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A clinician's guide to the neurobiology underlying the presentation and treatment of PTSD and subsequent growth

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Summary

While there has been an abundance of research on Post-Traumatic Stress Disorder (PTSD) in the past several decades, clinical studies on the neurobiological mechanisms involved in the disorder are only recently receiving attention. This paper will collate available information on the neurobiology of PTSD for clinical and lay audiences.

This paper reviews the literature surrounding typical symptoms of PTSD, with a specific focus on the neurobiological evidence suggesting altered brain functioning among those with the condition.

It will also present literature reviewing common treatment methods of PTSD and their potential effects on brain functioning, including attention, working memory, and emotional regulation.

The concept of post-traumatic growth will also be introduced, indicating an alternate trajectory of PTSD.

treatment / PTSD / neurobiology / post-traumatic growth

CONCLUSIONS

Neurological evidence suggesting that those with PTSD may experience better quality of life following a traumatic event will be presented.

In the last decade, the world has seen a shocking number of horrifying incidents: natural disasters, terrorist attacks, war, and egregious public acts of violence. Clinicians and researchers alike have been turning their attention more than ever to how individuals cope with the sometimes serious psychological effects that can arise from encounters with traumatic situations [1]. Exposure to trauma can have many impacts on both direct and vicarious survivors and, in some cases, can develop into a severe, debilitating condition which may have lifelong implications for those affected: Post-Traumatic Stress Disorder (PTSD). Since its addition to the DSM-III in 1980, the psychological community has examined and explored the aetiology, clinical, and neurobiological presentation, and treatment of PTSD. In particular, there has been an increase in research on how the disorder results in disruption of the neural systems associated with attention, working memory, and the processing of affective stimuli [2]. In spite of much of this work, the lay perception of PTSD is still catastrophic, holding closely the assumption that trauma has the power to 'throw life off course' and alter it, negatively, forever. This paper is intended for both clinicians and lay-readers as an accessible review of some of the neurology underlying the disorder and its treatment, as well as an intro-

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duction to the literature that supports post-traumatic growth after trauma.

THE NORMAL STRESS RESPONSE

The experience of trauma is fundamentally different from the ways in which we respond to everyday stressors. While the stress response and subsequent homeostatic mechanisms are normal [3], if the response is recurrent or continues for an extended period of time, or if the stressful event is so overwhelming that it overtaxes homeostatic mechanisms, it may lead to a disorder [4]. Stress is a state of arousal accompanied by physiological and behavioural responses that aim to restore homeostasis [5] in the face of a potential perceived threat [6, 7]. The stress response begins when the brain perceives a stressor (a factor that triggers arousal). The response consists of two separate biochemical sequences, one fast and the other slow. The fast response involves the release of epinephrine, whereas the slow response activates cortisol. Epinephrine is responsible for the energy surge that is triggered during a stressful event, preparing the body for a sudden burst of activity. The cortisol pathway by contrast is activated in minutes to hours, preparing the body for longer lasting adaptations, such as the restoration of cells or tissues after energy expenditure. Cortisol has a wide range of functions; it can turn off all bodily systems (like insulin, so that the liver begins releasing glucose), inhibit reproductive functions, and impede the immune system in order to help the body concentrate on dealing with the stress. Normally, stressors are short-acting events, with the body mobilizing its resources to manage challenges as needed.

At the termination of a stressor, the brain instructs the hypothalamus to turn off the stress response [5]. The hippocampus has a high density of cortisol receptors and has axons that project to the hypothalamus; it detects cortisol in the blood and instructs the hypothalamus to slow its release. There are a variety of mechanisms in the normal stress response which may malfunction when an individual is presented with trauma and can result in PTSD which encompasses a wide variety of neurological changes.

THE NEUROBIOLOGY OF POST-TRAUMATIC STRESS DISORDER

One of the most interesting findings with respect to trauma and neurobiology is the marked changes in the brain's neural circuitry and neurochemistry which can occur after exposure to a traumatic event. Early animal models have shown alterations in the hippocampus, amygdala, and medial prefrontal cortex as a result of exposure to excessive stress [8]. Human studies have indicated that there are also functional changes in these and other brain regions after exposure to a traumatic event [7, 9]; however, the exact mechanism of these changes remains unknown [8]. This section will describe the observed changes in the key regions associated with PTSD: the prefrontal cortex, amygdala, and hippocampus. It will also explore the implicated endocrinology of stress, focusing on alterations in cortisol levels in patients with PTSD.

Prefrontal Cortex (PFC). The PFC is the region of the brain commonly implicated in complex thought and operations, such as decision making, attention, impulsivity, personality, and emotionality [10]. The PFC also plays a role in the memory storage and personal expression of emotionally salient experiences. Of particular relevance to its role in responding to stress is the medial prefrontal cortex (mPFC), which serves to inhibit the amygdala and extinguish fear responses [8]. Research has shown that PTSD patients show decreased activity in their prefrontal cortex [11]. Shin and colleagues [12] conducted a comparative study of PTSD patients versus trauma-exposed patients without PTSD using functional magnetic resonance imaging (fMRI), and found a decreased function in the medial PFC in those patients with PTSD when exposed to fearful and happy faces. This study also indicated that symptom severity was correlated with activity in the PFC, such that higher hypoactivity is related to more severe symptoms.

Amygdala. Another brain region commonly implicated in the onset and maintenance of PTSD is the amygdala. This region of the brain acts as the filter through which threatening stimuli are interpreted and paired with appropriate emotion, such as fear [10]. The amygdala is a key part of the circuitry that alerts the body to impending danger and helps activate the systems

required for an individual to protect him/herself or escape the situation [10]. Shin and colleagues [12] demonstrated that in addition to decreased PFC activation to facial stimuli, patients with PTSD experienced hyperreactivity of the amygdala when presented with either happy or fearful facial stimuli. Liberzon and colleagues [13] demonstrated similar results, with amygdaloid hyperreactivity to trauma-related auditory stimuli in PTSD patients when compared to neutral auditory stimuli. In this study, SPECT analysis was used with three different sample groups: 14 Vietnam War veterans with PTSD, 11 combat exposed controls (without PTSD), and 14 controls. Participants were tested at two time points: in time one they were exposed to white noise, and in time two they were presented with combat related sounds. When presented with combat related stimuli, PTSD patients showed significantly higher activity in the amygdala than either of the control groups. Patients with PTSD have also been shown to demonstrate decreased left amygdala volumes when compared to controls [8].

Amygdala and PFC interaction. Rauch and colleagues [14], among others [e.g., 15], suggest that an interaction between the amygdala and the PFC contributes to the maintenance of PTSD. The Neurocircuitry Model of PTSD [16] suggests that the PFC does not adequately modulate the amygdala, resulting in amygdaloid hyperactivity. To date, however, causality has yet to be established. Amygdala hyperactivity mediates many of the positive symptoms of PTSD, such as hyperarousal. The hypoactivity of the PFC is implicated in this symptoms cluster, as it does not elicit extinction or suppress attention to traumatic stimuli, as it would in a non-PTSD brain. This amygdaloid/PFC interaction has been replicated in multiple studies [e.g., 12, 17].

Hippocampus. The hippocampus is another brain region commonly implicated in the onset and symptoms of PTSD [18]. In normal situations, the hippocampus is a necessary component of memory formation and the regulation of emotion. It situates events and experiences within a context in order that they might be processed [8]. Decreased hippocampal function has been implicated in such PTSD symptoms as difficulty identifying safe contexts and memory problems [19]. Bremner and colleagues [20] demonstrated that abuse survivors who had developed PTSD had decreased hippocampal activation when compared to controls. In this study, the authors used PET scanning, which demonstrated decreased left hippocampal activation in patients with PTSD (N=10) when compared to trauma exposed non-PTSD (N=12) and normal controls (N=11). Shin et al. [21] replicated these results in firefighters.

It has been suggested that adults with PTSD may not only show decreased activation of the hippocampus but also decreased hippocampular volume. Bremner and colleagues [20] employed MRI techniques to explore volume of the hippocampus in women with PTSD, trauma exposed women without PTSD, and non-trauma exposed controls. Their results indicated that women with PTSD have less right and left hippocampal volume than controls. A meta-analysis conducted by Kitayama and colleagues [22] indicated that both males and females with chronic PTSD demonstrated smaller hippocampal volumes across various types of trauma. Karl et al. [23] used meta-analysis to demonstrate that individuals who develop PTSD have decreased hippocampal volume when compared to both non-trauma exposed, trauma-exposed, and non-PTSD controls. Those participants exposed to trauma without PTSD had smaller hippocampi than non-trauma exposed controls. The authors also reported that increased PTSD severity is related to decreased hippocampal volume. It is important to note the same was not demonstrated in children and adolescents [16]. Twin studies indicate that decreased hippocampal volume may also be a predispositional factor for the development of PTSD [24]; however, many of these twin sets had experienced childhood trauma. It is therefore difficult to determine whether the decreased hippocampal volume predated or resulted from earlier traumas. Further research is required to elucidate the role of hippocampal volume in the development and maintenance of PTSD.

HPA axis and cortisol. Cortisol plays a key role in the body's immediate response to a stressor, and is released upon encountering a stressor to elicit a variety of changes throughout the body to increase the likelihood of surviving a perceived threat. In the case of traumatic stress, research has shown that there are fundamental changes to the way the HPA axis reacts to stress

with respect to cortisol release. Weewisse and colleagues [25] conducted a systematic review and meta-analysis to explore the pre- and post-trauma plasma levels of cortisol in individuals with PTSD compared to controls. Their research demonstrated that under certain conditions, individuals who develop PTSD have lower basal levels of cortisol than individuals not exposed to trauma. This meta-analysis also demonstrated that gender may play a role: men with PTSD were not different from male controls with respect to cortisol levels, whereas women with PTSD showed lower cortisol concentrations than female controls. Type of trauma also appeared to have implications for cortisol production; individuals exposed to sexual or physical abuse demonstrated lower plasma cortisol levels than controls, but these differences were not observed for war veterans or refugees. It is important to note that the differences in the levels of cortisol between PTSD participants and controls disappeared when comparing those with PTSD to trauma-exposed, non-PTSD controls. Olff and colleagues [26] explored a variety of endocrine implications in PTSD. They assessed plasma hormone levels of cortisol, DHEA and DHEA-S, prolactin, thyrotropin, and free thyroxin. Their results indicated that participants with PTSD demonstrated significantly lower levels of cortisol when compared to healthy volunteers.

Hippocampus and cortisol. Kolb and Whishaw [5] suggest that there may be an insidious relationship between the hippocampus and cortisol. They reviewed animal studies involving monkeys that demonstrated that monkeys who were chronically subjected to passive or subordinate roles in the cage showed exaggerated hippocampal degeneration. The authors explained that chronic high levels of cortisol eventually lead to damage of the neurons in the hippocampus, which can no longer inhibit cortisol production in the adrenal glands; cortisol production is not tempered. Excessive stress in humans can also lead to hippocampal damage [27].

TREATMENT OF PTSD

Pharmacotherapy. One of the modes through which helping professionals can treat PTSD is using pharmacotherapies. Fernandez and colleagues [28] explored the impacts of Prozac (Fluoxetine), a selective reuptake inhibitor (SSRI), on regional cerebral blood flow during activation of PTSD symptoms in patients who had torture and war related PTSD. They reported that for unmedicated patients, activation of PTSD symptoms results in increased blood flow to the cerebellum, precuneus, and the supplementary motor cortex, and decreased flow to the insula, prefrontal, and inferior frontal cortices. Hence, there was an increase in blood flow to the areas of the brain responsible for more physiological, automatic responses, and less to the areas responsible for higher levels of processing and critical thought. After administration of the SSRI, these changes in blood flow normalized.

Other research has shown that Propranolol, an anxiolytic, may be useful in managing enduring chronic symptoms of PTSD. Taylor and Cahill [29] report a case study in which Propranolol was administered to a patient with a history of chronic, recurrent PTSD. Propranolol was administered 48 hours after the most recent trauma, and resulted in a substantial decrease in PTSD symptoms, in comparison to prior trauma experiences. Further, Taylor and Cahill suggest that the combined use of Propranolol and psychotherapy may be most effective in mitigating PTSD, as the medication may offset the risks of re-exposure in the therapeutic space. More research is required to understand the impact of covariates, like gender, which may indicate interactions and contraindications for utilization of Propranolol in treating PTSD with female children [30].

Research has indicated that even early administration of Propranolol to some individuals who have recently experienced trauma can decrease the likelihood of them developing PTSD [31]. Propranalol acts to alter the memory storage processes in the brain in the event of a trauma. Bioethicists question the ethics of using medication to alter painful memories [32]. More research is required to determine the viability of memory modification using Propranolol.

Cognitive Behavioural Therapy (CBT). Hyperarousal, avoidant behaviours, and negative cognitions are typical among those who have experienced a trauma [33]. While psychodynamic and supportive counselling approaches are also employed, cognitive behavioural models have

been the most studied and empirically validated psychosocial interventions for those with PTSD [34]. Cognitive behavioural models rest on three fundamental assumptions: first, cognitive processes can be accessed with practice and awareness; second, the way we think mediates the way we respond to our environment; and third, our cognitions can be changed to become more balanced and rational [35]. Research has demonstrated that the way individuals emotionally and cognitively process a traumatic event is related to the onset and maintenance of PTSD [36, 37]. How an individual interprets and appraises a trauma has bearing on their memory of it that can contribute to persistent PTSD [35].

In their review of PTSD, Nemeroff and colleagues [1] discuss how the CBT model aims to teach clients how to identify, evaluate, and reframe the dysfunctional thoughts that contribute to intense negative emotional and behavioural reactions through exposure therapy, anxiety management, and challenging dysfunctional cognitions. Exposure therapy includes systematic desensitization and flooding where PTSD patients are required to confront their fears, memories, and triggers with progressively less anxiety and cognitive distortions. The anxiety management component of the CBT approach involves exercises designed to reduce anxiety through relaxation, controlled breathing, and self-distraction (thought stopping). Self-blame and negative thoughts about the self and the world are common among those with PTSD, particularly the use of overgeneralizations (e.g., 'no place is safe'), and labeling (e.g., 'I am weak and incompetent'), with the traumatic incident serving as evidence for these beliefs. Identifying and challenging patients' dysfunctional cognitions and replacing them with more adaptive ways of thinking is an integral component of the CBT approach. González-Prendes and Resko [35] add that many of these erroneous thoughts can lead to fear and avoidance of adversity, and so poor coping strategies result and help perpetuate symptoms; addressing maladaptive coping strategies and replacing them with more adaptive ones are also central to this approach.

After the onset of PTSD symptoms, the neurons of the amygdala have formed new pathways which reinforce, and are reinforced by, triggers. Though CBT cannot deaden these pathways, it is suggested that this type of therapy may form new inhibitory pathways which decrease the hyperactivity of the amygdala, leading to decreased symptoms severity [10]. CBT may also be effective in eliciting change in the PFC, as this treatment has been shown to elicit meaningful change in symptoms of other anxiety-related disorders.

Transcranial Magnetic Stimulation. Transcranial Magnetic Stimulation (TMS) has recently been applied to those with PTSD in an effort to reduce their core symptoms. This noninvasive, painless technique uses electrical energy to directly stimulate cortical neurons, leading to a depolarization of neurons [38] and cortical changes in monoamines [39]. Among those diagnosed with PTSD, it has been shown to decrease depressive symptoms [40], lower avoidance, anxiety, and somatization [41], and improve hyperarousal symptoms [42].

Cohen and colleagues [43] sought to evaluate the therapeutic effectiveness of active repetitive TMS at different frequencies of PTSD patients. They assigned 24 patients with PTSD (17 men and 7 women) to receive rTMS at low frequency (1 Hz), high frequency (10 Hz), or sham rTMS administered to the right dorsolateral prefrontal cortex in a double-blind design. Participant trauma included combat reaction, motor vehicle accident, sexual abuse, assault, work accident, and unexpected death of a relative. They administered treatment in 10 daily sessions. Patients were assessed at baseline, at day 5, at day 10, and at day 24 (14 days after the intervention). The 10 daily treatments of 10-Hz rTMS at 80% motor threshold over the right dorsolateral prefrontal cortex had therapeutic effects on PTSD patients, with PTSD core symptoms (re-experiencing and avoidance) markedly improving with this treatment. Moreover, high-frequency rTMS over the right dorsolateral prefrontal cortex alleviated anxiety symptoms in PTSD patients. The effect of 10-Hz rTMS was significant and stable for at least 14 days after the last treatment. The authors suggested that in future studies, the treatment could be used as maintenance therapy, similar to ECT procedures. Ten daily sessions of right dorsolateral prefrontal rTMS at a frequency of 10 Hz was shown to have greater therapeutic effects than slow-frequency or sham stimulation.

Future directions for treatment. Nemeroff and colleagues [1] explain that there will be further studies needed to determine brain mechanisms underlying successful response to treatment, including changes in brain receptor and neurotransmitter systems. Further assessment is needed to improve our understanding of what increases our susceptibility, genetically and biologically, to developing PTSD. A better understanding of the changes that occur in the brain throughout treatment will be facilitated with the help of a variety of animal models for PTSD. With better understanding of the complex aetiology of PTSD, new therapeutic targets and treatments with improved short- and long-term efficacy may emerge. Predictors of treatment response (e.g., psychotherapy, pharmacotherapy, combination treatments) may also be identified among those with PTSD. The authors also argue that PTSD requires an operational definition of remission (not just reduction of symptoms), as the final goal of treatment is ideally full remission from the condition.

In their review of CBT treatment and PTSD, González-Prendes and Resko [35] suggest that further research could eventually identify those clients who are most likely to benefit from the various cognitive-behavioural approaches for PTSD, perhaps according to the type of trauma they have suffered. This is particularly important given attrition rates that demonstrate that not all PTSD patients respond the same way to treatment. They also recommend that longer-term follow-up assessments be done to provide stronger evidence for the long-term effects of treatment.

Because only a subset of individuals exposed to trauma go on to develop PTSD, researchers are turning their attention to the identification of risk and protective factors that can inform treatment of PTSD [44], including more research on the nature of the trauma, individual characteristics, neurological soft signs, peri- and post-trauma variables, history of brain injury, and level of intellectual functioning. Like many other mental disorders, there are disorder- and population-related risks, resilience, comorbidity, and iatrogenic variables that can influence neuropsychological performance [35]. If we can identify these risk and protective factors, we may be able to develop earlier interventions or prevent the onset of PTSD [44]. Longitudinal studies of at-risk populations and cross-sectional approaches like twin methodologies will be needed. Future research must continue to investigate the links between PTSD and post-traumatic growth, including the most effective ways to elicit said growth in a variety of populations.

POST-TRAUMATIC GROWTH

Current research is beginning to indicate that patients can not only recover from their traumatic experience, but actually experience post-traumatic growth, or better quality of life, after the trauma when compared to before the traumatic event [45]. Post-traumatic growth occurs when persons struggle with their traumatic experience, and engage with it on a deep and meaningful level [46]. Van der Kolk and McFarlane [47] argue that the meaning people ascribe to their traumatic incident can contribute to the severity of their experience of the trauma. Interestingly, research has indicated that making meaning can be an essential component in recovering from trauma [48].

While the results of the relationship between PTSD and post-traumatic growth are somewhat inconclusive, trends in the literature indicate that post-traumatic growth is more likely when severity of PTSD symptoms is higher [49]. Hence, those patients who previously may have been thought to be irrevocably harmed by trauma may in fact be most likely to grow as a result of it. Factors which can contribute to post-traumatic growth may include degree of rumination on the trauma, openness to religion [50], and personality variables such as openness, conscientiousness, and agreeableness [51]. Preliminary research indicates that individuals experiencing post-traumatic growth may have increased left frontal brain activation [52]. Additionally, Warnick [53] cautions that use of Propranalol to inhibit formation of traumatic memories may decrease the likelihood of survivors being able to attain later post-traumatic growth. Further research is required to explore the neurobiological correlates of post-traumatic growth, which may further illuminate connections between PTSD and growth, in addition to the mechanisms by which growth occurs.

CONCLUSION

This paper has provided an overview of the neurobiology of PTSD, its treatment, and the potential for post-traumatic growth. In order for clinicians to adequately treat PTSD, it is essential that they understand the presentation of the disorder and the neurological correlates of these symptoms, in order that they can adequately validate patient experience and understand the impacts of their chosen treatments. It is also essential for practitioners to understand the potential positive outcomes for patients, so that they can work to foster not only a return to wellness, but also possibilities for post-traumatic growth.

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Regulations on the papers accepted to "Archives of Psychiatry and Psychotherapy"

INFORMATION FOR AUTHORS

Archives of Psychiatry and Psychotherapy accept experimental, clinical, theoretical papers, case reports and studies only written in English, which have not been published previously in any other journals or considered for publication elsewhere; as well as invited papers. The editors accept also a) letters to the editor, concerning the articles printed in the journal as well as letters on important issues connected with the theme of the journal and, b) book reviews.

All submissions should be made online via an electronic submission system **http://www.editorialsystem.com/APP**. New users should first create an account. Once logged in to the site, you will be guided step by step through the creation and uploading of the various files. After correct and complete fulfillment of all elements of the submitted paper, the last option "Send to Editor" will appear in the bottom, which will enable the final transfer of the manuscript to the editor. The system will send the notification at the author's e-mail address with the confirmation of receiving the manuscript and its registration number.

All papers will undergo a rigorous peer review, based on initial editor screening and anonymous refereeing by at least two independent expert referees. Journal Policy regulates a double-blind review process; authors and reviewers remain anonymous. To permit anonymous review, identifying information about the authors and their affiliations should not appear in the body of the manuscript. These details must be entered when proceeding through submission At least one of the reviewers should be affiliated in a foreign institution than the author(s).

Authors may also track the status of their manuscript using the online submission system. After receiving the reviews, the author is asked to send a paper including the reviewers' remarks by entering the manuscript in the same way as during submission. For all successfully published articles, a PDF file of the paper will be send in the corresponding author's email address at no cost.

All papers submitted to the journal should follow the below directive:

Manuscripts have to be presented in Word up to 16 MB and should not exceed 20 standard pages (1800 signs per page, spacing included), including illustrations, tables and references. The length of the letters to the editor should not exceed 5 pages of normalized text, whilst the book reviews should not exceed 2 pages.

The first page of the paper should contain: the title (very brief, if necessary a subtitle may be used), key words (3–5) and abstract minimum 100 up to 250 words, which need to be entered in the appropriate window in the submission system. The abstract of the research paper should include the below structure: the aim of the study, subject or material and methods, results, discussion, conclusions.

The font should be Times New Roman 12, double-spaced; minimum margins: left 3.5 cm, right 1 cm, top 3.5 cm, bottom 3 cm. Pages should be numbered in the middle of the page heading. Titles and sub-titles should not be written in capital letters. As regards numbers, decimal fractions should be separated from units with a period and not a coma.

The text cannot include any special layout tools like double spacing, bold, or capital letters. The layout of the mid-titles and that of the

tables is selected by the Editor according to the homogeneous layout of the journal.

The authors are obliged to mention if they have been aided by any grant in their research. The information on this should be place in the window under additional information in the submission system. Also all potential conflicts of interest for all authors must be disclosed. If authors have no interests to disclose, this must be explicitly stated. This should be placed in a separate note in the statement window in the submission system. In the same way authors must inform on their given participation scope in the work (eg. author of the conception, aims, methods, study protocol). In case of an even participation in the making of the publication, this should be clearly noted alongside each of the authors' names. The corresponding author should affirm that he or she has access to all data from the study, both what is reported and what is unreported. The corresponding authors also confirm that there was no editorial direction or censorship from the sponsors. Manuscripts including the results of examination of patients (involving a risk element) must have a copy of the written approval issued by the ethical committee attached or the statement that author received such approval. **All this information should be placed under the author's statement document in the separate window in the submission system.**

The authors are requested to use proper psychiatric vocabulary and international names of medicines (not trade ones). SI abbreviations should be used. Tables and drawings should be added at the end of the manuscript or as the separately named documents numbered consecutively, and their placement in the text should be clearly indicated.

Tables should be prepared in MS Word for Windows, graphs in MS Excel and drawings in Corel Draw. Drawings and tables should not be wider than 13 cm and should be capable of reduction.

Drawings should be saved as black and white (256 shades of grey) in the EPS or TIFF format, 300 dpi and the size in which they will be printed. Shades of grey or patterns should be used for filling the drawings and graphs. Illustrations can be submitted as halftone or colorful. They will be reproduced in black and white in the printed version of the journal, however, they will be saved in original colors in the Internet issue.

Content of the tables and descriptions of drawings should be written in Arial Narrow 10. The number of tables and drawings should be reduced to minimum. The author must obtain a written permission from the copyright holder of the previously published tables, illustrations and figures.

Tables, drawings, figures and illustrations should be added as the separately named documents, numbered consecutively, entered in the appropriate window in the submission system. Their placement in the text should be clearly indicated.

References should be presented in Vancouver System. The authors are requested to cite only necessary references, which are clearly referred to in the text. In the reference list, each item should start in a new line and be numbered according to the appearance in the text. For references with no author, the term "anonymous" should be used.

For papers published in journals the references should preserve the following sequence: surnames of the authors followed by their name initials, title of the article, name of the journal **(abbreviated according to Index Medicus at http://nlm.nih.gov; journals not indexed there should not be abbreviated),** year, volume, pages; **Example:** Kowalski N, Nowak A. Schizophrenia case-study. Psychiatr Pol. 1919; 33(6): 210–223.

For books: surnames of the authors followed by their initials, title of the book, place of publication, publisher, year of publication. **Example**: Kowalski ZG. Psychiatry. London: Press; 1923.

For a chapter of a book: surnames of the authors followed by their name initials, title. In: surnames and name initials of the editor of the book, title, place of publication, publisher, year of publication pages. **Example**: Szymański BM. Depressive states. In: Kowalski AM, Głogowski P, editors. Psychiatry Manual. 2nd ed. Paris: Psyche; 1972. p. 203–248.

For website: Author/Editor/Organisation's name. Title of the page [homepage on the Internet]. Place of publication: Publisher's name; [updated year, month, day; cited year, month, day]. Available from: (url). **Example:** Polskie Towarzystwo Psychiatryczne [homepage on the Internet]. Warszawa: Grupa Medforum sp. z o.o.; [updated 2011 Sept 07; cited 2012 Sept 15]. Available from: http://psychiatria.hosp.pl/

Be careful about punctuation (as in examples).