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Nonvalvular atrial fibrillation during chronic stress in the context of war in Ukraine: integrating mental health, pathophysiology, and pharmacotherapy in to a future-oriented model of care

Maryna Dolzhenko[1], Natalia Anatoliyivna Bilousova[1*], Vitalii Nesukai[1], Nataliia Kozhuharyova[1], Lidia Lobach[1], Larysa Konoplianyk[1], Tamara Mahanova[2] and Natalia Tkachenko[2]

Abstract

Mental health disorders resulting from war-related stress may interact with cardiovascular risk factors, highlighting the importance of understanding the course of nonvalvular atrial fibrillation (nAF) and the organization of medical care in resource-limited settings.

Objective To analyze evidence-based medicine (EBM) data on the mutual influence of atrial fibrillation (AF), chronic psychosocial stress, and mental health disorders with subsequent modeling of a future-oriented conceptual model of integrated patient-centered medical care for patients with nAF in wartime and post-war reconstruction of the Healthcare system in Ukraine.

Methods A narrative review of EBM data on epidemiological trends, pathophysiology of nAF, mental health, pharmacotherapy, Drug-Drug Interactions (DDI), patient-oriented, and digital interventions was conducted.

Results The relationships of psycho-emotional, cardiometabolic, behavioral and socioeconomic factors with the risk of onset and course of nAF were identified. Potential common mechanisms are dysregulation of the autonomic and hypothalamic-pituitary-adrenal systems, inflammation, oxidative stress, endothelial dysfunction and atrial remodeling. Mental health disorders can affect symptom burden, adherence to treatment, quality of life and safety of pharmacotherapy. A future-oriented conceptual integrated multidisciplinary model of Healthcare system was modeled.

Conclusions The analyzed data confirm the associative biopsychosocial links of nAF in conditions of chronic stress, but do not allow us to unambiguously establish the causal effect of chronic war stress on the development and progression of nAF. A future-oriented integrated conceptual model can be the basis for adapting medical care to war conditions and the post-war period in Healthcare system.

Keywords Atrial fibrillation, Mental health, War, Polypharmacy, Digital health, Future healthcare

*Correspondence:
Natalia Anatoliyivna Bilousova
arinatala@gmail.com

Full list of author information is available at the end of the article

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Introduction

Cardiac arrhythmias, in particular AF, are common and can lead to thromboembolic complications, Heart Failure (HF), premature cardiovascular events and mortality with a high probability. Considering that during the war in Ukraine up to 83% of the population is in a state of stress, psycho-emotional burnout, and a decrease in socio-economic status for a long time, this problem becomes particularly urgent [1–3]. In previous studies, we have confirmed the deterioration of the standard of living and its negative impact on adherence to treatment, quality of life, and the spread of anxiety and depressive disorders [4–6]. Taken together, the above factors require a revision of traditional approaches to providing medical care to patients with AF. It should be noted that a feature of nAF is the absence of rheumatic mitral valve disease or mechanical valve prostheses [7–9]. According to the results of our analysis of scientific sources, anxiety, depression, and emotional exhaustion are associated with the occurrence and complicated course of cardiovascular diseases (CVD), in particular AF. The results of the prospective Atherosclerosis Risk in Communities Study demonstrated that emotional exhaustion is associated with an increased risk of arrhythmia [10]. According to the clinical guidelines of the European Society of Cardiology (ESC), regular screening for anxiety and depression is recommended [11, 12]. However, the treatment of nAF is significantly complicated by the presence of comorbidities and polypharmacy [13–15]. According to EBM, pharmacological correction of mental health disorders does not always provide improved cardiovascular outcomes [16, 17]. Thus, there is a need for non-pharmacological approaches. Psychological, behavioral, and digital interventions are considered by current clinical guidelines as potential tools for integrated care for patients with AF in settings with limited access to Healthcare [18–20]. Current EBM suggests an association between chronic war-related stress, anxiety, depression, and nAF. However, the available evidence for these associations is mixed, with no definitive causal mechanisms. However, the organization of integrated, sustainable care for such patients in wartime settings requires improvement, particularly with regard to adherence to treatment, safety of pharmacotherapy, mental health, digital technologies, and sustainability of the Healthcare system. Therefore, there is a need to substantiate and identify promising areas for the development of integrated care for patients with AF in wartime and post-war periods.

Methods

This study was conducted as a narrative review to summarize current EBM data and substantiate the conceptual foundations of a future integrated model of medical care in war and martial law. The search for EBM data was conducted in the scientometric databases PubMed/MEDLINE, Scopus, Web of Science. Google Scholar data was used for additional search. The search was conducted in January – March 2026. An analysis of international clinical guidelines addressing the specified research problem was conducted. The EBM data search strategy included the use of the keywords "atrial fibrillation", "non-valvular atrial fibrillation", "mental health", "anxiety", "depression", "psychological stress", "chronic stress", "emotional exhaustion", "war", "conflict", "Ukraine", "drug-drug interactions", "polypharmacy", "pharmacotherapy", "medication adherence", "digital health", "self-care", "patient-oriented care", "healthcare system resilience", "future health care", "prediction" using logical operators AND and OR. The search strategies were adapted to the syntax and vocabulary of the scientometric database. The search queries were structured. The lists of literature sources were checked manually. Preference was given to literature sources from the last 5–10 years, but fundamental studies of pathophysiological and pharmacological mechanisms of action from an earlier period were also included.

The inclusion criteria were original studies, systematic reviews and meta-analyses, clinical guidelines, consensus documents in Ukrainian and English on adult patients with nAF or CVD, psychological and psychosocial risk factors, mechanisms of mutual influence of stress and nAF, pharmacotherapy, drug-related problems, digital and behavioral interventions, models of Healthcare in conditions of war or prolonged psychosocial stress.

The exclusion criteria were EBM data not related to nAF, mental health, Healthcare models, as well as publications in languages other than Ukrainian and English, duplicates, conference proceedings, abstracts, paid publications, and studies of low methodological quality.

After selecting scientific sources, a thematic and critical analysis of the EBM date was conducted, grouping the material by main areas: pathophysiological mechanisms, clinical manifestations, pharmacotherapy, mental health, digital technologies, and prospects for the development of integrated medical care. Particular attention was paid to the consistency of results, contradictory data, methodological limitations of the studies, and possible directions for the development of the Healthcare system in the war and post-war periods.

The analysis of the extracted data included comparison of results, identification of gaps and prospects for future research. The associations between mental health and AF were not interpreted as EBM date of causal relationships without confirmation by clinical studies.

The extracted EBM date used to develop a future-oriented conceptual model was analyzed, systematized, and structured. Factors influencing the care of patients with nAF in clinical practice were further identified, taking into account psychosocial, behavioral risk factors in

technological, socio-economic areas, and various Healthcare systems. Gaps in existing models of Healthcare that have an impact on risk factors for the development of nAF and mental health disorders were identified. The trajectories of existing fragmented care with a forecast of further development were modeled; digital care with unequal access; integrated sustainable patient-oriented medical and pharmaceutical care with future prospects and integration of cardiovascular, psychiatric, and psychosocial care, equity, optimization of pharmacotherapy, and digital inclusion.

Research results and discussion

Epidemiological trends and mental health burden in patients with nAF under chronic war-related stress: a perspective for Healthcare systems development

Due to the restricted access to official epidemiological data during the war in Ukraine, the assessment of the burden of CVD is based on indirect epidemiological indicators and the results of clinical studies, which indicate an increase in the prevalence of cardiometabolic and psychoemotional risk factors. According to the World Health Organization and the Ministry of Health of Ukraine, in 2025, approximately 83% of the adult population reported chronic stress and emotional burnout. Thus, an increase of 58% in anxiety, 49% in depression, 50% in sleep disorders, and 49% in emotional exhaustion was recorded [1–3]. At the same time, there is an increase in the number of hospitalizations to 37.5 per 1000 population (+8.6%), in particular, the number of cases of arterial hypertension (AH) increased by 59%, myocardial infarction - by 28%, strokes - by 78% [1–3]. These trends are most evident in regions affected by hostilities with reduced access to medical and pharmaceutical care [1–3].

Analysis of scientific sources indicates the consistency of EBM date regarding the deterioration of mental health of the Ukrainian population during the war. However, epidemiological indicators of the impact of war-related stress on the incidence and course of AF remain limited. The studies we have identified are observational and describe associative relationships. At the same time, cause-and-effect relationships require further confirmation by prospective clinical studies.

AF is a common form of arrhythmia, has an impact on the risks of thromboembolism and stroke, leads to thromboembolic complications, stroke, HF and increased mortality. Depressive and anxiety conditions often coexist with AF, but the relationships between them remain ambiguous [21, 22]. As of 2021, there were over 52.6 million cases of AF reported worldwide, increasing by 4.48 million cases annually [21]. It is projected to increase to 17.9 million cases in Europe by 2060 [23]. The relationship between mental health and AF is bidirectional. Mental disorders may be associated with an increased risk of AF onset and recurrence. However, AF and its symptoms, with uncertain prognoses, may contribute to the development or deterioration of mental health. In addition, most of the EBM date is observational, which does not allow us to establish cause-and-effect relationships. An analysis of scientific publications showed that mental disorders retained a prognostic relationship with AF after taking into account cardiovascular risk factors, but the magnitude and independence of this effect depend on population characteristics and study methodology [24]. Thus, in a population-based study ($n > 2.5$ million), it was found that depression, anxiety and insomnia, AH, chronic kidney disease are associated with a significantly increased risk of AF. However, the large size of the study population does not allow for residual confounding due to the presence of comorbid conditions, pharmacotherapy, and behavioral risk factors [25].

Mental health in AF: prevalence, heterogeneity of research findings, and clinical significance

The prevalence of anxiety and depression in patients with CVD is higher than in the general population (Table 1). It has been studied that 22% of patients with AF have depression and 13% have anxiety [26]. According to other studies, the prevalence of depression in such patients ranges from 38% to 42.7% [27].

At the same time, the development and progression of AF is associated with cardiometabolic risk factors and mental health and social well-being, which have an impact on patients' perception of symptoms, timely seeking medical care, and further progression of the disease [30].

Potential pathophysiological mechanisms of the interaction between chronic stress, mental health, and AF

The interaction between stress and AF occurs through interconnected biological pathways, which include activation of the sympathetic nervous system (SNS), dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation, oxidative stress, the influence of the autonomic nervous system (ANS), and structural

Table 1 Prevalence of anxiety and depression in patients with CVD and AF

Mental health condition	Prevalence in AF	Population / evidence source	Interpretation
Depression	18,4%	Adults with AF; meta-analysis [28]	High prevalence, substantial heterogeneity
Anxiety	28,9%	Adults with AF; meta-analysis [29]	Prevalence varies by age, sex and region
Anxiety/Depression	30,2%	European AF populations [26]	Higher regional estimate

and electrical remodeling of the atrium [31, 32]. Systematic reviews and meta-analyses have shown statistically significant associations between anxiety, depression, stress and the risk of AF, supporting the psychocardiological hypothesis [31, 32]. However, the results of the studies analyzed indicate an association but do not establish causal effects. However, the nature of the association may be nonlinear: the magnitude of the association between the severity of anxiety and depression and the risk of AF onset and progression did not increase monotonically with increasing symptom severity [27]. Such heterogeneity may reflect differences in patients' comorbid conditions, the methods used to assess mental status, or the influence of concomitant factors and requires further research [27] (Fig. 1).

Furthermore, depressive states are associated with a doubling of the risk of cognitive impairment in such patients [33]. The UK Biobank study further supports the possible causal role of personality (neuroticism) in the development of AF. These associations are observed predominantly among younger people and those with lower body mass index without generally accepted risk factors [34]. Such results may indicate the heterogeneity of the impact of psychological characteristics on the risk profile of patients.

Thus, most of the studies reviewed found associations between mental health disorders and AF. However, Mendelian randomization results [34] provided EBM date supporting a causal hypothesis for neuroticism. However, the results of this study [34] cannot be extrapolated to all mental health disorders and war-related stress conditions.

Mental Health and cardiovascular risk factors for AF in Ukraine during wartime

The war in Ukraine is associated with the formation of long-term psycho-emotional stress, which is accompanied by a high prevalence of symptoms of anxiety, depression and other manifestations of psychological distress [1–3]. According to Ukrainian epidemiological studies, 36.3% of the population meets the criteria for one mental disorder, and generalized anxiety disorder is observed in 15.2% of patients [35]. However, cardiovascular and metabolic risk factors remain very common: AH is 83.7%, obesity is 67.4% [36]. According to clinical studies conducted in Ukraine, war-related stress significantly worsens the consequences of somatic diseases, which leads to an additional burden on the Healthcare system and an increase in the burden of symptoms [37]. However, epidemiological data on the may impact of war-related stress on the prevalence and progression of nAF in Ukraine remain limited.

Pathophysiological aspects of the relationship between anxiety-depressive states and AF in conditions of War-Related Stress

The analyzed data indicate a biological relationship between psycho-emotional stress and nAF, which may develop through neurohumoral, immunoinflammatory, metabolic and neurocognitive mechanisms [38]. Therefore, the above data allow us to consider this interaction

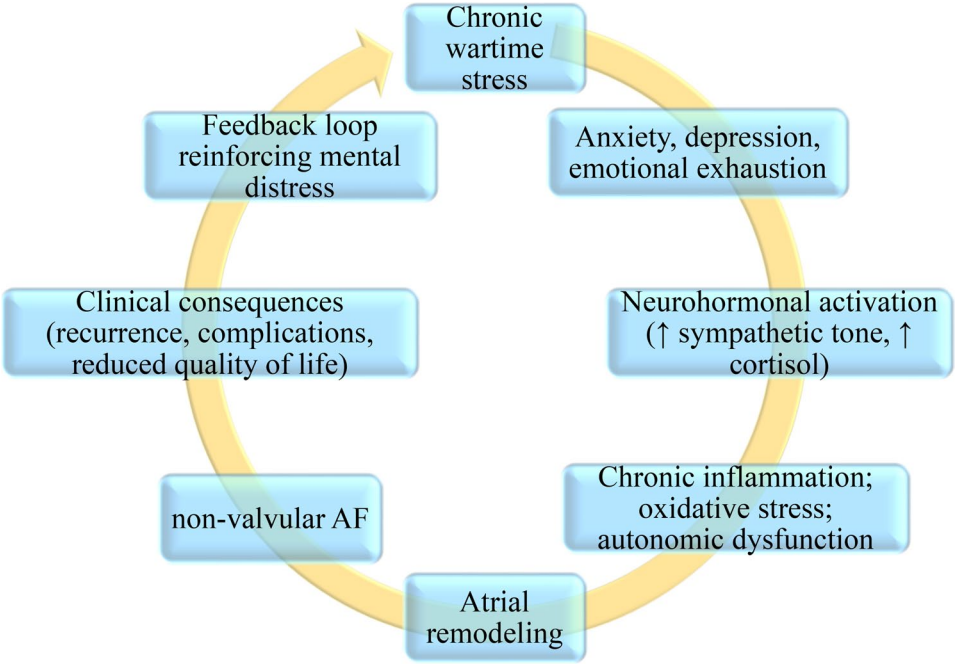


Fig. 1 Interaction between chronic stress, mental health disorders, and nAF

as multilevel, but do not prove the equal contribution of individual pathways to the development of nAF. The concept of the "Heart–Brain" axis provides a holistic basis for understanding the relationships between mental state and nAF, which may have common neuroendocrine and autonomic mechanisms [38]. Thus, the presented data allow us to consider neurohumoral, inflammatory, metabolic and behavioral pathways as potential links in the interaction between mental health and nAF. AF occurs due to electrophysiological instability of the myocardium, which is significantly exacerbated by acute and chronic stress [39]. Clinical studies have shown an association between depression, anxiety, and adverse outcomes in AF. However, heterogeneity in study cohorts, mental health disorder criteria, and clinical endpoints limits its direct comparison of effect sizes across studies [40]. Also, more severe forms of depression were associated with persistent and paroxysmal forms of AF. Furthermore, affective disorders have also been associated with reduced efficacy of pharmacotherapy, cardioversion, and catheter ablation [40]. Thus, the relationship between AF and depressive states should be viewed as a potentially bidirectional neurocardiac continuum, although EBM date to support a causal effect of treatment of one condition on the other is currently insufficient [40].

Neurocardiac regulation and the ANS: mechanisms of action

The interaction between the heart and brain is mediated by regulation that involves the central nervous system (CNS) and the ANS. Afferent impulses from cardiac baro- and chemoreceptors are transmitted to the medulla oblongata via sympathetic and vagal pathways. Further, primary integration occurs in the CNS [39]. Further mechanisms affect the insular cortex, amygdala, hypothalamus and hippocampus, which coordinate emotional, autonomic and neuroendocrine responses [41]. Dysfunction of the above structures may be associated with heart rhythm dysregulation and increased arrhythmogenicity [39]. Neuroinflammation and neurotrophic dysregulation may contribute to emotional dysregulation and the development of anxiety and depression [41]. Chronic autonomic dysregulation, namely the predominance of sympathetic activation, is accompanied by increased catecholaminergic stimulation, heart rate and blood pressure (BP). At the cardiomyocyte level, these changes may affect calcium homeostasis and action potential duration, which creates conditions for electrical remodeling of the atria and increased their arrhythmogenicity [41]. At the same time, the available data indicate pathophysiological plausibility and associative relationships, while the impact of war-related stress on the development of nAF requires further prospective studies.

Endocrine and neurohumoral activation

As noted above, chronic stress is associated with dysregulation of the HPA axis and the SNS, which may be accompanied by alterations in catecholaminergic and glucocorticoid responses [39, 42–45]. Further neuroendocrine responses may contribute to atrial electrical instability and increase the susceptibility to arrhythmias. At the same time, activation of the renin-angiotensin-aldosterone system may accelerate the process of atrial fibrosis through mechanisms mediated by TGF-β and matrix metalloproteinase dysregulation. In this case, conduction may slow down and myocardial re-entry may develop [40]. Persistent hyperactivation of the HPA axis is associated with excessive cortisol release, which may have an impact on hippocampal atrophy, cognitive impairment, and increased susceptibility to depression [46, 47].

Inflammatory and oxidative pathways in the development of nAF

Chronic inflammation may combine mechanisms associated with AF and depressive states. Elevated levels of inflammatory markers, including C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α, have been associated with atrial remodeling and increased thrombogenic potential [42, 45]. Elevated IL-6 and CRP levels have also been reported in patients with depression. The magnitude of these associations may depend on the severity of symptoms and clinical context [48]. However, such correlations do not allow us to determine the cause of psychiatric symptoms, inflammation, and their consequences [48]. Oxidative stress potentially contributes to the development of arrhythmias. Reactive oxygen species generated by Nicotinamide Adenine Dinucleotide Phosphate oxidases and mitochondria can disrupt calcium homeostasis and damage cardiomyocytes [48, 49]. Oxidation of ryanodine receptors can lead to calcium leakage and after depolarization, which causes the onset of AF [48, 49]. Endothelial dysfunction is characterized by reduced nitric oxide bioavailability and contributes to vascular dysregulation, increased risk of thrombosis and impaired cerebral perfusion, possibly influencing the association of AF with cognitive and affective disorders [49].

Genetic, metabolic and behavioral risk factors for AF

Recent genetic studies, including Mendelian randomization, indicate possible shared genetic risk factors for cardiovascular and mental health disorders [50]. Some genetic studies suggest a possible causal component of the association between genetic predisposition to anxiety and depression and risk of AF, but these results depend on the genetic tools used and the assumptions of the MR analysis [50]. Alterations in glucose and lipid metabolism, mitochondrial dysfunction, and energy imbalance

contribute to myocardial remodeling and electrophysiological instability [51]. At the same time, AF may be associated with subsequent metabolic dysregulation, suggesting a potentially bidirectional nature of this relationship [51]. At the same time, chronic stress and depressive states may be accompanied by changes in behavior and related cardiovascular risk factors [43].

Cardio-cerebral continuum and cognitive decline

A review of the literature suggests that AF may be part of a cardiovascular-cerebral continuum that links CVD with cognitive and affective disorders [52]. According to the data of a systematic review and meta-analysis ($n > 1.6$ million), it was found that the combination of AF and depression is associated with a twofold increase in the risk of cognitive impairment (OR ~ 2.23; 95%CI 1.54–3.21) (Fig. 2) [53]. Therefore, the analyzed data support the concept of a multilevel and potentially bidirectional interaction between mental health and AF, in which neurohumoral, inflammatory, metabolic, and behavioral factors may interact. Thus, in the context of war-related stress, this interaction becomes particularly relevant. However, the extent and scope of influence of individual pathophysiological mechanisms remain heterogeneous and require further investigation.

Features of the clinical course of nAF in conditions of war-related stress: a biopsychosocial perspective

War-related chronic stress in Ukraine likely acts as a powerful modifiable risk factor and alters the clinical course of nAF. The results of the conducted analysis of scientific data indicate a possible connection of chronic psycho-emotional stress with the features of the clinical course of AF, in particular symptom burden, relapses and disease progression [54]. In patients who experience prolonged psycho-emotional stress, the onset or relapse of AF may be associated with acute emotional events. At the same time, prolonged stress potentially contributes to the formation of conditions for further progression of the arrhythmia [54, 55]. Such variability in clinical debut may indicate heterogeneity of the response of the cardiovascular system to stress factors.

Stages of the clinical course of nAF in conditions of chronic stress

The clinical phenotype of nAF in patients with prolonged stress can vary from nonspecific symptoms in the early stages of development to more pronounced symptom burden and functional limitations as the disease progresses. In the preclinical phase of nAF, symptoms are often nonspecific and may include generalized fatigue, anxiety, and sleep disturbances. These manifestations are often mistakenly associated with psychological overload

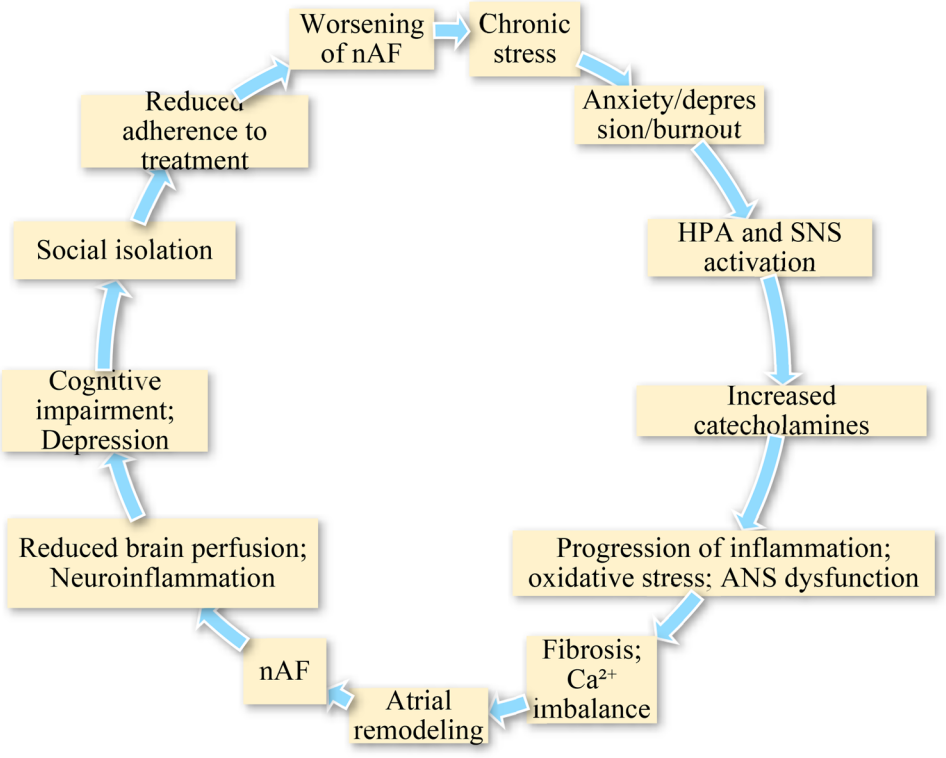


Fig. 2 Bidirectional pathophysiological interaction

and are not recognized as early manifestations of CVD [56]. The stage of clinical manifestation of nAF is characterized by classic symptoms of arrhythmia. Palpitations, shortness of breath, dizziness, and reduced tolerance to physical exertion may be observed. Moreover, in patients in states of anxiety and depression, the perception of these symptoms is significantly exaggerated [57]. Over time, the disease may partially regress or turn into a recurrent or chronic state characterized by repeated episodes of arrhythmia. Such progression of the disease is largely due to constant psycho-emotional stress and persistent autonomic dysregulation [58].

Progression and "AF burden"

In chronic stress, AF is characterized by relapses and its course progressively worsens. According to the ESC clinical guidelines, AF is a dynamic condition that progresses from paroxysmal to persistent and long-lasting and reflects cumulative atrial remodeling [11, 59, 60]. Psycho-emotional stress increases the so-called "AF burden", which is defined as the frequency, duration and overall impact of arrhythmia episodes. An increase in AF burden is a major factor in disease progression and is associated with a decrease in the effectiveness of heart rhythm control strategies [60, 61]. At the pathophysiological level, the progression of nAF is driven by electrical remodeling of the myocardium and is characterized by shortened refractory periods with conduction delays, structural remodeling, fibrosis, and disruption of intercellular connections [61–63]. Such changes create stable re-entry circuits that sustain the progression of the arrhythmia and reduce the likelihood of its spontaneous termination [64].

Symptom perception and psycho-emotional modulation

Patients with AF who are under chronic stress demonstrate distinct clinical manifestations of the disease. These manifestations are characterized by increased symptom variability and sensitivity to their perception. Psychological distress can alter the perception of AF symptoms, with the result that subjective symptom burden does not always correspond to objective arrhythmia severity [55, 65]. Patients may report fatigue, dyspnea, sleep disturbances, and decreased physical activity, which impairs quality of life [66, 67]. Sleep disorders are significantly more common in patients with AF and are associated with more severe symptoms and reduced physical activity [67].

Quality of life and psychosocial aspects

Patients with AF and comorbid anxiety or depression report a lower health-related quality of life. Importantly, improved rhythm control is associated with reduced arrhythmia-focused anxiety, general anxiety, and depression, and improved quality of life [68]. However, these improvements do not always correlate with objective heart rhythm parameters. Data from the SWEDEHEART registry suggest that psycho-emotional states may complement cardiometabolic risk factors in predicting adverse cardiovascular events [69]. However, these results do not allow us to determine the independent causal contribution of anxiety or depression compared with comorbid conditions [69].

Complications and burden on the Healthcare system

Chronic stress significantly increases the risk of complications in nAF. Thromboembolic events, including ischemic stroke, caused by nAF occur as a result of impaired intracardiac hemodynamics and thrombus formation in the left atrial appendage [11]. Disruption of the Healthcare system due to targeted attacks during the war in Ukraine leads to limited monitoring of treatment. This situation potentially contributes to rehospitalization due to recurrent arrhythmias, cardiovascular complications, and decompensation of comorbidities [70, 71]. An additional stress-related factor is posttraumatic stress disorder (PTSD). PTSD is associated with the development of AF and early onset of the disease (OR 1.13; 95% CI 1.02–1.24) [72].

Prognosis and transition of nAF into a chronic state

The clinical course of nAF in patients under chronic stress is associated with unfavorable prognostic dynamics. There is a reduced probability of restoring a stable sinus rhythm, which leads to progressive remodeling of the atria and reduced response to pharmacotherapy [11]. However, the impact of war-related stress remains poorly understood. The progression of AF may be accompanied by a transition from paroxysmal to persistent arrhythmia. Psycho-emotional disorders may be one of the modifying factors of the adverse course of AF [72, 73].

Behavioral patterns and social determinants

Patients with paroxysmal AF often develop "cardiac anxiety," characterized by hypervigilance of symptoms and an exaggerated perception of the severity of the arrhythmia. This perception of symptoms can lead to avoidance behaviors, limitation of physical and social activity, physical deconditioning, and social isolation [74]. Decreased physical activity and functional capacity may be associated with greater AF symptom burden and poorer quality of life, and depressive symptoms are further associated with decreased physical activity [74]. Social factors may also influence the course of nAF. Living alone is associated with an increased relative risk of AF recurrence after catheter ablation (HR 1.07; 95% CI 1.00–1.13) and higher recurrence rates (360.2 vs. 316.2 per 1000 person-years) [75]. Low socioeconomic status and perceived

social disadvantage are independently associated with increased cardiovascular risk [76–78].

Adherence to treatment

Adherence to treatment has a direct impact on clinical outcomes in patients with nAF. In contrast to compliance, adherence to treatment involves active participation of patients in treatment [79]. Studies conducted in Ukraine during the war show that patients with one or two socioeconomic risk factors demonstrate the lowest rates of adherence to treatment (76.2% [76.2 ± 0.04; $p < 0.001$]) [4; 5]. In addition, anxiety and depression ($p < 0.05$), especially among women, reduce adherence to treatment by 54.8% compared to men (B = −0.794; Exp(B) = 0.452; $p = 0.044$) [90]. These results are consistent with international data, where only 31.02% of patients in a depressed state adherence to prescribed antidepressant therapy [80].

Thus, the analyzed data allow us to identify several clinical features of nAF, potentially related to psychoemotional stress. The clinical features of nAF include variability in symptom burden, deterioration in quality of life, decreased physical activity, impaired adherence to treatment, and possible progression of arrhythmia. At the same time, most of the available evidence is observational studies. However, the impact of war-related stress on these clinical trajectories remains poorly defined. This situation justifies the need for a comprehensive assessment of mental state, symptom burden, and social determinants during the treatment of patients with nAF.

Optimizing pharmacotherapy in patients with nAF under war-related stress: integrating mental health and precision medicine

When optimizing pharmacotherapy for nAF, the mental state of patients, behavioral factors, adherence to treatment, and social factors that may affect the efficacy and safety of therapy should be taken into account.

Mental health screening as a main element in optimizing pharmacotherapy

The ESC and Ukrainian clinical guidelines emphasize that screening for anxiety and depression is an important component of comprehensive care for CVD together with nAF [11, 12]. Standardized quality of life, anxiety, and depression questionnaires (PHQ-2/PHQ-9 and HADS-A/D) are currently recommended by Ukrainian clinical guidelines for inpatients and outpatients with reassessment at follow-up. Importantly, AF-specific quality of life assessment (AFEQT, AF-QoL, AFQLQ, QLAF) is recognized as a clinically relevant endpoint [11, 12] and reflects subjective well-being as an integral part of clinical decision-making. Therefore, the diagnosis of comorbid anxiety or depression in patients with nAF may lead to the initiation of a review of pharmacotherapy for safety and efficacy with an assessment of adherence to treatment, potential DDIs, and the determination of indications for prescribing pharmacotherapy for psychiatric disorders.

Emotional exhaustion as an independent risk modifier

A prospective cohort study ($n = 11{,}445$; follow-up period 1990–2017) demonstrated that emotional exhaustion is associated with an independent risk factor for AF [10]. The mean Vulnerability Experiences Quotient score was 10.3 ± 8.6. Patients with AF in the highest quartile had a significantly increased risk of developing arrhythmia (HR 1.20; 95% CI 1.06–1.35) compared with those in the lowest quartile and the overall cohort (HR 1.13; 95% CI 1.02–1.25) [10]. These results emphasize that emotional exhaustion should be considered as a potential psychological symptom and biological risk factor associated with the development and progression of arrhythmias.

Limitations of pharmacotherapeutic treatment of psychiatric disorders in nAF

Pharmacotherapy aimed at improving anxiety and depression in patients with nAF does not always consistently improve cardiovascular outcomes. Clinical trials have shown that antidepressants do not significantly reduce AF recurrence or the risk of thromboembolism [81]. For example, SSRIs have been shown to reduce AF burden (incidence ratio 0.07 [0.03–0.15], $p < 0.001$) and have no significant effect on the frequency of arrhythmia episodes [16]. In addition, depressive states negatively affect the effectiveness of invasive and pharmacotherapeutic interventions. For example, according to a systematic review and meta-analysis ($n = 1070$), pre-procedural depression doubled the risk of AF recurrence after catheter ablation (HR 2.24; 95% CI 1.75–2.88) [17]. Therefore, these data do not support the use of SSRIs as a secondary prevention strategy for AF. In such cases, antidepressant therapy in patients with nAF should be guided by the indications for the treatment of anxiety and depression, tolerability, and potential DDIs.

Polypharmacy and the complexity of drug pharmacology

According to the GLORIA-AF registry, 83.1% of patients receive multiple medications simultaneously [82]. The presence of comorbid mental health conditions can further complicate pharmacotherapy. The potential for pharmacokinetic and pharmacodynamic DDIs increases with the number of medications. The potential for DDIs increases significantly with the concomitant use of medications that affect CYP450 activity and the P-gp and OATP1B1 transport systems [11, 14, 77]. DDIs may result in altered drug exposure, increased risk of bleeding, proarrhythmic effects, or DDI toxicity [15, 83, 84]. Particular attention should be paid to combinations with

amiodarone, which may alter the exposure of a number of concomitant medications through CYP and P-gp inhibition [15, 83, 84]. Therefore, in patients with nAF with comorbid mental health conditions, the prescription of new psychotropic medications should be accompanied by ongoing monitoring and review of the entire pharmacotherapy (Table 2).

According to the FDA database, 177,896 reports of adverse drug reactions related to arrhythmias were registered for 2016–2022. Some of them were associated with DDIs, which highlights the clinical importance of optimizing pharmacotherapy [13].

Thus, the clinical challenge is the use of multiple medicines in pharmacotherapy and the accumulation of potential pharmacokinetic and pharmacodynamic DDIs. However, mental health disorders do not prove a causal relationship between polypharmacy and adverse cardiovascular events, as the risks of DDIs and adverse drug reactions may be influenced by age, comorbid conditions, renal and hepatic function, severity of AF, and pharmacotherapy regimen. Therefore, pharmacotherapy monitoring should be considered as part of personalized approaches to the treatment of patients with nAF and mental health disorders.

Non-pharmacological interventions as components of comprehensive approaches to the treatment of nAF

Complex pharmacotherapy regimens, high risk of DDIs, and mental health impacts suggest that pharmacotherapy alone is not sufficient to achieve optimal clinical outcomes. In accordance with the ESC clinical guidelines, non-pharmacological approaches may be used. These include psychological interventions, psychological education, stress management, sleep hygiene, lifestyle modification, and physical activity [77]. A systematic review and meta-analysis of 21 randomized controlled trials ($n = 2591$) found that psychological interventions significantly reduce anxiety and depression, improve quality of life over 6–12 months [18]. Cognitive behavioral therapy has been shown to improve quality of life in patients with nAF and reduce the burden on the Healthcare system [77, 85].

Therefore, psychological and behavioral interventions have the potential to reduce symptoms of anxiety, depression, and subjective distress. They also have the potential to improve quality of life in patients with AF. However, improvements in emotional well-being should not be interpreted as EBM date of antiarrhythmic effects. The data reviewed do not establish whether reducing anxiety and depression reduces the frequency of AF recurrences, its burden, or the need for cardioversion and ablation. Therefore, such interventions should be considered as a component of comprehensive approaches to patient management.

Patient-oriented and digital approaches

In patients with nAF and mental health disorders, digital patient-oriented tools can be considered as a means of supporting treatment adherence, monitoring symptoms, and ensuring continuity of comprehensive medical care in settings with limited access to healthcare services. A randomized controlled trial ($n = 392$) demonstrated that nurse-led behavioral activation was associated with improvements in quality of life and adherence to pharmacotherapy that were maintained over 6 months [19]. A systematic review and meta-analysis of 27 studies showed that self-care combined with education, AF symptom monitoring, and digital tools can improve selected clinical and behavioral outcomes [20]. In wartime, digital tools have the potential to support remote screening for anxiety and depression, symptom monitoring, adherence to pharmacotherapy, and timely communication between the patient and members of the multidisciplinary team in conditions of limited physical

Table 2 Clinically relevant drug–drug interactions in patients with naf and anxiety-depressive disorders [11, 13, 77]

№	Clinically relevant combination	Mechanism action	Main risk	Practical solution
1	DOAC + strong CYP3A4/P-gp inhibitors	Increase DOAC exposure	Bleeding	Review concomitant therapy; follow product-specific recommendations
2	DOAC + strong CYP3A4/P-gp inducers (rifampicin, carbamazepine, St John's wort)	Decrease DOAC exposure	Reduced anticoagulant effect / thromboembolic risk	Avoid where possible; consider alternative therapy
3	SSRI/SNRI + oral anticoagulant	Impaired platelet serotonin-mediated haemostasis	Bleeding	Assess bleeding risk and concomitant antithrombotic therapy
4	Fluoxetine/paroxetine + metoprolol	CYP2D6 inhibition leads to increased metoprolol exposure	Bradycardia, hypotension	Monitor HR/BP; consider alternative antidepressant or β-blocker
5	Citalopram/escitalopram + QT-prolonging antiarrhythmics	Additive QT prolongation	Ventricular proarrhythmia	Review QT-prolonging drugs; ECG/electrolyte monitoring when indicated
6	Amiodarone + warfarin	CYP2C9 inhibition	Excess anticoagulation / bleeding	INR monitoring and dose adjustment
7	Amiodarone + digoxin	P-gp inhibition	Increased digoxin exposure/toxicity	Clinical and, when appropriate, concentration monitoring

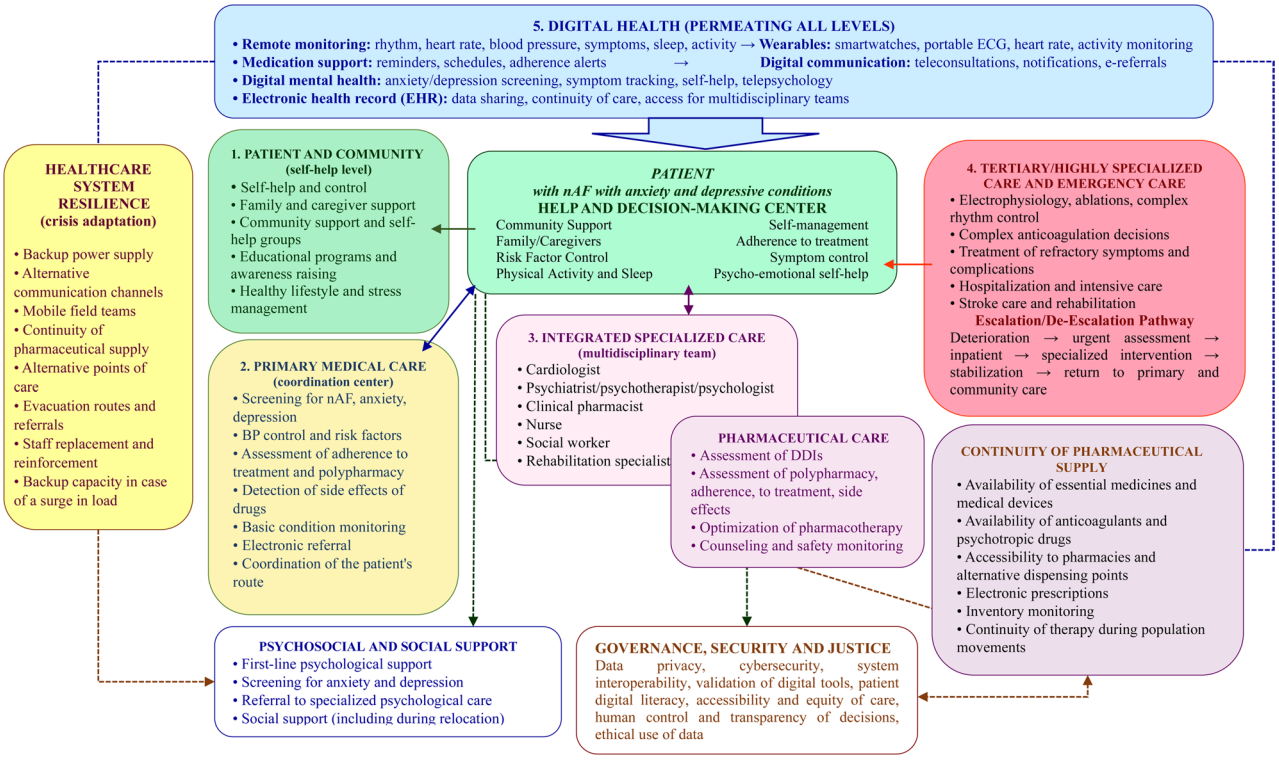


Fig. 3 Conceptual model of patient-oriented care for patients with nAF with anxiety and depressive conditions

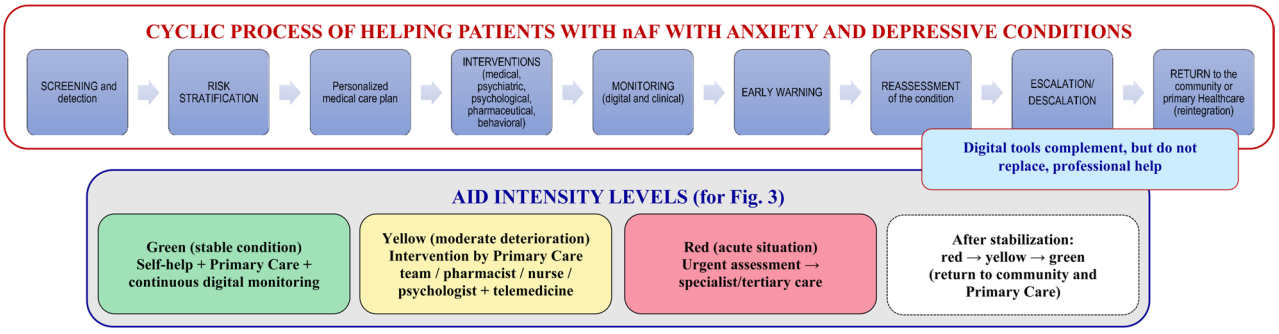


Fig. 4 Cyclic process of helping patients with nAF with anxiety and depressive conditions

accessibility of medical care. At the same time, the implementation of such approaches may be limited by digital inequalities due to access to the Internet, digital devices, digital literacy, and health services in different social and territorial communities. Therefore, the development of integrated models of multidisciplinary care that can combine digital monitoring with cardiac, pharmaceutical, psychological, and social support with adaptation to different levels of access to resources in wartime and post-war periods is promising.

A future-oriented conceptual model of integrated multidisciplinary health care

Taking into account the predominantly associative interconnected impact of nAF, anxiety and depressive states, polypharmacy and restrictions on access to medical care in war or crisis situations, a conceptual model of patient-oriented Healthcare was modeled. Its basis is the integration of cardiological, psychiatric, pharmaceutical, psychological care with primary medical care, nursing and community support and digital monitoring tools (Fig. 3).

The model involves a cyclical process of assessment, risk stratification, personalized interventions, patient monitoring and reassessment with the possibility of transition to specialized or emergency medical care and subsequent return to primary and community levels of care (Fig. 4).

The digital content of the model includes remote monitoring of heart rate, BP, symptoms, adherence to

treatment, and psycho-emotional status. In addition, the use of wearable devices, electronic medical records, digital reminders, tele-medicine, tele-pharmaceutical consultations is provided. At the same time, digital technologies are considered as a tool to supplement medical care. Adapting the model to crisis or wartime conditions involves emergency routes of medical care, mobile and mobile teams, continuity of supply of medicines, alternative access points to health services and support for patients in communities. Such a structure can provide a flexible response to changes in patients' clinical conditions, psychosocial burden and access to resources in the war and post-war periods.

Strengths, limitations, and research perspectives

A strength of this narrative review is the integration of cardiological, psychiatric, psychologic and socio-economic factors of AF in the context of chronic war-related stress. This approach allows us to consider AF through cardiometabolic risk factors. Furthermore, the course of AF may be influenced by psycho-emotional states, behavioral factors, socioeconomic conditions, and access to Healthcare. Also, the combination of evidence on pathophysiological mechanisms, clinical factors, and pharmacotherapy with the perspectives of digital and patient-oriented care are additional advantages.

The conducted narrative review does not ensure reproducibility and does not allow to assess the risks of bias of the results. The selection and interpretation of EBM date depended on the availability of publications and the professional interpretation of the authors. The number of studies devoted to the mutual influence of AF and mental health in war conditions remains limited. The results of studies conducted without the influence of war were used to substantiate possible pathophysiological mechanisms, risk factors, modeling the organization of medical care and were not considered for extrapolation to the Ukrainian population. In addition, the conceptual part of the study, focused on the future, is scientifically sound, is not standardized and predictive. However, this model can be used to develop and further standardize alternative directions for the development of integrated multidisciplinary medical care.

We see the prospect of further research as long-term observational studies on the Ukrainian cohort with the assessment of mental health, cardiometabolic risk factors and clinical characteristics of nAF. The effectiveness and safety of the developed integrated model of medical care in the real conditions of the Ukrainian Healthcare system require separate assessment. The effectiveness of the proposed model should be assessed by the clinical outcomes of the course of nAF, adherence to treatment, quality of life, mental health, frequency of hospitalizations, safety of pharmacotherapy and accessibility of medical care. Such an approach can ensure the transition from the description of the relationships between mental health and nAF to an evidence-based model of medical care organization adapted to the chronic war-related stress and limited resources.

Conclusions

It was found that the relationship between AF, mental health and chronic stress in the context of chronic war-related stress and limited Healthcare system resources should be considered in a biopsychosocial context.

It was determined that psycho-emotional, cardiometabolic, behavioral and socio-economic factors can shape the risks of AF. Pathophysiological mechanisms can provide a bidirectional relationship between mental disorders and AF. At the same time, the predominance of observational EBM data and the lack of long-term Ukarainian data do not allow us to establish the causal effect of chronic war-related stress or individual mental disorders on the occurrence and progression of AF.

The clinical significance of the relationship between nAF and mental health is found to lie in the potential impact on the risks of arrhythmias, possible consequences of treatment adherence, quality of life, symptom burden, safe use of medicines and access to Healthcare.

The transition from a highly specialized to an integrated patient-oriented interdisciplinary model of Healthcare, adapted to the conditions of chronic war-related stress, limited resources and variable access to health services, is justified. A future-oriented integrated conceptual model is proposed, combining primary, specialized and tertiary Healthcare, Pharmaceutical care, Psychological support, self-help in communities, digital monitoring and mechanisms for the integration of Healthcare and creates a basis for its further adaptation in the conditions of war and post-war recovery of the Healthcare system.

Abbreviations

AF	Atrial Fibrillation
AH	Arterial Hypertension
ANS	Autonomic Nervous System
ANS	Autonomic Nervous System
BP	Blood Pressure
CNS	Central Nervous System
CRP	C–Reactive Protein
CVD	Cardiovascular Diseases
DDIs	Drug–Drug Interactions
EBM	Evidence–Based Medicine
ESC	European Society Of Cardiology
HF	Heart Failure
HPA	Hypothalamic–Pituitary–Adrenal
HR	Heart Rate
nAF	non–valvular Atrial Fibrillation
PTSD	Posttraumatic Stress Disorder
SNS	Sympathetic Nervous System
SSRIS	Selective Serotonin Reuptake Inhibitors

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Data availability
No new datasets were generated or analysed during the current study. All information supporting the conclusions of this review is derived from published articles cited in the reference list.

Declarations

Ethics approval and consent to participate
Not applicable. This manuscript is a narrative review based exclusively on previously published literature and did not involve human participants, animals, human tissue, or identifiable personal data. Therefore, ethics committee approval and informed consent to participate were not required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Cardiology Department, Shupyk National Healthcare University of Ukraine, Dorohozhytska 9, Kyiv, Ukraine
[2]Department of Management and Economics of Pharmacy, Zaporizhzhia State Medical and Pharmaceutical University, Maria Pryimachenko Boulevard, 26, Zaporizhzhia, Ukraine

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