناول الأدوية فقط عند الشعور بالمرض، إيقافها عند الشعور بتحسن أو تفاقم المرض، إنكار الشعور بمزيد من الاسترخاء أو أكثر طبيعية أو أن تكون أفكارهم أكثر وضوحاً عند استخدام الأدوية، تناول الأدوية ضد الإرادة الحرة، الاعتقاد بأنه من غير الطبيعي أن يتم التحكم بالذهن والجسد عن طريق الأدوية، الاعتقاد بأن مساوئ الأدوية أكثر من الفوائد، والاعتقاد بأنه لا يمكن للأدوية أن تمنع حدوث الانهيار العقلي. **الاستنتاج:** عدم الالتزام بتناول الأدوية لدى مرضى الفصام في العيادات الاستشارية أمر شائع ومن المتوقع أن يكون أعلى بكثير لدى المرضى الراقدين. العوامل الرئيسية المرتبطة بعدم الالتزام هي الفئة العمرية الأصغر، العيش في المناطق الريفية، قصر مدة المرض، الجهل بالمرض ووجود الاضطرابات النفسية في العائلة.

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Role of Oral versus Long-Acting, Second-Generation Medications for Enhancing Adherence and Preventing Rehospitalization in Patients with Schizophrenia

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مقارنة مضادات الذهان الفموية اليومية بمضادات الذهان طويلة المفعول بمرضى الفصام لتحسين الالتزام بالعلاج وتقليل الحاجة للتنويم بالمستشفى

منى السيد، هايدي حسن سيد

Abstract

As psychopathology and social functioning can worsen with repeated psychotic episodes, relapse prevention is critical in schizophrenia and because non-adherence decreases response to pharmacotherapy, the use of long-acting, injectable (LAI) antipsychotics is considered an important treatment option. **Aims:** The current study aims to assess the experience of adherence and rehospitalization in patients with schizophrenia who receive second-generation, oral or long-acting injectable antipsychotics following hospital discharge. **Method:** A prospective comparative study was carried out from April 2018 to March 2019 in an outpatient psychiatry clinic in Ismailia, Egypt. In total, 70 patients with a diagnosis of schizophrenia were recruited; ages ranged from 18 to 40 years; and all were allocated to one of two groups. Group A consisted of 35 patients maintained on oral, second-generation antipsychotic (SGA). Group B consisted of 35 patients maintained on long-acting injection second generation antipsychotic. Patients were followed up for one year to assess adherence, discontinuation and rehospitalization. **Results:** Patients on long-acting, second generation antipsychotic injection (LAI) were more adherent and required fewer rehospitalizations than those on oral, second-generation antipsychotics (OAP). **Conclusion:** Long-acting antipsychotic injections may have a role in enhancing medication adherence for patients with a diagnosis of schizophrenia and may also decrease the need for hospitalization.

Keywords: Long acting second generation antipsychotic, oral second-generation antipsychotic, hospitalization, schizophrenia

Declaration of interest: None

Introduction

Schizophrenia is chronic debilitating mental disorder and the leading cause of psychiatric disability in adults, which can result in considerable economic burden. According to some studies, an estimated 50% of patients diagnosed with schizophrenia are non-adherent to oral antipsychotic medication (OAM) after one year of treatment.^{1,2}

Poor medication adherence to antipsychotics is a predictor of relapse and hospitalizations. The initial five years after diagnosis of schizophrenia can result in higher relapse rates.³

Some factors contributing to non-adherence to oral antipsychotic include daily medication routine, complex medication regimen, missing doses, availability of medication, lack of insight that led to missed doses.⁴

As psychopathology and social functioning can worsen with repeated psychotic episodes, relapse prevention is critical in schizophrenia. Because more nonadherence decreases the efficacy of pharmacotherapy, the use of

long-acting injectable (LAI) antipsychotics is considered an important treatment option.⁵

Achieving greater continuation of treatment is a key element to improve treatment outcomes in patients with schizophrenia. Treatment discontinuation has been determined as a reliable and strong predictor of relapse.⁶

Delivery of continuous, assured medication through long-acting injectable (LAI) antipsychotic formulations has a long history of use to minimize non-adherence. This potential clinical effect is not pharmacodynamics although there may be pharmacokinetic advantages based on lower and less variable plasma concentrations with LAI administration.⁷

The LAIs were previously recommended when there was poor medication adherence or symptoms exacerbation or in maintenance phase of therapy.⁷

The results of comparing long-acting antipsychotic with oral antipsychotic regarding relapsing and hospitalization

could be affected by methodology of study. While proactive studies show LAIs and oral antipsychotics to have similar effects, whereas mirror-image and some large cohort studies showed LAIs to be superior to oral antipsychotics.⁹

Long-acting antipsychotic medication in many studies associated with less relapses and lower hospitalization rates after initiation of treatment as compared to patients treated with oral antipsychotic medication (OAP).⁸ resulting in a lower total healthcare cost.⁹

Aim of the study

The aim of the current study was to assess experiences of adherence and rehospitalization in patients with a diagnosis of schizophrenia who received second

generation, oral or long-acting injectable antipsychotics following hospital discharge.

Method

A prospective comparative design was used to compare second generation antipsychotic medication, oral versus long-acting injection regarding non-adherence, discontinuation, and the need for hospitalization in patients with a diagnosis of schizophrenia.

The study was carried out between April 2018 to March 2019 in a psychiatry outpatient clinic in Ismailia, Egypt, which is situated in the Suez Canal region.

Sampling

Participants were selected using a convenience sampling method with the following inclusion criteria: participants who were easy to contact and who provided their consent to take part in the study. All were selected at patient follow up from a psychiatric outpatient clinic at Suez Canal University Hospital.

The study included 70 patients fulfilling DSM-5 criteria for schizophrenia with duration of less than five years; and included those who were aged 18 to 40 years and without history of hospitalization six months prior to the study. Group A comprised 35 patients maintained on oral, second-generation antipsychotic (SGA) and group B comprised 35 patients maintained on long-acting injection, second generation antipsychotic. All were selected via psychiatric outpatient clinic at routine follow-up. Written consent was obtained from all patients with one family member from each also providing consent.

Exclusion criteria included patients with schizoaffective, bipolar, other mood disorder and/or difficulties associated with substance use. Also, patients with IQ<80, organic brain injury, first episode psychosis, refractory schizophrenia, chronic medical illness, pregnancy, and lactation were also excluded. Patients hospitalized due to serious suicidal ideation, self-harming behaviors, or high levels of aggression were excluded from study as were those requiring ECT or clozapine to control symptoms.

All patients were assessed every month for symptoms and signs of positive psychotic symptoms, suicide, self-injury behavior, tendency for aggression and intolerance of side effects. Dose modification was acceptable in accordance with assessment. Anticholinergic medications were prescribed for extrapyramidal symptoms with Inderal being prescribed for akathisia and Benzodiazepine prescribed for insomnia.

Basic laboratory investigation included CBC, RBS, KFT, and LFT. Lipid profile was performed initially with follow up every three months.

Non-adherence is considered when the proportion of days covered is less than 0.80, and discontinuation is considered when there was continuation gap ≥ 60 days, relapse and schizophrenia-related hospitalization is also recorded.⁸

Psychiatric hospitalization is needed due to relapse of psychotic symptoms, suicidal ideation, aggressive and disorganized behavior.

The need for hospitalization alone was not considered cause for discontinuation participation in the study.

Ethics

1. Written consent was taken from patients and one of caregiver
2. Patients evaluated by two consultant psychiatry for diagnosis and plan of management and follow up sessions
3. All needed investigation was offered free for patients
4. Monthly follow up by consultant to all patients and phone contact was available to caregiver as needed.

5. Patients requiring hospitalization for serious suicidal ideation, self-harm behavioral or aggressive behavioral were excluded from the

study and re-assessed for the appropriate level of care and management

Results

Table 1. Comparison between the two studied groups, according to sociodemographic data

	Group A (n=35)	Group B (n=35)	Test of Sig.	p
Gender				
Male	22(62.9%)	22(62.9%)	$\chi^2=0.0$	1.000
Female	13(37.1%)	13(37.1%)		
Age				
Mean \pm SD.	29.1 \pm 6.2	28.6 \pm 6.1	t=0.351	0.727
Median (Min.-Max.)	29(19-40)	28(19-40)		
Education				
No education	2(5.7%)	3(8.6%)	$\chi^2=1.601$	^{MC} p=0.716
Primary school	9(25.7%)	7(20%)		
Secondary school	21(60%)	19(54.3%)		
University graduate	3(8.6%)	6(17.1%)		
Marital status				
Single	18(51.4%)	19(54.3%)	$\chi^2=0.514$	^{MC} p=1.000
Married	9(25.7%)	9(25.7%)		
Divorced	6(17.1%)	6(17.1%)		
Widow	2(5.7%)	1(2.9%)		
Financial income				
Low	8(22.9%)	7(20%)	$\chi^2=0.085$	0.771
Average	27(77.1%)	28(80%)		

χ^2 : Chi square test MC: Monte Carlo

*: Statistically significant at $p \leq 0.05$

There was no significant different between the two studied groups regarding socio-demographic date

Table 2. Comparison between the two studied groups, according to duration of illness

Duration of illness	Group A (n=35)	Group B (n=35)	χ^2	p
Less 3 years	16(45.7%)	20(57.1%)	0.915	0.339
3 to 5 years	19(54.3%)	15(42.9%)		

χ^2 : Chi square test
p: p value for comparing between the studied groups

There was no significant difference between the two studied groups regarding duration of illness

Table 3. Comparison between the two studied groups, according to adherence and discontinuation

	Group A (n=35)	Group B (n=35)	χ^2	<i>p</i>
Adherence				
No	16(45.7%)	7(20%)	5.245*	0.022*
Yes	19(54.3%)	28(80%)		
Discontinuation				
No	20(57.1%)	26(74.3%)	2.283	0.131
Yes	15(42.9%)	9(25.7%)		

χ^2 : Chi square test

p: p value for comparing between the studied groups

*: Statistically significant at $p \leq 0.05$

The above table shows a significant difference between two groups regarding adherence. Patients on second generation, long-acting antipsychotic (Group B) were

more adherent to medication than patients on oral, second-generation antipsychotic (Group A).

Table 4. Comparison between the two studied groups, according to re-hospitalization

Hospitalization	Group A (n=35)	Group B (n=35)	χ^2	<i>p</i>
No	12(34.3%)	21(60%)	4.644*	0.031*
Yes	23(65.7%)	14(40%)		
Once	16(69.6%)	11(78.6%)	0.358	^{FE} $p=0.710$
Twice	7(30.4%)	3(21.4%)		

χ^2 : Chi square test

Fisher Exact

*: Statistically significant at $p \leq 0.05$

The above table shows significant difference between the two studied groups regarding re-hospitalization. The patients on second generation long-acting antipsychotic

(Group B) needed less rehospitalization than patients on oral second-generation antipsychotic medication (Group A).

Discussion

Approximately 40-60% of patients with schizophrenia are non-adherent to oral antipsychotic medication (OAM) in the first year of treatment. Although oral, second-

generation antipsychotics have fewer side-effects than the first-generation, non-adherence is still significant issue.^{2,9}

Achieving greater continuation of treatment and improving outcomes for patients diagnosed with schizophrenia, treatment non-adherence and discontinuation are strong predictor of relapse; each relapse having determined clinical impact, economic burden, hospitalization with its high-cost burden while continuation on antipsychotic medication linked with less risk of relapse and better outcomes.²¹

Many factors contributing to medication non-adherence in patients with schizophrenia include complex medication regimen, missing doses, irregular daily routine, and clinician's lack of awareness on adherence.¹⁰

Long-acting antipsychotic were designed to overcome non-adherence issue by decreasing the dosing frequency. Recent guidelines recommend LAIs in all phases of schizophrenia including first-line therapy as well as the initial 2-5 years.¹¹

Characteristics of the two research groups

Both groups were comparable at a baseline regarding age, gender, marital status, education, diagnosis, and duration of illness (Tables 1 and 2).

Adherence and discontinuation and hospitalization:

There is significant difference between the two studied groups regarding adherence and hospitalization. Over the one-year follow-up period, patients in group B (LAI) of second-generation antipsychotic had more adherence and less hospitalization than those in Group A on oral, second-generation antipsychotic, (Tables 3 and 4).

This result supports Tianmei Si *et al.*, 2019, which compared 108 patients who were prescribed oral antipsychotic and the same group of patients after shifting to long-acting antipsychotic (Paliperidone) for 18 months. Their mirror-analysis revealed that the percentage of patients' hospitalization in the period of one-year post long-acting medication therapy was lower than that in the retrospective period. The cause of less need to hospitalization in both studies could be more adherence to medication. The long acting medication given one/month or every two weeks enable less insight schizophrenic patients to compliance on their antipsychotic medication. Also, long-acting antipsychotic medication decrease burden on care giver to these patients.¹²

These results are supported also in Zhang F *et al.*, 2015, which found that patients with recent-onset schizophrenia, who had previous failed on the oral antipsychotics medication, show good respond to 18 months long acting Paliperidone therapy.¹³ Also, similar results were found by Chiou *et al.*, 2015 which suggested that a lowered direct health care cost may be expected as a benefit of long-term therapy.¹⁴ Many retrospective studies

show the main explanation for such differences is the improvement of continuation and adherence to treatment.^{15,16}

Delivery of continuous, assured medication through long-acting injectable (LAI) antipsychotic formulations has a long history of use to minimize non-adherence. This potential clinical effect is not pharmacodynamics although there may be pharmacokinetic advantages based on lower and less variable plasma concentrations with LAI administration.¹⁷ Kane *et al.*, 2010 revealed that long-acting antipsychotic medication (LAI) has a long history of use to minimize non-adherence. This clinical effect could be having pharmacokinetic causes on lower and less variable plasma concentrations with LAI administration the main explanation for such differences is the improvement of continuation and adherence to treatment.¹⁷

Similar results by Baweja *et al.*, 2012 they found long-acting antipsychotic agents could improve compliance especially for patients experiencing a first-psychotic episode and, also in patients with comorbid substance use or patients with severe and enduring psychopathology.¹⁸ Steven *et al.*, 2015 also found long-acting injection both first- and second-generation antipsychotic had lower odds for being non-adherent and as relates to discontinuation when compared with patients receiving oral medications. Second-generation LAI therapy showed more significant advantages relative to oral medications.⁸

In contrast with our results, one prospective US study on 305 patients follow up 30 months, included both schizophrenia and schizoaffective comparing risperidone as long acting second generation SGA with oral SGAs. Differences between long-acting injection risperidone and oral, second-generation antipsychotic regarding first relapse and hospitalization were not significant.¹⁹ Also, one retrospective observational study from Italy included all patients discharged from psychiatric hospital for two years either on long-acting injection or oral antipsychotic. The study reported no significant differences between the two group of patients regarding rehospitalization rate in a 24-month period.²⁰

The causes of these mixed results could be due to adherence to antipsychotic medication by patients with schizophrenia. The rate of relapse and re-hospitalization could be decreased if the patients had better adherence to their medication whether it was long-acting injection or oral. Close follow-up of patients in these studies could be enhancing factors that may explain why adherence had improved. However, use of long-acting injection can help caregivers and patients with medication adherence and decrease relapse and rehospitalization. Long-acting injection need only one or two visits to outpatients per

month. The LAI can overcome many difficulties when dealing with patients who have a diagnosis of schizophrenia patient and who may, therefore, lack

insight, decline follow-up visits and/or decline daily medication.

Conclusion

Patients with a diagnosis of schizophrenia who received second generation LAIs were more adherent to medication and required less re-hospitalization compared with those

patients who received oral, second-generation antipsychotic medications.

Recommendations

Long-acting, antipsychotic medication is recommended for patients with a diagnosis of schizophrenia who are non-adherent to their medications because it is found to enhance adherence and decrease the need for rehospitalization.

Strength of the study

1. All patients are diagnosed as having schizophrenia according to DSM-5 criteria and patients with other co-occurring mental health or psychosocial difficulties, such as schizoaffective and problematic substance use were excluded from study to avoid confounding the results.
2. Both study groups were comparable regarding sociodemographic data and duration of illness.
3. Monthly follow-up was arranged for both groups for one year to enhance adherence to their medication.

4. Early detection of relapsing symptoms and observation of all common causes associated with discontinuation and non-adherence to antipsychotic medication, such as frequency of dose, lack of insight, high cost of medications, availability of medications have been considered.

Limitation of the study

- 1- Small sample size.
- 2- High cost of long-acting, antipsychotic medication.
- 3- Supporting patients and their caregivers to attend regular follow up monthly for one year.
- 4- Six patients were excluded from the study due to hospitalization after relapse and high levels of aggression.

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المخلص

تهدف الدراسة الي المقارنة بين استخدام مضادات الذهان الفموية اليومية الجيل الثاني، بمضادات الذهان طويلة المفعول الجيل الثاني بمرضي الفصام، المترددين على العيادات النفسية بمنطقة قناة السويس للحد من الانتظام بالعلاج وتقليل الحاجة للتتويج بالمستشفى

اجريت الدراسة على 70 مريض مصاب بداء الفصام حسب التصنيف الرابع للأمراض النفسية

تم تقسيمهم الي مجموعة أ الذين عولجوا بمضادات الذهان الفموية اليومية ومجموعة ب الذين عولجوا بمضادات الذهان طويلة المفعول بواسطة الحقن كل اسبوعين او شهريا. وقد اسفرت النتائج ان المرضى مجموعة ب الذين استمروا على مضادات الذهان طويلة المفعول كانوا أكثر التزاما باستخدام الدواء واكل حاجة لإعادة التتويج بالمستشفى من مرضي مجموعة ا. وخلصت الدراسة ان استخدام مضادات الذهان طويلة المفعول بمرضي الفصام تحسن من عملية انتظام المريض على الدواء وتقلل من الحاجة لإعادة التتويج.

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Roles of oral versus long-acting, second-generation medications for enhancing adherence and preventing rehospitalization in patients with schizophrenia

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Impact of COVID-19 on Patients with Mental Health Conditions Reported by Caregivers in Saudi Arabia

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تأثير جائحة كوفيد 19 على المرضى النفسيين حسب إفادة مقدمي الرعاية لهم .

مستشفى الصحة النفسية في الطائف , المملكة العربية السعودية

وسيم مرعي مرعي، أحمد سالم الطويرقي، فريد المالكي، طلال محفوظ

Abstract

Objective: The current study aims to measure the perceived effects of COVID-19 on patients with mental health conditions and their families. **Methods:** Using a descriptive cross-sectional survey design, a random sample of 1,168 caregivers were recruited to the study. Caregivers were identified via the Patient Affairs Department database with every third person invited via WhatsApp to complete an online questionnaire. The structured questionnaire was based on published research during the COVID-19 pandemic. **Results:** Of the 1,168 people recruited, 246 participated in the study; nearly 50% were caregivers for patients who were women. One out of two caregivers reported a deterioration in patients' mental health symptoms. Four out of ten participants reported that the pandemic negatively affected home care support by family members of mental health patients. Around 50% reported they would decline hospital admission if a psychiatric doctor recommended it during the pandemic and 71.3% reported believing that medications were unsafe if prescribed without a consultation. **Conclusion:** The COVID-19 pandemic has had a pronounced effect on Saudi mental health patients. Decisions whether to seek psychiatric care were also greatly influenced COVID-19. There is a clear need for adaptation and monitoring of the current emergency response psychiatric services as well as for further research to explore the knowledge of psychiatric patients and their caregivers regarding COVID-19.

Keywords Psychiatry: COVID-19, Coronavirus, mental illness

Declaration of interest: None

Introduction

In December 2019, a new disease emerged in a wet market in Wuhan province in China.^{1,2} The coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) and it is thought to be of zoonotic in origin.^{3,4} By March 2020, the World Health Organization (WHO) announced a global emergency and the situation escalated to become a global pandemic.⁵ According to a WHO situation report, the pandemic reached 216 countries, around 209 million confirmed cases of COVID-19 were detected, and the pandemic has already led to 4.4 million deaths.^{6,7} Compared to other Middle Eastern countries, Saudi Arabia was hit hard with the COVID-19 pandemic.⁸ The first confirmed cases of COVID-19 in Saudi Arabia were discovered on March 2, 2020.⁹ According to the Saudi Ministry of Health statistics, as of August 19, 2021, more than a half a million COVID-19 cases were detected; 384 people were still hospitalized with COVID-19 and there have been approximately 8000 deaths.¹⁰ The Saudi

government emergency response measures included complete country lockdown, and wide-scale awareness campaigns regarding social distances and handwashing practices.^{11,12}

COVID-19 pandemic has profound effects on psychiatric patients.^{2,4} Underprivileged living conditions, poor personal hygiene, and lack of insight for social distances practices are all possible risk factors for COVID-19 infection among mental health patients.^{13,14} In addition, the high prevalence of tobacco smoking among mental health patients increases their vulnerability to the SARS-CoV-2 virus.¹⁵

Three incidences of COVID-19 spread among inpatient psychiatric patients and workers at mental health facilities were reported in China, South Korea, and the United States.^{1,5,16} Healthcare providers and hospitals around the world have adapted their psychiatric care procedures to match the requirements of infection control and social

distancing measures.^{2,5} As part of these new procedures, the Mental Health Hospital in Taif (largest mental health institute in the Kingdom of Saudi Arabia) started to provide telemedicine (virtual clinics) for chronic psychiatric patients and new drug delivery services were introduced. These new procedures might have positive or negative effects on care-seeking behaviors for psychiatric patients and their families. To the best of our knowledge, there have been no previous assessments for the effects of COVID-19 response procedures in a mental health hospital in the Middle East.

It was estimated that one in every five adult Saudi individuals might have mental health difficulties.¹⁷ Therefore, the estimated impact of COVID-19 on Saudi patients with mental health conditions would be in the

vital interest of the general population and several stakeholders. Saudi Arabia is considered one of the high-income countries and the health expenditures is around 5% of the Gross Domestic Product (GDP).¹⁷ Thus, focusing the vast response resources on mental health interventions with positive impact could be cost-effective and crucial for future planning of pandemic responses.

The current study aims to measure the perceived effects of COVID-19 on patients with mental health conditions, their families, and the impact of newly introduced measures on the quality of psychiatric care. In addition, the aim is to explore psychiatric care-seeking behaviors at OPD, IPD, and emergency levels, to explore the impact of COVID-19 on medication adherence, and to explore its impact on psychiatric home care.

Methods

Ethics

Ethical approval was obtained from the Research Ethics Committee of the Ministry of Health (MoH) in Saudi Arabia. Participants provided written consent following a brief explanation of the purpose of the study. No identifying data were collected for caregivers or patients. The research was carried out in accordance with the Helsinki Declaration and according to Saudi MoH regulation to protect human research participants.

Using a descriptive cross-sectional survey, a random sample of 1,168 caregivers, from a pool of 4,900, were recruited to the study. Participants were selected via systematic sampling method with every third caregiver in the database of the Patient Affairs Department also being invited to participate. Information was obtained from both genders using one single database, which included access to WhatsApp numbers. The study invitation was sent to caregivers via WhatsApp, and they were asked to answer the study questionnaire online. The principal investigators developed a structured questionnaire based on previously published research during the COVID-19 pandemic. A self-administered questionnaire consisted of twenty-six close-ended questions. The questionnaire included questions about participants' demographics, questions about care-seeking behavior during COVID-19 pandemic, questions about changes in patients' mental health status

and symptoms during the pandemic, and questions about caregivers' feedback regarding the new COVID-19 measures.

Study inclusion criteria were: being a caregiver of a patient with mental health illness who has been diagnosed before the COVID-19 pandemic and a native Arabic speaker. A mental health illness was defined as bipolar disorders (including mania), schizophrenia and other chronic psychosis disorders, and anxiety disorders. At the time of sample selection, around 4,900 caregivers' WhatsApp numbers were registered in the database, which included all patients who received psychiatric services over three months during lockdown, according to the Patient Affairs Department. Non-respondents were either the caregivers who selected "no" when they were asked to participate or those who ignored the invitation sent to them.

Data collection was carried out in June 2020, three months after the WHO announced the pandemic status and during the response measures. Data was analyzed using the Statistical Package for the Social Sciences - SPSS (IBM Corporation, version 25.0, USA). Pearson's chi-square (χ^2) test or Fisher's exact test were used to analyze the data. Data were interpreted as statistically significant when a *p*-value is less than 0.05.

Results

Out of 1,168 invited caregivers, 246 participated in the study with a response rate of 21%. Almost half of the study participants were caregivers of women and 52.2% of the participants were caregivers of patients older than

39 years of age. The characteristics of study participants are described in Table 1. The most common reported diagnosis was depression, followed by schizophrenia (30.7% and 25.6%, respectively).

Table 1. Characteristics of study participants

		n	%	p-value of univariate analysis
Patient gender	Male	111	45.5	0.179
	Female	133	54.5	
Patient age	< 18 years old	7	2.9	<0.001
	18 – 29 years old	30	12.2	
	30 – 39 years old	80	32.7	
	40+ years old	128	52.2	
Patient address	Taif city	176	72.1	<0.001
	Outside of Taif city	68	27.9	
Number of family members living in the same household	0	12	5.0	<0.001
	1-3	60	24.8	
	4-7	128	52.9	
	8 or more	42	17.4	
Household financial status	Low income (less than 3,000 SAR)	111	46.6	<0.001
	Moderate (3,000 – 7,999 SAR)	81	34.0	
	High income (8,000-11,999 SAR)	18	11.8	
	Very high income (12,000 SAR or more)	28	7.6	
Marital status of the patient	Married	105	42.9	0.021
	Single	104	42.4	
	Widowed	12	4.9	
	Divorced	24	9.8	
Number of household members with a psychiatric diagnosis	1	63	26.7	<0.001
	2	30	12.7	
	3	14	5.9	
	More than 3	6	2.5	
Patient diagnosis	Schizophrenia	61	25.6	<0.001
	Bipolar Mood Disorder	32	13.4	
	Depression	73	30.7	
	Anxiety disorder	44	18.5	
	Other	28	11.8	
Last OPD visit	Within 2 weeks	41	16.9	<0.001
	Within 2 months	85	35.1	
	Within 6 months	89	36.8	
	More than 6 months ago	24	11.2	

One out of two caregivers reported a deterioration on patients' mental health symptoms and 38.8% of study participants reported a negative effect of COVID-19 on patients' medication adherence. Similarly, four out of ten participants reported that the pandemic affected home care

provision by family members to mental health patients (Table 2).

The bivariate analysis revealed that more than half of caregivers of patients with anxiety disorder, depression, or bipolar mood disorder reported a deterioration in patients' symptoms during the pandemic compared with 38.3% of

caregivers of patients living with schizophrenia. The type of patient mental health diagnosis was a statistically significant factor (p -value 0.023) in reporting a deterioration of patient’s symptoms.

Additionally, patient gender was one of the statistically significant factors that were associated with reporting a negative effect of COVID-19 in relation to providing home care for psychiatric patients by a family member (p -value 0.009), with caregivers of men reporting 44.2% of negative effect on home care compared with 27.8% of caregivers of women. In addition, the number of household members was another significant factor for

reporting a negative effect of COVID-19 on home care (p -value 0.005). Around 40% of households with eight or more members reported a negative effect on home care compared with 54.2% of households with one to three household members who reported a negative effect on home care. Meanwhile, households, with zero and four to seven members reported 25% and 27.9% negative effect on home care, respectively.

In addition, half of the participants reported that patients were afraid of being isolated during the quarantine and 57.4% reported that patients were afraid of getting the infection (Table 2).

Table 2. COVID-19 effect on patients' mental health status

		N	%
COVID-19 deteriorated patient’s psychiatric symptoms	Yes	119	49.6
COVID-19 affected patient’s adherence to medication	Yes	93	38.8
COVID-19 affected home care provided by family members to the patient	Yes	87	36.7
The patient has fears of being isolated during the quarantine	Yes	119	50.4
The patient has a fear of being infected with Coronavirus	Yes	139	57.4

Study participants reported several causes for seeking emergency psychiatric care during the pandemic. Around one-quarter of participants reported aggressive behaviors as a cause for seeking emergency care and 29.9% reported mild symptoms like mild restlessness or inability to fall asleep as a cause for seeking emergency care. On the other hand, 47.6% reported they would decline any hospital admission if a psychiatric doctor recommended it during the pandemic.

Seven out of ten participants considered the patients’ knowledge regarding COVID-19 as fair, good, or very good. On the other hand, 12% had a perception that psychiatric medications increase the risk of getting the Coronavirus infection.

Multivariate analysis was used to identify the adjusted effect of study variables on reporting fair, good, or very good patients’ knowledge regarding COVID-19 (Table 3). The stepwise logistic regression model revealed that patients between 18 and 29 years old were 12.9 times more likely to have good knowledge about COVID-19 compared with the pediatric age group (<18 years old) after controlling for other variables (p -value 0.049). On the contrary to that, patients with a diagnosis of schizophrenia were 0.2 less likely to have a good knowledge regarding COVID-19 compared with bipolar patients after controlling for other variable, and this was statistically significant (p -value 0.005).

Table 3. Multivariate analysis of factors associated with reporting fair or good on patients' knowledge about COVID-19

Variable	Odd Ratio	p -value
< 18 years old	Reference	
18 – 29 years old	12.9 (1.0 – 164.9)	0.049*
30 – 39 years old	7.4 (0.7 – 80.5)	0.101
40+ years old	15.5 (1.5 – 163.9)	0.023*
Bipolar mood disorder	Reference	

Anxiety disorder	1.7 (0.5 – 6.8)	0.426
Depression	1.7 (0.5 – 5.9)	0.389
Schizophrenia	0.2 (0.1 – 0.6)	0.005*
Other mental health disorder	0.3 (0.1 – 0.9)	0.046*

* Statistically significant *p*-value in the regression model

Around half of the participants rated the telepsychiatry consultation as good or excellent, but 71.3% of the participants reported feeling that the medications were unsafe when they received them without a consultation. In the same way, 54.1% of the participants rated home

delivery of medications as good or excellent and four out of five caregivers reported receiving all or most of psychiatric medications. The hospital health education regarding COVID-19 was rated as good or excellent by 53.6% of the participants (Table 4).

Table 4. Rating of COVID-19 response measures

		N	%
Caregiver evaluation of virtual psychiatric clinics	Bad or acceptable	128	55.4
	Good or excellent	103	44.6
Caregivers perception that the prescriptions are not safe if received without a consultation	Yes	169	71.3
	No	68	28.7
Caregivers rating of medications home delivery service	Bad or acceptable	95	45.9
	Good or excellent	112	54.1
Number of caregivers who reported receiving all or most of psychiatric medication if the OPD visit was within the last 2 months	Yes	104	83.2
	No	21	16.8
Caregivers rating of hospital COVID-19 health education	Bad or acceptable	109	46.4
	Good or excellent	126	53.6
Caregivers rating of hospital COVID-19 health education	Bad or acceptable	109	46.4
	Good or excellent	126	53.6

Discussion

Patients living with mental health conditions are a vulnerable group for COVID-19 infection.¹⁸ Several recent articles have revealed that there is an increase in demand for mental health services during COVID-19.^{19,20} Despite strict movement measures, 52.0% of study participants reported visiting Taif Hospital OPD department during the pandemic. This continued demand for mental health services could be explained by the deterioration of the mental status of our study cohort during the pandemic. These results are in line with Agyapong *et al.* and Iasevoli *et al.* findings were both

reported an increase in mental health services demand by the general population and mental health patients during the current pandemic in both China and Italy.^{3,21}

So many mental health patients rely on a small network of relatives and family members who provide them with essential physical and psychological support.^{15,22} The lockdown measures could affect the ability of family members to reach those patients, increase their loneliness fears, and affect their living conditions.^{23,24}

Although a German study reported a decrease in utilization of emergency psychiatric visits during the COVID-19 pandemic, our findings suggest that the

psychiatric patients will continue to utilize the emergency services even for mild or moderate situations such as inability to fall asleep or refusal to take the medication.²⁵ Saudi Arabia went through several phases during the COVID-19 response and these phases included an alteration between lockdown and release of lockdown measures, especially in the Maccab Region.^{26,27} One possible explanation for this difference was the fear of losing future access to the emergency services so that caregivers would seek the services while they are still accessible.

With recurrent news about a cluster of COVID-19 cases in psychiatric and general hospitals, it is not surprising that half of the study participants refrained from using inpatient services during the pandemic.^{1,28} This would require new psychiatric care procedures to provide the patients with possible alternatives for inpatient services and to prevent or decrease the need for inpatient services as much as possible.²⁵

Having a high perception of proper knowledge regarding COVID-19 could be interpreted in two different ways. Caregivers overestimate the knowledge level of mental health patients and that would increase the risk of those patients getting the infection due to the lack of adequate

protection from caregivers.²⁹ Alternatively, the high perception of good knowledge could be actual good knowledge and patients living with mental health illness are fully capable of obtaining good knowledge and have adequate hygiene practices and social distance practices.¹³

In addition, having slightly positive feedback regarding the implementation of telepsychology or telepsychiatry services is in line with overwhelming evidence about the effectiveness of these services.^{22,30} It was estimated that eight out of ten stable psychiatric patients could ultimately benefit from these teleservices.²⁹ However, if these new virtual clinic services need to continue or expand in the future, it needs to be associated with reassurance about the safety of receiving psychiatric prescriptions without seeing the doctor in a face-to-face consultation.

To the best of our knowledge, this was the first study to measure the psychiatric effects of COVID-19 on patients living with mental health illness. Conducting the study in the largest mental health institute in KSA and the random selection of study participants could help with generalization of study results on all Saudi mental health patients. Additionally, online data collection of de-identified information could eliminate interviewer bias.

Limitations

The criteria used in selecting caregivers did not include their mental and medical fitness for reporting the mental impact of COVID-19 on their patients, regarding methodology; we depended on the caregivers to measure the impact of COVID-19 without interviewing the patients themselves and, due to cross-sectional study designs, it is

not possible to measure the causal effects of study variables. Although a low response rate for online surveys is expected in the literature, taking into consideration the short data collection duration, a 21% response rate is considered a satisfactory response rate.^{31,32}

Conclusion

The COVID-19 pandemic has had a pronounced effect on Saudi mental health patients and the quality of homecare provided by family members. The behavior of seeking psychiatric care was also affected by COVID-19 and a higher number of inpatients refrained from using services against the medical advice was expected during the pandemic response. Therefore, there is a clear need for adaptation and monitoring of the current emergency response psychiatric services.^{5,22} In general, the study cohort was satisfied with virtual clinics and there has been no interruption in medication supply for the patients but the hospital health education regarding COVID-19 could be improved.

There is a need for further research to explore the knowledge of psychiatric patients and their caregivers regarding COVID-19. Health workers at mental health

institutes could be a valuable source of information regarding COVID-19 for mental health patients.¹⁵ Awareness messages for all mental health patients with a particular focus on pediatric cases could reduce the risk of infection. However, infection prevention and control (IPC) measures should be applied and strictly followed at all psychiatric hospitals.³³

Policymakers and community leaders should allocate adequate financial and human resources for the continued demand for mental health services.³⁰ The results of this study could be used for future planning regarding pandemic responses and its effects on mental health patients and their families.

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ملخص

الأهداف: تهدف هذه الدراسة الى قياس مدى تأثير جائحة كورونا على المرضى النفسيين وذويهم وكذلك تأثير ما حصل من تغيير في طريقة تقديم الخدمة للمرضى على نوعية تلك الخدمة، بالإضافة لتأثير الجائحة على طريقة طلب الخدمة النفسية والالتزام في العلاج وكذلك مستوى الرعاية المقدمة في منازلهم. **آلية البحث:** هذه دراسة وصفية ومقطعية تمت من خلال دعوة 1,168 من مقدمي الرعاية (نوي المرضى) للمشاركة كعينة عشوائية، واستخدمت فيها الطريقة المنهجية لاختيار المشاركين في الدراسة بحيث تم اختيار كل ثالث شخص حسب قاعدة بيانات المرضى الموجودة في قسم شؤون المرضى، وتم ارسال الدعوة لمقدمي الرعاية بواسطة رسائل التواصل الاجتماعي (الواتس اب) للإجابة على أسئلة الاستبيان المحدد الاختيارات الذي تم تصميمه اعتماداً على دراسات سابقة منشورة ومتعلقة بالجائحة ويتم تعبئته ذاتياً ومكون من ستة وعشرين سؤال. **النتائج:** 246 مقدم رعاية أو من ذوي المرضى من اصل 1,168 قد شارك في هذه الدراسة بمعدل استجابة بلغ 21%، نصف المشاركين تقريباً كانوا من مقدمي الرعاية لمرضى اناث، 52% كانوا لمرضى أعمارهم اكبر من 39 سنة، واحد من كل اثنين من مقدمي الرعاية أشاروا الى وجود تدهور في الأعراض الخاصة في الأمراض النفسية و38% من المشاركين في الدراسة أفادوا بوجود أثر سلبي على مدى التزام المرضى بالعلاجات النفسية و 4 من كل 10 مشاركين أفادوا بوجود تأثير سلبي للجائحة على مستوى الرعاية المنزلية للمريض النفسي، نصف المشاركين أفادوا بوجود قلق لدى المرضى النفسيين من العزلة الناتجة عن إجراءات الحجر الصحي، و50% من المشاركين أفادوا بأنهم سوف يرفضون ادخال مرضاهم الى المستشفى في حال قرر الطبيب ذلك خلال الجائحة، 71.3% من المشاركين أفادوا بعدم الشعور بالاطمئنان لصرف الدواء للمريض دون مقابلة المريض بسبب الجائحة. **الاستنتاجات:** جائحة كورونا لها تأثير سلبي على الصحة النفسية لدى المرضى النفسيين المراجعين لمستشفى الصحة النفسية بالطائف وعلى مستوى الرعاية المنزلية المقدمة لهم من قبل ذويهم. وطريقة الحصول على الخدمة النفسية تأثرت أيضاً، لذلك ظهرت الحاجة الملحة لتغيير طريقة تقديم الخدمة للمرضى النفسيين بما يتناغم مع ظروف الجائحة، و ملاحظة ومتابعة الاستجابة الحالية الطارئة في خدمة الطب النفسي، وبرزت الحاجة لعمل دراسات علمية أكثر عن مدى ثقافة المرضى وذويهم بظروف الجائحة، وقد يكون للعاملين في منشآت الطب النفسي دور كبير في تثقيف المرضى النفسيين عن الجائحة، وللقائمين على الخدمة النفسية من أصحاب القرار دور كبير في توفير الدعم المادي وتوفير الكوادر البشرية لمقابلة احتياجات تطور قطاع الخدمة النفسية.

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Mental Health of Syrian Refugees: Translating Epidemiology and Research into Policy and Practice

Mohammed T Abou-Saleh and Mamoun Mobayed

الصحة النفسية للاجئين السوريين: ترجمة بحوث علم الوبائيات والتدخلات إلى سياسات وممارسات صحية

محمد أبو صالح، مأمون مبييض

Abstract

B **ackground:** The Syrian conflict, now in its eleventh year, has been described by the United Nations as the worst complex humanitarian emergency since World War II. It has resulted in widespread and profound adverse mental health and psychosocial consequences for Syrians who were internally displaced and refugees in neighboring countries. **Aims:** The aims of this narrative overview are to examine the epidemiology research on the burden of mental disorders in displaced Syrians; to review the evidence base for psychosocial interventions and to translate these findings into effective health policies and practice. **Method:** Databases were searched for this review, including PubMed and Google Scholar. Search terms included conflict, epidemiology, mental disorders, cultural issues, intervention, mental health, capacity building, policy, practice, psychosocial support, Syrian refugees, and treatment. We included only English language papers. The final search was done on 17 May 2021. **Results:** Many relevant studies, reviews and UN and WHO resources were identified and included in this review. The findings were summarized into the following subcategories: epidemiology and burden of mental disorders among Syrians, MHPSS interventions for Syrian refugees, building capacity for MHPSS for Syrian refugees and translating research evidence into policy and best practice. **Conclusions:** There are formidable challenges to the provision of MHPSS for Syrian refugees. There is need for more research on the long-term consequences of the conflict on all Syrians, on evaluation of MHPSS within complex interventions and models of care and on the challenges of their implementation to inform optimal health policies and best practice.

Keywords: Conflict, epidemiology, intervention, mental health, policy, psychosocial support, Syrian refugees, treatment

Declaration of interest: None

Introduction

The conflict in Syria, now in its eleventh year, has been described by the United Nations as the worst complex humanitarian emergency since World War II. What started as a peaceful civilian protest for freedom, democracy, rule of law and human rights following the emergence of the Arab Spring, rapidly evolved into violence and armed conflict that was initiated and perpetrated by the Syrian regime.

The Syrian conflict is unprecedented in the magnitude of humanitarian and public health catastrophe with extensive deaths, displacement, widespread destruction of the country's infrastructure and devastating health consequences. Nearly 600,000 have died in this conflict and millions are displaced, inside Syria with millions also being displaced to mostly Turkey, Lebanon, and Jordan.¹⁻⁵

This complex humanitarian emergency crisis features large in the contemporary global refugee crisis and Syrian refugees remain in protracted situations living in conditions of insecurity, socioeconomic instability, and political adversity. Weaponization of health care, including

attacks on healthcare facilities and targeting of healthcare workers, has been a defining feature.⁶

The Lancet-American University of Beirut Commission on Syria documented the extensive and unprecedented deliberate targeting of health workers and healthcare facilities by the Syrian Government and allied forces “the weaponization of healthcare - a strategy of using people's need for healthcare as a weapon against them by violently depriving them of it - has translated into hundreds of health workers killed, hundreds more incarcerated or tortured, and hundreds of health facilities deliberately and systematically attacked”.^{7,8}

The conflict impacted health professionals resulting in high rates of burnout on 3350 resident physicians in specialties, including psychiatry in 12 different hospitals spread over eight governorates in Syria who reported a very high level (94%) in at least one of the three domains (emotional exhaustion, depersonalization and reduced personal accomplishment) with 19% of the residents reporting a high level of burnout in all three domains.⁹ Syrian mental

health professionals have experienced trauma, loss and violations, adding to the literature of the professional issues and ethical duty to protect health workers in conflict settings.¹⁰ In Syria and refugee-hosting neighboring countries, more than 23 million people need humanitarian assistance.¹¹

The Global Burden of Disease study (2013) reported that the crisis in Syria resulted in a reduction in life expectancy.¹² The Syrian conflict has been marked by indiscriminate violence, the use of chemical warfare and the use of health and sexual violence as weapons in the wanton terrorizing and demoralizing of Syrian civilians.

Moreover, the Independent International Commission of Inquiry on the Syrian Arab Republic documented how civilians have been subjected to various forms of sexual violence in government detention facilities.¹³

Finally, a recent Gallup World Poll, from 2008 to 2015, showed that Syrians' physical, mental, and social well-being declined substantially. Importantly the poll indicated that "global data covering 1.7 million participants across 163 countries from 2006 to 2016 show during the conflict, Syria's precipitous decline in well-being is unparalleled in the world, even when compared to countries similarly experiencing war, protests, and disasters".¹⁴

The aims of this narrative overview are to review research on epidemiology of mental disorders and psychosocial consequences of the Syrian conflict in Syrians who are IDPs and refugees in neighboring countries (Turkey, Lebanon, Jordan); to review the evidence base for psychosocial interventions; to consider the treatment gap in mental health, and manpower requirements of these Syrian populations and to translate these findings into effective health policies and practice.

Epidemiology, determinants, and burden of mental disorders among Syrians

Early studies and reviews of the prevalence of mental disorders in Syrian populations showed high rates of depressive, anxiety, and posttraumatic stress disorders.^{15,16}

A systematic review reported that Syrians exposed to the conflict may suffer from exacerbations of pre-existing mental disorders incidence cases following conflict related violence, displacement, and multiple losses; and mental health issues related to stresses of adaptation to the post-emergency context with some populations being particularly vulnerable, such as women survivors of sexual or gender-based violence, and children who have experienced violence and exploitation.¹⁷

A recent systematic review of the burden of mental disorders in Syria and among Syrian refugees in neighboring countries, identified 28 eligible studies including two studies that involved conflict-affected populations within Syria including eight studies focused on children and adolescents.¹⁸ The studies were cross-sectional, 10 studies took place in refugee camps, 10 in non-camp settings and four in both settings. Levels of post-traumatic stress disorder ranged from 16-84%, depression from 11-49%, and anxiety disorder from 49-55% with common risk factors of exposures to trauma and having a personal or family history of mental disorder. PTSD was associated with war-related violence and/or traumatic-related experiences, cumulative trauma exposure, displacement in a camp, trauma centrality (degree to which experienced trauma lends meaning and identity), lower self-efficacy, personal or family history of mental health problems, poor physical health and previous chronic conditions (unspecified), being a housewife or student, lack of coverage of basic needs, unavailability of medication, and being unemployed. Female gender was

associated with higher posttraumatic stress disorder (PTSD) rates in two studies but not in others. PTSD was also associated with anxiety, depression, and physical health problems.

A pilot study of the prevalence of mental disorders in Syrian refugees in Lebanon who were accepted for resettlement in the UK using the Global Mental Health Assessment Tool - led by the first author and Hala Kerbage for the UK Home Office and Public Health England - showed a low prevalence (9%) of mental disorders.¹⁹ All of the assessed applicants for resettlement in UK, reported a high level of psychosocial stressors and adverse living conditions. Despite this high level of adversity, the majority of the applicants assessed were able to manage their daily functioning and cope with distress with available community and family resources. The majority of those with diagnosable mental disorder, suffered from depression and anxiety disorders with few experiencing comorbid PTSD. The low rate of PTSD is in accordance with findings of other studies in acute displacement settings (compared to post-resettlement settings) and PTSD might arise later on, when the life conditions become more stable. A recent study conducted in Syria during wartime, reported similar findings.²⁰ These findings are in tune with new WHO prevalence estimates of mental disorders in conflict settings: the systematic review reported the high burden of mental disorders, including bipolar disorder and schizophrenia (22.1%) at any point in time in the conflict-affected populations with comorbidity of 5.1%.²¹

Syrian refugees in Turkey showed higher rates of major depressive disorder than internally displaced persons in Syria whilst PTSD was more prevalent in the latter than the

former and was also associated with postmigration factors.²²

The massive disruption to family and social networks in the context of extreme violence may perpetrate domestic violence, familial child abuse and transgenerational mental ill health, arguing for ecological epidemiology.²³

Overall, the reviewed studies are informative but have limitations of being cross-sectional, use of self-reported measures some of which were not validated in Syrian populations resulting in high rates of mental disorders, sampling designs and predominant setting of camps. Moreover, the studies do not allow a clear distinction to be made between situational forms of distress and frank mental disorder, a shortcoming that may be addressed by longitudinal studies.²³

Mental health of Syrian children and adolescents

The systematic review reported the results of eight studies conducted on Syrian children and adolescents showing high rates of depression (18-74%), anxiety (14%) and PTSD (23-45%).¹⁸

Syrian refugee children and adolescents in Istanbul showed prevalence estimates for depression, PTSD, and anxiety of 12.5%, 11.5% and 9.2% respectively.²⁵ Depression and PTSD were significantly more common in older adolescents, whilst anxiety and PTSD were significantly more common in girls. Depression was more common in children from poorer households and those who had received no education. Children coming from larger households were less likely to show symptoms of PTSD. In Damascus schools, 53% of students suffered from PTSD; 62% from problematic anger; 46% declared a fair or worse general health and 61% had moderate or severe mental health problem.²⁶

In a pivotal study, Karam *et al.*²⁷ investigated the etiological interplay of childhood adversities and environmental sensitivity in the development of post-traumatic stress disorder in war-exposed Syrian refugee children and adolescents in Lebanon. The authors concluded that “when considering the effects of war on PTSD in refugee children, it is important to take account of the presence of other adversities as well as of children's sensitivity. Sensitive children may be more vulnerable to the negative effects of war exposure, but only in contexts that are characterized by low childhood adversities”.

In Syrian refugee children, experiences of depression and anxiety were associated with PTSD, particularly in those with physical health problems; in those who lost their mothers in the war; lost their fathers and separated from their families.²⁸

Importantly Syrian refugees have experienced trauma, loss, gross violations of their human rights resulting in grief, frustration, and anger for the injustice of their situations compounded by post-migration difficulties resulting in a sizeable minority suffering from depression, anxiety, and PTSD.

It is anticipated that future studies may uncover syndemic effects in the complex humanitarian Syrian emergency in view of occurrence of multimorbidity, including mental conditions in contexts of the extreme political violence as shown in case studies in Nepal (co-occurrence of depression and PTSD in girl soldiers in communities of mixed castes and religions) and in Ethiopia with appropriate interventions.²⁴

The impact of war on family processes, particularly parenting behavior and, *inter alia*, on child psychosocial outcomes in Syrian refugees in Lebanon indicated that exposure to war-related events was directly associated with maternal posttraumatic stress (PTS) and general psychological distress, as well as indirectly via daily stressors. Mothers' general psychological distress, but not PTS, was directly associated with negative parenting and child psychosocial difficulties.

Economic strain and loss of educational opportunities during displacement had a negative impact on the well-being of adolescent Syrian refugees in Lebanon.³⁰ For girls the displacement increased risks of child marriage and limitations in mobility. Moreover, adolescents themselves expressed tensions with their Lebanese counterparts and feared verbal attacks and beatings from school-aged Lebanese male youth.

Chen *et al.*³¹ studied the impact of war and displacement on executive function - what the authors call the cognitive signatures of minds under siege in Syrian adolescent refugees in Jordan in comparison with Jordanian non-refugees. Associations were observed between poverty and working memory suggesting that even in populations exposed to substantial violence and fear, poverty is a specific pathway to working memory deficit.

In primary school-aged Syrian refugee children in Lebanon, attending a lower grade than their age-expected grade level, uniquely predict Syrian refugee children's developmental processes and academic outcomes. Moreover, children's executive function and behavioral regulation, but not internalizing symptoms, partially mediated the relations between risk factors and academic outcomes.

In summary, for Syrian children, “the complex emergency has brought on massive social change both at the structural level of legal, socioeconomic, educational, and health systems, and at the intimate heart of everyday family life”.³³ Moreover, the dire socioeconomic changes

following displacement have compounded their adverse experiences, including loss of educational opportunities rendering children “the lost generation” with longstanding if not lifelong mental health difficulties.

MHPSS interventions for Syrian refugees

The provision of Mental Health and Psychosocial Support (MHPSS) to meet the escalating demand following the onset of the Syrian conflict has been extremely challenging against the background of a rudimentary pre-conflict, mostly institutional mental health services in Syria.¹⁶ There is minimal coverage of MHPSS in view of the continuing violence within Syria³⁴ and in hosting countries³⁵ indicating the need to integrate MHPSS into routine primary care services.³⁶

In Turkey, the burden of mental disorders faced with barriers to service provision, has been shown to be related to stigma, language, financial difficulties, legal status, social and cultural beliefs, challenges that are compounded by restrictive migration policies and issues related to poverty and social exclusion.³⁷

Syrian refugees in Istanbul rarely access MHPSS services despite formally having access to the public mental health system in Turkey.³⁸

The treatment gap in MHPSS for Syrian refugees has led to the widespread adoption by policy makers in neighboring countries of the WHO Mental Health Gap Action Program (mhGAP). The mhGAP aims at scaling up services for mental, neurological and substance use disorders in low- and middle-income countries (LMIC). The mhGAP was implemented in Turkey.³⁷ with training 1468 Syrian and Turkish doctors, serving in primary health care during 2016-2019.³⁷

The Lebanese Ministry of Public Health, in collaboration with WHO, UNICEF, and the International Medical Corps, launched the first National Mental Health Program to reform the mental health system and scale up services. The program has coordinated the work of more than 62 organizations working to provide MHPSS in primary health care centers using mhGAP and psychological first aid in response to the Syrian crisis.³⁹

Syrian healthcare workers (HCWs) are among those who fled the Syrian conflict to Lebanon and have been working informally providing services to Syrian refugees filling a gap in the formal health system.⁴⁰ The authors recommend “that policy decision makers within humanitarian agencies and the Government of Lebanon explore the possibilities for allowing temporary registration of displaced Syrian IHCW to benefit local host communities and refugee populations until their return to Syria”.

A pivotal study of the perceptions and experiences of professionals and of Syrian refugees accessing mental health services in Lebanon, reported important and informative findings.⁴¹ Firstly, whilst refugees viewed their distress as a normal shared reaction to adversity, mental health practitioners considered it as diagnostic of mental illness. Secondly, mental health practitioners viewed Syrian culture as a barrier to providing care and thus advocated educating refugees about mental health issues. Thirdly, policymakers invoked the state of crisis to justify short-term interventions, while Syrian refugees requested community interventions and considered resettlement in a third country the only solution to their adverse living conditions. The authors opined that “the therapeutic relationship seems threatened by mistrust, since refugees change their narratives as an adaptive mechanism in response to the humanitarian system, which professionals consider manipulative and discussed the implications of their findings for mental health practice in humanitarian settings”.

The mhGAP was also implemented within Syria and Iraq. Training non-specialist health workers was shown to improve their knowledge and skills for managing mental health disorders in primary healthcare.⁴²

Besides the primacy of mhGAP, the WHO has developed a range of scalable psychological interventions aimed at reducing psychological distress and improving functioning in people living in communities affected by adversity. These interventions, including Problem Management Plus (PM+) and its variants, are intended to be delivered through individual or group face-to-face or smartphone formats by lay, non-professional people who have not received specialized mental health training. Scalable PM+ oriented programs have been adapted for the mental health needs of Syrian refugees in both neighboring and European countries hosting Syrian refugees.⁴³ There is an ongoing randomized controlled trial of peer-to-peer Group Problem Management Plus (PM+) for adult Syrian refugees in Turkey.⁴⁴

Research priorities on the mental health of Syrian refugees, include strengthening MHPSS with monitoring and evaluation, epidemiological studies and implementation research focused on testing interventions.⁴⁵

Cultural issues in MHPSS assessment and interventions

The UNHCR provided a guide on the sociocultural background and MHPSS of the Syrian population within the context of the armed conflict primarily to inform MHPSS staff. The guide complements the more generic guidance of the Inter-Agency Standing Committee (IASC) Guidelines for Mental Health and Psychosocial Support in Emergency Settings and “provides detailed information on the role of social, cultural, and contextual factors in the presentation and expression of mental and psychosocial distress and how this is interwoven with cultural and religious notions of personhood”.⁴⁶

Wells *et al.*,⁴⁷ in ground-breaking research, developed an ecological model of adaptation to displacement based on the experience of Syrian and Jordanian psychosocial workers supporting the Syrian refugee community in Jordan. The emergent themes, including adaptive functions of a culturally significant concept of dignity (karama) moderated by gender and displacement were in tune with the five ADAPT pillars identified by Silove.⁴⁸ The authors concluded “the transactional concepts in this model can help clinicians working with displaced people to consider and formulate a broader range of causal factors than is commonly included in individualistic therapy approaches. Researchers may use this model to develop testable hypotheses”.

Arabic speaking refugees, mostly Syrians resettled in Germany, presented with somatic symptoms.⁴⁹ However, and importantly internalized stigma of mental ill health were not related to somatic symptoms, but were related to psychological symptoms, results that provide the “first empirical indications for the relationship of symptom expression with the use of explanatory models and conceptualizations of mental illness within the Arabic culture and language” A further study of the impact of faith

on the mental health of refugees in Germany showed that those with stronger faith used faith-based coping strategies with implications for providing culturally-sensitive mental healthcare.⁵⁰

A practical cross-cultural guide was developed for MHPSS practitioners working with resettled Syrian refugees⁵¹ that provided the following key recommendations (quoted verbatim):

- Focusing efforts on advocacy for human rights and improvement of living conditions (e.g., housing, employment, food) and fostering coping skills and resilience are key to effective mental health services for Syrian refugees.
- Healthcare providers should be careful not to over-diagnose mental disorders among displaced Syrians, especially in the early post-settlement phase when refugees face insecurity and have many ongoing daily stressors.
- Providers are advised to avoid psychiatric labelling because this can be especially alienating and stigmatizing for survivors of violence and injustice. Using easy-to-understand terms is recommended.
- Healthcare practitioners should avoid being overly directive. Instead, listening closely to the wishes and views of the person who seeks help will empower them to make their own decisions.
- Services for sexual and gender-based violence survivors may be more acceptable if they are provided within a non-stigmatizing setting, such as general health care or women’s centers, without initially addressing the issue of abuse explicitly.

Effectiveness of MHPSS in Syrian adults and children

A systematic review of MHPSS interventions in Syrian refugees reported the results of eight studies that evaluated the effectiveness of eye movement desensitization and reprocessing (EMDR), cognitive behavioral therapy (CBT), psychological first aid (PFA) and other interventions.¹⁸ Six studies were conducted in Turkey, including two studies in children, one study in Lebanon and one in Jordan. Six studies were pre-post design involving urban populations and two RCTs conducted in camps in Turkey. Overall, the studies reported improved clinical outcomes, well-being and improved competency of service providers. The authors recognized the limitations of these studies: interventions were brief with few weeks follow-up, small scale, using no measures of cost-effectiveness, and no evaluations of larger-scale interventions

implemented across different cities or camps were identified.

Experimental and randomized controlled trials of a psychosocial intervention for youth affected by the Syrian crisis reported informative findings.⁵² The study demonstrated the effectiveness of an 8-week program of structured activities informed by a profound stress attunement (PSA) framework (Advancing Adolescents), delivered in group-format to 12–18-year-olds in communities heavily affected by the Syrian crisis including both Syrian refugee and Jordanian youth. This study is pivotal in advancing “an implementation science agenda on mental health and psychosocial responses in war-affected settings: using an innovative approach, this work

demonstrates that a thoughtful, ethical, and scientifically valid trial can be carried out amid mass displacement”.⁵³

Promoting positive parenting of Syrian refugees in Lebanon and Jordan using interactive and educational sessions was shown to improve parents’ wellbeing, skills and to reduce their children’s difficulties and conduct problems.⁵⁴

In a pilot randomized controlled trial (RCT) of the War Child Holland’s Caregiver Support Intervention (CSI) in Syrian refugees in Lebanon reported that the CSI group showed significantly increased parental warmth and responsiveness, decreased harsh parenting, lowered stress, and distress, improved psychosocial wellbeing, and improved stress management⁵⁵ Moreover, CSI parents reported increased child psychosocial wellbeing. The authors are conducting a definitive large scale RCT of CSI in Syrian refugees in Lebanon.⁵⁶

The effectiveness of a classroom-based group psychosocial intervention in children and adolescents exposed to war in Lebanon has not been proven in a large-scale study.⁵⁷

An epidemiologic study of resilience-promoting factors in war-exposed adolescents, reported that resilience was related to being male, using problem-solving techniques, having leisure activities, and having parents who spent time with their adolescents and who supported them with schoolwork.⁵ The authors concluded that “interventions designed for war-traumatized youth must build individual coping skills of children and adolescents, yet at the same time target parents and teachers in an integrated manner”.

A recent study of children’s protection concerns and MHPSS outcomes, conducted in schools in real-time in northwest Syria, showed the highly complex nature of MHPSS variables, needs and outcomes in Syria.⁵⁹ The findings call “for the need to implement far-reaching and intersectoral approaches in children’s protection projects, and for the integration of protection standards across various projects and sectors”.

Global and regional action

The WHO Comprehensive Mental Health Plan 2013-2020, proposed that member countries: work with national emergency committees and mental health providers to include MHPSS needs in emergency preparedness; enable access to safe and supportive services, that address psychological trauma and promote recovery and resilience, for persons with mental disorders or psychosocial problems and provide services for health and humanitarian workers, during and following emergencies, with due attention to the longer-term funding required to build or rebuild a community-based mental health system after the emergency.⁶¹ In 2017, the WHO produced a draft global action plan, 2019-2023 for promoting the health of refugees and migrants.⁶²

The WHO Eastern Mediterranean Office (EMRO) has adopted these action plans for the provision of MHPSS for Syrians within Syria including North West Syria with “broad recommendations for the ministry of health to embed mental health and psychosocial support in national health and emergency preparedness plans; put in place national guidelines, standards and supporting tools for the provision of mental health and psychosocial support during emergencies; strengthen the capacity of health professionals to identify and manage priority mental disorders during emergencies; and utilize opportunities generated by the emergency response to contribute to development of sustainable mental healthcare services”.⁶³

Moreover, in 2020 and in the context of the emergence of the COVID-19 pandemic, EMRO advocated the introduction of WHO-supported mobile teams to deliver mental health care in Syria. These efforts were broadly

supported by the EMRO commissioned report, Build Back Fairer: Achieving Health Equity in the Eastern Mediterranean Region.⁶⁴

The report is timely in identifying the stark health and social inequities in the 22 countries in the region including the impact of COVID-19 in exposing and amplifying these inequities. Importantly, the report focused on the impact of conflicts and complex emergencies in the East Mediterranean: the high number of conflict-related deaths of more than 150,000 deaths per year since 2014, conflicts that cause high rates of disability, communicable and noncommunicable diseases and poor mental health. The conflicts exacerbate existing inequities and adversely affect all aspects of the social determinants of health, including the availability of early years support, education, health services, employment, incomes, social protection systems, shelter, water, sanitation, electricity and basic human rights, and often leads to high levels of migration and the collapse of governance systems.

The Commission has delivered the research evidence for social determinants of health including mental health and produced a roadmap for transformative action and priorities for implementation. It is incumbent on all stakeholders to take responsible action to Do Something, Do More, Do Better. Psychiatrists as members of professional associations, leaders of mental health in their countries, service providers, teachers, trainers, researchers, and advocates have a major role in facilitating the implementation of these recommendations.⁶⁵

An analysis of the effects of conflicts in Iraq and Syria showed how wars have resulted in both the militarization and regionalization of healthcare, conditions that complicate the rebuilding of previously robust national healthcare systems.⁶⁶ Moreover, it showed how historical and transnational frameworks can be used to show the long-term consequences of war and conflict on health and healthcare. The report introduced the concept of therapeutic geographies - defined as the geographic reorganization of healthcare within and across borders under conditions of war.

International collaborative work produced the IASC and the Sphere project that set universal minimum standards in core areas of humanitarian response. Importantly international collaborative work produced the Research for Health in Humanitarian Crisis (R2HC) program that aims to strengthen humanitarian health practice and policy through research.⁶⁷ The findings of research have both challenged and confirmed widely-held assumptions about the effectiveness of mental health and psychosocial interventions in humanitarian settings. Further research needs “to fill knowledge gaps regarding how to: scale-up interventions that have been found to be effective (e.g.,

questions related to integration across sectors, adaptation of interventions across different contexts, and optimal care systems); address neglected mental health conditions and populations (e.g., elderly, people with disabilities, sexual minorities, people with severe, pre-existing mental disorders); build on available local resources and supports (e.g., how to build on traditional, religious healing and community-wide social support practices); and ensure equity, quality, fidelity, and sustainability for interventions in real-world contexts (e.g., answering questions about how interventions from controlled studies can be transferred to more representative humanitarian contexts)”.

Against the background of rudimentary mental health services in conflict zones in the Arab region, it has become incumbent on international relief agencies to provide MHPSS to refugees that is often short term: it is advocated that for a sustainable framework, that there should be a larger role for regional and local actors and for development of expertise that is culturally and socially grounded that could take the initiative in research, training and deployment in collaboration with non-governmental organizations, allowing for comprehensive development of the mental health sector.⁶⁸

Building capacity and capability for MHPSS for Syrian refugees

Capacity building for MHPSS for Syrians is guided by the WHO pyramid of the optimal mix and hierarchy of mental health services that recommend: promotion of self-care; developing informal community care; integration of mental health into primary care services; developing community specialist mental health services, inpatient mental health units in general hospitals and inpatient units for people with severe and complex mental conditions.

Notwithstanding the ongoing conflict in northwest Syria, the OCHA report in 2020 stated that there are 157 health facilities with MHPSS Programs with 163 mhGAP-trained doctors that are supported by weekly online psychiatrists in capacity building, including online training in child psychiatry and addictions.⁶⁹ Of concern is that there was a 38% increase in suicide cases in the last quarter.

Self-care has been advocated for Syrians⁷⁰ and the WHO has recently introduced an illustrated mental health self-care intervention, “Doing what matters in times of stress”.⁷¹ A user-centered app adaptation of a low-intensity E-mental health intervention for Syrian refugees was shown to be acceptable to Syrians who were found to have high technical literacy.⁷ An important cluster randomized trial of guided self-help to reduce distress in Sudanese female refugees in Uganda showed that Self-Help Plus is an innovative, facilitator-guided, group-based self-help intervention that can be rapidly deployed to large numbers of participants and resulted in meaningful reductions in psychological distress at three months.⁷³

Charlson *et al.*⁷⁴ applied epidemiological modelling of outputs of the burden of major depression and PTSD in the Syrian population and their MHPSS needs and the human resources requirements to scale-up recommended packages of care for PTSD and depression in Syria over a 15-year period using the World Health Organization mhGAP costing tool. The total number of cases of PTSD in Syria was estimated at approximately 2.2 million, and approximately 1.1 million for depression. The human resource requirements estimated the need for a steady increase from 0.3 FTE at baseline to 7.6 FTE per 100,000 population after scale-up and the linear scale-up over 15 years could see 7-9% of disease burden being averted. However, the needs for increased professional human resources are likely to be greater as these estimations were for the provision of care to people with depression and PTSD.

A systematic review of the health needs of Syrian refugees in Lebanon and Syria's neighboring countries identified 63 informative articles.³⁵ Mental health was identified as one of the greatest health needs in the region with a high gap in services and sub-optimal training and availability of health workers, particularly in Syria. The findings highlighted the need for an enhanced synchronized approach in Syria's refugee hosting neighboring countries to reduce the existing gaps in responding to the mental health needs of Syrian refugees. This mainly includes training of healthcare workers to ensure a skilled workforce and

community-based efforts to overcome barriers to access, including lack of knowledge and awareness about highly prevalent health conditions.

The protracted Syrian conflict has impacted on the provision of healthcare workers (HCWs), undergraduate and post-graduate education and training in non-government-controlled areas in northwest Syria.⁷⁵

A review of policies on return and reintegration of displaced healthcare workers towards rebuilding conflict-affected health systems for the Lancet-AUB Commission

on Syria, reported few specific policies and the limited information available explicitly focused on the repatriation and reintegration of such workers to their home country in the post-conflict period.⁷⁶

In view of dire and rudimentary state of mental health services in pre-conflict Syria, there is a case of need to Building Back Better in post-conflict Syria as demonstrated in the WHO publication on how this was done in 10 diverse emergency-affected areas using a longer-term perspective.⁷⁷

The Syrian Association for Mental Health

The Syrian Association for Mental Health (SAMH), a mental health multi-professional association established in 2012 has been concerned with the mental health of all Syrians and the provision of MHPSS with focus on the need for community services and enforcement of the prime resource of resilience, self-management and promoting recovery.⁷⁰ SAMH has risen to the challenges in contributing to essential MHPSS and training for specialist and non-specialist health workers in evidence-based interventions. Moreover, SAMH has produced the Ethical Code for Syrian Mental Health Practitioners. Last but not least and with funding from the World Psychiatric

Association and in collaboration with The EU ARTIP (Awareness Raising and Training for the Istanbul Protocol) project lead by Thomas Wenzel,⁷⁸ SAMH organized training for Syrian health professionals in the use and application of the Istanbul Protocol (Manual on Effective Investigation and Documentation of Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment), the United Nations standard for training in the assessment of persons who allege torture and ill treatment, for investigating cases of alleged torture, and for reporting such findings to the judiciary and any other investigative body.

Translating research evidence into policy and best practice

The Syrian complex emergency with extreme unprecedented violence, weaponization of health, torture and extensive violation of human rights has resulted in an epidemic of mental distress, loss and high rates of mental ill health. Moreover, there is evidence for effectiveness of MHPSS. Whilst the MHPSS needs of Syrians refugees in neighboring countries are partially met, the needs of Syrians within Syria, particularly those internally displaced, are largely unmet.

Translating this evidence into policy and practice in conflict situations is challenging, particularly in the case of Syria: there are no long-term studies of the impact of the conflict on the mental health of Syrian refugees in the contexts they are unsettled or resettled in. Silove *et al.*²³ addressed this issue in refugees in low-income countries and posited that it is not realistic to expect refugees to access general or specialist mental health services and that “creative solutions are thus necessary, including networking of all agencies to ensure the sharing of responsibility of care for refugees with mental disorder, and task-shifting, i.e., the transfer of skills to primary care and lay workers in order to undertake specific mental health interventions of various types under supervision”.

Implementation of WHO guidelines for acute stress, PTSD, and bereavement faces barriers recommending

strengthening knowledge on effectiveness of existing cultural practices for improving mental health; improving supervision capacity of current mental health staff to address shortage in human resources; and increasing awareness of help-seeking clients on the potential effectiveness of psychological versus pharmacological interventions.⁷⁹

The mhGAP intervention guide has been shown to be highly effective in building capacity and capability in Syria and neighboring countries. Moreover, it has been fine tuned by engaging culture and context for optimal implementation and thus fostering reflexive deliberation in practice.⁸⁰ An updated systematic review on the evidence and impact of the mhGAP-IG demonstrated the substantial impact on training, patient care, research and practice. Priorities for future research should be less-studied regions, severe mental illness, and contextual adaptation of brief psychological interventions.⁸¹

Further, a major advance has been the introduction of Problem Management Plus (PM+) and its variants that are delivered through individual or group face-to-face or smartphone formats by lay, non-professional people who have not received specialized mental health training and peer-refugees.⁸² The use of the scalable PM+ oriented programs that has been adapted for Syrian refugees in the

newly launched STRENGTHS program for adapting, testing, and scaling up of PM+ in various modalities in both neighboring and European countries hosting Syrian refugees.⁴³

Problem Management Plus has been successfully implemented in hard-to-reach areas with trained psychosocial workers in Syria through humanitarian agencies using remote supervision.⁸³

A recent study of integrated physical and mental health awareness education intervention reported a reduction in non-communicable diseases among Syrian refugees and Jordanians in host communities.⁸⁴ A review of the mental health impact of social capital interventions (community engagement and educative programs, cognitive processing therapy and sociotherapy for trauma survivors, and neighborhood projects), showed improved mental health outcomes, but there was little evidence of benefit compared to control groups in the long term.⁸⁵

For scaling up MHPSS interventions there is need for four types of necessary evidence: effectiveness with sociocultural relevance; cost-effectiveness; process evidence and evidence on the broader health system and policy context in which the intervention is to be scaled up.⁸⁶ Moreover, “process information should go beyond what is being delivered (e.g., fidelity, dose, and adaptation) and include data on mechanisms of impact (e.g., participant responses and unexpected consequences) and local contextual factors affecting the intervention and its delivery”.

The challenges of planning the scale up of brief psychological interventions for conflict-affected populations have been addressed using theory of change (ToC). Three ToC workshops were conducted in Turkey, the Netherlands, and Lebanon in which Management Plus (PM+) and the Early Adolescent Skills for Emotions (EASE) interventions are implemented for Syrian refugees.⁸⁷ Two distinct causal pathways for scale up were identified (a policy and financing pathway, and a health services pathway) which are interdependent on each other. These findings highlight that scaling up brief psychological interventions for refugees builds on structural changes and reforms in policy and in health systems. Both horizontal and vertical scale up approaches are required to achieve sustainability.

A review of barriers and facilitators for scaling up MHPSS in LMIC for populations affected by humanitarian crises identified fourteen eligible studies, seven of which were in conflict situation.⁸⁸ The findings were that few MHPSS interventions appear to have been scaled up horizontally (replicated or expanded), integrating services into primary and community care through staff training, task-sharing, and establishing referral and supervision mechanisms. There is also need for vertical (where policies or legal

action are used to institutionalize innovations into regulatory frameworks), or diversification (where new innovations are added to existing interventions) to secure their long-term sustainability.

A study of low-intensity transdiagnostic family intervention for common mental disorders in health and non-health sector settings using a task-sharing approach highlighted the need for innovative collaborative and multidisciplinary approaches to understanding and addressing many sociocultural, contextual, practical, and scientific challenges.⁸⁹

The complex Syrian emergency has unfolded in a variety of settings and contexts: Syrians in-situ, those internally displaced and those who have become refugees in neighboring countries and beyond. The challenges to developing, delivering, and implementing policies are formidable. These challenges call on implementation science meeting complexity science for optimal translation of epidemiology into effective policies and best practice, including the adoption of the Consolidated Framework for Implementation Research.^{90,91,92}

Indeed, in an innovative ground-breaking study, Médecins sans Frontières reported their experiences of providing multidisciplinary primary level non-communicable disease (NCD) care including MHPSS for Syrian refugees and the host population in Jordan.⁹³ They examined the program’s Reach, Effectiveness, Adoption and Acceptance, Implementation and Maintenance over time (RE-AIM). The multidisciplinary program was largely acceptable, achieving good clinical outcomes, but for a limited number of patients and at relatively high cost. RE-AIM proved to be a valuable tool in evaluating a complex intervention in a protracted humanitarian crisis setting and they proposed that model simplification, adapted procurement practices and use of technology could improve cost effectiveness without reducing acceptability and may facilitate replication.

Policy makers face tough choices for psychological interventions in crisis situations. At the 2019 second global inter-ministerial meeting held in Amsterdam, 35 countries and organizations signed a declaration to integrate mental health and psychosocial support services in crisis situations.⁹⁴ However, policy makers are left with the challenge of what psychological services to select and how to implement them. There is a growing range of psychological treatments, implementation modalities, and options to use with non-specialist community health workers, teachers, or peers. The conference in its declaration provided “recommendations for researchers conducting multi-site studies to foster the research-policy nexus: involvement of policy makers in planning multi-site studies; integration of implementation science theory and measures; comprehensively document usual care and incremental cost-effectiveness across sites and evaluate

moderators and mediators across sites”. Guided by these issues, the authors produced a practicable roadmap with a sequence of measurable indicators as an important step to

delivering interventions at scale and reducing the mental health treatment gap.⁹⁵

Future actions and lessons learned

It is not realistic to consider future actions for the provision of MHPSS within Syria whilst the conflict is ongoing save for supporting the present efforts of WHO EMRO and humanitarian agencies within Syria. Moreover, it is premature to produce a mental health national plan for post-conflict Syria except to invoke the WHO action on Building Back Better and the recent WHO EMRO report on Build Back Fairer introducing social injustice agenda for action. Pre-conflict mental health services were very rudimentary and comprised of two large mental hospitals in Damascus and Aleppo and few small inpatient units with no community mental health services.

It is evident that there is a large treatment gap in MHPSS for all Syrian populations, particularly those within Syria whether in government and non-government areas and those internally displaced that are uprooted from their home communities.

As we previously advocated that, the provision of MHPSS services for refugees and people displaced in Syria requires a protracted, humanitarian inter-agency collaborative model of care of accessible community based MHPSS services, as well as more specialized mental health systems and an increasingly efficient use of minimal resources. The current centralization of services in certain urban areas restricts access. Efforts are needed to attain a better geographical coverage of MHPSS services nationwide, which requires advocacy and effective involvement of the existing infrastructure. The further development of holistic MHPSS services and effective inter-agency cooperation systems is crucial and requires a response that is coordinated and inclusive of all stakeholders: humanitarian agencies, national NGOs, community-based support groups, traditional and religious healers. Improved coordination will remain a primary need among national partners working in the protection, health, social services, education, and livelihood sectors, to maximize the efficacy of limited resources and the sustainability of required MHPSS programming.^{96,97} There is need for conflict-

affected and post-conflict Syria to develop policies and initiatives that address factors within and beyond the health sector to encourage displaced HCWs to return and provide sustainable reintegration solutions for those who return to post-conflict health systems.⁷⁶

For Syrian refugees in neighboring countries, we endorse the recommendations of The UNHCR Assessment of Mental Health and Psychosocial Support Services for Syrian Refugees in Lebanon.⁹⁸ The Syrian American Medical Society for Mental Health undertook a mission to Jordan and Lebanon to address the MHPSS needs of Syrian refugees in 2019.⁹⁹ The mission engaged government authorities and NGOs and identified “two key elements for the advancement of humanitarian mental health care: the need for community-based mental health services, and the importance of transitioning from a crisis-response model in humanitarian mental health towards a model of resilience and post-traumatic growth”.

For building capacity, there is need to expand and scale up essential interventions, particularly mhGAP-IG and PM+ provided by non-specialist health workers in community health services, interventions that have been provided to Syrians within Syria and in neighboring countries. For developing capability, there is need for re-instating professional training programs for psychiatrists, psychologists, and other professional workers.

There is need to provide Tier 3 and 4 services for people with severe mental health difficulties and those with learning disabilities

We endorse the recommendations of Silove *et al.*,¹⁰⁰ that “low-cost mobile emergency teams led by psychiatrists and other mental health professionals, supported by community health teams of workers provided with intensive training and ongoing supervision, can provide psychotropic medications and social and family support in these unstable settings, averting the need for inpatient care except in the extreme instances”

Conclusions

The Syrian armed conflict now in its eleventh year, is almost unprecedented in the magnitude of humanitarian and public health catastrophe with widespread devastation of the country’s health infrastructure and profound adverse mental health and psychosocial consequences for Syrians who were internally displaced and refugees in neighboring countries. The conflict is unprecedented in the weaponization and health and sexual violence that were

used as tactics of war against civilians with violation of human rights, including the rights to health that amounted to war crimes.

Syrian refugees have experienced trauma, loss, gross violations of their human rights resulting in grief, frustration, and anger for the injustice of their situations compounded by post-migration difficulties resulting in a

sizeable minority suffering from depression, anxiety, and PTSD.

There is growing evidence for effective mental health and psychosocial support (MHPSS) services in the neighboring countries that hosted the refugees. Cultural issues should be considered in relation to the mental health assessment and the provision of MHPSS for Syrian refugees.

Notwithstanding the UN and WHO global and regional action plans for refugees, translating these research findings into optimal models of service, health policies and best practice for Syrians has been very challenging. Whilst there is growing evidence for the effectiveness of MHPSS that are integrated into primary care and community mental health services for refugees in neighboring countries, the provision of MHPSS within Syria, particularly for the

internally displaced is minimal, unstable, and governed by the acute emergency.

Optimally, displaced Syrian refugees need the provision of sustainable comprehensive evidence based MHPSS interventions within primary care, mainstream community mental health services and access to institutional care for people experiencing severe mental health difficulties.

There is need for more research on the long-term consequences of the conflict on all Syrians, on evaluation of MHPSS within complex interventions, on sustainable models of care and on the challenges of their implementation to inform optimal health policies and best practice.

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الملخص

خلفية البحث: وصفت الأمم المتحدة الصراع السوري الذي دخل عامه الحادي عشر بأنه أسوأ حالة طوارئ إنسانية معقدة منذ الحرب العالمية الثانية. وقد أدى ذلك إلى عواقب صحية نفسية سلبية واسعة النطاق وعميقة على السوريين الذين نزحوا داخليا، والذين لجأوا للبلدان المجاورة. **الأهداف:** تهدف هذه المراجعة العامة إلى دراسة أبحاث علم الوبائيات حول عبء الاضطرابات النفسية على النازحين السوريين؛ ومراجعة قاعدة الأدلة للتدخلات النفسية الاجتماعية، وترجمة هذه النتائج إلى سياسات وممارسات صحية فعالة. **الطريقة:** تم البحث عن قواعد البيانات لهذه المراجعة، بما في ذلك PubMed ومحرك بحث غوغل. وشملت مصطلحات البحث: النزاع، وعلم الوبائيات، والاضطرابات النفسية، والقضايا الثقافية، والتدخلات، والصحة العقلية، وبناء القدرات، والسياسات، والممارسات، والدعم النفسي الاجتماعي، والملاجئين السوريين، والعلاج. وقد أدرجنا فقط الأوراق باللغة الإنجليزية. وتم البحث النهائي في 17 مايو 2021. **النتائج:** تم تحديد العديد من الدراسات والمراجعات ذات الصلة، ومصادر الأمم المتحدة ومنظمة الصحة العالمية والتي تم إدراجها في هذه المراجعة. وقد تم تلخيص هذه النتائج في الفئات الفرعية التالية: علم الوبائيات، وعبء الاضطرابات النفسية بين السوريين، وتدخلات الدعم النفسي الاجتماعي للصحة النفسية (MHPSS) للملاجئين السوريين، وبناء القدرة على تقديم الدعم النفسي الاجتماعي للصحة النفسية (MHPSS) للملاجئين السوريين، وتم ترجمة هذه الأدلة البحثية إلى سياسات وأفضل الممارسات. **الاستنتاجات:** لقد ظهرت تحديات هائلة أمام توفير خدمات الدعم النفسي الاجتماعي للصحة النفسية (MHPSS) الخاصة للملاجئين السوريين. وأن هناك حاجة لإجراء المزيد من الأبحاث حول العواقب طويلة الأمد للنزاع على جميع السوريين، وحول تقييم خدمات الدعم النفسي الاجتماعي للصحة النفسية (MHPSS) ضمن التدخلات المعقدة ونماذج تقديم الرعاية، وحول التحديات التي تواجه تنفيذ هذه الخدمات من أجل إثراء السياسات الصحية المثلى وتوفير أفضل الممارسات.

الكلمات المفتاحية: النزاع، علم الوبائيات، التدخلات، الصحة النفسية، السياسات، الممارسات، الدعم النفسي الاجتماعي، اللاجئين السوريين، العلاج.

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Implementing Outcomes in Specialist Psychiatric Rehabilitation Mental Health Services: A Routine Clinical Audit

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مراقبة وقياس النتائج في خدمات الصحة النفسية لإعادة التأهيل، استناداً إلى الملاحظات والقياسات السريرية الروتينية

سامر داوود، ديرك تريسي، شارلوت هاريسون

Abstract

Objective: There is no standardized methodology to evaluate the effectiveness of psychiatric rehabilitation services. We aimed to achieve this using empirical indicators for efficacy. **Method:** Data were collected from routine clinical electronic notes. The subjective experience of recovery was explored using the Recovery Assessment Scale (RAS-24) questionnaire and meta-cognitive abilities using the Meta-Cognitions Questionnaire (MCQ-30) questionnaire, in twenty-three individuals in an NHS Trust rehabilitation service. **Results:** All clients were independent in their daily living skills. However, their main social interactions were limited. None of the individuals had finished any higher education; one person was able to secure a paid job. The rate of stepping down care from the rehabilitation team was low. The MCQ-30 and the RAS-24 scores were satisfactory. **Conclusion:** Social and psychological functioning and reduction in the amount of support needed can be measured using everyday practice indicators combined with self-rated questionnaires to determine subjective recovery experience.

Keywords: Rehabilitation, psychosis, outcomes, Schizophrenia, recovery

Declaration of interest: None

Introduction

The goals of rehabilitation services are to empower patients and to enhance recovery.¹ Recovery typically requires a variety of interventions to address the multifaceted nature of chronic severe mental health problems and their psychosocial consequences.^{2,3} However, the financial costs of these interventions are high⁴ and auditing such services and demonstrating effectiveness is crucial. In the UK, guidance for commissioners of rehabilitation services for people with complex mental health recommends the collection of routine outcome measurements to monitor the quality of care,¹ though this is not always done in practice. In part, this may be due to a lack of agreement on methodologies by which to audit and measure rehabilitation services, and debate on how well some research maps onto real-world

tools and practice.⁵⁻⁸ Additionally, providing good quality of care to clients with chronic mental health problems might not rapidly or easily lend itself to a clear sense of wellbeing or achieve the ethos of recovery. The recovery pathway includes, in addition to the well-studied therapeutic factors, important but perhaps more nebulous personal factors, for example, attitudes and beliefs, previous life experiences, emotions, cultural issues, and positive psychology.^{8,9} Taking in consideration the aforementioned challenges, we sought to audit recovery by naturalistic measuring of the outcomes of a rehabilitation service that depict topographies of everyday life tasks, and endpoints of real-world functional abilities, as well as clients' inner self-efficiency, keeping in mind simplicity and practicality.

Methodology

At the time of completing the audit in December 2017, Wandsworth Rehabilitation and Recovery Community Service provided specialist rehabilitation for people with very complex and enduring mental difficulties who lived in the Wandsworth borough in London, and for whom

previous placements and services had been unable to meet their needs. The Rehab Community team provided care for clients living in supported housing with on-site based staff support for up to 24 hours a day with time-limited

tenancy and clients living in houses with off-site outreach floating staff support who have an unlimited tenancy.

It was anticipated that clients should move on to more independent accommodation when they gained adequate skills that enabled them to live as independently as possible. The audit invited 60 community clients to participate, of whom 23 gave informed consent and took part. The audit collected data from the patients' electronic clinical notes that covered the clinical notes over a period of six months. The work was undertaken as part of an audit/service evaluation, to improve our quality of care. All patients were receiving routine care following national and local guidelines and the paper does not report on the use of experimental or new protocols. Hence, we did not require ethical approval for a study but rather project approval from the local mental health trust authority, South West London and St George's NHS Trust.

Because of the diversity of outcomes in rehabilitation psychiatry, we addressed three practical domains.

1. We reviewed six months' clinical documentation retrospectively about housing, financial situation, employment, education, connectedness with significant others, alcohol, and drugs problems. This was to capture the domains of social functioning, and living environments, which are recognized as important parameters in rehabilitation care. We also collected the following information from the clinical notes: any admissions to a psychiatric hospital, usage of the Mental Health Act, adherence to medications, and physical health follow up; all clinical indicators for our sample wellbeing.¹⁰
2. To measure the flow of our clients through the care pathway and the rate of 'stepping down' the level of care, we reviewed notes for active discharge planning to their GP or a transfer to a generic/psychosis community mental health team.¹

3. A key principle in the recovery concept is regaining a sense of self-purpose with meaningful and effective mental capacities.⁹ Therefore, we sought to measure the patients' perspectives of recovery with RAS-24 questionnaire and their strategic cognitive abilities by MCQ-30 questionnaire. The Recovery Assessment Scale-revised (RAS-R) is a self-reflective 24 items instrument that has been designed to gauge and yield five domains: personal confidence and hope, willingness to ask for help, goal and success orientation, reliance on others, not dominated by symptoms. It helps clients and staff to recognize and to spot opportunities for development and improvement.¹¹⁻¹³ Also, it is the most common measurement of personal recovery used in research and has been recommended for routine use in practice.^{14,15} A recent systemic review concluded The Recovery Assessment Scale is possibly the best currently available measure of personal recovery as it is the most widely evaluated and published instrument, and it is easy to be administered.¹⁶

The Metacognition Questionnaire-30 (MCQ-30) is a self-report measure that assesses a person's general inclination in a selection of certain metacognitive beliefs.¹⁷ Metacognition in schizophrenia has been receiving growing attention, notably its correlations with symptomatology and psychosocial aspects of schizophrenia.^{18,19} Further, recent work has identified intrinsic motivations as being mediated by the relationship between metacognition deficits and impaired functioning.²⁰ We measured our clients' metacognitive abilities using MCQ-30. Higher scores on MCQ-30 indicate less functional metacognitions. It contains five subscales, which are: cognitive confidence, negative beliefs (about the danger and uncontrollability of thoughts), beliefs about the need to control thoughts, positive beliefs about worry, and cognitive self-consciousness.¹⁷

Results

The sample consist of 23 patients. Ten were white, six were black, two South Asian, two East Asian, and the rest of other ethnicities. Twelve were women. The sample distribution of age ranged between 37 to 64 years and the mean was 50.7 years. Of the sample, 91% were suffering from schizophrenia and the remaining 9% were suffering from a schizoaffective disorder, with psychotic features more prominent than affective. Two patients had problems with alcohol and substance use. All clients had stable housing circumstances, which was expected.

All patients were on statutory benefit. According to the Occupational Therapist reports during the care review meetings, all patients in the sample were independent in their daily living skills and had a reasonable level of social activities. However, their main social interactions were with their families, and with their housemates, and there were fewer outside contacts. Living with other clients thus provided a significant and important social network to most of our clients. Five of them had connections with external friendships, mostly from their original

neighborhoods. The staff provided significant social support, including outdoors activities and companionship for shopping and other domestic activities.

None of the people in the sample had any formal education above GCSE level. One person in the sample was able to secure a paid job (as a secretary), with another two having part-time volunteer jobs (at a charity shop and a local public library). All had been offered education and vocational training (which was mainly IT training and catering). The majority accepted the offer and showed interest in attending appropriate courses. Only two stated clearly that they had no interest in finding a job and did not want to attend any training, demonstrating a clear desire for such self-improvement in a large majority. Two were clinically considered to be suffering at that time from psychotic symptoms to a degree that halted any reasonable abilities to work. Those who expressed interest in finding jobs were specifically interested in volunteer jobs at charity shops, catering, and clerical jobs. Disappointingly, despite the training and educational input, this had not resulted in positive outcomes, highlighting the challenging gap between aspirations and support, and actual real-world outcomes.

The entire sample was on antipsychotic medications. Fifty nine percent (thirteen patients) were on clozapine, and 36% (eight patients) were on a combination of two antipsychotics (seven patients on a combination of

clozapine with another antipsychotic). Eleven patients were on mood stabilizers and another two persons were receiving an antidepressant. All were adherent to their medications and were encouraged to take the responsibility for administering their medications by themselves. Clinical notes showed that clear arrangements were in place to liaise with the primary and secondary care services to manage physical health comorbidities. Furthermore, systematic screening for medication side effects was a regular practice during the CPA reviews and other medical contacts. One of the 23 patients in the sample was admitted to a psychiatric hospital during the six months of the audit and this was under the Mental Health Act.

Regarding stepping down care, three clients within the sample were under active discharge planning to their GP or a community mental health team.

The total scores on each of the MCQ-30 and the Recovery Assessment Scale subscales were calculated. Means and standard deviations were extracted and reported in Table 1 (MCQ-30) and Table 2 (the Recovery Assessment Scale subscales). We used unadjusted Pearson's *r* statistic (Table 3) to test the strength, and the direction of a possible association between each Recovery Assessment Scale-subscale individual's scoring, with each MCQ-30 subscales individual's scorings.

Discussion

Firstly, concerning social functioning, the key social deficits identified by the current audit were in the domains of education and occupational status. Only one client had a paid job. Clients were offered vocational training and were usually enthusiastic about this, but it did not appear effective. Nevertheless, the employment rate in schizophrenia is very low, even in well-developed countries, and a recent study estimated the employment rate among working-age individuals with schizophrenia in Norway to be around 10%.²¹ Furthermore, we should take into consideration that people in our sample represent individuals with chronic treatment-resistant conditions, also they had a history of repeated relapses which hindered them from finishing education or gaining vocational skills. However, this indicates that more efforts are required in these aspects of care. Generally, in psychiatry, the problem of unemployment is well recognized and different interventions were studied and implemented with some encouraging results including recent attempts to use virtual reality training.^{22,23} Yet, research suggests that direct entry into competitive employment with provided individualized workplace

support is the most effective,²⁴ and supported employment programs within mental health services have proven to be successful as well.²⁵ Additionally, cognitive remediation and so-called 'apathy minimization' should be considered as important facilitators to improve vocational and formal education in populations similar to our sample.²⁶

Secondly, regarding the flow rate of our clients to other mental health teams, a low rate of stepping down the level of care was identified. A review in 2005 advocated for extended rehabilitation input for people with chronic and severe treatment resistance with mental health problems who are experiencing continuing symptomatology or social disability.²⁷ An Italian intensive psychiatric rehabilitation program commenced specifically to treat long-term psychiatric patients, who were deemed to be "difficult to treat" by the mainstream psychiatric services, reported significant clinical improvement, but stated referral back to mainstream services did not occur.⁹

Thirdly, cognitive resilience appeared to be a factor that promotes independence and recovery. Metacognitions are a form of higher thinking which involves self-regulation,

executive control of thinking, planning, evaluating and monitoring problem-solving activities, and learning.²⁸ Metacognitions' role in recovery from psychosis has been investigated extensively including their associations with symptomatology, loss of motivations, social skills, coping capacity and subjective sense of recovery.^{29,30} We used the Meta-Cognitions Questionnaire (MCQ-30) to gauge patients' level of unhelpful metacognitive beliefs (Table 1). Our sample scored high on the following subscales of the MCQ-30: 1- positive beliefs about worry; 2- negative beliefs concerning uncontrollability and danger of worry, and 3- cognitive consciousness and the need to be aware constantly of thinking. These scores indicated a tendency

to perceive worry as helpful to avoid problems and dangers, at the same time with a tendency towards ruminations. Our sample scores on 4- cognitive confidence and 5- need to control worry, were lower than on the previous subscales but still high, indicating poor confidence in self-thinking and the tendency to self-punishment and taking irrational responsibility about misshapen. These results are beneficial to build an idea about the psychological well-being of the sample as a whole and to evaluate the service. However, interrupting these results on the individual level and linking them with the specific biopsychosocial circumstances of that patient is more beneficial in shaping specific interventions.

Table 1

Questionnaire	Our sample		Sellers R (2018)	
	Mean	SD	Mean	SD
MCQ-30 subscales				
Cognitive Confidence	9.30	3.91	11.92	4.70
Positive Beliefs about Worry	10.12	5.52	10.40	4.67
Cognitive Self-Consciousness	11.01	5.00	14.98	4.90
Negative Beliefs about Uncontrollability and Danger	10.10	4.69	14.30	5.47
Need to Control Thoughts	9.80	4.12	11.79	4.27

MCQ-30 subscales scoring compared with scoring Personal Confidence & Hope (Mean of items 7, 8, 9, 10, 11, 12, 13, 14 & 21). Willingness to ask for help (mean of items 18, 19 & 20). Goal and Success Orientation (Mean of items 1, 2, 3, 4 & 5). Reliance on Others (Mean of items 6, 22, 23 & 24). Not Dominated by Symptoms (Mean of items 15, 16 & 17).

Results of the Meta-Cognitions Questionnaire (MCQ-30) in comparison with Sellers R (2018) and Bright M (2017) using Mean and Standard Deviation. The Means in our sample are less than in other samples on all items of the questions. The Standard Deviations were sandwiched between 3.9 and 5.5 which means the variation in data is within the same range in all samples and on all items.

A meta-analysis investigated the relationship between metacognitive beliefs as captured by the Meta-Cognitions Questionnaire (MCQ-30) and its variants with psychosis. Data from 11 studies went through analyses, which showed the five sub-scales of the MCQ-30 were significantly elevated in psychosis compared to non-psychiatric controls. Also, it was found that people with psychosis had higher scores on the positive beliefs about worry subscale compared to people with emotional disorders.³¹ We cannot compare our results directly with other studies because of the differences in samples but it might be useful to review findings on MCQ-30 in another

study as an illustration. Seller (2017) found metacognitive beliefs to be independent cross-sectional predictors of negative affect in a sample that encompassed 159 who had either a diagnosis of psychotic disorder or met the threshold for early intervention in psychosis using the Positive and Negative Syndrome Scale (PANAS). Of the metacognitive subscales that predicted negative affect, negative beliefs about the uncontrollability and danger of thoughts and the need to control thoughts emerged as a consistent predictor for distress.

Lastly, Recovery involves the development of new meaning and purpose in one’s life as one grows beyond the effects of mental illness. We used RAS-24 to measure the subjective sense of recovery in our sample. RAS-24 scores range between 24-120. Higher scores indicate a more positive attitude toward personal recovery. Our sample gradings on RAS-24 subscales were as follows: the mean of the scores on the Personal Confidence & Hope was 23.5 which is above the median. Hope is common to all factors of recovery. While the mean of the scores on

the domination of symptoms, was 9.2, which indicates less attention to symptomatology. Scores on Goal and Success Orientation which point to having meanings and aims were good (Mean 16.2). ‘Reliance on others’ and ‘Willingness to ask for help’, are associated with hope and the sample scored well on them as well (Table 2). These findings are in concordance with previous conclusions that living semi-independently, in two to three-person accommodations with regular case manager visits would help in achieving psychological stability.³²

Table 2. Scores on RAS-24 subscales

Subscales	Mean	SD
Personal Confidence & Hope (Mean of items 7, 8, 9, 10, 11, 12, 13, 14 & 21; scores range 9-45)	23.5	3.86
Willingness to Ask for Help (Mean of items 18, 19 & 20; score range 3-15)	11.5	2.42
Goal & Success Orientation (Mean of items 1, 2, 3, 4 & 5; score range 5-25)	16.7	4.83
Reliance on Others (Mean of items 6, 22, 23 & 24; score range 4-20)	15.4	3.00
Not Dominated by Symptoms) (Mean of items 15, 16 & 17; score range 3-15)	9.2	2.42

Table 2. Scores on RAS-24 subscales.

Personal Confidence & Hope (Mean of items 7, 8, 9, 10, 11, 12, 13, 14 & 21) 3.5 0.68 1.67-5 3.40; 3.58. Willingness to Ask for Help (Mean of items 18, 19 & 20) 4.0 0.89 1-5 3.84; 4.07. Goal & Success Orientation (Mean of items 1, 2, 3, 4 & 5) 4.1 0.63 1.4-5 3.99; 4.15. Reliance on Others (Mean of items 6, 22, 23 & 24) 4.0 0.68 2-5 3.88; 4.06. Not Dominated by Symptoms (Mean of items 15, 16 & 17) 3.3 0.95 1-5 3.21; 3.45 Total scale (Mean of items) 3.7 0.56 1.92-5 3.66; 3.80. Total scale (sum of items) 89.5 13.39 46-120 87.75; 91.2

Furthermore, a previous study used The Recovery Assessment Scale-41, and the abbreviated Metacognition Assessment Scale (MAS-A) to explore the correlation between RAS subscales scores and performances on metacognitions subscales.³³ Accordingly, this paper sought to apply and test the same hypothesis. We used the Pearson correlation coefficient to test the association between the two questioners. Values in (Table 3) suggest

that ‘Positive Beliefs about Worry’, ‘Cognitive Self-Consciousness’, and ‘Negative Beliefs about Uncontrollability and Danger’ have the most detrimental effects on recovery with negative correlations with ‘Personal Confidence & Hope’, ‘Willingness to Ask for Help’, and ‘Goal & Success Orientation’; on the other hand, they have a positive correlation with ‘Reliance on Others’. ‘Need to Control Thoughts’ has no or very

limited correlations with all RAS subscales. No domination by symptoms correlated negatively with all MCQ-30 subscales, which means less healthy Metacognition increase the domination of symptoms.

These results suggest that such measurements can help guide therapists to help patients develop skills to cope with their unhelpful negative thoughts and negative affect.

Table 3

	Personal Confidence & Hope RAS-24 subscale	Willing to Ask for Help RAS-24 subscale	Goal & Success Orientation RAS-24 subscale	Reliance on Others RAS-24 subscale	Not Dominated by Symptoms RAS-24 subscale
Cognitive Confidence Meta-Cognitions Questionnaire (MCQ-30) subscale	-0.14	0.04	-0.06	0.21	-0.19
Positive Beliefs about Worry Meta-Cognitions Questionnaire (MCQ-30) subscale	-0.51	-0.33	-0.35	0.30	-0.22
Cognitive Self-Consciousness Meta-Cognitions Questionnaire (MCQ-30) subscale	-0.45	-0.26	-0.35	0.37	-0.19
Negative Beliefs about Uncontrollability and Danger Meta-Cognitions Questionnaire (MCQ-30) subscale	-0.44	-0.29	-0.30	0.23	-0.14
Need to Control Thoughts Meta-Cognitions Questionnaire (MCQ-30) subscale	0.03	0.13	0.12	0.00	-0.02

Pearson correlation coefficient values to show the association between the scoring on two questioners (Meta-Cognitions Questionnaire (MCQ-30) subscale and the RAS-24 subscale). Values showed Positive Beliefs about Worry, Cognitive Self-Consciousness, and Negative Beliefs about Uncontrollability and Danger have negative correlations with Personal Confidence & Hope, Willingness to Ask for Help, and Goal & Success Orientation, and they have a positive correlation with Reliance on Others. Not dominated by Symptoms correlated negatively with all MCQ-30 subscales

Limitation

Our study presented three main limitations. First, a cross-sectional design was adopted, which does not allow for inferences of causality. Second, the generalization of our

results is limited by the small sample and the fact that not all our service users participated in this study. Third, there was no control sample for comparison.

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contributed: we hope these positive results encourage all about the care they give and receive, and further that this might prove of value to others.

Ethical statement

This paper collected data from patients' clinical notes, and this was done internally as part of an audit/service evaluation, to improve our quality of care. Those patients were receiving routine care and had been treated already according to the national and the local guidelines and the paper does not report on the use of experimental or new

protocols. Hence, we did not seek/obtain ethical approval for a study but rather project approval from the local mental health trust authority, South West London and St George's NHS Trust. No individually identifying information is contained within.

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المخلص

الأهداف: لا توجد منهجية موحدة لتقييم فعالية خدمة إعادة التأهيل النفسي. حاولنا تحقيق ذلك باستخدام المؤشرات السريرية الروتينية اليومية. **المنهجية:** تم جمع البيانات من الملاحظات الإلكترونية السريرية الروتينية. بينما تم استكشاف التجربة الشخصية للتعافي باستخدام استبيان RAS-24 واستكشاف القدرات المعرفية الفوقية باستخدام استبيان MCQ-30 في ثلاثة وعشرين فردًا. **النتائج:** كان جميع المرضى مستقلين في مهاراتهم المعيشية اليومية. ومع ذلك، كانت تفاعلاتهم الاجتماعية الرئيسية محدودة. لم يكمل أي من الأفراد أي تعليم عالٍ؛ تمكن شخص واحد من الحصول على وظيفة مدفوعة الأجر. كان معدل ترك الرعاية من فريق إعادة التأهيل منخفضًا. كان معدل النتائج مرضي في مقياس التجربة الشخصية للتعافي و في مقياس المعرفية الفوقية. **الاستنتاج:** يمكن قياس التحسينات في الأداء

الاجتماعي والنفسي للمرضى الخاضعين لرعاية خدمات إعادة التأهيل باستخدام مؤشرات الممارسة السريرية اليومية جنبًا إلى جنب مع الاستبيانات المصنفة ذاتيًا لقياس التعافي الشخصي.

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Viewpoint

'Mental Health in an Unequal World': Women in the Eastern Mediterranean Region After the Covid Pandemic

Unaiza Niaz

الصحة النفسية في عالم غير متساوي: النساء والأطفال في منطقة شرق البحر الابيض المتوسط بعد جائحة الكورونا 19

عنيزه نياز

The COVID-19 outbreak has had an unprecedented impact on societies worldwide. However, not everyone, in every place, is affected in the same way. Understanding how the pandemic has affected certain groups may help increase the effectiveness of containment efforts and minimize potential negative impact. The current viewpoint considers the impact of COVID-19 on women and girls. Experiences from previous pandemics demonstrate how women and girls can be especially active actors for change although also demonstrates how they can also experience the effects of the crisis in different (and often more negative) ways than men might. COVID-19 is not gender-blind. The response to it should not be either. Based on existing evidence and emerging trends the current viewpoint summarizes key gender differentiated transmission channels and impacts on outcomes across three areas: endowments, economic conditions, and agency.

Gender implications: Data from China, Spain, and Italy regarding the COVID-19¹ outbreak indicate that men are dying from the virus in much higher numbers than women. This also appears to be the worldwide trend. In China, the fatality rate for men was approximately 65% higher than for women. Reasons for this trend remain unclear although initial research suggests higher incidence of chronic diseases (e.g., hypertension), and risky and/or health-seeking behaviors (e.g., smoking) among men,² as well as immunological differences. Among SARS patients, men also appeared to be more severely affected by the disease than women, which may partly reflect gender differences in tobacco use.⁶ Similarly, gender differences in physical activity, eating habits, occupational exposure to smoke and dust, etc. and associated comorbidities could play a role. Research on animals, such as mice, also show that males generate less robust immune responses than females to infections with SARS-CoV and perhaps other coronaviruses.

Summary of key messages, gender implications and recommendations for health

- **Health vulnerabilities are especially related to disease exposure in the short-term.** There is a larger share of women in the health sector, and as home and family caregivers, which makes them more exposed to contagion. Occupational gender-segregation might also bring different levels of exposure. As an example, women are more present in client-facing roles while men are more likely to concentrate on logistics or security. Providing protective equipment and materials and COVID-19 testing to higher-risk populations will be key to prevent contagion.
- **However, and likely in connection with differences in the incidence of chronic conditions, risky and preventive behaviors or in immune systems, men seem to be over-represented among the fatalities of COVID-19.** This trend may also have gendered implications, for instance as the women and girls left behind face further difficulties.
- **The shift in resources towards addressing the public health emergency can entail disruptions to key health services for women and girls, such as reproductive and sexual health services.** There is for instance evidence of increases in both teenage pregnancy among girls no longer attending education and maternal mortality due to lack of critical resources in similar crises.

Pregnant women can be particularly vulnerable in this context.

- **A minimum package of these services should be maintained during confinement, while virtual programs for adolescents can be considered.** Pregnant women and maternity wards require particular attention during the containment phase. In the longer term, programs aimed at reducing teenage pregnancy and encouraging girls to go back to school will be necessary, especially in contexts where pressures to drop out of education are higher.
- **Social and gender norms will play a role in educational investment decisions. Intra-household allocation of resources for home schooling and/or at the community-level might be redirected to boys over girls.** These dynamics need to be considered in efforts aimed at offering home-schooling, and in related social messaging. Targeted measures for the most vulnerable girls (i.e., with no access to information and communication technologies or ICTs) will also be necessary.
- **The disruption of services with school closures can lead to an increase in the burden of care-related tasks - likely impacting girls more than boys in many contexts.** This will affect their ability to stay engaged in education in the longer term. Among boys, pressure to contribute to the family income may also increase with the tightening economic conditions, leading to permanent school dropout. Financial incentive programs can help encourage families to send children back to school when the confinement phase is over. Adolescent empowerment programs have also shown to be effective in keeping girls in education. Gender implications for economic conditions:
- **Globally, women will likely experience a significant burden on their time given their multiple care responsibilities as school closures and confinement measures are adopted, possibly leading to reductions in working time and permanent exit from the labor market.** In some contexts, and due to food insecurity, girls and women would decrease their caloric intake in favor of men and boys. Social messaging as part of the

emergency response can contribute to a more balanced distribution of household responsibilities and resources.

- **Especially in lower income countries, women are largely engaged in informal work and other vulnerable forms of employment (e.g., self-employment in small subsistence businesses, domestic work), which often leaves them out of formal social protection measures targeted to workers.** Female cross-border traders and small-holder farmers can particularly suffer the consequences of the declines in food and crop production, increases in food prices and closed borders.
- **Gender segregation in sectors and occupations will also lead to differential impacts depending on whether the jobs are sustained, for instance when they allow for telecommuting or are in counter-cyclical industries (government and education), or at higher-risk to be lost.** Women are over-represented in some of the occupations that will be hardest hit, such as retail, travel, leisure and hospitality, and men in construction or manufacturing.
- **The effectiveness of social protection responses to the crisis will improve if these gender dimensions are considered.** Cash transfer programs to the most vulnerable groups including women only households (e.g., single mothers with children, widows or women farmers) will be necessary both as part of the emergency response and in the longer term. Specific programs to support women's return to economic activity will also play a central role (e.g., public works, access to training and credit, direct provision of productive inputs to women farmers). Ensuring access to care support when work outside of the house is resumed will also be necessary.

Women make up large parts of the health workforce, but they may have less decision-making capacity within the sector and less access to protective equipment in times of crisis compared to health workers who are men. Globally, between 65% (Africa) and 86% (Americas) of nurses are women³ while physicians are disproportionately men (except for some countries in Europe). In addition, the hierarchical relationship between nurses and doctors may undermine the perspective of (female) nurses.

Nurses participating in focus group discussions conducted in Canada after the SARS epidemic argued that physicians' non-compliance with infection control protocols jeopardized their health and safety. During the 2014 Ebola outbreak in Nigeria, nurses, traditional birth attendants, and cleaners/laundry workers in health facilities (most of whom were women) were not provided with the same amount of protective gear

given to doctors (most of whom were men) and other high-ranking hospital officials. Women are also vulnerable in more informal parts of the health workforce, such as home health care, aids or community health workers. Indeed, and as part of the response to the COVID-19 crisis, some countries are mobilizing large unpaid community health care forces.

Conclusion

At the time the current review was being written, a 4th wave of Covid variant, had led to chaos and absolute disaster in some countries. Travelling has been almost negligible, economic crises continues to loom globally. In EMRO countries, it is about time the people wake up to this crises and support women and girls to survive and live a reasonably descent lives. In most of the countries, lockdown has led to inability of

domestic helpers to help large extended families, or even a young nuclear family with small children to look after. Men and adolescents must share in the household responsibilities that are so often left for women to do. For to do otherwise will likely perpetuate oppression and the maintain the workload burden that women manage and this, in turn, becoming a greater at-risk group with calamitous consequences.

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سعادة أ. د. رئيس تحرير المجلة العربية للطب النفسي المحترم
اتحاد الأطباء النفسيين العرب، عمان / الأردن
تحية طيبة وبعد،،،

يسر معامل التأثير والاستشهادات المرجعية للمجلات العلمية العربية (ارسیف - ARCIF)، أحد مبادرات قاعدة بيانات "معرفة" للإنتاج والمحتوى العلمي، إعلامكم بأنه قد أطلق التقرير السنوي السادس للمجلات للعام ٢٠٢١.

يخضع معامل التأثير "ارسیف Arcif" لإشراف "مجلس الإشراف والتنسيق" الذي يتكون من ممثلين لعدة جهات عربية ودولية: (مكتب اليونيسكو الإقليمي للتربية في الدول العربية ببيروت، لجنة الأمم المتحدة لغرب آسيا (الإسكوا)، مكتبة الإسكندرية، قاعدة بيانات معرفة، جمعية المكتبات المتخصصة العالمية/ فرع الخليج). بالإضافة للجنة علمية من خبراء وأكاديميين ذوي سمعة علمية رائدة من عدة دول عربية وبريطانيا.

ومن الجدير بالذكر بأن معامل "ارسیف Arcif" قام بالعمل على فحص ودراسة بيانات ما يزيد عن (٥١٠٠) عنوان مجلة عربية علمية أوبحثية في مختلف التخصصات، والصادرة عن أكثر من (١٤٠٠) هيئة علمية أو بحثية في (٢٠) دولة عربية (باستثناء دولة جيبوتي وجزر القمر لعدم توفر البيانات). ونجح منها (877) مجلة علمية فقط لتكون معتمدة ضمن المعايير العالمية لمعامل "ارسیف Arcif" في تقرير عام ٢٠٢١ .

ويسرنا تهنئكم وإعلامكم بأن **The Arab Journal of Psychiatry : المجلة العربية للطب النفسي** الصادرة عن **اتحاد الأطباء النفسيين العرب، عمان / الأردن** قد نجحت في تحقيق معايير اعتماد معامل "ارسیف Arcif" المتوافقة مع المعايير العالمية، والتي يبلغ عددها (٣٢) معياراً، وللاطلاع على هذه المعايير يمكنك الدخول إلى الرابط التالي: <http://e-marefa.net/arcif/criteria>

وكان معامل "ارسیف Arcif" لمجلتكم لسنة ٢٠٢١ (لم نرصد أية استشهادات)، و صنفتم في تخصصها ضمن الفئة (الرابعة Q4).

ونأمل حصول مجلتكم على معامل تأثير متقدم في تقرير عام ٢٠٢٢. وبإمكانكم الإعلان عن نجاحكم في الحصول على معايير اعتماد معامل "ارسیف Arcif" العالمية سواء على موقعكم الإلكتروني، أو على مواقع التواصل الاجتماعي، وكذلك الإشارة في النسخة الورقية لمجلتكم إلى معامل أرسيف Arcif الخاص بمجلتكم.

ختاماً، نرجو في حال رغبتكم الحصول على شهادة رسمية إلكترونية خاصة بنجاحكم في معامل "ارسیف"، التواصل معنا مشكورين.

وتفضلوا بقبول فائق الاحترام والتقدير

أ.د. سامي الخزندار

رئيس مبادرة معامل التأثير

" ارسيف Arcif "

