Founded 1897 • New Series

Vol. 128 • No. 3/2025 • May

Romanian Journal of Military Medicine

REVISTA DE MEDICINĂ MILITARĂ

REDACTION

Strada Mircea Vulcanescu, Nr. 88, Sector 1, București, Email: office@rjmm.ro
www.revistamedicinamilitara.ro

Romanian Journal of Military Medicine, New Series, vol. 128, No 3/2025, May
ISSN-L1222-5126; eISSN 2501-2312; pISSN 1222-5126

Romanian Journal of
Military
Medicine

Founded 1897•New Series
Vol. 128 • No. 3/2025, May

Contents

https://doi.org/10.55453/rjmm.2025.128.3.1

ORIGINAL ARTICLE

Off-Label Percutaneous Solution for Primary Degeneration of a Bioprosthetic Valve in the Tricuspid Position: Case Report and Literature Review on Transcatheter Valve-in-Valve Insertion

Horațiu Moldovan[1,2,3], Vlad A. Iliescu[1,4], Andrada Guță[2], Elena Nechifor[5], Aida Badea[2], Alexandru Zăman[2], Maria S. Safta[1,2], Gabriel Gorecki[6,7], Mircea Robu[1,4], Andrada Bogdan[5]

[1] Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; h_moldovan@hotmail.com (H.M.); vladanton.iliescu@gmail.com (V.A.I.); mariasabinasafta@gmail.com (M.S.S); mircea.robu@drd.umfcd.ro (M.R.)
[2] Department of Cardiovascular Surgery, Bucharest Clinical Emergency Hospital, Bucharest, Romania; Sanador Clinical Hospital, 010991 Bucharest, Romania; andrada_guta@yahoo.com (A.G.); aidafirtade@gmail.com (A.B.); alexandrusebastianzaman@gmail.com (A.Z.)
[3] Academy of Romanian Scientists, Bucharest, Romania
[4] Department of Cardiovascular Surgery, Prof. Dr. C.C. Iliescu Emergency Institute for Cardiovascular Diseases, Bucharest, Romania
[5] Department of Cardiovascular Surgery, Sanador Clinical Hospital, Bucharest, Romania; nechiforelena21@yahoo.com (E.N.); bogdan_andrada@ymail.com (A.B.)
[6] Faculty of Medicine, Titu Maiorescu University, Bucharest, Romania; gabriel.gorecki@prof.utm.ro (G.G.)
[7] Department of Anesthesia and Intensive Care, CF2 Clinical Hospital, Bucharest, Romania

Correspondence: Maria Sabina Safta, mariasabinasafta@gmail.com

Abstract: Transcatheter valve-in-valve implantation in failing bioprosthesis is an emerging field in cardio-vascular surgery and cardiology. If a valve plasty is not possible, a biological valve is implanted with limited durability. Due to valve degeneration repeated valve exchanges are necessary in some patients. To expand the lifetime of a bioprosthesis in the tricuspid position percutaneous transcatheter valve-in-valve implantation was introduced recently. This is a promising new catheter interventional technology. There are no published outcomes of repeat surgical, but overall early mortality after tricuspid valve replacement (TVR) was 37% in patients undergoing TVR after prior tricuspid valve (TV) repair. The off-label use of transcatheter aortic valve prostheses for tri-cuspid valve–in–valve implantation within dysfunctional surgical tricuspid valve bioprosthesis has been described in small reports but has become of interest nowadays.

Keywords: valve-in-valve tricuspid, redo-surgery, endovascular surgery, off-label valve implantation

INTRODUCTION

A severely diseased tricuspid valve (TV) is classically treated by tricuspid valve repair (TVr) or, when the valve is too damaged, by tricuspid valve replacement (TVR) in classical open-heart surgery. In the case of TVR usually, a biological valve is used considering the thrombo-embolic risk, however, the life expectancy of this valve is limited due to degeneration [1]. Tricuspid stenosis is not an infrequent late complication of TVR. The 8-year follow-up of 31 patients showed that 1 out of 3 patients developed degeneration of the prosthesis with an average gradient above 5 mmHg, and 21% of patients needed surgical redo [2]. Redo surgery is associated with very high risk, with reported early mortality after TVR being 37% in patients undergoing TVR after prior TV repair [3,4]. The off-label use of transcatheter aortic valve prostheses for tricuspid valve–in–valve implantation within dysfunctional surgical tricuspid valve bioprosthetics has been described in small reports and has become of interest nowadays [5,6] especially in patients with high surgical risk or contraindications for surgery [7,8].

Case report

We describe the case of a 64-year-old female patient who presented in our department for fatigability and dyspnea with mild exertion. She had a past medical history of surgical excision of a right ventricle myxoma in 2008, followed by TVR with a biological prosthesis for residual severe tricuspid regurgitation in 2011, VVI pacemaker for iatrogenic grade III atrioventricular (AV) block in 2011 followed by lead fracture and DDD pacemaker upgrade with one lead in the right atrium and second lead in the coronary sinus in 2016. Between 2016 and 2021 the patient had several admissions for heart failure symptoms and degeneration of the tricuspid

Citation: Moldovan H, Iliescu VA, Guță A, Nechifor E, Badea A, Zăman A, Safta MS, Gorecki G, Robu M, Bogdan A. *Off-Label Percutaneous Solution for Primary Degeneration of a Bioprosthetic Valve in the Tricuspid Position: Case Report and Literature Review on Transcatheter Valve-in-Valve Insertion*. R. J. Mil. Med. 2025, 128(3): 177-181; https://doi.org/10.55453/rjmm.2025.128.3.1

Academic Editor: Remus Nica

Received: 23 December 2024
Revised: 19 February 2025
Accepted: 13 March 2025

valve bioprothesis was diagnosed with moderate-severe regurgitation and moderate stenosis. The patient developed progressive signs of cardiac failure despite the administration of high doses of diuretics.

At the time of admission, the patient had signs of peripheral congestion and hepatomegaly. Lab tests showed hepatic failure, low albumin, thrombocytopenia, prolonged prothrombin time, and a BNP of 144 pg/mL. Repeated echocardiography showed severe stenosis of the bioprosthesis (max/medium gradient of 20/10 mmHg) and moderate-severe regurgitation. After a careful evaluation of the case by our Heart Team (which includes cardiac surgeons, a cardiologist, an interventional cardiologist, and an anesthesiologist), the patient was contraindicated for open heart cardiac surgery due to an evaluated very high surgical risk. An off-label transcatheter valve–in–valve procedure was considered and an Angio-CT was performed to confirm the feasibility. After careful clinical, biological, and anatomical evaluation, the procedure was scheduled, with the patient's consent.

The procedure was performed by transfemoral right vein approach with a percutaneous Proglide suture implanted before sheath insertion. The 16 F system delivery sheath was inserted without events. A long 0.035 regular wire was advanced with the aid of a JR catheter, passing the wire through the stenotic TV, and positioning a Pigtail catheter in the right ventricle (RV). An exchange was performed with the p of a Safari wire in the apex of the RV. A 26 mm balloon valvuloplasty catheter was then advanced and pre-dilatation was performed with good expansion of the balloon. Then the valve system was introduced into the sheath with a 180-degree counterclockwise turn by inserting the valve system with the Edwards E logo facing downward. The passage through the valve proved to be very difficult with prolapse of the guidewire in the superior vena cava (SVC) even with the use of the flex features of the system.

After several maneuvers, a 90-degree clockwise turn allowed us to obtain a loop into the RV as seen in Figure 1 (a), that stabilized the system and proved to be useful to cross with adequate alignment the degenerated valve, 3 mm below the ventricular edge of the surgical valve frame. A very slow inflation during implantation was performed. This gave us the possibility in the last part of the implant, when the valve tended to protrusion into the RV, to control the position and obtain a good final result as observed in Figure 1 (b, c). The procedure was finalized with the closure of the implanted Proglide suture. There was a good postprocedural result with no para-valvular leak and a mean gradient of 2 mmHg as observed in Figure 2. No vascular complications were encountered during and after the procedure.

Figure 1: Angiographic images during intervention: a – Loop of the system with valve; b – Valve implantation crossing the degenerated prosthesis; c – Final position of the valve-in-valve prosthesis

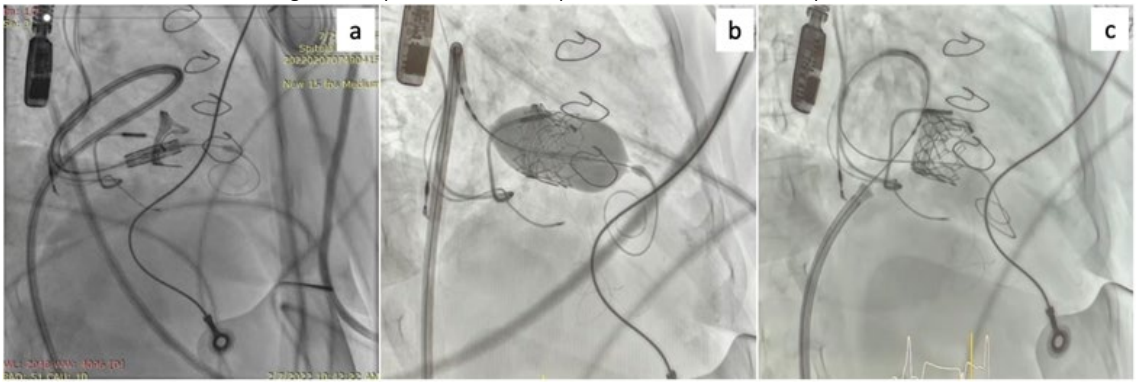
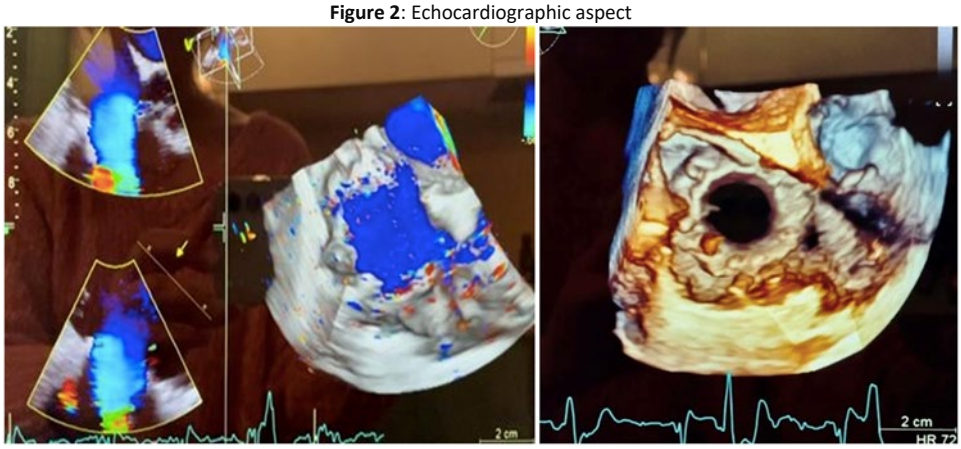


Figure 2: Echocardiographic aspect



The patient had a favorable postprocedural evolution with symptom improvement. She was discharged on the 4th postprocedural day. At 1 month follow-up the patient had good clinical status (NYHA functional class II). Biologically, there was a significant decrease

in natriuretic peptides and normalization of the hepatic markers. On echocardiography, there was no para-valvular leak, with a stationary mean gradient of 2 mmHg.

DISCUSSION

With the technical evolution of percutaneous valvular systems and clinically proven real benefits of transcatheter aortic valve implantation, a new treatment option has become available for patients with inoperable tricuspid valve stenosis [9]. The calcified degenerated native valves have a rough inner surface that acts as an effective anchor for the prosthesis [10]. The irregular inner surface and metal frame of a degenerated bio-prosthetic have similar characteristics and form an ideal docking station for a transcatheter valve. This has allowed valve-in-valve implants, mostly in the aortic position [11-13]. The first case of transcatheter valve-in-valve tricuspid valve replacement was described by Hon et al [14]. Their approach was through a thoracotomy and direct puncture of the right atrium [14]. This has definite advantages regarding the delivery of the device but remains more invasive. The first transcatheter tricuspid valve-in-valve procedure was performed by Leen van Garsse, aided by an extracorporeal circulation machine [15]. Today, with the aid Edwards Sapien valve system, the procedure result is similar and offers real benefits in severe clinical cases.

A successful procedure is highly dependent on the preprocedural evaluation of the patient. A good selection is mandatory in out-of-label cases. Confirmation of the tricuspid stenosis can be made by echocardiography with additional data from the trans-esophageal evaluation. A transvalvular gradient across the tricuspid valve of more than 5-10 mmHg at a heart rate of 70 beats per minute suggests severe stenosis. Gradients are affected by the patient's current hemodynamic status and evaluation needs to be performed with the patient under maximal medical therapy. Additional parameters may be evaluated: a pressure half-time of more than 190 msec, right atrial enlargement, and plethoric inferior vena cava suggest severe TS. Right ventricular performance is exceedingly difficult to assess after surgical tricuspid valvular replacement. Published data suggests that TAPSE and S' wave may be inaccurate parameters when we need to evaluate right ventricular function, at least in the first year after surgery, being highly dependent on the load volume [16]. However free wall longitudinal strain is a valid parameter even after immediate surgery. The mechanism of the prosthesis failure can be analyzed by echo and additional data on the stability of the surgical implanted prosthesis and paravalvular leak are mandatory to evaluate the procedural success. Also, clinical and echocardiographic assessment needs to eliminate the presence of acute endocarditis which is often caused by bacteria entering the bloodstream, adhering to damaged or abnormal heart tissue, and forming colonies [17-19].

The sizing of the valve is made considering three aspects: the dimensions and type of the surgically implanted valve with the aid of the ViV software developed by the Minneapolis Heart Institute Foundation, the Angio-CT sizing, and the echocardiographic findings.

As we demonstrated in this case the presence of hepatic failure appears to regress after the treatment, and this preprocedural condition should not be a contraindication.

The presence of cardiac stimulation leads may need judgment before the procedure, but several case reports suggest that the presence of a transvalvular lead in a valve-in-valve tricuspid procedure is safe and does not affect the functionality of the pacemaker. In our case, however, the ventricular lead was positioned in the coronary sinus, a position that reduced the risk of electric disturbances and paravalvular leak after the implant.

The procedure is done by general anesthesia considering the high dependency of the atrioventricular plane during positioning and implant of the valve with the respiratory activity, general anesthesia allows the control of respiratory movements with apnea if needed during the implant. Conscious sedation and local anesthesia may be considered in selected cases when good anatomy indicates a straightforward procedure.

There are three ways for valve delivery: the transfemoral, transjugular, and direct surgical trans-atrial approach. The decision is made considering the anatomy of the tri-cuspid plane: the valve is vertical, and the transfemoral approach is indicated. Nowadays, with the complex features of the systems that allow us flex movements, the trans-atrial and transjugular approaches are almost abandoned, transfemoral approach allowing good crossing and alignment in the valve [20]. The transjugular approach may remain a good option in case of inferior vena cava thrombosis. The trans-atrial approach is nowadays considered too invasive and is almost abandoned.

The transfemoral approach that we perform is a gradual one, with a first 7F approach, one Proglide suture implanted, and an 8F sheath insertion. As demonstrated in MitraClip studies [21], pre-closure of the femoral vein with Proglide suture is feasible and safe for the 14-16 F access needed for a tricuspid valve-in-valve procedure, considering the pressure and volume vein overload status before the valve treatment.

The insertion of the 16 F large system sheath is performed by gentle movements on a stiff wire, with the positioning of the sheath 5 to 10 cm below the entrance into the right atrium to allow free movement without tension of the system.

The crossing of the valve may be done with the aid of an angulated catheter (JR or vertebral catheter) with a regular J wire, a strait wire, or a hydrophilic wire depending on the degree and anatomy of the valvular complex. After the passage into the right ventricle, two final positions of the wire can be chosen: one in the apex of the RV and another one in the pulmonary artery. There are significant differences between the two positions: the RV position has a higher risk of complications by ventricular rupture and pericardial effusion but allows a better coaxially of the system in the valve with better control during the implant; the pulmonary position may give better support with the minus of poor coaxially and a higher risk of distal pulmonary perforation with pulmonary hemorrhage.

The more vertical the tricuspid plane is, the more the RV position is indicated. The positioning of the stiff wire should be made on a pigtail catheter to diminish the possible trauma on the RV muscle.

If many studies proved the benefit of a direct implant in the aortic position without pre-dilatation, in a tricuspid position during a valve-in-valve procedure we consider that pre-dilatation with a similar-sized balloon is mandatory to anticipate the behavior of the system in the valve, to facilitate the passage through the valve with the system and to anticipate the movement of the system during the gentle inflation.

As we already anticipated for the Edwards systems the insertion should be made opposite to an aortic implant so that the flex movement is possible on the left and not on the right side. This allows typical anatomies to align and cross into the valve without major difficulties. As we presented in our case prolapse of the wire into the right atrium (RA), especially in enlarged anatomies, is possible and in such case, there are two strategies to be tried: one is using a stiffer wire such as Lunderquist Extra-stiff wire by Cook Medical, eventually positioned into the PA- this strategy needs to be prepared in advance because once the system is inserted repositioning of another wire is virtually impossible. If this doesn't allow the positioning of the system in the TV the technique that we used was a gentle two-people synchronized maneuver with the return of the system in an aortic position, developing a loop with the wire in the RA and crossing the valve from the lateral wall of the RA using the loop as a stabilizer to increase pushability (a maneuver similar for the right heart catheterization by femoral approach in severe tricuspid regurgitation (TR) with the loop-technique with the Swan-Ganz catheter).

Once the system is positioned there is no need for rapid pacing during inflation, but several aspects may be considered: the inflation needs to be very slow to allow small adjustments, especially in the last part of the inflation when the rigidity of the full inflated balloon may change the position of the valve in the AV plane. Small movements of the wire and the system in slow inflations can achieve perpendicular lines on the valvular plane with a perfect result. Also, during implantation, apnea may help in maintaining the position.

We consider that transesophageal echocardiography (TEE) during the implant is mandatory to evaluate the result of the procedure, and the presence of the paravalvular leak, and evaluate complications such as pericardial effusion. There is no consensus about an antithrombotic treatment after a valve-in-valve procedure in the tricuspid position. We believe that the low regimen pressure of the right heart indicates us to consider oral anticoagulant treatment (OAC) treatment (without consideration of the presence or absence of sinus rhythm) associated with at least 6 months of clopidogrel. The regimen should be adapted to the patient, evaluating the bleeding risk. This strategy is highly debatable and further studies are needed to define the correct antithrombotic treatment.

CONCLUSION

In conclusion, tricuspid valve-in-valve implantation using the Edwards SAPIEN valve system is a feasible and effective procedure for selected patients with failing bio-prosthesis where redo open heart surgery presents considerable risk. The procedure proved a good clinical improvement for the patients in NYHA III or IV functional class at baseline, with consistent results at 1-year follow-up. Further studies are needed to analyze patient selection, implant technique, results, and antithrombotic treatment following a valve-in-valve procedure in the tricuspid position.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, H.M. and M.R.; methodology, H.M., V.A.I., A.G., E.N., G.G. and M.R.; software, A.G., E.N., A.B., A.Z., M.S.S. and A.B.; validation H.M., V.A.I., A.G., E.N., A.B., A.Z., M.S.S., G.G., M.R. and A.B.; formal analysis, H.M., V.A.I., A.G., E.N., A.B., A.Z., M.S.S., G.G., M.R. and A.B.; investigation, H.M., V.A.I., A.G., E.N., A.B., A.Z., M.S.S., G.G., M.R. and A.B.; resources, H.M., A.B., M.R. and A.B.; data curation, H.M., V.A.I., A.G., E.N., G.G. and M.R.; writing—original draft preparation, H.M., A.G., A.B., A.Z., M.S.S., M.R. and A.B.; writing—review and editing, H.M., V.A.I., A.G., E.N., A.B., A.Z., M.S.S., G.G., M.R. and A.B.; visualization, H.M., V.A.I., A.G., E.N., A.B., A.Z., M.S.S., G.G., M.R. and A.B.; supervision, H.M., V.A.I. and G.G.; project administration, H.M., G.G. and M.R; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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https://doi.org/10.55453/rjmm.2025.128.3.2

REVIEW

Asymptomatic Bacteriuria – A Permanent Challenge in Clinical Practice: When Should We Treat It?

Flavia L. Turcu[1,2], Ileana A. Vacaroiu[1,2], Ana R. Mitrea[3], Dragos E. Georgescu[4,5], Mihaela R. Mititelu[6,7], Alina M. Stanigut[8,9], Andra E. Balcangiu-Stroescu[10]

[1] Department of Nephrology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2] Department of Nephrology, Sfantul Ioan Clinical Emergency Hospital, Bucharest, Romania
[3] Discipline of Physical Medicine and Rehabilitation (Medical Recovery Neurology), Elias Clinical Emergency Hospital, Bucharest, Romania
[4] Department of General Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[5] Department of General Surgery, Dr. I. Cantacuzino Clinical Hospital, Nephrology Department, Faculty of Medicine, Bucharest, Romania
[6] Department of Nuclear Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[7] Clinic of Nuclear Medicine, Central Clinical Emergency Military Hospital, Bucharest, Romania
[8] Faculty of Medicine, "Ovidius" University of Constanta, Constanta, Romania
[9] Department of Nephrology, County Emergency Clinical Hospital of Constanta, Constanta, Romania
[10] Discipline of Physiology, Faculty of Dental Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Correspondence: Mihaela Raluca Mititelu, raluca.mititelu@umfcd.ro

Abstract: Asymptomatic bacteriuria (ABU) is a common finding in everyday clinical practice. Many patients, many of them with significant comorbidities, will present, when tested, with bacterial colonization of the urine even if they have no lower urinary tract symptoms at all. Therefore, the clinician is having a dilemma: Should I prescribe antibiotics to sterilize the urine or not? This article aims to update and eventually support physicians in the difficult decision of whether to treat or not to treat patients with ABS and when.

Keywords: asymptomatic bacteriuria, urinary tract infections, antibiotics, pregnant women, elderly patients

INTRODUCTION

Bacterial infections represent a serious health problem worldwide [1]. The growth of bacteria in the urine of a patient who has no symptoms is named as asymptomatic bacteriuria (ABU). ABU is quite a common finding in clinical practice and corresponds to a commensal colonization of the urinary tract [2]. Enterobacterales, B Streptococcus group, and gram-negative bacilli are often met in the urine of ABU patients [3]. Among these species, Escherichia coli, followed by Klebsiella sp, were frequently detected in ABU-urine patients [3-5]. Studies have reported ABU may potentially protect against superinfecting organisms that can determine urinary tract infections (UTIs), therefore the treatment of ABU should be offered only to selected patients. Avoiding unnecessary antibiotic treatment in a significant number of patients with ABU is highly likely to avoid the potential risk of acquired antimicrobial resistance and the risk of removing a potentially effective defense mechanism [4,5]. On the other hand, in some categories of patients, the treatment of ABU proved to be beneficial, avoiding possible serious complications, some of them life-threatening like urosepsis. ABU is quite common in everyday practice. It can be identified in healthy pre-menopausal women(1-5%), with the incidence increasing to 4-19% in postmenopausal women. The ABU varies between 0.7 and 27% in diabetic patients, up to 10% in pregnant patients, and impressive rates varying between 15 and 50% are found in patients living in care homes, and in those who have had spinal cord injuries between 23 and 89% [6]. The bacteria identified in patients with ABU are not different than those found in patients with symptomatic uncomplicated or complicated UTIs.

Citation: Turcu FL, Vacaroiu IA, Mitrea AR, Georgescu DE, Mititelu MR, Stanigut AM, Balcangiu-Stroescu AE. *Asymptomatic Bacteriuria – A Permanent Challenge in Clinical Practice: When Should We Treat It?*. R. J. Mil. Med. 2025, 128(3): 182-187; https://doi.org/10.55453/rjmm.2025.128.3.2

Academic Editor: Octavian Vasiliu

Received: 20 December 2024
Revised: 12 February 2025
Accepted: 11 March 2025

DISCUSSIONS

ABU diagnosis

By definition, ABU is characterized by a mid-stream urine sample (MSU) culture with a bacterial growth of more than 105 colony-forming units/mL in a patient without any urinary tract symptoms. Two consecutive samples should be positive in female patients and only one in males [7,8].

No further investigations are required if the history is unremarkable. However, if the urine cultures confirm the presence of urease-producing bacteria, an ultrasound of the kidneys and urinary tract might be performed to rule out the urinary tract stones [8,9]. Digital rectal examination (DRE) needs to be performed in men to exclude the risk of prostate pathology, either infectious or benign/malignant. In selected cases, cystoscopy, either flexible or rigid, can offer a significant diagnostic or sometimes even treatment benefit when bladder wash-out, biopsies, or bladder stone laser disintegration is needed.

ABU management in patients with no identified risk factors

Studies have shown that ABU by itself in patients without any risk factors does not cause any urinary tract infections, or renal disease and does not determine acute or chronic pyelonephritis that can potentially alter the kidney function [10].

One study investigated the value of antibiotic treatment in adult, non-diabetic, non-pregnant women with ABU the incidence of symptomatic UTI was similar in both treated and not treated groups[4]. It was concluded that screening for ABU and the antibiotic treatment of ABU are not routinely recommended in patients with no risk factors and no lower urinary tract symptoms.

A study published in 2012 reviewed the ABU treatment in women with recurrent symptomatic UTIs otherwise healthy and demonstrated an increased risk of symptomatic UTIs in treated patients, compared to non-treated ones. This observation proves that ABU can play a prophylactic role in female patients with recurrent UTIs. Hence the treatment of ABU is not recommended in patients with no risk factors[5].

ABU management in pregnant women

ABU is present in pregnant women in between 2 to 10% of cases. Many studies were dedicated to this category of complex patients when potentially both the mother and the fetus can be affected.

A couple of RCTs [9,10] have been performed on pregnant women trying to identify if ASB treatment is needed or not. Those RCTs compared the groups with ABU treated with antibiotics versus placebo and versus no-treatment patients, also using various antibiotics and regimens. Therefore, these trials reported that the antibiotic treatment has significantly reduced the number of symptomatic UTIs in this group, versus placebo or no treatment ones. Another conclusion of these trials was that the ABU treatment has significantly decreased the rates of low birth weight and the rates of preterm delivery.

Other authors have remarked that the ABU treatment in pregnant women induces decreased incidence of symptomatic UTIs, pyelonephritis, and low birthweight or preterm delivery [11-14]. In conclusion, it seems that it is beneficial for both mother and fetus if the screening for ABU is used in pregnant women and, if bacterial growth is found in the urine, the patients should be subsequently treated appropriately. On the other hand, considering the variety and complexity of pregnant women as patients, it is always advisable to consult national guidelines and recommendations but also to consider each patient on a case-by-case basis.

As it seems that the ABU treatment in pregnant women is generally accepted, another question is which antibiotics and for how long should be used in pregnancy. A significant number of randomized clinical trials have been performed trying to answer these questions. [11-21]. These trials essentially compared different antibiotics, different regimens, or the same antibiotic prescribed in different doses or various durations. Many antibiotics have been used including mainly Nitrofurantoin, Sulphamethopirazine, Pivmecillinam, Amoxicillin, Amoxicillin associated with Clavulanic Acid, Cephalexin, Co-trimoxazole, Fosfomycin [13-15, 17, 18]. Different treatment groups were identified and used for comparison when the treatment length was considered: single dose; short course varying from 2 days to 7 days); long course considered between 8 and 14 days; and long-term course until delivery [17-20]. The data showed that single-dose treatment determined fewer side effects but more babies with low birth weight compared with the short course of treatment.

The value of Fosfomycin single dose was reviewed in a meta-analysis which compared the use of it in pregnant women with uncomplicated UTIs or ABU versus short-term courses of treatment with various antibiotics. The successful treatment of ABU was found to be not significantly different between the patients who received short-term courses of antibiotics, whatever the antibiotic used was. It was also apparent that both standard short-course treatment with various antibiotics and single dose Fosfomycin could be effective options in treating ABU in pregnant patients; however, further studies are needed [21,22].

ABU management in patients with identified risk factors- Diabetes Mellitus

If in 2019, worldwide 463 million people were diagnosed with diabetes mellitus (DM), in 2045 the number can increase to 700 million [23]. Long-term hyperglycemia induces several side effects affecting the eyes, nervous system, kidneys, cardiovascular disorders, [24], and periodontal disease [25]. Therefore, the diabetic patient has an increased risk of developing ABU. Even if diabetes is well controlled with the appropriate medication and diet, a significant proportion of cases with ABU [26]. A randomized control trial was addressed to these patients and found that the ABU treatment, with consecutive negative mid-stream urine, did not reduce the risk of symptomatic UTIs or pyelonephritis. On the other hand, the lack of ABU antibiotic treatment did not correlate with an increased risk of developing diabetic nephropathy [27]. It is now accepted that the ABU screening and treatment in well-controlled DM patients is not routinely recommended.

However, poorly controlled diabetes represents a significant risk factor for various infectious complications. In these patients, the doctors and nurses should make every effort to get the diabetes controlled using both medication and diet. If ABU and infectious complications are present, sounds sensible to not only treat the ABU but also further investigate these patients to rule out urological

causes.

ABU management in patients with identified risk factors – Postmenopausal women

Another category of patients who have an increased incidence of ABU is represented by postmenopausal women. Randomized control trials were addressed to these patients and compared the groups with ABU antibiotic treatment vs the placebo or no treatment groups, using different antibiotics and regimens [28]. There were no reported benefits of antibiotic treatment regarding both the incidence rate of symptomatic UTIs and the incidence of bacteriuria resolution [29, 30]. Therefore, as currently there is no demonstrated benefit of ABU antibiotic treatment in post-menopausal women, ASB should be managed the same in both pre-menopausal and post-menopausal women and the screening and treatment of ABU are not recommended.

ABU management in patients with identified risk factors –Elderly/institutionalized patients

Studies have revealed that in elderly institutionalized patients, the rate of ABU is significantly elevated, varying between 15% to 50% [4,5]. Considering that the differential diagnosis between ABU and UTIs is extremely difficult or even impossible in bed-bound, poor mobility patients who also have multiple comorbidities and are potentially mentally deteriorated, it seems that unfortunately unnecessary antibiotic treatments are prescribed in a significant number of patients [30, 31].

An important number of randomized control trials were addressed to the elderly patient population (either institutionalized or not). They were divided into three groups and the group in whom they were treated with antibiotics (different antibiotics, different doses, and regimens were prescribed), was compared with placebo controls or no-treatment groups [30-34]. These RCTs reported that the ABU treatment did not show any significant benefit, compared to placebo or no treatment groups, in reducing the rate of symptomatic UTIs. Also, there was no reported benefit of the antibiotic treatment versus placebo in obtaining a persistently negative MSU culture and sensitivity. One randomized control study compared the incidence of urinary incontinence before and after the resolution of ABU and found no effect in the group of patients who were treated with antibiotics. Even more, other studies reported that the antibiotic treatment of ABU determined significant side effects without any clinical benefit [34]. Therefore, based on the current scientific literature, we can conclude that the screening and treatment of ASB are not recommended in this group.

ABU management in patients with identified risk factors - Renal Transplant Patients

Renal transplant patients represent a very important category, as they are complex patients with associated pathology and sophisticated medication frequently [35-38]. A meta-analysis including randomized control trials and retrospective studies compared the effect of antibiotic treatment to no treatment in renal transplant patients and did not find any benefit in decreasing the risk of symptomatic UTIs between 12 and 22 months after transplant. No benefit was reported in ABU resolution, graft loss, or renal function preservation for up to 24 months [38].

Other publications reported that the incidence of UTIs and pyelonephritis (15% vs. 2.5%) was higher in patients receiving antibiotic treatment for ABU compared to no treatment group [37]. In another RCT, in the first year after transplantation, no difference in the acute graft pyelonephritis was found, but, not surprisingly, the incidence of antimicrobial resistance was higher in the treatment group [36]. Therefore, routine screening and treatment are not routinely recommended in patients who had renal transplantation.

ABU management in patients with identified risk factors – Patients with dysfunctional or reconstructed lower urinary tract

Patients with dysfunctional or reconstructed lower urinary tracts become frequently colonized having ABU [39, 40]. A study reported that the incidence of ABU varies from 25 to 86% for intestinal urinary conduits and from 9.1 to 85% for orthotopic neobladders. It has demonstrated no long-term benefit of ABU treatment in this group [40]. Interestingly, the deliberate colonization with an ABU strain (Escherichia coli 83972) has shown a protective effect against symptomatic UTI recurrences [41]. ABU screening and treatment in these patients is therefore generally not recommended.

ABU management in patients with identified risk factors –Patients with urethral/suprapubic catheters, nephrectomies, or ureteral stents

Patients with urethral or suprapubic catheters and nephrostomy tubes routinely become colonized with bacteria and is generally accepted nowadays that antibiotic treatment is not needed as determines no benefit. No screening for ABU or antibiotic treatment is recommended for patients with indwelling ureteral stents. Hence routine antibiotics for ABU are not recommended, as offer no benefit and determine a significant risk of acquired antibiotic resistance.

In patients who need routine urethral/suprapubic catheter changes, there is no need to be screened for ABU or to have antibiotics. On the other hand, in patients subjected to nephrostomy tube replacement or ureteral stent change, ABU is a risk factor, and therefore prophylactic antibiotics or treatment of ABU are needed [42,43].

ABU management in patients with identified risk factors – Chronic Kidney Disease (CKD)

Worldwide, kidney failure represents another serious complication, especially among diabetic patients [44]. Studies reported an incidence between 9-20% of UTI among female DM patients, while for male DM patients, the incidence is between 3-11% [45].

Patients with CKD are another group in whom ABU can be present. There is no study to investigate if ABU is identified in patients with CKD needs to be treated or not. As it seems that in this group there is an increased risk of antimicrobial resistance, highly likely no routine screening and treatment is needed [46]. This physician should not forget that, if treatment is needed, then it will be necessary

to prescribe the antibiotics in renal dose, considering the patients' kidney function test.

ABU Treatment options

If the clinician decides to treat ABU, the same antibiotics, regimens, and duration as in uncomplicated UTIs can be offered, depending on multiple characteristics like gender, co-morbidities, risk factors, allergy status, other medication the patient is taking, potential medication interactions, etc. Treatment should be always tailored on a case-by-case approach based on mid-stream urine culture and sensitivity and should not be empirical.

CONCLUSION

ABU is a clinical entity frequently found in everyday practice. Despite this, there are only a few indications to treat it. Unfortunately, even though the guidelines are clear, inappropriate antibiotic treatment is still offered and determines antimicrobial resistance and selection of extremely aggressive uropathogens. As we presented above, the screening and the antibiotic treatment of ABU are recommended only in pregnant women and in selected individuals who will have endourological procedures that can potentially determine the urothelial mucosa trauma. It remains that future studies could identify alternative methods and treatments, to better manage the patients with asymptomatic bacteriuria.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, F.L.T.M and I.A.V., methodology, A-R.M., D.E.G., M.R.M., and A.E.B-S., software, A.M.S., M.R.M.., I.A.V., and F.L.T., validation, I.A.V., and M.R.M.., formal analysis, F.L.T., A-R.M., D.E.G., A.M.S., and A.E.B-S., investigation, F.L.T., I.A.V., and M.R.M., resources, F.L.T., and I.A.V., data curation, A-R.M., D.E.G., and A.M.S writing—original draft preparation F.L.T.M and I.A.V., writing—review and editing, F.L.T.M, D.M., A.E.B-S., and I.A.V., visualization, F.L.T.M and I.A.V.; supervision, I.A.V., and D.M.; project administration F.L.T.M and I.A.V.; funding acquisition, F.L.T.M. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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https://doi.org/10.55453/rjmm.2025.128.3.3

REVIEW

Conventional and Modern Methods in the Diagnosis of Sepsis and Septic Shock: A Narrative Review

Gabriel P. Gorecki[1,2], Daniel Cochior[3,4], Andrei Bodor[5], Carmen Pantiș[6,7], Romina M. Sima[8,9], Liana Pleș[8,9], Dan G. Costea[10], Daniel O. Costache[8,11], Dana R. Tomescu[12,13]

1 Department of Anesthesia and Intensive Care, Faculty of Medicine, "Titu Maiorescu" University, Bucharest, Romania; gabriel.gorecki@prof.utm.ro
2 Department of Anesthesia and Intensive Care, CF2 Clinical Hospital, Bucharest, Romania
3 Department of General Surgery, Faculty of Medicine, "Titu Maiorescu" University, Bucharest, Romania; rector@univ.utm.ro
4 Monza Clinical Hospital, Department of General Surgery, Bucharest, Romania
5 1st Department of Cardiovascular Anesthesiology and Intensive Care, Prof. Dr. C. C. Iliescu Emergency Institute for Cardiovascular Diseases, Bucharest, Romania; andreibodor96@gmail.com
6 Department of General Surgery, University of Oradea. Faculty of Medicine and Pharmacy, Oradea, Romania; carmen.pantis@didactic.uoradea.ro
7 Department of Anesthesia and Intensive Care, Emergency County Hospital Oradea, Oradea, Romania
8 "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; romina.sima@umfcd.ro (RMS), liana.ples@umfcd.ro (LP), daniel.costache@umfcd.ro (DOC)
9 Department of Obstetrics and Gynecology The "Bucur" Maternity, "Saint John" Hospital, Bucharest, Romania
10 Department of General Surgery, Clinical Hospital CF2, Bucharest, Romania; dancostea2006@yahoo.com
11 Research Department, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania
12 Department of Anesthesia and Intensive Care, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; danatomescu@gmail.com
13 Department of Anesthesia and Intensive Care, Fundeni Clinical Institute, Bucharest, Romania

Correspondence: Daniel O. Costache, daniel.costache@umfcd.ro

Abstract: Background/Objectives: Sepsis and septic shock are critical conditions associated with high mortality rates and substantial impacts on healthcare systems. Accurate and rapid diagnosis is essential for the management of these conditions. The objective of this study is to assess the accuracy of contemporary and traditional methods for diagnosing sepsis and to determine whether improvements have been made concerning the integration of novel diagnostic approaches, to facilitate a prompt diagnosis, taking into account the rapid progression of complications associated with this disease. For this purpose, studies published between 2014 and 2024 were examined to highlight the benefits and limitations of each approach. Methods: A systematic literature review was conducted, including randomized clinical trials, observational studies, and retrospective studies assessing both conventional diagnostic methods (blood cultures and clinical scoring systems) and modern methods (rapid molecular tests, specific biomarkers, and machine learning algorithms). The studies included were selected based on strict design and methodology criteria to ensure a rigorous comparative evaluation of the interventions and technologies used in diagnosing and monitoring patients with sepsis. Results: A total of 23,822 patients were reviewed across the studies included in this systematic analysis. Modern methods, such as continuous monitoring through integrated biosensors and the use of molecular panels for pathogen detection, demonstrated high potential for the early and accurate diagnosis of sepsis. The reviewed studies suggest that these methods can significantly reduce diagnostic time and improve the ability to stratify mortality risk compared to conventional methods. Conclusions: Integrating modern diagnostic technologies, such as rapid pathogen identification tests and specific biomarkers, may complement traditional methods and bring significant benefits in the management of sepsis.

Keywords: sepsis; septic shock; diagnostic methods; biomarkers; rapid pathogen detection; machine learning; clinical outcomes; intensive care; advanced monitoring; mortality prediction

Citation: Gorecki GP, Cochior D, Bodor A, Pantiș C, Sima RM, Pleș L, Costea DG, Costache DO, Tomescu DR. *Conventional and Modern Methods in the Diagnosis of Sepsis and Septic Shock: A Narrative Review*. R. J. Mil. Med. 2025, 128(3): 188-199; https://doi.org/10.55453/rjmm.2025.128.3.3

Academic Editor: Raluca Mititelu

Received: 15 January 2025
Revised: 6 March 2025
Accepted: 11 April 2025

INTRODUCTION

Sepsis and septic shock are critical medical conditions that occur as a systemic inflammatory response to severe infections and have a devastating impact on global public health [1,2]. These conditions are considered medical emergencies, as they can quickly lead to multiple organ dysfunction and death, with mortality rates reaching up to 40% in severe cases [1,3].

Sepsis is triggered by the presence of pathogenic microorganisms, such as bacteria, viruses, or fungi, which activate a complex and often excessive immune response [4]. The initial immune response to infection involves the activation of macrophages and other immune cells, which release cytokines and other inflammatory substances [5]. These proinflammatory molecules play a crucial role in defending the body; however, in sepsis, this response becomes disproportionate, damaging tissues and organs [6]. This excessive activation leads to vasodilation, increased vascular permeability, microvascular dysfunction, and, ultimately, multiple organ failure [7].

In essence, sepsis represents an overreaction of the immune system to an infection which, rather than protecting the body, causes extensive tissue and organ damage [8]. When this reaction escalates, resulting in a severe drop in blood pressure and inadequate perfusion of vital organs, septic shock occurs—an extreme form of sepsis that requires urgent and complex therapeutic interventions to prevent patient death [9].

The challenge of sepsis is compounded by the variability of symptoms, which can differ significantly from one patient to another, and the difficulty in quickly identifying the responsible infection [10]. This clinical heterogeneity makes timely diagnosis of sepsis challenging, contributing to its high mortality rate [11]. The fact that sepsis presents with symptoms common to other conditions—fever [12], tachycardia [13], rapid breathing [14], and low blood pressure [15]—can delay intervention.

In light of the aforementioned evidence, it can be surmised that the specific manifestations of sepsis fall within the differential diagnosis of other pathologies. In such cases, the therapeutic approach to sepsis (volemic repletion) may precipitate a worsening of the patient's condition if the underlying diagnosis is not correctly identified. This could potentially lead to delays in establishing an accurate diagnosis and initiating appropriate treatment. It is therefore imperative to identify more rapid and efficient diagnostic methods, to save lives and reduce the significant costs associated with the care of patients with sepsis and septic shock.

MATERIALS AND METHODS

Given the significant impact of sepsis and septic shock on public health and the limitations of current diagnostic methods, this study aims to identify the efficacy and clinical relevance of conventional diagnostic methods and modern approaches. This comparison will be conducted through a systematic review of the literature from 2014 to 2024, providing insights into the benefits, limitations, and potential of each clinical approach.

The study will synthesize evidence regarding the accuracy of diagnoses obtained through conventional methods, such as blood cultures and modern methods, including advanced molecular tests and specific biomarkers associated with sepsis. Additionally, it will examine the practical aspects of integrating these methods into clinical practice, with a focus on their potential to reduce diagnostic time and improve patient prognosis.

By highlighting how recent innovations can complement or even replace traditional methods, the study will provide a solid evidence base to support informed clinical decision-making. Ultimately, this review aims to contribute to the discussion on the broader integration of modern diagnostic methods within healthcare systems and to support the development of standardized practices that incorporate these advanced technologies in the management of sepsis and septic shock.

The methodology for this systematic review has been designed in accordance with the PRISMA guidelines to ensure transparency and rigor in the search, selection, and analysis process. This approach facilitates a detailed and comparative assessment of conventional and modern methods used in the diagnosis of sepsis and septic shock [16].

Article Identification Strategy

In our search strategy, we explored renowned international databases to obtain a representative and up-to-date selection of relevant scientific articles. The primary databases included MDPI and PubMed, as these provide access to a wide range of clinical studies, research articles, and other academic sources addressing the diagnosis of sepsis and septic shock.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were rigorously established to maintain the quality and relevance of selected articles. Only studies that include specific diagnostic methods for sepsis, whether conventional or modern, were included. Additionally, only articles published in peer-reviewed journals with complete data available were selected for analysis to ensure a robust data foundation and minimize publication bias.

Regarding exclusion criteria, review articles, opinion pieces, case reports, and studies lacking clinical validation were excluded. These types of publications do not provide direct comparative data or are not based on systematic evaluations of diagnostic methods, and their inclusion would have distorted the analysis results.

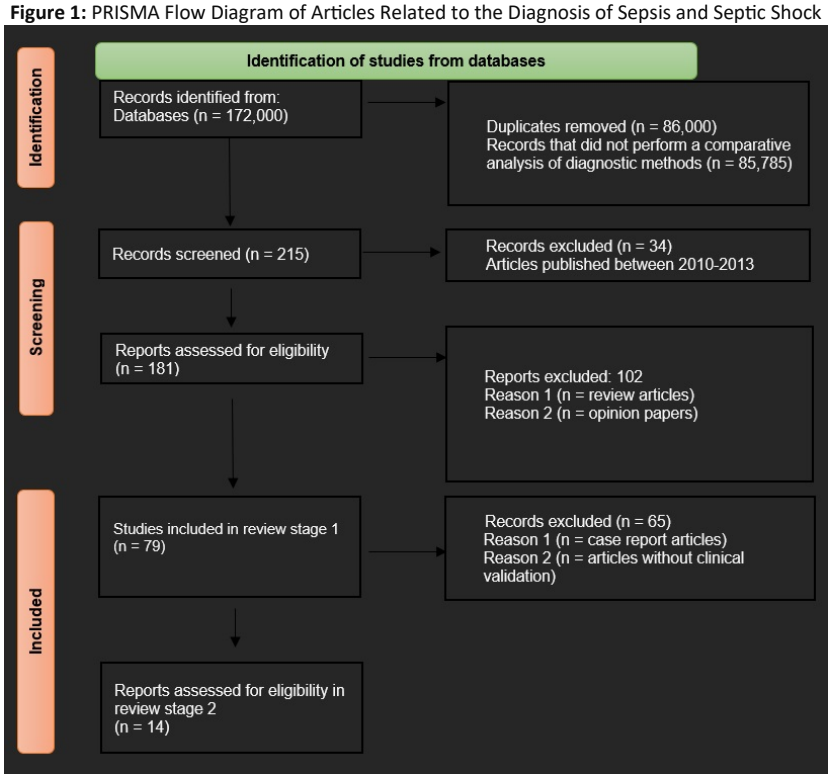
To ensure transparency and traceability in the selection process, we included a PRISMA flow diagram in the study, detailing the number of studies identified and filtered at each stage. The diagram specifically illustrates the initial number of articles obtained from the search, the number excluded after reviewing titles and abstracts, and finally, the number included in the detailed analysis. The reasons for excluding articles are also specified to clarify why certain studies were not included in the final analysis.

The PRISMA diagram is an essential tool for transparency, as it enables readers to follow the decision-making process behind article selection, ensuring that the criteria established at the beginning of the review are adhered to [16,17].

Keywords and Boolean operators were used in the search process to refine the results and select only articles relevant to the study objectives. The main search terms included phrases such as “sepsis diagnosis” (29,700 results), “septic shock” (21,800 results), “conventional methods sepsis and septic shock” (17,300 results), and “modern methods sepsis and septic shock” (17,200 results). These terms were combined using the AND, OR, and NOT operators to ensure a highly precise selection.

The timeframe set for the included articles was 2010–2024 to reflect recent developments in sepsis diagnosis and ensure the relevance and currency of the data analyzed.

Figure 1: PRISMA Flow Diagram of Articles Related to the Diagnosis of Sepsis and Septic Shock



In Figure 1, we can see that the study identification process from the databases began with the selection of two main databases. In the course of this process, a total of 172,000 studies were identified. Of these, 86,000 records were eliminated as duplicates, as well as a further 85,785 records that did not perform a comparative analysis of diagnostic methods. Following these initial exclusions, 215 records remained for screening.

Of these, 34 were excluded after the selection process. These were articles published before 2014. We chose a period of 10 years rather than 14 because the literature on sepsis is constantly changing and the period 2010-2013 seemed outdated for today's requirements. A total of 181 reports were assessed for eligibility. At this stage, reports were excluded for several reasons, including review articles, and opinion pieces.

In the end, 79 were included in the phase 1 review, with studies without clinical validation and case reports being discarded. 14 studies were selected for inclusion in stage 2 of the review.

RESULTS

Two distinct groups of modern and conventional methods were generated. The conventional methods included: basic immunophenotyping, cardiac function monitoring and histopathology, manual assessment of CRT, serum lactate, MAP, vasopressor use, standard intravenous fluid administration, ICD-9 coding for sepsis, clinical scores (e.g., SOFA, APACHE II, SAPS II/III), standard biomarkers (CRP, PCT, lactate), and blood clutches and antibiogram. Modern methods included: PAR2 receptor inhibition with 1-PPA, proteomic analysis (2D-nanoUPLC-UDMSE), restrictive intravenous fluid administration, SOFA score and albumin combination, NLR, PLR, MLR, PLT/MPV ratio, AR stimulation (PediSepsisAR), remote photoplethysmography (rPPG) and aCRT, T2Bacteria® panel and T2MR®, continuous monitoring with biosensors (PO, NIRS, ST), advanced biomarkers (e. (e.g. IL-6, suPAR, irisin), ML (machine learning) algorithms.

In Table 1, we present a detailed analysis of 14 studies, each examining innovative interventions, biomarkers, and technologies used in the diagnosis and management of sepsis and septic shock. Data were extracted from recently published articles and structured according to study design, type of intervention, methodology, and key results.

Table 1: Comparison of Conventional and Modern Diagnostic Methods for Sepsis and Septic Shock

Author(s) and Year	Study Design	Sample	Intervention	Intervention Duration	Conventional Methods	Modern Methods	Key Results	Conclusions
Meyhoff et al., 2022 [18]	International, randomized, open-label study (CLASSIC trial)	1554 ICU patients with septic shock	Restriction of IV fluids vs. standard fluids	Until ICU discharge (max. 90 days)	Standard IV fluid administration according to guidelines	Restrictive IV fluid administration	Similar mortality between groups: 42.3% (restrictive) vs. 42.1% (standard). Similar incidence of adverse events: 29.4% (restrictive) vs. 30.8% (standard). Similar life support-free days and out-of-hospital days between groups	Fluid restriction did not improve survival rates compared to standard therapy. Fluid restriction did not reduce the incidence of severe adverse events. Restrictive intervention showed no significant benefits over standard intervention in the ICU.
Liberski, Szewczyk, & Krzych, 2020 [19]	Retrospective case-control study	138 ICU patients	Evaluation of NLR, PLR, MLR, PLT/MPV ratios vs. CRP, PCT, and lactate	On ICU admission	CRP, PCT, lactate	NLR, PLR, MLR, PLT/MPV	High NLR has predictive value for septic shock (AUROC = 0.66); combining NLR + CRP improves septic shock prediction (AUROC = 0.88)	NLR can identify patients with septic shock but must be interpreted alongside CRP/PCT; no index predicts ICU mortality
Toto et al., 2021 [20]	Randomized controlled feasibility study	50 paediatric participants	Simulation of septic shock with and without AR (PediSepsisAR)	Short-term simulation (per exercise)	Traditional mannequin simulation	AR simulation (PediSepsisAR)	Fluid administration time and volume were measurable in both groups; no significant differences in patient status recognition or fluid administration.	PediSepsisAR is feasible for simulation; improved perception of perfusion in most participants, but no impact on response times.

Wang et al., 2023 [21]	Retrospective bioinformatics study	98 sepsis patients (GSE26440) and 32 control; external test: 51 sepsis patients, 22 control	Diagnostic model using PCD-associated genes	Retrospective, pre-existing data	SOFA score and traditional inflammatory biomarkers	ML algorithms (RF, SVM, DNN) for gene-based diagnosis	ML models based on 10 genes (e.g., ITGAM, KIF1B) achieved AUC=0.7951 (internal) and AUC=0.9627 (external); analysis of immune cell infiltration in sepsis	Gene-based ML models show high diagnostic capacity for sepsis; potential to improve diagnosis and identify therapeutic targets
Lungu et al., 2024 [22]	Longitudinal observational study	121 neonates (39 late-onset sepsis, 35 early-onset sepsis, 47 control)	Multimodal monitoring (pulse oximetry - PO, near-infrared spectroscopy - NIRS, skin temperature - ST) with biosensor signal integration through ML algorithm	Max 72 hours of continuous monitoring	Standard biomarkers (CRP, PCT), cultures	Continuous monitoring with PO, NIRS, ST, ML algorithm	The model had 87.67% accuracy and detected sepsis 6-48 hours before clinical diagnosis; NIRS and ST had the highest predictive accuracy (0.90 and 0.85)	Non-invasive monitoring methods (NIRS, PO, ST) significantly improve early neonatal sepsis detection, complementing conventional tests and reducing the potential for clinical deterioration; require validation in varied clinical settings
Pipitò et al., 2024 [23]	Retrospective study	15,373 sepsis patients admitted to hospitals in Sicily between 2016-2020	Retrospective data collection from standard discharge forms for all sepsis cases in hospitals	5 years	ICD-9 for coding and identifying sepsis and septic shock	Temporal trend analysis through regression	Overall in-hospital mortality was 36.3%, higher in septic shock cases (66.7%) and ICU patients (74%). Rates increased over the analyzed years.	Sepsis and septic shock significantly contribute to in-hospital mortality; and require a focus on infection prevention, antimicrobial stewardship, and improved diagnostic coding.

Luka et al., 2024 [24]	Prospective observational study	67 sepsis and septic shock patients, ED, Cluj-Napoca, Romania	Evaluation of 6 biomarkers (IL-6, suPAR, AZU1, hsCRP, sTREM-1, PCT) combined with severity	28 days	Severity scores: SOFA, APACHE II, SAPS II/III, NEWS, CCI, GCS, qSOFA, SIRS, MEDS	Advanced biomarkers (IL-6, suPAR, AZU1) combined with clinical scores	Mortality was 49.25%; IL-6 was the most accurate biomarker, and SAPS II/III were the most predictive scores for mortality	IL-6 and SAPS II/III are the best predictors of 28-day mortality in ED sepsis cases; using biomarkers with clinical scores improves prognostic accuracy
Klibus et al., 2024 [25]	Prospective observational study	20 patients with bacterial septic shock or COVID-19-associated sepsis, ICU, Latvia	Evaluation of microcirculation via remote photoplethysmography (rPPG) and automated capillary refill time (aCRT) analysis in infusion	Various stages during the protocol	MAP, manual CRT, serum lactate levels, skin temperature	rPPG, aCRT	rPPG and aCRT detected perfusion changes more sensitively than manual CRT, highlighting significant differences between bacterial and COVID-19-associated sepsis	rPPG and aCRT are promising tools for microcirculation monitoring in intensive care, providing more precise assessments than conventional methods, useful for sepsis patient management
Bonura et al., 2024 [26]	Retrospective observational study	85 patients with septic shock or sepsis-induced hypotension, ICU	Evaluation of T2 Magnetic Resonance (T2MR®) technology for early ESKAPE pathogen detection using T2Bacteria®	First 6 hours after sepsis onset	Blood cultures and antibiogram	T2Bacteria® Panel for rapid bacterial identification	81% concordance rate between T2Bacteria® and blood cultures; T2Bacteria® detects pathogens in 5.15 hours vs. 94.62 hours for traditional cultures	T2Bacteria® Panel provides rapid and concordant ESKAPE pathogen detection, allowing faster decisions on antibiotic escalation or de-escalation in severe sepsis cases

Ayenew Mekuria et al., 2024 [27]	Retrospective cohort study	386 ICU septic shock patients	Septic shock management in ICU	2019-2023	Vasopressors (adrenaline, dopamine)	ICU surveillance, continuous monitoring	Mortality rate of 58.29%; predictive factors: age >60 years, delayed ICU admission, low MAP, comorbidities, unidentified pathogen	ICU mortality for septic shock remains high; need for early recognition and treatment protocols, in line with sepsis survival guidelines
Karampela et al., 2024 [28]	Prospective observational study	102 critical patients with sepsis or septic shock, 102 healthy control	No specific intervention, comparative analysis	28 days	CRP, procalcitonin as standard biomarkers	Serum irisin determination via ELISA	Patients with low circulating irisin had significantly higher 28-day mortality; irisin was negatively associated with sepsis severity and APACHE II and SOFA scores.	Circulating irisin decreases at sepsis onset and could be a promising biomarker for prognosis and diagnosis; needs confirmation in larger studies.
Alves et al., 2024 [29]	Observational proteomic study	5 septic shock patients, 10 healthy control	No specific intervention	N/A (not applicable)	Monocyte immunophenotyping	Proteomic analysis via 2D-nanoUPLC-UDMSE	Identified 67 proteins with altered expression in septic shock patients' monocytes, linked to immune dysfunction, hypotension, vasodilation, and endothelial damage	Identified proteins could serve as biomarkers for diagnosis, prognosis, and treatment of septic shock, offering new insights into this condition's pathophysiology.
Kim et al., 2024 [30]	Retrospective observational study	5805 septic shock patients from 12 EDs in South Korea	No specific intervention	N/A (not applicable)	Initial SOFA assessment	Combination of SOFA with serum albumin level	28-day mortality inversely proportional to albumin level; SOFA with albumin improved mortality prediction (AUC 0.71 vs. 0.68 SOFA alone)	Combining initial SOFA score with albumin level may enhance prognostic accuracy, providing a risk stratification tool in septic shock

Luisetto, Scarpa, Villano, Martini, et al., 2024 [31]	Experimental study, in vitro and in vivo	Mouse model of LPS-induced endotoxemia	Administration of 1-PPA molecule to inhibit PAR2 receptor	1 and 3 hours post-LPS injection (early and delayed administration)	Survival monitoring, cardiac function analysis, histopathological assessments	Real-time PCR, Western blot, cardiac ultrasound, flow cytometry	1-PPA administration reduced mortality and sepsis symptoms, improved cardiac function, and decreased inflammation via PAR2 inhibition	1-PPA demonstrates efficacy in reducing sepsis effects by blocking PAR2, preventing pro-inflammatory pathway activation, and reducing multiorgan dysfunction

*ICU: Intensive Care Unit; CRP: C-Reactive Protein, an inflammatory marker; PCT: Procalcitonin – Procalcitonin, a specific biomarker for bacterial infections; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; MLR: Monocyte-to-Lymphocyte Ratio; PLT/MPV: Platelet to Mean Platelet Volume Ratio; AR: Augmented Reality; PediSepsisAR: AR simulation for paediatric septic shock recognition; PCD: Programmed Cell Death; ML: Machine Learning; RF: Random Forest classification algorithm; SVM: Support Vector Machine classification algorithm; DNN: Deep Neural Network; AUC: Area Under the Curve; PO: Pulse Oximetry; NIRS: Near-Infrared Spectroscopy; ST: Skin Temperature; ICD-9: International Classification of Diseases, 9th Revision; AUROC: Area Under the Receiver Operating Characteristic; IL-6: Interleukin-6, an inflammatory biomarker; suPAR: Soluble Urokinase Plasminogen Activator Receptor; AZU1: Azurocidin 1 – Protein associated with inflammation and immune response; sTREM-1: Soluble Triggering Receptor Expressed on Myeloid Cells-1 – Triggering Receptor on Myeloid Cells-1; MAP: Mean Arterial Pressure – Mean Arterial Pressure; CRT: Capillary Refill Time; rPPG: Remote Photoplethysmography; aCRT: Automated Capillary Refill Time; T2MR®: T2 Magnetic Resonance; CCI: Charlson Comorbidity Index; GCS: Glasgow Coma Scale; NEWS: National Early Warning Score; qSOFA: Quick Sequential Organ Failure Assessment; SIRS: Systemic Inflammatory Response Syndrome; MEDS: Mortality in Emergency Department Sepsis; 2D-nanoUPLC-UDMSE: Two-dimensional Ultra Performance Liquid Chromatography-Ultimate Data-Independent Mass Spectrometry Enhancer – Advanced proteomic technology for monocyte analysis; ELISA: Enzyme-Linked Immunosorbent Assay – Enzyme-Linked Immunosorbent Assay, used for irisin determination; PAR2: Protease-Activated Receptor 2 – Protease-Activated Receptor 2, associated with inflammation.

The analyzed studies included ICU patients who were assessed and monitored for sepsis and septic shock using both conventional and modern methods. These studies comprised randomized, observational, retrospective, and prospective designs, with data covering clinical variables such as mortality, incidence of adverse events, length of hospital stay, and response to various interventions.

The interventions analyzed included techniques for intravenous fluid administration, the use of inflammatory biomarkers (NLR, PLR, MLR, CRP, PCT, lactate), machine learning algorithms for continuous monitoring (e.g., photoplethysmography, capillary refill time analysis), and gene expression-based models for diagnostics (e.g., using a panel of PCD genes in machine learning algorithms). Each study employed specific statistical analysis methods and regression models to evaluate the effect of these interventions on mortality and clinical outcomes of patients.

For biomarkers and continuous monitoring, predictive analysis methods were used, combining clinical scores (SOFA, APACHE II, SAPS II/III, qSOFA) with advanced biomarkers (IL-6, suPAR, sTREM-1). Additionally, rapid molecular technologies for pathogen identification, such as the T2Bacteria® panel using magnetic resonance, were utilized to enable quick identification of infectious agents.

The analysis also included proteomic diagnostic technologies that identified altered proteins in septic shock, used as potential biomarkers for diagnosis and prognosis. Experimental studies also involved animal models to assess the efficacy of interventions such as blocking inflammatory receptors (e.g., PAR2) with specific molecules aimed at reducing sepsis effects by preventing organ dysfunction.

In Table 1, we also observe that recent studies emphasize the importance of personalized approaches and advanced monitoring in sepsis and septic shock, incorporating both conventional clinical interventions and innovative methods. Although fluid restriction and standard biomarkers have shown limitations in predicting and managing sepsis effectively, emerging technologies like monitoring through machine learning algorithms, rapid diagnostics with molecular panels, and the use of specific biomarkers, such as irisin, offer promising perspectives for improving diagnostic and prognostic accuracy. However, further studies are recommended to validate these methods across various clinical settings and to implement them into intensive care protocols.

In terms of conventional methods, the most frequently used are clinical scores (e.g. SOFA, APACHE II, SAPS II/III) and standard biomarkers (CRP, PCT, lactate). These are each mentioned four times across studies, which serves to underscore their central role in traditional clinical practice.

Other conventional methods, such as blood cultures and antibiograms, appear twice, while standard intravenous fluid administration, ICD-9 coding for sepsis, vasopressor use, and cardiac function monitoring are each mentioned only once.

The high frequency of clinical scores (e.g., SOFA, APACHE II, SAPS II/III) and standard biomarkers (CRP, PCT, lactate) in traditional clinical practice is because these methods are well-validated, accessible, and easy to apply across various clinical settings. These tools are an integral part of international guidelines for the diagnosis and monitoring of sepsis and septic shock, with widely recognized

utility in assessing patient severity and risk stratification [32,33].

Conversely, less frequently used conventional methods, such as blood cultures and antibiograms, standard intravenous fluid administration, ICD-9 coding for sepsis, vasopressor use, and cardiac function monitoring, are employed less often for various reasons. Blood cultures and antibiograms are useful for identifying pathogens but require a long time to yield results, making them less practical in emergencies. ICD-9 coding is important for epidemiological data collection but has a limited impact on immediate patient care.

Therefore, the more frequent use of clinical score assessment and standard biomarkers is due to their ability to provide rapid and reliable information about the patient's condition, making them suitable for initial assessment and real-time monitoring of patient progress.

On the other hand, among modern methods, the use of advanced biomarkers (e.g., IL-6, suPAR, irisin) has the highest frequency (3 mentions), followed by machine learning algorithms and continuous monitoring with biosensors (e.g., PO, NIRS, ST), each with two mentions. Other modern methods, such as molecular diagnostic panels (T2Bacteria® and T2MR®), remote photoplethysmography, AR simulations, and PAR2 receptor inhibition, were used less frequently, each mentioned only once, suggesting that they are either emerging technologies or applied only in specific contexts.

The high frequency of advanced biomarkers (e.g., IL-6, suPAR, irisin), machine learning algorithms, and continuous monitoring with biosensors (e.g., PO, NIRS, ST) as modern methods in the diagnosis and monitoring of sepsis and septic shock are due to their enhanced capacity for early detection and precise patient assessment. Advanced biomarkers are valued for their increased sensitivity in identifying inflammation and organ dysfunction associated with sepsis, and their inclusion in clinical practice is supported by growing evidence showing their predictive value.

Machine learning algorithms and continuous monitoring with biosensors are also highly attractive to researchers and clinicians, as they can analyze complex data and provide real-time alerts, enabling faster and more personalized interventions. In particular, machine learning algorithms can integrate information from multiple sources (biomarkers, vital signs) to improve risk stratification and allow continuous, proactive monitoring of patients.

On the other hand, modern methods with lower usage frequency, such as molecular diagnostic panels (T2Bacteria® and T2MR®), remote photoplethysmography, AR simulations, and PAR2 receptor inhibition, are relatively new and are typically used only in specific contexts or experimental studies. These technologies are still in the evaluation phase for widespread implementation and require additional studies to validate their effectiveness and cost-efficiency across various clinical settings. Additionally, the higher costs and infrastructure requirements for some of these emerging technologies limit their broad use in everyday clinical practice.

Thus, there is a continued preference for conventional methods in clinical practice, alongside a gradual trend towards the integration of more advanced modern methods, which have the potential to provide faster and more accurate detection of sepsis and septic shock.

DISCUSSIONS

A total of 23,822 patients were reviewed across the studies included in this systematic analysis. These patients come from various observational, randomized, and retrospective studies, each with different designs and intervention methods aimed at evaluating and monitoring sepsis and septic shock.

The results of this systematic analysis demonstrate that the treatment of sepsis and septic shock can be enhanced by combining conventional interventions with modern methods, including advanced biomarkers, digital monitoring, and artificial intelligence (AI) techniques. The studies reviewed cover a wide range of therapeutic approaches, from fluid therapy strategies and inflammatory biomarkers to continuous monitoring technologies and predictive genetic analyses.

A central aspect of the analysis is the impact of conventional and modern interventions. For example, the study by Meyhoff et al. (2022) shows that intravenous fluid restriction does not offer significant advantages over standard therapy in terms of mortality or reduction of severe adverse events [18]. Although fluid restriction may reduce the risk of volume overload, the results of this study indicate that there are no significant differences between restrictive intervention and the conventional approach regarding the survival of patients with septic shock. This suggests that the optimization of fluid volume should be evaluated based on the individual characteristics of each patient.

Similarly, the study by Liberski et al. (2020) highlights the role of biomarkers such as NLR (neutrophil-to-lymphocyte ratio) in assessing the risk of septic shock [19]. NLR has shown predictive value for identifying patients prone to septic shock, but its combination with conventional biomarkers like CRP and PCT significantly increases predictive accuracy. This suggests that advanced biomarkers may contribute to the early identification of high-risk patients, facilitating faster interventions. However, since no single biomarker directly predicted mortality, their optimal use remains as a complement to standard clinical measures, for more effective risk stratification.

Another essential aspect is the inclusion of modern monitoring technologies, such as near-infrared spectroscopy (NIRS) and remote photoplethysmography (rPPG). The study by Lungu et al. (2024) indicates that continuous monitoring using NIRS, PO, and skin temperature can detect sepsis 6–48 hours before clinical diagnosis, providing an important advantage in preventing the rapid progression of the disease [22]. NIRS and PO demonstrated the highest predictive accuracy, highlighting the potential of these non-invasive methods for continuous monitoring and early detection of neonatal sepsis. Microcirculation monitoring via

photoplethysmography (rPPG) showed greater sensitivity than conventional methods for assessing perfusion, which could have important implications for managing critically ill patients with septic shock, according to the study by Klibus et al. (2024) [25]. The use of these technologies offers a more sensitive way to monitor subtle changes in tissue perfusion, which could precede overt clinical deterioration.

AI-based methods also bring innovative contributions to the diagnosis and prognosis of sepsis. The study by Wang et al. (2023) highlights the capability of machine learning (ML) algorithms to identify sepsis-associated genes, such as ITGAM and KIF1B, with significant accuracy [21]. These models achieved high-performance scores (AUC), indicating that ML-based approaches can support diagnosis and risk stratification by identifying specific genetic profiles. Using AI to analyze genetic profiles paves the way for personalized treatments and improved identification of therapeutic targets.

Additionally, the administration of the molecule 1-PPA, investigated by Luisetto et al. (2024), demonstrated positive effects by reducing mortality and sepsis symptoms in animal models [31]. This molecule inhibits the PAR2 receptor, reducing systemic inflammation and protecting cardiac function, suggesting that interventions targeting specific molecular pathways could offer new therapeutic solutions for patients with septic shock. Although these results are preliminary and obtained from in vitro and in vivo animal studies, they show promising potential for developing targeted therapies capable of blocking inflammatory cascades at the molecular level.

Overall, the results of this analysis underscore the need for an integrated approach that combines conventional interventions, such as fluid administration and vasopressors, with modern diagnostic and monitoring methods. Continuous monitoring, advanced biomarkers, and AI algorithms have the potential to improve prognosis and reduce mortality in sepsis, although their widespread applicability depends on validation in extensive clinical studies. While some methods, such as fluid restriction, have shown limited results, others, like biomarkers or digital monitoring, have significant potential in risk stratification and early identification of patient deterioration.

Thus, the combination of conventional and modern methods allows for better adaptation of treatment to the individual specificities of each patient, while also offering opportunities to improve survival and quality of care in intensive care units.

CONCLUSION

This comparative study of conventional and modern methods for diagnosing and monitoring sepsis and septic shock highlights the importance of adopting advanced technologies in the care of critically ill patients. While traditional methods, such as blood cultures and standard biomarkers, remain fundamental, the results of the reviewed studies suggest that modern technologies – including rapid molecular tests, continuous monitoring through biosensors, and machine learning algorithms – offer greater accuracy in early diagnosis and superior risk stratification capabilities. These advanced tools enable faster and more informed interventions, thereby contributing to improved prognosis and reduced mortality in sepsis and septic shock.

The comparative analysis between conventional and modern methods of diagnosis and monitoring for sepsis and septic shock reveals several practical implications for clinical practice. Conventional methods, such as the use of standard biomarkers (CRP, PCT, lactate) and clinical scores (SOFA, APACHE II, SAPS II/III), remain essential due to their accessibility and the familiarity healthcare professionals have with them. These methods provide a solid foundation for the initial assessment of patients and risk stratification in intensive clinical settings.

However, integrating modern methods, such as machine learning algorithms, continuous monitoring with biosensors, and the use of molecular diagnostic panels (e.g., T2Bacteria®), has the potential to significantly transform clinical approaches. These advanced technologies can improve diagnostic accuracy, enable early detection of sepsis, and facilitate faster and more informed decision-making. For instance, rapid molecular panels can identify pathogens within hours, thereby reducing the time needed to initiate appropriate antibiotic therapy, which is crucial for improving patient prognosis.

Implementing these modern methods in hospitals requires initial investments in infrastructure and medical staff training, but the potential benefits are substantial, including reduced mortality, shortened hospital stays, and optimized resource utilization in intensive care units. The use of advanced biomarkers and machine learning algorithms could also facilitate continuous monitoring of patients with sepsis and septic shock, providing real-time alerts for patient deterioration and supporting early intervention.

In the long term, these innovations may contribute to the standardization of more effective clinical protocols and the personalization of treatments for sepsis patients, tailoring interventions to the specifics of each patient. Furthermore, the gradual integration of these modern technologies could help raise the quality of medical care and improve the overall efficiency of the healthcare system.

To fully integrate these technologies into clinical practice, further clinical studies are needed to validate their effectiveness across a variety of clinical settings. It is essential to develop standardized protocols that include rapid molecular tests and machine learning algorithms for early detection and personalized monitoring of patients. Additionally, future research should explore the potential of new biomarkers and non-invasive monitoring technologies to support rapid clinical decision-making and facilitate integrated sepsis management in intensive care units.

This systematic analysis included studies with varied designs (randomized, observational, and retrospective studies), which may impact the direct comparability of results. Differences in study design, patient populations, and clinical settings (pediatrics, adults,

ICU) make generalizing conclusions challenging, as each type of study may have its methodological limitations and biases. The present study encompasses a diverse range of patient populations, including neonates, children, adults, and the elderly. It is therefore evident that the newborn with sepsis has almost no defense mechanisms, whereas the middle-aged population demonstrates the most effective response to sepsis through early secretion of various mediators, a robust response to systemic inflammation, and a high capacity for regeneration. The elderly are included in the category of individuals who are considered to be frail, and as a result, may demonstrate a reduction in their ability to respond effectively to an encounter with a pathogen. Consequently, sepsis can be identified even in its most advanced stages in these patients. Furthermore, the capacity for regeneration is diminished in this population, resulting in more pronounced manifestations and consequences of sepsis and septic shock. Furthermore, patients with at least one additional health condition (such as autoimmune, cardiovascular, respiratory, or renal disease) are at significantly elevated risk of developing more severe forms of sepsis, including septic shock. Consequently, developing a diagnostic methodology for sepsis in the general population is challenging, necessitating the use of specific diagnostic techniques and combinations of traditional and modern methods adapted to the individual's age, associated diseases, and other factors.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, G.P.G. and A.N.D.; methodology, R.M.S and L.P; software, A.B. and I.S.C.; validation, V.T.G and D.R.T.; formal analysis, D.C, D.O.C. and E.F.L.; investigation, G.P.G, A.N.D and A.B.; data curation, V.T.G. and E.F.L ; writing—original draft preparation, A.B and R.M.S.; writing—review and editing G.P.G, D.O.C. and D.C.; visualization, L.P. and I.S.C.; supervision, G.P.G and D.R.T.; project administration, G.P.G and D.C. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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https://doi.org/10.55453/rjmm.2025.128.3.4

REVIEW

Assessment of Suicide Risk in the Civilian Population, Active Military Personnel and Veterans Using Psychometric Instruments – A Literature Review

Octavian Vasiliu[1,2]

[1] Discipline of Psychiatry, Neurosciences Department, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Clinical Department of Psychiatry, "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest

Correspondence: Octavian Vasiliu, octavian.vasiliu@umfcd.ro

Abstract: The assessment of suicide risk is a highly debated topic in the literature due to the complex interplay between social, psychological, cultural, and biological factors that contribute to the pathogenesis of self-harm. There is no unanimously accepted predictive model of suicide and no widely recognized evidence-based algorithm for psychiatric and psychological evaluation in clinical and non-clinical populations for early detection of self-harm. Therefore, this narrative review is focused on identifying the validated clinical instruments that may contribute to the construction of a possible screening and monitoring plan for suicide risk in military and civilian populations. Four electronic databases were searched (PubMed, CINAHL, Google Scholar, and Clarivate/Web of Science) for relevant reports on psychometric tools for detecting suicide risk published between the inception of each archive and January 2025. Seventeen instruments dedicated to the measurement of suicide and suicide-related aspects were reviewed, as well as three tools for the evaluation of depression severity that include specific items for assessing self-harm. The advantages and vulnerabilities of each instrument were assessed, and the particular features of using these tools in the military population were also explored. In conclusion, although a large number of validated instruments for the assessment of suicide risk exist, it is not possible to recommend the use of a single tool, either for clinical and nonclinical populations or for military and civilian personnel. The endeavor of finding an algorithm for the assessment of suicide risk is still far from reaching its end, as new psychometric instruments and possibly a new paradigm for the phenomenon of self-harm are sorely needed.

Keywords: suicide risk, self-harm, depression, military personnel, veterans, suicide prevention

INTRODUCTION

Suicide prevention is one of the most challenging phenomena in clinical psychiatry due to the social impact of self-harm, its high prevalence, and the lack of unanimously accepted predictive models. More than 720000 individuals die by suicide each year, and self-aggression is the third leading cause of death among individuals aged 15 to 29 years old [1]. More than one in every 100 deaths worldwide occurs due to suicide, and methodological improvements are needed in order to increase the accuracy of reports regarding complete suicide and suicide attempts [2]. In this context, structured assessment of suicidal ideation and behaviors is an important aspect of the psychiatric clinical practice, and the development of validated instruments (scales, inventories, and questionnaires) for assessment of suicidal risk is essential for both civilian and military populations.

Suicide rates are still high among military personnel, both active and retired [3]. The Army Study To Assess Risk and rEsilience in Servicemembers (Army STARRS) is a large investigation targeting the prediction of suicide in active duty soldiers who were hospitalized (N=53769 participants), in the next year after discharge [4]. The incidence of suicide in this population was 12% of all US Army suicides, equivalent to 263.9 suicides per 100,000 person-years vs. 18.5 suicides per 100,000 person-years in the entire US Army [4]. This data indicates the need for more careful post-discharge monitoring of active duty soldiers, but the specific means to be implemented for this purpose are far from being clear. A potential contributor to the higher risk of suicide among military personnel has been the existence of stigmatizing beliefs since these can act as deterrents for help-seeking [3]. In a cohort study (N=153,736 patients) of US veterans, the risk assessment suggested that only a few variables were associated with subsequent suicide, especially suicidal ideation, firearm access, and preparatory behaviors, which is completely insufficient to develop a risk prediction algorithm [5]. According to the US Department of Veterans Affairs, the risk of suicide in veterans was 1.57 to 1.66 higher than in non-veterans between 2017 and 2020 [6].

Citation: Vasiliu O. *Assessment of Suicide Risk in the Civilian Population, Active Military Personnel and Veterans Using Psychometric Instruments – A Literature Review*. R. J. Mil. Med. 2025, 128(3): 200-214; https://doi.org/10.55453/rjmm.2025.128.3.4

Academic Editor: Daniel O. Costache

Received: 25 January 2025
Revised: 21 February 2025
Accepted: 3 April 2025

Searching for psychological predictors of suicide is but only one side of the complex process of identifying relevant contributors to the pathogenesis of suicide. Biological factors, such as chronic diseases, and social vulnerability factors, like stigmatization, migration, or bullying, cultural and economic influences, e.g., poverty, acculturation stress, being part of a cultural minority, transgenerational conflicts, etc. [7-12]. However, all these potential pathogenetic factors have intricate relationships, and disentangling them is necessary as part of constructing an evidence-based approach to a predictive model for self-harm behavior.

Based on all these data, it becomes clear that finding adequate tools for detecting the risk of suicide is essential for creating preventative measures and thus decreasing the incidence of completed suicide. To attain this objective, the current review focuses on the detection of the most validated and widely used psychometric instruments for the detection of suicide risk in military personnel, veterans, and civilians. It is expected that such an endeavor could provide the basis of an algorithm for the evaluation of vulnerable populations, as a screening strategy, and for the monitoring of at-risk groups during and after exposure to severe stressors. This review does not target only clinical populations derived from civilian or military environments but also non-clinical populations, which may be exposed to significant risk of suicide ideation and behavior.

MATERIALS AND METHODS

A narrative literature review was conducted by searching four major databases – PubMed, CINAHL, Google Scholar, and Clarivate/Web of Science – for all primary and secondary reports published between the inception of each archive and January 2025, using as keywords “suicide” OR “self-harm” AND “scale” OR “inventory” OR “questionnaire” OR “profile” OR “psychometric instrument” OR “psychometric tool” AND “civilian” OR “military personnel” OR “veterans. Only papers in English were selected. The inclusion criteria were adolescents and adults, clinical and nonclinical groups, civilian and military populations, primary outcomes related to suicide, clinician-rated and self-rated instruments, both prospective and retrospective studies, but also systematic reviews, narrative reviews, and meta-analyses. Exclusion criteria were undefined measurement methods, exclusively non-structured methods of evaluation, poorly defined study design, and children or unspecified population characteristics.

RESULTS

A number of 17 instruments dedicated to the measurement of suicide and suicide-related aspects were found during the literature search, and three tools that include at least one item related to suicide, that were investigated in multiple studies were also included in the analysis.

The **Suicide Attempt Self-Injury Interview** (SASII) was developed by Linehan et al. (2006) to assess the multiple factors associated with suicide attempts and self-aggressive behaviors without a clear suicidal intent [13]. According to the authors of this instrument, its major strength is the use of a standardized definition of suicidal and other self-injurious activities, allowing the practitioners to assess the suicidality/suicide intent regardless of the particular aspects and consequences of the acts themselves [13]. This tool also offers individual ratings for the components of lethality, such as the method used, the consequences of the gesture, and the therapy needed [13]. The scales of SASII are „suicide intent”, „lethality”, „rescue likelihood”, „risk/rescue ratio”, „suicide communication”, „interpersonal influence”, and „emotional relief” [13]. SASII allows for each episode of non-suicidal self-injury behavior to be coded separately and described by its characteristic details. The major variables are assessed by the interview and the frequency of self-injury behaviors, the medical treatment required secondary to the behaviors, and a set of four factors for each episode of non-suicidal behavior - medical risk, suicidal intent, instrumental intent, and impulsivity [13].

A study investigating patients (N=60) with repetitive nonsuicidal self-injury (NSSI) tried to validate subtypes of these behaviors, based on multiple self-report scales, and two structured interviews, SCID-5-CV (Structured Clinical Interview for DSM-5 Clinical Version) and SASII [14]. The results supported a two-subtype model, i.e., (a) substance abuse and suicide attempt subtype- with a higher rate of lifetime suicide plans, number of lifetime suicide attempts, higher severity of self-harm, borderline personality features, anger, posttraumatic manifestations, and difficulties in regulation of own emotions; (b) cutting and scratching subtype [14]. The use of SASII in this study supported the validity of this model and, consequently, the existence of clinical heterogeneity of individuals with NSSI [14].

In another study, SASII was combined with the Beck Scale for Suicide Ideation (BSI), Beck Depression Inventory (BDI), and Beck Hopelessness Scale (BHS), to characterize the self-harm behaviors in a group of Pakistani patients (N=221) [15]. The results showed the possibility of common causal mechanisms and processes underlying self-harm between the investigated population and other groups, with factors such as financial, relationship, or interpersonal difficulties being considered [15]. SASII was administered to collect data on details regarding the time, methods, circumstances, motivations, and treatment for self-harming behaviors [15].

According to a systematic review that explored self-harm measuring tools, seven such validated instruments were identified, but there was a high variation detected in their overall quality [16]. Out of the identified tools, SASII appeared to be the most detailed and psychometrically solid instrument currently available for measuring self-harm behaviors [16]. The other instruments identified were Self-Harm Inventory (SHI), Deliberate Self-Harm Inventory (DSHI), Self-Harm Behavior Questionnaire (SHBQ), Self-Injury Questionnaire (SIQ), Self-Injurious Thoughts and Behaviors Interview (SITBI), and Inventory of Statements About Self-Injury (ISAS) [16]. The reported reliability of SASII was α=0.63-0.93, and the convergent validity with therapist notes (r=0.76-0.86) and the medical records (r=0.75-0.82) were also high [16].

A study investigating the influence of NSSI onset age in adolescents is associated with the frequency of subsequent episodes of self-

harm (N=103 participants) showed that a lower age of onset and a longer duration of self-harm were both associated with an increased frequency of other NSSI episodes and a higher risk of a first suicide attempt [17]. Therefore, early identification of NSSI using validated instruments is an essential way to create adequate management strategies for these behaviors [17]. In this important study, SASII was used to collect data on most of the parameters targeted, including time, modality, and frequency of self-harm behavior [17].

A recent cross-sectional study evaluated the presence of factors associated with self-harm behavior during military service in the Israel Defense Forces and used SASII and the Columbia Suicide Severity Rating Scale (C-SSRS) to characterize this population [18]. A number of 1238 episodes of self-harm behavior were identified between 2017 and 2021 and included in the analysis [18]. NSSIs correlated with the presence of adjustment difficulties, and higher rates of previous psychiatric diagnoses were found in individuals with suicide attempts [18]. The risk of dying by suicide during military service was twice as high in soldiers with previous suicide attempts and psychiatric diagnoses [18]. Also, if these soldiers were serving in a combat unit, the risk of suicide was four times higher [18].

Another two-year prospective study explored the predictive value of NSSI for suicide attempts in a clinical sample of US active duty military personnel (N=152, mean age=27.53 years), using SASII and Beck Scale for Suicide Ideation (BSSI-C) [19]. All participants reported current suicidal ideation and/or had a suicide attempt during the last month [19]. The results showed 40% of soldiers with a history of NSSI and 25% of those with a history of suicide attempt made a suicide attempt during the two years of follow-up [19]. Soldiers with a history of NSSI were twice as likely to engage in another suicide attempt, but those with a previous suicide attempt had no increase in suicidal behavior vs. soldiers without a history of suicide attempts [19]. However, 30% of the soldiers with a suicide attempt in their history had engaged in NSSIs, and the total number of NSSIs was significantly associated with an increased risk for future suicide attempts [19].

The **Columbia Suicide Severity Rating Scale** (C-SSRS) is one of the most widely used instruments in Psychiatry to determine suicide risk, but it must be noted that it cannot replace a complete clinical assessment. The C-SSRS has very good convergent and divergent validity with other scales for assessing suicidal ideation and behavior, its subscales are sensitive to changes over time, and the suicidal ideation subscale has a moderately high internal consistency [20]. The C-SSRS is structured in such a way that it allows separate assessments of the severity and intensity of suicidal ideation, autolytic behavior, and lethality of the attempt [20]. The severity of ideation is rated on a five-point scale, the intensity of ideation subscale also on a 5-point ordinal scale (i.e., frequency, duration, controllability, deterrents, and reason for ideation), the behavior subscale is rated on a nominal scale (i.e., aborted, actual, and interrupted attempts, preparatory behavior, and NSSI), while the fourth scale is the lethality subscale for the assessment of actual attempts (there is a 6-point ordinal scale, and if the current lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale) [20].

The cut-off value of 27 on C-SSRS has very good sensitivity and specificity for classifying suicide attempts in the first three months, according to a prospective multicenter cohort study (N=804 patients with a recent episode of self-harm) [21]. The CSSRS and the Suicide Assessment Scale (SUAS) had a better chance to classify the suicide attempts in the first months but also during a one-year follow-up, although the cut-off value for long-term monitoring could not be established for either instrument [21]. The same study showed that the Suicide Intent Scale (SIS) was the only instrument able to classify suicides adequately at 3 and 12 months, with a cut-off score of at least 21 and at least 17, respectively [21].

C-SSRS had proven a sensitivity of 67% and a specificity of 76% for identifying suicidal behaviors at the follow-up (mean period of 64 days) in a large study (N=3776 patients) [22]. Negative life events were associated with a 2.4% subsequent risk of suicidal behavior, and patients reporting lifetime suicidal ideation with intent/prior suicide attempt had a 4 to 9 times higher risk to report prospectively suicidal behavior [22].

C-SSRS score includes information collected from the patient, but also from other significant sources, and has been validated in emergency settings, as well as in the outpatient population [23]. Also, C-SSRS has been validated in children and adolescents, military veterans, and patients with different psychiatric disorders [23]. The US Food and Drug Administration recommends the use of C-SSRS for clinical trials, and it has been approved by the Centers for Disease Control and Prevention to define and monitor suicidal ideation and behavior [23,24].

The administration of C-SSRS in a large sample of US veterans (N=15373) resulted in confirmation of concurrent validity by comparison with self-reports from the last three months and attempts documented in medical records [25]. Nevertheless, a significant number of discordant responses were reported [25]. The predictive value for future attempts was more than 80% [25]. Another study evaluated the psychometric assessment of C-SSRS and Suicidal Behaviors Questionnaire-Revised (SBQ-R) in 200 active-duty personnel and concluded acceptable reliability for both SBQ-R and C-SSRS ideation severity subscale, while the confirmatory factor analysis supported the SBQ-R, but not the self-reported version of C-SSRS [26]. Yet another study that included US military personnel with lifetime attempted suicide (N=121) used C-SSRS to test the hypothesis that NSSIs elevate the suicide risk; the results showed that a history of NSSI is relevant for increasing the service member's social alienation and acquired tendency for suicide, but did not correlate with the number of lifetime suicide attempts or the controllability of suicide ideation [27].

The **Scale for Suicide Ideation** (SSI) and its self-administered version, Beck Suicidal Ideation Scale (B-SSI), were developed by Beck et al. and are widely used in clinical studies, although their dimensional structure is debated in the literature [28-30]. For SSI, the internal consistency was high, and there were recorded moderately high correlations with clinical ratings of suicidal risk and self-administered measures of self-harm, while the sensitivity to changes in hopelessness and depression over time was also good [28]. For B-SSI, the

Cronbach alpha coefficient was 0.90, indicating high internal consistency for both paper-pencil and computer versions [29]. B-SSI has 21 items, and its items are scored on a 3-point Likert scale, with a total score varying from 0 to 38 [29,31]. The cut-off score of 6 for B-SSI was defined in a prospective study as presenting accuracy for future suicidal behavior, and a reduction to less than eight items with stochastic curtailment was sufficient for this purpose [32]. There is a version for the assessment of current ideation, i.e., the SSI-C, and another for the worst moment in the patient's life, i.e., the SSI-W, both with 19 items [33]. Both SSI-C and SSI-W were positively correlated with a diagnosis of mood disorder, a personality disorder, and measures of depression and hopelessness [33]. The internal consistencies of both scales were high, i.e., alpha 0.84 for SSI-C and 0.89 for SSI-W [33].

A study that involved US military service members showed that summing up five items of the B-SSI (i.e., 1, 2, 4, 6, and 15) is an acceptable strategy to shorten this tool while preserving the predictive value of 74% for a cut-off score ≥1 [34]. A study that included 39 Israeli soldiers (mean age 19 years) who were suicide attempters during their military service included evaluations using B-SSI, C-SSRS, and Suicide Intent Scale (SIS); the results supported seven items of the B-SSI, one of the C-SSRS and two of the SIS were associated with severe suicide attempts [35].

The **Beck Hopelessness Scale** (BHS) explains hopelessness through the concept of a cognitive schema focused on unfavorable expectations, both in terms of the short-term and long-term perspective. This instrument, developed by Beck et al. in 1974, includes 20 items with a dichotomous format, and its primary use is the evaluation of suicide risk in clinical and non-clinical adult populations [36,37]. The original version has three factors, i.e., affective, motivational, and cognitive, but other alternative factorial structures have been suggested [37]. The BHS can be self-administered, as well as administered by the clinician, to hospitalized and non-hospitalized subjects, in specialized outpatient clinics or in emergency hospitals [37]. The predictive validity of BHS has been confirmed by multiple studies in patients with psychiatric disorders [38]. The Cronbach alpha was 0.81 in the general population, according to a study (N=1500 participants) [39]. Shorter versions of BHS have been created, in order to increase its applicability for clinical populations, such as BHS-9 or BHS-4 [38,40,41].

A study focused on improving the detection and prediction of suicidal behavior among military personnel by measuring suicidal beliefs used a set of tools, BHS included, in order to evaluate a new instrument, i.e., the Suicide Cognitions Scale (SCS) [42]. Another study included BHS in the set of instruments dedicated to the assessment of psychological pain in suicidal veterans and concluded that psychological pain accounted for the most shared variance for suicidality, but most relevant correlations were determined for the C-SSRS [43].

The **SAD PERSONS scale** is a mnemonic with each letter representing a risk for suicide, and the total score varies from 0 to 10 [44]. The interpretation is low risk for scores from 0 to 4, medium risk from 5 to 6, and high risk from 7 to 10 [44]. Modified SPS (M-SPS) is characterized by a substitution of new factors and changes in scoring (low risk = 0-5, medium risk = 6-8, and high risk = 9-14) [45]. These are simple and easy-to-administer instruments developed for screening suicide risk in community mental health settings [46].

The SAD PERSONS Scale (SPS) was assessed in a systematic review (N=9 studies) and the data were considered insufficient to support its use in the assessment or prediction of suicidal behavior [47]. In a large study (N=5462 consecutive adults evaluated by psychiatrists in tertiary emergency departments), the suicide rates at six months, 12 months, and five years were determined [48]. Low-risk assessed by SPS at baseline died by suicide at 6 and 12 months, while high-risk scores were significantly associated with death by suicide over the five-year interval by both SPS and M-SPS [48]. Another study (N=4019 consecutive referrals to psychiatric services in emergency departments) used both SPS and M-SPS and showed that high-risk baseline values presented low sensitivity and low positive predictive power [49]. SPS did not predict suicide better than chance in this study, but when only the five original scale items that accounted for the higher proportion of suicide attempt variance were used, the sensitivity was 93.5%, and the predictability was 5-fold higher for suicide attempt presentation [49].

To evaluate the possibility of using SAD PERSONS in veterans, a study (N=271 participants from the Midwest Veterans Affairs Medical Center) concluded that the rate of false-positive and false-negative results is unacceptable [46].

The **Reasons for Living Inventory** (RFLI) was created by M. Linehan in 1983, and it consists of a checklist of motives for choosing to continue living, instead of self-harming with suicidal intent [50]. RFLI has 72 items (long version) or 48 items (short version). The six factors originally describing the structure were replicated by other authors, the internal consistency was proven acceptable (Cronbach alpha = 0.72-0.92), and the test-retest reliability was also demonstrated [51]. A high score on RFLI predicted fewer future suicide attempts in the next two years interval for initially hospitalized women with depression, but not for men, in a study (N=386 participants) [52].

RFLI was administered in a veteran male population (N=421) with various combat exposures and a history of suicide attempts, and the initial results were supportive of this tool being used in the specified population [53]. The reliability and validity of RFLI were confirmed by exploratory factor analysis and bi-factor analysis, correlates between total scores and subscale scores, and estimates of internal consistency reliability on the original instrument subscale scores [53].

The **Reasons for Living Scale-Military Version** (RFL-MV) was created later by Deutsch & Lande, who added 20 items to the items of RFLI-SV, items specifically designed to reflect the military environment characteristics [54]. RFLI-MV was evaluated on 200 patients from the military personnel, and a six-factor structure was defined, with the subscale of "Military Values" reflecting the coherence of the new dimension added to Linehan's version of the tool [54].

The **Reasons for Living versus Reasons for Dying Assessment** is another tool that combines the protective factors and triggers for

suicide, to offer a more complete interpretation of the individual's risk [55]. In a study (N=49 suicidal university counseling center patients), 173 reasons for living and 145 reasons for dying were obtained and structured in eight and, respectively, nine categories, and different chi-square results for the two dimensions were obtained, suggesting a different salience of those dimensions for suicidal patients [55]. The evaluation of the reasons for dying vs. reasons for living (RFD-RFL) index in military psychiatric inpatients (N=167) following a suicide event showed that family was the most reported supporting factor (40% of the participants), while the most frequently invoked reasons for dying were general descriptors of self (27%), general statements about escape (19%), and others/relationships (19%) [56]. Higher values of this index were associated with a more significant wish to die vs. wish to live, higher levels of hopelessness, and a history of multiple suicide attempts [56]. When individuals can find more reasons for dying than for living, this could be indicative of a higher suicide risk [56].

Another study evaluated the risks of dying vs. the risks of living in patients admitted after a suicide attempt (N=60) and a monitoring period of 24 months, showing that the number of reasons for dying was the most relevant predictor for increased suicidal ideation at baseline, and reasons for dying, depressive symptoms and baseline suicide ideation predicted suicide reattempt up to 12 months later [57]. In the mediation analysis, reasons for dying mediated the effect of depressive symptoms at baseline and one-year follow-up on suicidal ideation [57]. However, reasons for living did not prove themselves a protective factor against suicide risk [57].

The **Suicide Opinion Questionnaire** (SOQ) was designed to assess the different approaches to the event of suicide in different cultures and demographic groups, being administered in multiple settings and populations, e.g., college students, medical students, and mental health professionals [58,59]. The test-retest reliability coefficient for SOQ was r=0.78 to 0.91, and the intercorrelations between the scales were in the range of r=0.20 [59]. An exploratory factor analysis detected a weak 2-factor structure in one study, and this model failed in the second study, thus raising doubts about the factorial structure of this instrument [60].

In a group of undergraduate volunteers (N=738), the responses to SOQ were compared between attempters, contemplators, and nonattempters, and a factor analysis indicated the existence of seven factors, with two significant functions discriminating between the respondents based on their gender and prior suicide history [61]. In another study (N=91 psychiatric inpatients admitted for suicidality), the SOQ was included in a battery of tests focused on suicidality, and the results showed that 20 items differed between patients with suicide attempts vs. those without at baseline and follow-up [58]. The linear discriminant analysis supported the sensitivity and specificity of the test for post-discharge suicide attempts for the 9-item scale [61]. The potential of SOQ to be useful in identifying prospectively the individuals with a risk of suicide is supported by the available data, but maybe including it in a module of tests would be more beneficial than using it alone, and using it in high-risk patients would increase its predictive power [58].

In a study (N=1758 Marine Non-Commissioned Officers) that evaluated the usefulness of SOQ in military personnel, a 4-factor structure was detected, which accounted for approximately 30% of the total variance, with sex, education, and prior exposure to suicide within the individual's military unit being significantly associated with suicide options [62].

The **Suicide Trigger Scale** (STS) is a self-report instrument to assess the trigger states for suicide, which showed a strong internal consistency, with a Cronbach alpha of 0.94, and good validity related to past suicidal behavior [63,64]. Its third version, STS-3, showed that scores may be predictive for post-discharge suicide attempts [63]. This scale has 42 items and three factors explaining 43% of the variance- Frantic Hopelessness, Ruminative Flooding, and Near-Psychotic Somatization [64]. In a validation study (N=183 adult psychiatric patients with suicidal ideation/attempt in the psychiatric emergency room) with a 1-year follow-up, suicidal subjects with suicide attempt history had a mean of 7 points more than those without such a history, and Frantic Hopelessness was a significant predictor for current suicide attempt, if only attempters requiring at least some medical attention were considered [64].

A subset of six items on the STS-3 improved the prediction of post-discharge suicide attempts, and patients with ultra-high scores differed significantly from those with ultra-low scores on mood intensity, depression, impulsiveness, abuse history, and attachment security, in a validation study (N=161 adult psychiatric patients admitted to hospital for suicidal ideation or attempt) [63].

The **Manchester Self-Harm Rule** (MSHR) was based on an exploration of multiple variables related to self-harm, i.e., those which include the nature of the act, details of self-harm episode, the main reason for current distress/precipitant to the episode of self-harm, social and demographic information, clinical history, and current medical state [65]. The four questions of MSHR refer to the history of self-harm, previous psychiatric treatment, current psychiatric treatment, and benzodiazepine taken as an overdose [65]. The tool has a sensitivity of 97%, a specificity of 26%, and a positive predictive value of 22% [65]. A related tool is the ReACT Self-Harm Rule, derived from a prospective cohort study, which analyzed 29571 self-harm presentations to hospital Emergency Departments [66]. Recent self-harm (in the last year), living alone/homelessness, cutting as a method of self-harm, and treatment for an ongoing psychiatric disorder were factors associated with higher risk [66]. This tool had 95% sensitivity and 21% specificity, with a positive predictive value of 30%, identifying 83 out of the subsequent 92 suicides [66].

The **Suicidal Behaviors Questionnaire** (SBQ) is a 34-item self-assessment instrument for suicidal thoughts and behaviors, developed by Linehan in 1981 [67]. Another, much shorter form of SBQ, containing only four items, and another 14-item tool [67-60]. Other versions of SBQ are available, but this multitude of variants precludes the finding of definite recommendations and psychometric properties for each population (adolescents vs. adults, clinical vs. nonclinical) [70,71]. SBQ 4-item version correlated with SSI scores significantly and it is recommended as a screening tool [71]. A revised version exists, SBQ-R, with four items, which benefits from empirical support as a risk measurement tool that differentiates between suicide-risk and non-suicidal risk individuals at a cut-off value of 7 (nonsuicidal sample) or 8 (clinical samples) [70]. SBQ-R has good internal consistency (Cronbach alpha = 0.97), convergent validity, a one-factor solution (89.5% of the total variance), good sensitivity (82%), and specificity (63%) when differentiating between

serious planner/ideator and attempter groups [70]. SBQ-R has been translated and validated in numerous languages due to its brevity, ease of administration, and good psychometric properties [72,73].

The first item ("Have you ever thought about or attempted to kill yourself?") of the SBQ-R and the total scores have been recommended for use in both clinical and non-clinical populations [70]. A Bayesian approach to the SBQ-R supports the usefulness of item 1 for identifying other parameters of suicide, e.g., thoughts and behaviors [74]. The same analysis showed the relevance of each SBQ-R item when exploring the suicide elements and suggests that the individual item evaluation can offer clinically meaningful insights [74].

SBQ-R and the Risk-Taking Questionnaire 18 (RT-18) helped differentiate between individuals with suicide attempts and healthy controls by the variable "risk-taking" [75]. Individuals who reported a recent suicide attempt also had a higher tendency to sensation-seeking and impulsive behavior as correlates to risk-taking behaviors [75]. SBQ-R and other instruments were administered in a study (N=1310 medical graduate students) that suggested a significant risk of suicide (6.7%) among specific populations of students in China [76]. Poor relationships with the supervisor increased the risk of suicidality, suggesting more care is needed when educators are interacting with medical students, especially if the last ones are coming from families with low socio-economic status [76]. The administration of the original SBQ version in clinical populations was also explored in a study with patients diagnosed with bipolar disorder (N=98 participants); the association between anxiety dimensions and SBQ scores was relevant in a similar way to the association with depressive rumination [77]. Depressive rumination was a significant predictor of higher SBQ scores, and emotional processing was a significant predictor for lower SBQ scores for women and the entire sample [77].

In an exploration of the temperament dimensions most associated with the progression from ideation to suicide attempts, an adapted version of SBQ with 17 items was used together with the Affective and Emotional Composite Temperament Scale (AFECTS) [78]. The depressive, cyclothymic, and volatile were the most frequently associated temperaments with suicide attempters, while the cyclothymic, depressive, and euphoric temperaments were associated more with progression from ideation to suicide attempt [78].

The use of SBQ-R in a study that included post-9/11 veterans and service members seeking treatment for psychiatric symptoms (N=261 participants) reflected the high rates of suicidal ideation and behavior in this population [79]. A rate of 40% was obtained in this sample, based on the SBQ-R, indicating a high risk of suicide [79]. Negative posttraumatic thoughts about self, gender, military branch of service, higher levels of severity, anger and anger expression, less impulse control, and lower rank, all these factors were associated with a higher risk of suicidal ideation and behavior [79].

Another retrospective analysis included 3356 cases (age 55+) collected from the US National Health and Resilience in Veterans Study (2019-2020) and used SBQ-R in correlation with various demographical and personal history data [80]. The rate of suicidal ideation during the last year was 6.6%, for lifetime suicide plans was 4.1%, and for future suicide intent 0.9% [80]. A higher level of loneliness and a lower level of purpose in life was most strongly associated with last year's suicide ideation, while a lifetime history of major depressive disorder correlated with suicide plans and suicide attempts [80].

In another cohort study (N=3078 US military veterans), the rates of suicide ideation and suicide attempts did not present higher values during the COVID-19 pandemic vs. pre-pandemic level, but a small percentage of veterans (2.6%) developed new-onset suicidal ideation during the pandemic [81]. SBQ-R items 1 and 2 were used in this study, together with the UCLA Loneliness Scale, Alcohol Use Disorders Identification Test, Life Events Checklist for DSM-5, Adverse Childhood Experience Questionnaire, Medical Outcome Study Social Support Scale-5, and the Coronavirus Health and Impact Survey [81].

The **Military Suicide Attitudes Questionnaire** (MSAQ) is a 32-item instrument with a four-factor structure designed to be used by military service members [82]. The confirmatory analysis included 317 US military personnel, and good levels of test-retest reliability were found; the four factors identified were "individual-based rejection vs. acceptance", "psychache vs. pathological", "unit-based acceptance vs. rejection", and "moral vs. immoral" [82]. The validation study did not control for social desirability, which may be an important limitation [82].

Two different studies of MSAQ validation included 200 and 1116 individuals, respectively, from the military environments, and factorial analyses support the previously reported four-factor structure [3]. The reliabilities ranged from 0.77 to 0.83; men had more negative suicide-related beliefs vs. women, and discomfort and unacceptability beliefs were more positively associated with perceived barriers to care [3].

The **Suicide Probability Scale** was developed in 1982, it contains 36 items and is a self-report tool [83]. This scale was designed to assess suicide risk in adolescents and adults, and it only takes 5 to 10 minutes to complete [83]. The score is obtained by adding the answers using a 4-point scale; there are four factors: Hopelessness, Suicide Ideation, Negative Self-evaluation, and Hostility [83]. The Cronbach alpha for this scale was 0.92 in a sample of hospitalized patients with psychiatric disorders, and the results correlated with the scores on the Beck Depression Inventory-II and Adult Suicidal Ideation Questionnaire [83,84]. The utility of this scale did not confirm its utility in adolescents to assess suicide potential, and the factorial structure was not confirmed [85]. However, other studies support its utility for this population, with good convergent and discriminant validity [86].

The **Sheehan Suicidality Tracking Scale** (SSTS) has a standard version with 16 items that assess the seriousness of suicidality, the frequency of key phenomena, and the overall time spent in suicidality on a Likert scale (0-4) [87]. It is available in a patient and clinician-rated format, but a version that reconciles the eventual discrepancies between the previous two in specific items also exists [87]. There is a clinically meaningful change version of the SSTS and a pediatric version (P-SSTS) [87,88]. Another version of SSTS (v.10)

has an 8-item instrument that measures variables related to self-injury, self-harm, suicide ideation and suicide attempt, with each item being scored on a Likert scale, from 0 (absent) to 4 (extremely) [89]. SSTS proved good convergent, divergent, internal consistency, and test-retest stability, according to a cross-sectional study (N=303 undergraduate students) [89]. All SSTS items were loaded on a single factor, suggesting it could be useful as a screening tool [89].

In a clinical study (N=82 subjects with generalized anxiety disorder) that assessed an experimental corticotropin-releasing factor antagonist vs. placebo and an active comparator (escitalopram), SSTS had a good sensitivity, as well as item 3 on the Hamilton Depression Rating Scale for Depression (HAMD) for identification suicidal thoughts or behaviors (100% and 63%, respectively) [90].

In another clinical trial, which investigated the evolution of depressive symptoms during citalopram + lithium vs. citalopram + placebo (N=80 patients), SSTS and Montgomery Asberg Depression Rating Scale (MADRS) were administered as primary measures, and the results showed a larger reduction on SSTS vs. MADRS (43% vs. 25%) [91]. A subgroup of patients who received lithium and citalopram had higher SSTS remission rates (45% vs. 19%) [91].

The **InterSePT scale for suicidal thinking** (ISST) has 12 items and assesses the current suicidal ideation in patients with chronic psychosis [92]. In two studies, with 22 inpatients with schizophrenia and schizoaffective disorders who had a recent suicide attempt or ideation, and 980 patients with the same disorders and a history of suicidal ideation in the past 36 months, respectively, ISST was used as a monitoring tool for two years, together with Clinical Global Impression for Severity of Suicide (CGI-SS), Calgary Depression Scale (CDS), Scale of Functioning (SOF) and Positive and Negative Symptom Scale (PANSS) [92]. The Cronbach alpha was high (0.86-0.89) for individual items, as well as the overall value (0.88) [92].

The ISST total score was highly correlated with the CGI-SS by the blind rater [92]. During the InterSePT trial that evaluated clozapine efficacy, ISST and CDS were administered to predict suicide attempts or hospitalizations [93,94]. The results of the InterSePT trial suggest both tools may be useful for assisting clinical decision-making regarding the suicide risk in patients with chronic psychoses [93].

The **Acquired Capability for Suicide Scale** (ACSS) is a 20-item tool administered based on the Interpersonal Psychology Theory of Suicide and assesses factors that facilitate individuals to acquire the ability to engage in suicidal acts, such as fearlessness about death and habituation to pain (which are considered needed to overcome the self-preservation reflexes) [95]. The items are scored on a Likert scale, from 0 to 4, and the reliability of the scale was calculated in a study to be alpha=0.80 [95]. In a study that included suicide ideators, depressed suicide attempters, and control participants (N=44 participants), based on the ACSS administration, suicide attempters showed the highest level of fearlessness and pain insensitivity and a greater history of painful and provocative life events [96].

A systematic review evaluated the use of ACSS among US military personnel and veteran samples (n=31 studies), and the results, based on a high risk of bias sources, indicated inconsistent findings across studies [97]. The authors of the respective analysis recommended caution in the interpretation of ACSS empirical data [97].

Regarding the instruments for the assessment of depression, which include items specific for suicidality, three tools were analyzed based on their wide use in clinical and epidemiological trials and their validated psychometric profile.

The **Beck Depression Inventory** (BDI) is among the most widely used self-rating scales for depression severity, with a long history of being administered in therapeutic and other various studies, starting from its publication in 1961 [98]. The internal reliability was confirmed in clinical and nonclinical samples and the average Cronbach alpha was 0.75; the factorial validity of this instrument showed a variable number of factors, from 1 to 9, and the convergent and discriminant validity was also proven [98]. Of interest for this review is the suicide item for its predictive value for deaths by suicide, which is scored from 0 (“I do not have any thoughts of killing myself”) to 3 (“I would kill myself if I had the chance”) [99].

A study that included 5319 patients showed that the single BDI item significantly predicted both deaths by suicide and repeated suicide attempts [100]. Each successive rating of the suicide item on BDI conferred greater risk, suggesting a direct proportionality between the two values, with an optimal cutoff score of ≥1 for suicide and ≥2 for suicide attempts providing the maximum equilibrium between sensitivity and specificity [100]. A value of ≥1 on item 9 on BDI-II was also used as a marker for suicide ideation in a study that concluded type D personality could be a risk factor for suicide ideation in individuals with major depression with (N=318) [101].

The **Hamilton Rating Scale for Depression** (HAMD) represents, in fact, a variety of scales that differ by the number of items and modalities of administration [102]. HAMD is a valid and sensitive clinimetric index and requires informed use, with the specific type of HAMD to be selected for each context [102]. The HAMD includes an item on the assessment of suicide risk (scored from 0 – “absent” to 4- “attempts at suicide”) [99]. It correlates significantly with the number of suicide attempts and the age at the first attempt in a study with 281 suicide attempters [103].

The **Montgomery Asberg Depression Rating Scale** (MADRS) is a 10-item tool dedicated to the measurement of depressive severity that includes an item dedicated to „suicidal thoughts” (scored from 0 – „enjoys life or takes it as it comes” to 6 – „explicit plans for suicide when there is an opportunity/active preparations for suicide”) [99]. This item of MADRS and the suicide item on HAMD correlated with the first five items on SSI at a significant level (r>0.80) in a study that assessed the efficacy of ketamine on the severity of depression [99].

DISCUSSION

Table 1 presents a synthesis of the instruments explored in this review. All of the reviewed instruments present benefits and shortcomings, making the unanimous recommendation of only one such instrument for evaluating suicide risk highly unlikely. However, based on the characteristics of each population or group that needs to be explored (screened or monitored) for suicide risk, a certain set of tools may be selected from the available resources, depending on their psychometric properties and previous studies' results available.

Table 1: Analysis of the psychometric tools for the assessment of suicide

Psychometric instrument	Studies on active military personnel and /or veterans	Studies on the civilian population	Advantages	Disadvantages	Observations
SASII	Yes [18,19]	Yes [14-17]	Standardized definition of suicidal and other self-injurious activities; individual ratings for the components of lethality, such as the method used, the consequences of the gesture, and the therapy needed.	More studies on military personnel are needed to confirm its psychometric properties in this population and its predictive power. The necessary time to administer is quite long.	Reliability and convergent validity were determined. Studies that compared this instrument with other validated instruments were performed. Evaluates both suicidal and non-suicidal self-injury behaviors.
C-SSRS	Yes [23,25-27]	Yes [21-23]	Separate assessments of the severity and intensity of suicidal ideation, autolytic behavior, and lethality of the attempt.	Data about the self-reported version of C-SSRS in military personnel is insufficient to recommend its use in this population.	Very good convergent and divergent validity with other scales used for the same purposes.
SSI, B-SSI, SSI-C, SSI-W	Yes [34,35]	Yes [28-20,33]	The set of SSI scales offers a more nuanced choice for different settings and populations.	The dimensional structure is debated.	Good internal consistency and sensitivity to changes for several important suicide factors.
BHS	Yes [42,43]	Yes [38]	Evaluation of suicide risk in clinical and non-clinical adult populations. Self-administered or clinician-administered.		Demonstrated predictive validity and reliability. Shorter versions of this tool have been created.
SPS, M-SPS	Yes [46]	Yes [47-49]	Ease of administration; the existence of a shorter version.	The predictive value of suicidal behavior was considered inconsistent.	A further refinement of the items included in this scale may be needed to increase its predictive value.
RFLI, RFL-MV	Yes [53,54]	Yes [51,52]	A self-administered version and a clinician-administered version exist. A military version of this scale also has been published.	The RFLI scales (both long and short versions) are quite long due to the large number of items.	A checklist of motives for living that can represent useful resources to work with in psychotherapy. Acceptable internal consistency and test-retest reliability.
RFD-RFL Index	Yes [56]	Yes [55,57]	It combines two distinct lists of reasons for living and reasons for dying.	It is a complex and long instrument to administer (17 domains).	Reasons for living are not a valid protective factor against suicide risk. However, reasons for dying may be useful as a predictor of suicide risk.
SOQ	Yes [62]	Yes [58,61]	It was constructed to be sensitive to cultural and demographic variability.	Different studies did not support the factorial structure.	Test-retest reliability was demonstrated. It was administered in different groups. It has the potential to help identify the risk of suicide.
STS	None were identified	Yes [63,64]	It has several versions, some of them presenting scores with good predictive values.	More studies are needed to support its utility, especially in military personnel.	Good internal consistency and validity related to past suicidal behavior. A subset of items could be further explored for higher predictive value than the overall scale.

MSHR	None were identified	Yes [65]	Based on multiple variables related to self-harm	Psychometric properties are poor.	Good sensitivity but poor specificity and low predictive value.
ReACT SHR	None were identified	Yes [66]	Based on a large populational study, and includes multiple variables related to suicide.	More research is needed to validate this instrument.	Good sensitivity but poor specificity and low predictive value.
SBQ, SBQ-R	Yes [79-81]	Yes [70,72,73,75-78]	Many versions of this instrument exist. It was explored in multiple studies that enrolled veterans.	Psychometric properties are poorly defined, except for SBQ-R.	It was extensively explored in both military and civilian populations.
MSAQ	Yes [3,82]	Not applicable	It was explored in two studies with US military personnel.	The currently available studies have methodological limitations.	More studies are needed to explore the validity of this instrument.
SUPS	None were identified	Yes [83-86]	It is a short instrument, easy to administer.	It is a self-report tool. The factorial structure is debated.	Good validity and reliability. The utility of this tool in adolescents to predict suicide was not confirmed.
SSTS	None were identified	Yes [89-91]	Patient and clinician-rated format, and a version that reconciles the differences between the two also exists. A shorter version exists.	No study was identified with military populations.	Good convergent, divergent, internal consistency, and test-retest stability. Only one factor was identified: good screening tools.
ISST	None were identified	Yes [92]	A valuable instrument for assessing suicidal ideation in patients with schizophrenia spectrum disorders.	It applies to a limited population, i.e., a clinical population with chronic psychoses.	High construct validity, good correlation with other scales.
ACSS	Yes [97]	Yes [95,96]	Short, easy-to-administer tool.	Caution is recommended in the interpretation of this scale's results in the military population.	Good validity and reliability.
Scales with single items evaluated for suicide predictive power					
BDI - item 9	None were identified	Yes [99-101]	The suicide item predicted deaths by suicide and suicide attempts.	Insufficient data to support scores on single items as independent predictors of suicide.	Good internal reliability in clinical and nonclinical samples for depressive disorders.
HAMD – item 3		Yes [103]	The suicide item correlated with the number of suicide attempts.		Valid and sensitive tool for depression.
MADRS – item 10		Yes [99]	Short and easy-to-administer tool. The suicide item correlated with items on SSI.		A useful tool for the quantification of depressive symptoms across age intervals.

SASII= Suicide Attempt Self-Injury Interview, C-SSRS= Columbia Suicide Severity Rating Scale, SSI= Scale for Suicide Ideation, B-SSI= Beck Suicidal Ideation Scale, BHS= Beck Hopelessness Scale, SPS= SAD PERSONS, M-SPS= Modified SAD PERSONS, RFLI= Reasons for Living Inventory, RFL-RFD= Reasons for Living versus Reasons for Dying Assessment, RFL-MV= Reasons for Living- Military Version, SOQ= Suicide Opinion Questionnaire, STS= Suicide Trigger Scale, MSHR= Manchester Self-Harm Rule, ReACT SHR= ReACT Self-Harm Rule, SBQ= Suicidal Behaviors Questionnaire, MSAQ= Military Suicide Attitudes Questionnaire, SSTS= Suicide Probability Scale Sheehan Suicidality Tracking Scale, ISST= InterSePT scale for suicidal thinking, ACSS= Acquired Capability for Suicide Scale, BDI= Beck Depression Inventory, HAMD= Hamilton Rating Scale for Depression, MADRS= Montgomery Asberg Depression Rating Scale

A prospective comparative analysis of multiple scales for the assessment of suicide risk included MSHR, ReACT Self-Harm Rule, SAD PERSONS, M-SPS, and Barratt Impulsivity Scale (BIS) in patients who would repeat self-harm within six months [104]. By evaluating 483 episodes of self-harm, the recurrence rate was 30%, and the sensitivity of these tools varied from 1% for SAD PERSONS, to 97% for MSHR [104]. The positive predictive value also varied, from 13% for M-SPS to 47% for the clinician assessment of risk [104]. The authors of the respective study concluded that risk scales for self-harm have limited clinical utility, as they are no better than clinician or patient ratings of risk [76]. A secondary analysis of data collected from multicenter prospective cohort studies showed that some individual items outperformed the scale in which they are included, but no items were superior to clinician or patient risk estimations

[105]. Based on the data from the same analysis, the use of suicide risk scales was less cost-effective than the clinician and patient ratings based on QALY (Quality-Adjusted Life Years) exploration [106].

A systematic review that evaluated the level of evidence for instruments assessing the suicide risk (n=21 studies) included 15 such tools and for the outcome suicide attempt, SPS had a sensitivity of 15% with a specificity of 97%, MSHR 97% and 20%, respectively, ReACT a similarly low specificity with MSHR; BHS presented a sensitivity of 89% and a specificity of 42% for the outcome suicide [107].

A direct comparison of the psychometric properties of CSSRS, STS, and SSTS in 199 psychiatric inpatients was conducted in a randomized manner by three trained judges [108]. All three assessments had very good accuracy for suicidal ideation and attempts (k=0.72 to 1.00, and 0.82 to 0.95, respectively), with an interrater agreement about CSSRS categories being more varied (k=0.48 to 1.00) [108]. Cronbach alpha value was less than 0.55 for CSSRS ideation and 0.78-0.92 for STS and SSTS [108]. The administration of any of these three instruments would improve reliability vs. unstructured assessment in the evaluation of suicidal ideation and behavior [108].

A study included 40 subjects with suicidal ideation and behavior who were interviewed using the InterSePT Scale for Suicidal Thinking-Plus, the SSTS, and the CSSRS, administered in a random sequence [109]. An agreement between these scales and the 2012 Food and Drug Administration (FDA) Classification Algorithm of Suicide Agreement categories was sought [109]. SSTS and InterSePT scale had an acceptable agreement with CSRSS in the detection of passive ideation, active ideation with method, intent, and plan, completed suicide, preparatory actions, and self-injurious behaviors [109]. However, these tools did not detect the presence or absence of other active suicidal ideation combination categories and aborted and interrupted attempts [109]. These results show the importance of validity exploration regarding the widely used scales for suicide risk assessment and the concordance with the FDA categories [109].

The use of single items from validated scales for depression as indicators for the assessment of suicidal ideation is a debated approach in clinical practice. A comparison of BDI and HAMD suicidal items and SSI scores was conducted in 281 suicide attempters and a positive correlation between the first two and the specific scale for suicide scores (SSI) [103].

The importance of searching for chronic diseases as predictors for suicide that can interfere with mental health due to negative impact on multiple levels (i.e., low functionality, poor quality of life, pain, low self-esteem) can not be overemphasized [110-113]. Therefore, any predictive model for suicide should take into account not only personality features, psychiatric symptoms, and actual psychological stressors but also organic diseases and their essential effects on mental health. This involves the necessity of a complex evaluation of individuals with a risk of suicide by a team of specialists, not only psychiatrists and clinical psychologists.

Treatment of the pathological background in patients with suicide risk can not be overemphasized [114-117]. Although significant advances in the field of psychopharmacology can be observed, as well as multiple psychotherapies focused on reducing the risk of self-harm, it is essential to note that no single intervention can be appropriate for all cases with self-harm tendencies, due to the unique configuration of vulnerability factors and triggers that exist in each case.

The current review's limitations are related to its narrative design, which explains why important sources may be missed from the analysis and the lack of assessing the quality of each report. The review's strengths are its focus on clinical tools used for military and civilian populations and the inclusion of psychometric properties together with relevant clinical and epidemiological studies for each instrument.

Directions for further research in this field are the need to further investigate the psychometric properties of some scales presented in this review, like MSAQ, which is dedicated to military personnel, and the comparative exploration of such instruments focused on clinical and non-clinical samples, to highlight the strengths and vulnerabilities of each. The final purpose of further research could be the construction of an algorithm able to detect individuals vulnerable to self-harm behavior.

CONCLUSION

Many good-quality, validated instruments allow for assessing the risk of suicide in civilian populations, and some of them have been explored in military personnel, like SBQ, C-SSRS, SASII, SOQ, etc., while others have been constructed especially for military populations, like MSAQ. Unfortunately, each of these tools has shortcomings that are expected to be corrected by further research.

Therefore, any algorithm for the detection of suicide risk based exclusively on the existing scales, interviews, and questionnaires would be vulnerable to a more rigorous analysis since the complex pathogenesis of the suicide phenomenon would impair its predictability.

Conflicts of interest and sources of funding

The author declares no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

As the only author, I assume the responsibility for data collection, writing, and revision of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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REVIEW

Oxidative Stress and Nutritional Antioxidants in Neurological Diseases

Iulia I. Enache[1,2], Dorin Dragos[1,3], Cosmina I. Stoican[2], Raluca Naum[2], Suzana M. Guberna[1,4], Maria M. Manea[1,2]

[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; iulia-ioana.enache@drd.umfcd.ro, maria.manea@umfcd.ro
[2] Department of Neurology, National Institute of Neurology and Neurovascular Diseases, Bucharest, Romania; iulia-ioana.enache@drd.umfcd.ro, iulia-cosmina.stoican@rez.umfcd.ro, raluca.naum0325@rez.umfcd.ro, maria.manea@umfcd.ro
[3] 1st Internal Medicine Department, Emergency University Hospital, Bucharest, Romania; dorin.dragos@umfcd.ro
[4] Cardiology Department, Emergency Clinical Hospital Prof. Dr. Bagdasar-Arseni, Bucharest, Romania; suzana.guberna@umfcd.ro

Correspondence: Dorin Dragos, dorin.dragos@umfcd.ro

Abstract: A significant number of neurological diseases are pathogenetically related to oxidative stress, including but not limited to cerebrovascular afflictions such as ischemic and hemorrhagic stroke, Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and so on. Natural nutrients may help limit the impact of oxidative stress and, therefore, delay or prevent the impairment of these diseases. Although these natural components have not entered routine use, many have been studied in preclinical or even clinical settings with promising results. Therefore, the need to find the stage of the research in the field of validating the properties and clinical usefulness of such nutrients represents the main reason this narrative review was conducted. This analysis explored the PubMed database for papers related to the influence of natural nutrients on the onset and evolution of some of the most severe neurological disorders. The results of the review provide an overview of the pathways oxidative stress may undertake and how the use of nutrients may counteract these pathways. In conclusion, natural nutrients may have beneficial effects that can be impactful on clinical outcomes, but more good quality research in this field is needed before formulating any clear recommendation.

Keywords: oxidative stress, neurodegeneration, antioxidants, nutrients

INTRODUCTION

This narrative review aims to provide readers with a brief, yet pinpointed overview as to the therapeutic potential of nutritional antioxidants. Given that oxidative stress has a key involvement in the pathogenesis of many neurological diseases (neurodegenerative, cerebrovascular, or inflammatory), targeting oxidative stress through such components (known to medicine for hundreds, if not thousands of years) may prove efficient. Moreover, this paper should be viewed as an incentive to inspire future research, preclinical and particularly clinical, in this field, so that the usage of such components may one day become a validated treatment with a probable wide spectrum. A step-by-step approach to nutrient intervention in neurological diseases is provided in Figure 1.

MATERIALS AND METHODS

Comprehensive research has been conducted by consulting the PubMed database for relevant reports published between the inception of the archive and January 2025.

The following keywords have been used by themselves or in various combinations to achieve optimal results: "Parkinson's disease", "amyotrophic lateral sclerosis", "Alzheimer's disease", "multiple sclerosis", "small vessel disease", "ischemic stroke", "hemorrhagic stroke", "inflammation", "oxidative stress", "reactive oxygen species", "mitochondrial dysfunction", "apoptosis", "necrosis", "excitotoxicity", "lipid peroxidation", "vitamin C", "vitamin E", "coenzyme Q10", "black tea", "green tea", "taurodeoxycholic acid", "flavonoids", "curcumin", "polyphenol", "antioxidant", "Ginkgo biloba", "mecasin", "citicoline", "Artemisia", "Silybum", "curcumin", "melatonin", "saffron", "vitamin D3", "Gastrodia elata", "lavender oil".

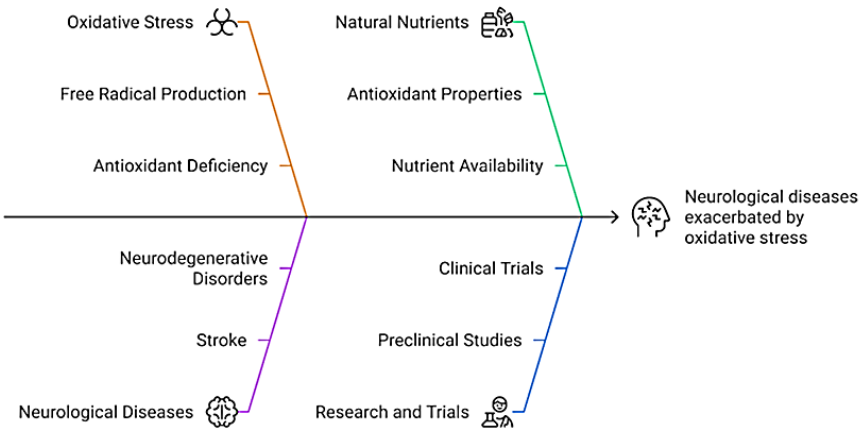
Case reports, preprints, and standalone abstracts have been excluded. Only papers published in English were included in the selection.

Citation: Enache II, Dragos D, Stoican CI, Naum R, Guberna SM, Manea MM. *Oxidative Stress and Nutritional Antioxidants in Neurological Diseases*. R. J. Mil. Med. 2025, 128(3): 215-224; https://doi.org/10.55453/rjmm.2025.128.3.5

Academic Editor: Octavian Vasiliu

Received: 18 December 2024
Revised: 28 February 2025
Accepted: 22 March 2025

Figure 1: Addressing neurological diseases through nutrient intervention



Oxidative stress is a central component in the pathophysiology of a plethora of neurological diseases. Nutrients may be an appealing method to target oxidative stress and, therefore, mitigate or perhaps even prevent these afflictions. However, the impact of nutrients has to be appropriately measured through validated, reproducible clinical trials before they can broadly enter therapeutic practice.
This figure has been generated using Napkin AI.

RESULTS AND DISCUSSIONS

Parkinson's Disease

Parkinson's disease (PD) is a chronic neurodegenerative disease with a characteristic loss of the dopaminergic neurons in the pars compacta of the substantia nigra [1]. Literature has shown that environmental factors (herbicides, pesticides (such as paraquat), industrial pollutants, neurotoxins (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine or MPTP) and its metabolite (1-methyl-4-phenylpyridinium), as well as genetic factors (mutations of DJ-1, Parkin, PINK1) [2] involved in PD pathogenesis induce oxidative stress (OxSt) in the mitochondria [3], reduce the production of adenosine triphosphate (ATP), facilitate the generation of reactive oxygen species (ROS), and finally lead to the apoptosis of dopaminergic cells [2].

Pathogenesis

1 Oxidative stress and mitochondrial dysfunction

OxSt contributes to the degeneration of dopaminergic cells in PD [4]. Also, OxSt is tightly linked to other pathogenic mechanisms involved in PD (mitochondrial dysfunction, excitotoxicity, and inflammation); therefore, it is difficult to ascertain whether it is a primary factor in PD or a consequence of the aforementioned mechanisms [3].

In PD, lipid peroxidation is upregulated, and antioxidant pathways (superoxide dismutase – SOD, catalase, glutathione peroxidase – GPx, ceruloplasmin, vitamin E, vitamin C, copper, zinc, selenium) may be insufficient to protect the cells from pathological oxidation [4]. Increased OxSt in association with diminished antioxidant protectors leads to the loss of neurons in the pars compacta, hence the development of PD [4]. Studies have proven lower levels of vitamin C and E in PD patients versus control groups, launching the hypothesis of increased consumption of these vitamins in PD due to OxSt [4].

Excessive ROS production, mitochondrial transport changes, and increased iron deposition in the pars compacta of the substantia nigra are key pathways in PD pathogenesis [1]. There is a close link between ROS formation and mitochondrial dysfunction [1]. Cellular death in PD is thought to be connected to excessive lipid peroxidation, occurring as a consequence of increased oxidation and expenditure of compensatory mechanisms [1]. ROS have a direct cytotoxic impact, as well as an indirect one by impacting mitochondrial complex I, with higher lipid peroxidation [1]. The reduction of this complex leads to the production of more ROS [1].

2 Neuroinflammation

In PD, α-synuclein deposition induces an activation of the microglia in the pars compacta, thus activating nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) [1]. The latter's consequences are, on the one hand, ROS production in the extracellular compartment afflicting nearby neurons, and on the other hand, redox signaling in the microglia, amplifying the pro-inflammatory response with the induction of chronic inflammation [6].

The presence of excessive OxSt in PD is supported by studies that have proven an increase in carbonyl derivatives [7], in indicators of lipid peroxidation [8], and 8-hydroxy-2'-deoxyguanosine (a marker of nucleic acid damage) [9].

Nutrients

Given the involvement of OxSt in the occurrence of PD and the fact that PD treatment (especially L-dopa) may determine, after a long period of usage, the appearance of free radicals, the administration of multiple antioxidant agents in high dosage along with L-dopa may increase the latter's efficiency [10,11].

In experimental studies, vitamin E was proven to protect cells from OxSt-related damage in PD and the chronic administration of high doses of vitamin E may be a therapeutic strategy in PD treatment or prevention [3,12]. In other experimental studies, vitamin E diminished the OxSt induced by midbrain iron deposits in PD patients, suggesting it may have neuroprotective effects in these patients [13].

Other observational studies on human subjects suggested that a combined administration of high doses of vitamins E and C may determine a slowed PD progression through their antioxidant effect (14), although their efficacy was not proven in double-blind randomized clinical trials (RCTs) [15].

Taurodeoxycholic acid is an antioxidant agent, decreasing ROS reduction, an effect that has been proven when in vivo PD lab models were used [16].

Coenzyme Q10 has an important antioxidant role in the mitochondria and the lipid membrane, some of its antioxidant effects being mediated by its interaction with α-tocopherol. A phase 2 clinical trial on the efficiency of the antioxidant effect of the coenzyme on early PD patients (i.e., patients who did not require specific therapy) versus placebo showed a decrease in the treated patients' disability [17].

Black and green tea, due to high polyphenol concentration, exert an antioxidant effect and may have a neuroprotective and neuroregenerative effect in this disease, although clear evidence to support this assertion, derived from clinical research, is scarce [18].

Flavonoids enhance the endogenous activation of antioxidant enzymes, inhibit the peroxidation of lipids, and reduce the production of inflammatory mediators [19]. Due to all these actions, flavonoids exert a favorable effect on dopaminergic neurons and mitigate PD manifestations in laboratory studies [19].

An association between PD and a lack of adherence to the Mediterranean diet suggests a potential neuroprotective effect of this diet, through an undetermined mechanism that may attenuate the OxSt and inflammation, which are both recognized pathogenetic factors in PD [20].

Alzheimer's disease and small vessel disease

Alzheimer's disease (AD) is a neurodegenerative affliction characterized by the dysfunction of memory, attention, and other cognitive processes; it is the most common form of dementia [21]. Small vessel disease (SVD) may affect microvasculature systemically or mainly in the brain, the latter constituting a devastating cause of stroke and dementia worldwide [22,23].

Pathogenesis

AD mainly determines a synapse affliction, with the development of senile plaques mainly containing β-amyloid (Aβ). Aβ derives from the proteolysis of the amyloid precursor protein performed mainly by the enzymatic actions of β- and γ-secretase, with an imbalance between production and clearance causing the Aβ buildup [21]. The lesions produced by OxSt in AD are associated with an accumulation of Aβ [11]. Aβ buildup is also a central feature of the cerebral amyloid angiopathy form of SVD, to which AD is intimately connected; some might argue that the two constitute an inseparable spectrum [22]. The other form of SVD, deep perforator arteriolosclerosis, centrally features a blood-brain barrier (BBB) dysfunction, subsequent morphological and functional changes to the vascular wall, as well as myelin impairment [22,23].

Aβ determines the release of ROS by attacking mitochondrial enzymes (particularly cytochrome c oxidase), leading to mitochondrial dysfunction, increasing superoxide radicals, conversion to hydrogen peroxide (H_2O_2), the release of cytochrome, affecting the production of ATP and cellular apoptosis [21].

OxSt increases with aging and it is an important causal factor in the appearance of AD and other neurodegenerative age-related diseases, such as SVD. Moreover, OxSt is thought to bridge the connection between SVD and AD [24]. It is not yet fully understood how neurochemical factors influence the appearance of age-related cerebral lesions, but more and more data has shown the involvement of biometals (Cu, Fe, Zn) in Aβ accumulation. Copper is a potent mediator for the hydroxyl radical, and the high-affinity link between copper and Aβ (via histidine and tyrosine), as well as between zinc and the amyloid precursor protein and Aβ may contribute to the increased OxSt in AD [11].

Apolipoprotein E is a lipid transport molecule believed to be related to ROS and directly to lipid peroxidation in AD [25]. Carriers of apolipoprotein E4 more often have cerebral amyloid angiopathy [24].

To conclude, the involvement of OxSt in AD pathogenesis is supported by the high concentrations of Cu, Fe, Al, and Hg in the brain parenchyma, a high level of lipid peroxidation and DNA oxidation, as well as a decrease in polyunsaturated fatty acids, in cytochrome c oxidase activity, and energy metabolism [11]. OxSt could become a promising link between AD and SVD; therefore, research focusing on OxSt may decrease the neurological manifestations of both illnesses [24].

Nutrients

In preclinical research, caffeine has been associated with a tendency to lower the Aβ levels in early (familial) AD, because of its antioxidant properties [26]. Studies on cerebral amyloid angiopathy models are lacking.

Curcumin is an antioxidant and anti-inflammatory agent (inhibiting cyclooxygenase and lipoxygenase) that has been shown to reduce carbonyl derivatives, facilitating Aβ disaggregation, with possible beneficial effects in AD in animal studies [26]. Curcumin may also aid endothelial function, which is frequently impaired in SVD, as it has been shown to diminish the risk of stroke in animal models [27].

Vitamin E is a potent antioxidant that prevents oxidizing lesions induced by Aβ in cell cultures; it also delays memory impairment in animal studies on AD [28]. Some RCTs suggested vitamin E, through its antioxidant effects, may delay functional disability in patients with mild to moderate AD [29]. Vitamin E tocotrienols have demonstrated a positive impact on white matter lesions (associated with SVD) in an RCT [30].

Polyphenols (such as anthocyanins from berries, catechins and flavonoids from tea, curcumin from turmeric, and resveratrol from grapes) have an antioxidant effect with possibly associated neuroprotection, observed in preclinical models of AD [26]. Dizziness improved in SVD patients taking polyphenols [31].

The association between AD and a lack of adherence to the Mediterranean diet indicates that the latter may have a neuroprotective effect through an as-of-yet incompletely understood mechanism, potentially including an influence on OxSt and inflammation, both involved in AD pathogenesis [32]. Compliance with a Mediterranean diet lowered the burden of white matter lesions in SVD patients [33].

Due to their antioxidant properties, alkaloids such as groenlandicine, berberine, and palmatine from Coptis chinensis rhizomes may find their use in AD treatment [26]. Berberine promotes endothelial health and has been proven to support proper arterial elasticity in human subjects [34].

Milk thistle (Silybum marianum) diminishes OxSt and memory decline in laboratory studies of AD [35]. Milk thistle extracts also favored proper endothelial function in mice [36].

Ginkgo biloba, through its capacity to purge ROS, may reduce Aβ aggregation in AD, which is suggested by certain in vitro studies [26], but on the other hand, this theory has been contested in the literature [37]. Currently, there is little proof to support the routine use of Ginkgo biloba in AD patients [26]. Ginkgo extract had a beneficial yet limited effect on cognitively impaired mice models of SVD [38].

Melatonin overcomes apoptosis, prevents Aβ from interfering with mitochondrial DNA, diminishes lipid peroxidation, and, in high concentrations, protects from the OxSt induced by Aβ [39]. However, more studies are needed to prove its efficiency in delaying progression in early AD stages or in AD prevention [39]. Melatonin was shown to be a potential BBB integrity protector in cell cultures [40].

Coenzyme Q10 is an antioxidant factor that maintains mitochondrial membrane potential during OxSt, while also protecting neural cells from excessive Aβ deposition in laboratory studies of AD [26]. It also eliminates peroxyl radicals and may prove efficacious in AD [17].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease defined by a loss of central and peripheral motor neurons [41].

Pathogenesis

The pathophysiology of ALS onset is quite complex, probably heterogeneous, and not fully understood [42]. OxSt is a common link between various pathogenetic mechanisms of ALS, contributing to: (a) mitochondrial dysfunction: high ROS levels may augment mutations in mitochondrial DNA, and mutations of the Cu-Zn-SOD1 mitochondrial gene are synchronous with increased OxSt;(b) protein aggregation: OxSt is a contributor to the mechanisms of abnormal aggregation of SOD1; (c) axonal transport: certain fragments of axonal neurofilaments are targeted by OxSt [43].

Environmental or modifiable risk factors may be the source of OxSt, incriminated in ALS pathogenesis: (a) smoking induces lipid peroxidation, DNA damage, and cellular death, smokers having a higher risk of ALS (sporadic form); (b) chemicals used in agriculture (pesticides, organophosphates) are linked to ALS and induce mitochondrial dysfunction and ROS production [44].

It is not clear whether OxSt is the main cause of ALS or if it is a consequence of all the other pathogenetic mechanisms involved, but the existence of SOD1 gene mutation among familial cases suggests OxSt is central to the pathophysiology of genetic forms of ALS, at the very least [43].

OxSt could also interfere with ALS pathophysiology by deteriorating the mitochondria that support presynaptic transportation and, hence, affecting presynaptic mechanisms involved in neurotransmission [45]. ROS and reactive nitrogen species (RNS) alter RNA processing, generating mitochondrial dysfunction that eventually leads to neuronal death [46].

In ALS, indicators of OxSt are increased, such as carbonyl derivatives (in sporadic forms), 3-nitrotyrosine (a marker of oxidative lesions, with a higher expression in sporadic forms as well as familial forms associated with SOD1 mutation), 8-hydroxy-2'-deoxyguanosine (a sign of damaged DNA), 4-hydroxynonenal (showing lipid peroxidation) [43].

Nutrients

Laboratory studies have proven that mecasin (also known as KCHO-1, a herbal extract) diminishes OxSt via the gp91phox and MAPK pathways in ALS patients. Mecasin improved motor function and delayed ALS onset in study models [47].

EGb761, a standardized Gingko biloba extract with antioxidant and neuroprotective effects, could prove useful in treating ALS patients [48].

To prevent OxSt from interfering in ALS pathogenesis, various antioxidant agents have been tested, such as vitamin E and vitamin B complex; however, there were no significant proven benefits [43].

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system [49,50], defined by perivenous lymphocytic infiltration and macrophage presence in the cerebral parenchyma [51].

Pathogenesis

MS neuropathology is characterized by focal demyelinating lesions and axonal lesions. Neurodegeneration is induced by inflammation and mitochondrial dysfunction, with ROS production as a common element. ROS promotes transendothelial migration of leukocytes, contributing to axon and oligodendrocyte degeneration [52].

ROS occurs mainly by the activation of macrophages, microglia, and astrocytes and are produced through NADPH-oxidase, myeloperoxidase, and inducible NO-synthase. ROS leads to neuron, axon, myelin, and oligodendrocyte destruction and may contribute to mitochondrial dysfunction, which in turn exacerbates ROS production, augmenting MS lesion appearance [52].

Through lipid, protein, and DNA oxidation, OxSt leads to cellular dysfunction and, finally, to necrosis or apoptosis [53]. In the early stages of MS, OxSt is associated with microglial activation and the inflammatory process, whereas in advanced stages, it is linked to mitochondrial dysfunction, pathological iron accumulation in cerebral structures and its release in demyelinating lesions [54]. Myelin and oligodendrocytes are the most damaged by OxSt in this disease, a phenomenon that has been supported by the cytoplasmic accumulation of oxidated lipids and nuclear DNA alterations [54].

Nutrients

Melatonin presents neuroprotective effects and may decrease the OxSt in individuals with secondary progressive MS [55] by ROS neutralization and induction of antioxidant enzymes [49].

Coenzyme Q10 potentially diminishes OxSt and stimulates the activity of antioxidant enzymes in relapsing-remitting MS [56].

Saffron extract attenuated OxSt in experimental studies on MS [57].

Vitamin D3 has antioxidant properties and has been shown to halt lipid peroxidation in MS literature [58].

Ischemic stroke and intracerebral hemorrhage

Ischemic stroke (IS) is the most widespread type of cerebrovascular affliction and a relevant cause of death and disability worldwide. Intracerebral hemorrhage (ICH) is about 30% of all non-traumatic strokes worldwide, with a higher disability rate compared to IS [59]. The major cause of ICH is small vessel disease, a complex microvascular affliction of the brain [23].

Pathogenesis

Normally, the BBB protects against neurotoxins. After ischemia occurs, various mediators of inflammation, as well as other potentially neurotoxic molecules, cross the altered BBB to the brain parenchyma, contributing to neuronal lesions [60]. A breakdown of the BBB also occurs in ICH, as well as an enhanced proinflammatory response with a release of ROS [61,62].

OxSt is an important factor involved in the pathophysiology of IS [63]. Immediately after a cerebral injury is produced in IS as a result of vascular obstruction, the rapid increase of ROS determines the extension of the ischemic area [64]. OxSt also occurs in ICH and may surprisingly have a disseminated impact, such as the induction of glomerular dysfunction [65].

The brain is particularly sensitive to oxidative lesions. The main sources of ROS in the brain are the mitochondrial respiratory chain, NADPH-oxidase (especially isoforms 2,3,4 that are notably expressed in the central nervous system) and xanthine oxidase (XO). Superoxide (O_2^-), physiologically produced by the mitochondria, is converted via SOD to H_2O_2 and acts as a cellular messenger, with a role in neuronal signaling in the central and peripheral nervous system. Oxygen depletion in ischemic neurons favors anaerobic glycolysis, with higher lactate levels and acidosis. The latter contributes to OxSt, providing H^+ and hence facilitating O_2^- conversion to H_2O_2 [60].

After cerebrovascular flow is reestablished, the mitochondrial respiratory chain is reestablished with the generation of a new peak of ROS [63], contributing to cerebral reperfusion lesions [60]. O_2^- is involved in reperfusion lesions and NADPH-oxidase contributes to its production [60]. Mitochondrial malfunction has also been detected in ICH around the hematoma [66].

During cerebral ischemia, ATP is broken down to hypoxanthine, which accumulates in the ischemic cerebral parenchyma, and during

the reperfusion phase, XO facilitates hypoxanthine oxidation to xanthine and subsequently to uric acid, a process during which O2− and H2O2 are generated [60].

An increase in excitotoxic amino acids such as glutamate in cerebral lesions as well as in the perihematoma region in ICH also favors the production of ROS [63,67].

Excessive ROS leads to lipid peroxidation and a deterioration of proteins and nucleic acids, hence the lesion area is extended and finally, necrosis and apoptosis occur [63]. Lipid peroxidation is the main pathway through which ROS impacts neurons: phospholipase A2 is activated by ROS and subsequently releases arachidonic acid, further enhancing the production of ROS. By impacting lipids, ROS produces aldehydes, dienals, and alkanes, thus provoking neuronal apoptosis. The process of DNA oxidation has an early onset in ischemia, and, although it is initially reversible, then an irreversible deterioration of DNA and cellular death appear due to all the ROS production pathways and a blockage of antioxidant mechanisms [60].

Nutrients

Vitamin C, playing the role of an oxygen donor, can revert oxidative processes [60]. Vitamin E is a lipid antioxidant capable of inhibiting lipid peroxidation and acting as a ROS scavenger [68]. In an experimental study, vitamin C and E administration diminished lipid peroxidation and IS volume [69], but their therapeutic effects were not proven in human observational studies [68,70,71]. Vitamin C plasma levels are reduced in ICH patients [72] and administering vitamin C and E in combination with ICH rat models had positive effects [73].

Coenzyme Q10 is a component of the mitochondrial transport chain, the latter being involved in ROS production [74]. Coenzyme Q10 builds up in the mitochondria, having a powerful antioxidant effect, proving its efficacy in neuronal protection in IS experimental models [75]. Coenzyme Q10 therapeutic strategies in ICH are also under investigation [76].

Citicoline is a natural component that may reduce the release of fatty acids during lipid peroxidation [74]. Citicoline has demonstrated protective effects in experimental IS studies [77], but these results were not obtained in IS patients [78]. Small double-blind trials on citicoline in ICH have shown an increase in muscular strength, however, this needs to be proven in larger studies [79].

Wormwood (Artemisia absinthium), a plant of the Asteraceae family, increases ROS purging and diminishes lipid peroxidation, managing to reduce IS volume in experimental literature [80]. Eupatilin, an Artemisia-derived flavone with antioxidant properties, had neuroprotective effects by reducing inflammation in the microglia in ICH cellular models [81].

Ginkgo biloba extract reduces lipid peroxidation and protects neurons against OxSt in experimental studies [82]. There is no convincing data to support its routine use in IS patients [83]. A systematic review on ginkgo biloba extract in ICH patients has recently shown promise for this therapy, but further validation is needed [84].

Gastrodia elata is a plant belonging to the Orchidaceae family with antioxidant activity, capable of inhibiting glutamate neurotoxicity [85]. In animal studies, it confers neuroprotection against cerebral lesions caused by ischemia and reperfusion [86].

In animal models, lavender oil proved to have antioxidant properties, reducing ROS levels in ischemic or reperfusion lesions [87].

Cannabinoids, mainly cannabidiol, have been associated with neuroprotective effects and the studies with rat cortical neuron cultures exposed to toxic levels of glutamate support a further investigation of these compounds in different pathologies, including ischemic stroke [88,89]. Also, cannabidiol is increasingly investigated in other disorders, including psychiatric illnesses, due to its anxiolytic, antidepressant, and antipsychotic properties, and the benefit of being administered as an adjuvant to current treatment, thus potentially decreasing the rate of treatment resistance [90,91].

CONCLUSION

To summarize, whereas it may play a variety of roles in the pathogenesis of various neurological diseases, oxidative stress is a worthy target to consider in future therapeutic strategies. Natural nutrients may have beneficial effects that can be impactful, pending more validation in the literature. Vitamin E appears as a versatile option, with potential neuroprotective effects in PD, a possible functional role in AD, and an antioxidant capacity in both ischemic and hemorrhagic stroke, although its clinical role requires further, solid proof. Coenzyme Q10 could also be useful to PD, AD, MS, and stroke patients, with a vast potential awaiting exploration. Ginkgo biloba might also hold promise in AD and stroke, but there is limited evidence to support its routine use, despite clinicians nowadays often adding it to therapeutic regimens. Pending improved technologies to refine and standardize natural extracts, as well as solid and validated methodology usage in RCTs, novel therapies may include nutrients in a plethora of neurological diseases.

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; ATP = adenosine triphosphate; BBB = blood-brain barrier; GPx = glutathione peroxidase; ICH = intracerebral hemorrhage; IS = ischemic stroke; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NADPH = nicotinamide adenine dinucleotide phosphate; OxSt = oxidative stress; PD = Parkinson's disease; RNS = reactive nitrogen species; ROS = reactive oxygen species; SOD = superoxide dismutase; SVD = small vessel disease; XO = xanthine oxidase.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization I.I.E., M.M.M., S.M.G., D.D.; methodology M.M.M, D.D, R.N., C.I.S., I.I.E; software M.M.M, I.I.E.; validation M.M.M, S.M.G., D.D,; formal analysis M.M, D.D., I.I.E, S.M.G; investigation M.M.M., I.I.E, resources I.I.E., M.M.M.; data curation M.M.M.; writing—original draft preparation, I.I.E., M.M.M., R.N., C.I.S., D.D.; writing—review and editing I.I.E., M.M.M., R.N., C.I.S, D.D.; visualization M.M.M.; supervision M.M.M, D.D., I.I.E; project administration M.M.M, D.D., S.M.G. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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https://doi.org/10.55453/rjmm.2025.128.3.6

REVIEW

A Review of the Ethical and Legal Challenges in Clinical Trials

Octavian Vasiliu[1,2], Andrei G. Mangalagiu[1,2], Bogdan M. Petrescu[1,2], Adela M. Ciobanu[1,3]

[1] Discipline of Psychiatry, Neurosciences Department, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Clinical Department of Psychiatry, Central Military Emergency University Hospital "Dr. Carol Davila", Bucharest
[3] Department of Psychiatry "Prof. Dr. Al. Obregia" Clinical Hospital of Psychiatry, Bucharest, Romania

Correspondence: Octavian Vasiliu, octavvasiliu@yahoo.com

Abstract: Clinical research is the cornerstone of the progress recorded in psychiatry in the last six decades, or of what is called the psychopharmacological revolution. Regardless of the stage of clinical research, there are sensitive ethical and legal aspects that may appear during this process, and such challenges have to be acknowledged in order to preserve its scientific value, integrity, and centered-on-the-patient-wellbeing core principles. Also, adequate strategies focused on preventing the risk of ethical misconduct and litigation have to be found to avoid a loss of trust in the results of clinical research, to protect vulnerable populations from abuse, and to ensure a legally stable environment for investigators. In order to explore these practical problems, a narrative review was performed through a search in PubMed and Google Scholar databases. The main ethical risks detected in clinical research were related to errors in the methodology of obtaining informed consent, monitoring the participant's safety during the clinical trial, and falsifying collected data. Several famous cases of ethical misconduct were found and analyzed, and methods to decrease the risk of the re-appearance of such problems have been listed. In conclusion, this review is an invitation to explore the complexity of the methodology of clinical research and its ethical and legal risks, as well as to find new ways to mitigate the possibility of such risks related to the research process.

Keywords: clinical trial; volunteers; informed consent; vulnerable population; pharmacological agents; psychopharmacology; ethical misconduct

INTRODUCTION

Clinical research is an essential component of the broader paradigm of evidence-based medicine that is focused on ensuring scientific progress in healthcare. Although the evolution of medicine is an important objective, it must always be kept in mind when discussing clinical trials that the ultimate goal is to increase the quality of services offered to patients and improve their prognosis and chances of regaining a normal life. To refer only to the field of psychiatry, the developments recorded in the armamentarium of psychotropics in the last six decades represent a veritable revolution that allowed a change in the nosological paradigm of psychiatric disorders. Due to this change, which showed there is a biological basis for mental illnesses and that pharmacological agents can mitigate their symptoms, the stigmatization and the tendency to institutionalize patients with such diagnoses decreased and are expected to diminish further in the near future.

The importance of clinical research is illustrated by the high number of trials identified by a search in the International Clinical Trials Registry Platform (ICTRP), a World Health Organization database, that reported the existence of 10606 depression studies in 2024 [1]. According to the US National Library of Medicine database for clinical trials (ClinicalTrials.gov), more than 530000 studies are registered, out of which over 200000 are exploring a drug or a biological product, regardless of the pathology targeted, at the beginning of 2025 [2].

The need to conduct clinical trials in psychiatry is supported by a large number of practical difficulties when confronting the reality of mental health problems. One of the most critical challenges for clinicians is to increase the rate of responsiveness in treatment-resistant psychiatric illnesses, being known that 30-35% of depressive disorders, 30% of schizophrenia spectrum disorders, and up to 25% of bipolar disorders do not respond well enough to the usually administered pharmacological agents [3-7]. Another significant motive to foster clinical research in the field of psychiatry is the continuous quest to find new formulae to enhance therapeutic adherence (e.g., other ways of administration for a particular substance, coupling

Citation: Vasiliu O, Mangalagiu AG, Petrescu BM, Ciobanu AM. *A Review of the Ethical and Legal Challenges in Clinical Trials*. R. J. Mil. Med. 2025, 128(3): 225-233 https://doi.org/10.55453/rjmm.2025.128.3.6

Academic Editor: Raluca Mititelu

Received: 4 January 2025
Revised: 26 February 2025
Accepted: 20 March 2025

the active drug with a vehicle that allows a slower release of the active substance so that the interval between administration could increase, or to find molecules with superior tolerability). Changes in the pharmacodynamic or pharmacokinetic properties of certain drugs that are already available for clinical use could lead to the discovery of new drugs with potentially superior properties. Covering emerging health needs, including mental health-related problems, such as the long COVID-19 syndrome, new psychoactive substances (NPS) use disorders, etc., is another important reason for conducting clinical trials.

Some of the above-mentioned directions of research have been more productive than others, while high expectations are related to the objectives insufficiently accomplished, like detecting pathogenic rather than symptomatic treatments or improving the tolerability of already existent drugs for treatment-resistant cases. For example, when discussing the improvement of treatment adherence, the discovery of long-acting antipsychotics that allow patients with schizophrenia to receive only two injections each year (i.e., paliperidone palmitate with 6-month release) could be considered significant progress [8-10]. The production of active metabolites as independent drugs, a process starting with tricyclic antidepressants, like nortriptyline from amitriptyline, or desipramine from imipramine, and continuing with new-generation antidepressants and atypical antipsychotics, like desvenlafaxine from venlafaxine, or paliperidone from risperidone, allowed for improving and diversification of pharmacokinetic and pharmacodynamic properties of the parent drugs [11-15]. Another direction of research is improving the pharmacodynamic properties of a racemic mixture by extracting only the most potent enantiomer, as was the case of escitalopram, levomilnacipran, or eszopiclone [16-20]. Even one of the most sensitive topics in psychopharmacology, i.e., the pathogenic vs. symptomatic treatments, acknowledged significant progress in the last years by the Food and Drug Administration (FDA) approval of monoclonal antibodies that target beta-amyloid peptides, like aducanumab, donanemab or lecanemab [20-23].

The responsibility for conducting clinical trials belongs to medical professionals, primarily doctors, but also to other categories of healthcare personnel – registered nurses, clinical psychologists, etc., who follow specific training programs before engaging in any research activity. Completing these training programs provides professionals with a common background of knowledge and skills necessary for participation in pharmacological studies. Specific certifications, such as Good Clinical Practice (GCP)– ICH Guidelines E6 R2, or qualifications for scoring scales and inventories used to measure the severity of clinical symptoms, have the aim to protect participants in clinical studies, reduce the risks of malpractice for investigators, increase the validity of data obtained from the research, and decrease the inter-rater variability of clinical scale results [24-27].

The Declaration of Helsinki regarding human experimentation originated in 1964 in the World Medical Association (WMA) statement and has been constantly revised ever since, with the last revision in 2024 [28-30]. This declaration is an essential step in the history of conducting research with human subjects, as it stipulates the fundamental principles of this domain, for example, the unconditioned respect for individuals and their right to self-determination and making informed decisions regarding their own health, including aspects pertaining to participation in clinical studies [28,30]. The primary duty of the investigators is to the patient or volunteer included in clinical studies, and the participant's well-being takes precedence over the interests of science and society [28-30]. This declaration also stipulates that ethical aspects are primordial and laws and regulations are only second in importance [28-30].

Ethical and legal errors in pharmacological research have the potential to harm not only study participants but also the integrity of the entire research process, thus indirectly affecting a very large number of patients who could benefit from a specific investigational product once it is approved. This narrative review is dedicated to highlighting the most relevant domains of clinical research that are vulnerable to malpractice risk and to investigate possible ways to decrease the probability of its onset.

MATERIALS AND METHODS

Two electronic databases (PubMed and Google Scholar) were searched for the terms „malpractice," OR „ethical issues," OR „methodological errors," OR „legal issues," AND „clinical trials," OR „pharmacological research," OR „drug research," OR „psychopharmacology." All primary and secondary reports published in English were selected if they corresponded to the inclusion criteria and did not meet the exclusion criteria. In order to ensure adequate coverage of this topic, grey literature was also searched for papers published in English. The period chosen for published papers was between the inception of each database and January 2025. Inclusion criteria: all types of research and commentaries, press releases and related sources of information; all stages of clinical trials, if related to the field of psychiatry; pharmacological interventions, either alone or in combination with other interventions. Exclusion criteria: non-pharmacological interventions used alone; reports that did not contain precise data on ethical or legal issues related to clinical trials in psychiatry; undefined outcomes or imprecise source of the referenced studies.

RESULTS

From the clinical research perspective, ethical and legal error problems appear when a doctor participating in clinical trials (hereinafter referred to as "investigator") does not comply with the correct way of obtaining adequate informed consent, mismanages patient safety measures, or falsifies research data. These actions can lead to serious consequences for participants, undermine the validity of clinical trial results, and negatively impact the medical community and society as a whole through the decrease of individuals' chances of getting the optimal cure.

Ethical and legal challenges related to obtaining informed consent

Signing informed consent is the first procedure a participant in a clinical trial has to perform prior to any study-related procedures [31]. This step is mandatory in the era of clinical trials conducted under rigorous ethical principles, according to the principles of the

Declaration of Helsinki [28-30]. The procedure of informed signed consent is mentioned in the GCP guidelines and reflects the principles of absolute respect for patients' autonomy and their right to be informed in every aspect of the trial that is relevant to their own health [24-27]. Also, the Declaration of Helsinki stipulates that whenever the participants are unable to give their own consent, surrogate consent may be obtained from an individual acting in the participant's best interest, but the consent of the participant still needs to be obtained if at all possible [28-30,32]. The cases when this procedure is applicable are also presented in the Declaration of Helsinki [28]. The investigator must ensure that this consent is given freely, without any form of coercion, and with a comprehensive understanding of the implications of the study [28].

Possible errors in this domain, which are compatible with a risk of malpractice, are (a) a failure to disclose potential risks of the trial, (b) providing false or intentionally incomplete information, and (c) coercing patients to participate in the study.

For example, if an investigator conducting a study fails to properly explain to participants the adverse events or health risks of the investigational product, patients could be exposed to a danger to their health that they did not voluntarily assume in the very beginning. A study exploring the proportion of participants in clinical trials (N=135 cohorts) who were aware of the different elements of informed consent showed that only 52-75.8% understood what they were signing [33]. According to this study, 74% of the participants were aware of potential benefits and less than 70% of the study's aim, while 66% understood the rule of confidentiality [33]. Also, the proportion of participants who understood the informed consent did not increase during the 30 years of the studies included in the review [33]. These data indicate the need for better communication between investigators and participants during the signing of the informed consent form.

According to the GCP-ICH, both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the testing hypothesis process involved by the clinical trial, which is the purpose of the trial, understanding the fact that the treatment is not validated and what is the probability of random assignment to each treatment/placebo [24-27]. Also, the participant must receive adequate information about the study procedures to be followed, including all invasive procedures, which are his/her responsibilities, those aspects of the trial that are experimental, and the reasonable risks that can be anticipated or inconveniences to the subject and, also, the reasonably expected benefits [24-27]. Other elements included in the informed consent, according to the same source, refer to the alternative procedure(s) or treatment(s) that may be available to the subject, and their potential significant benefits and risks, the compensation and/or treatment available to the subject in the event of study-related harm, and the anticipated payment, if any, to the subject for participation in the study [24-27]. The list of all elements that constitute an informed consent form is too extensive to be reproduced here, but this complexity explains the long time necessary for the investigator to explain the totality of the relevant aspects to each participant in order to obtain his/her approval to participate in the trial.

Patient safety and monitoring of adverse events

Investigators are responsible for carefully monitoring the psychobiological parameters of each participant in a trial, ensuring that subjects are not exposed to avoidable health risks [24-27]. This process presumes a regular verification for the existence of adverse reactions, offering adequate interventions if these appear and discontinuing participants' involvement if they develop a serious adverse event. Failure to comply with this principle is a severe form of malpractice and a clear violation of the core principles of the Declaration of Helsinki [28-30].

For example, if an investigator continues to administer an investigational product to a patient despite clear signs suggesting the onset of severe side effects, he or she is engaging in a form of negligence that can have severe legal consequences far beyond the violations of ethical conduct. In this area are placed the cases when participants who remain pregnant during the clinical trials are still receiving the investigational product or when adverse events to the experimental drugs are treated with medications not allowed by the study protocol, thus disregarding the potential of pharmacologically dangerous interactions. According to a study [34] focused on the understanding of potential trial participants regarding the monitoring and communication of serious adverse events during a clinical trial, it was observed that their awareness of safeguards or regulations in this domain was very scarce; also, many of them expressed the desire to be more informed about the potentially serious adverse events and short reporting deadlines. The same study reported on the concerns of participants about potential financial conflicts of interest in monitoring and further reporting serious adverse events during a clinical trial [34].

In the same direction, the 2024 revision of the Declaration of Helsinki notes that unproven interventions focused on alleviating pain or suffering must not bypass ethical safety measures or avoid evaluation by controlled clinical trials [35], highlighting the importance of conducting an accurate assessment of all health parameters even in the most severe patients.

New tools have been suggested for the most accurate monitoring of safety in clinical trials, including those using graphical visualizations that are congruent with the FDA/EMA (European Medicines Agency) guidelines [36]. Such tools are interactive and support regular medical monitoring and oversight [36]. The National Institutes of Health in the US require data and safety monitoring boards for all phase III clinical trials, which are conceived as a supplementary barrier to errors in safety monitoring [37].

Data falsification and breaking the research integrity

The accuracy of data collection in the clinical research process and the integrity of the analysis of information regarding the efficacy and tolerability of the investigational product are essential to provide valid results. Ethical breaks and legal issues can be detected in this field when an investigator manipulates or falsifies clinical data to obtain some desired results [38,39]. Data falsification exerts

significant prejudice on the validity of research, endangers the patient's safety, and violates the core ethical principles of medicine.

For example, such an unethical approach can lead to the approval by competent institutions of harmful or ineffective treatments for clinical use, which can significantly endanger future patients [38-41]. Furthermore, new research could be based on a false presumption, and this could exponentially amplify the negative economic and medical consequences of a single false study [38-41].

Several examples of data falsification and research integrity break are: (a) selective reporting, which is a form of reporting only data that supports the drug's efficacy while omitting negative or inconclusive results; (b) data harvesting, a phenomenon that refers to the selective analysis of certain variables that fit a desired outcome, ignoring others; (c) partial monitoring of tolerability data, which may be observed when there is a lack of monitoring or inadequate reporting of adverse effects that occur during the study; (d) lack of adequate monitoring of participants after the study ends to confirm that the investigator ensures that any long-term effects of the drug are documented and managed appropriately; (e) underestimation of risks, which refers to the situation when the investigators minimize or ignore potential risks that expose participants to short, medium, and long-term negative effects [38-43].

Another example of phenomena that negatively interact with research integrity is the participation in clinical trials of investigators with insufficient experience or without enough credentials, and this is a direct violation of the Declaration of Helsinki [28-30]. Thus, allowing individuals without the necessary certifications or knowledge to conduct or supervise critical aspects of a trial is an example of ethical misconduct [28-30]. Failure to provide adequate training to staff on ethical practices, safety protocols, or specific clinical trial procedures is also a breach of research integrity [28-30].

Ethical integrity can also be breached by improper recruitment and enrollment of participants [28-30,38]. For example, the inclusion of ineligible participants might refer to the enrollment of individuals who do not meet the inclusion criteria for the study, such as those with contraindicated health conditions or who are already taking other medications prohibited by the study protocol. On the other hand, but in the same category of ethical breaches, the exclusion of eligible participants refers to discrimination against specific populations, such as vulnerable groups, in order to distort results or save time. Such examples are the inclusion of participants diagnosed with major depression and active suicide ideation, although the study protocol prohibits their enrollment, and, on the other hand, exclusion of patients with severe depression due to the investigator's fear they will be challenging to manage, although the study protocol allows their participation.

Ethical breaches may be derived from protocol deviations and protocol violations [44,45]. The first case refers to divergences between the study activities from the institutional review board (IRB)-approved protocol with minimal impact, while the second refers to divergences that reduce the quality or completeness of the data, inaccuracies in the informed consent form, or endanger the subject's safety, rights, or welfare [45]. For example, if the test procedures are modified or the treatment administration algorithm is changed during the trial without a clear rationale, these may affect the results and induce harmful reactions in the participants. Also, failure to adequately document protocol changes or deviations makes it impossible to assess their potential impact on the trial. Failure to report or address ethical concerns is a significant methodological and ethical or legal error that can be observed, for example, when an ethical review is neglected by failing to obtain approval from an IRB or ethics committee before the trial begins or failing to address ethical concerns raised during the review process [46].

Several ways to decrease the risk of protocol deviations are enhanced training for the investigators, regular monitoring visits, involvement of the Ethics committee in site monitoring, etc. [44]. In a study that explored 80 postgraduate dissertations, representing observational studies (74%) and interventional trials (10%), a significant proportion of protocol deviations (more than 42%) were due to nonreporting and incomplete documentation of the divergencies [47].

Consequences of malpractice in clinical trials

Clinical trial litigation has been rapidly escalating during the last decades, and defendants are not only principal investigators or sponsors but also IRBs, individual IRB members, study coordinators, etc. [48,49]. Beyond the legal repercussions, malpractice in clinical trials can have long-lasting effects on public opinion about medical research. Patients may become hesitant to participate in future clinical trials, fearing that their health may be at risk. As a consequence, the interest of the general public in research could decrease, and thus, the availability of new treatments for various disorders could be delayed, or potentially valuable drugs may even be abandoned.

Furthermore, the reputation of healthcare practitioners can be significantly damaged when cases of malpractice in clinical trials are discovered and exploited by mass media [50,51]. Such phenomena can fuel an environment of skepticism and mistrust, leading to the erosion of the relationship between the patient and the healthcare specialists. The impact is, consequently, negative not only at an individual level but also at a macro-social level, with consequences beyond the level of a research site or a certain clinical trial.

Examples of famous cases when ethical and legal violations of clinical research were detected

One of the first cases of ethical misconduct after the Nuremberg Trials, which brought to the general interest the dangers of experiments without ethical restraints, was related to the MKUltra studies (1955–1967) [52,53]. These involved „mind-control" techniques using LSD-25, and were sponsored by the CIA [52]. Many of the subjects were given LSD and other psychoactive substances without consent, and some were subjected to psychological manipulation; also, not all of the „investigators" were healthcare specialists, but they came from very diverse professional backgrounds, e.g., one of them was a magician, i.e., a student of Harry Houdini, while another was a CIA consultant with a shady history; tragically, this so-called experiment for mental illnesses became

medical torture not very unlikely to the Nuremberg Trials [52,53]. Different reports describe the effects of these experiments on mental health, including the Veterans Health Initiative Report in 2003 [53].

The study 329 (1994–2001) investigated the use of paroxetine and imipramine in adolescents, and this research was later found to have serious ethical and scientific flaws, including selective reporting of results [54,55]. An independent reanalysis of the data from Study 329 (the RIAT initiative) showed that acute and long-term paroxetine and imipramine were harmful and ineffective in adolescents with major depression [54]. In the original study, paroxetine proved itself well-tolerated and effective in that population on multiple outcomes, i.e., the Hamilton Depression Rating Scale (HAMD), Schedule for Affective Disorders and Schizophrenia for Adolescents-Lifetime version (K-SADS-L), and Clinical Global Impression (CGI), while the withdrawal rates due to adverse events were 9.7% vs. 6.9% (paroxetine vs. placebo) [55]. The RIAT analysis presented several ways in which the presentation of safety data in clinical trials may influence the apparent tolerability of a drug, e.g., the use of an idiosyncratic coding system, failure to transcribe all adverse events from clinical records to an adverse event database, or filtering data on adverse events through statistical techniques [55]. This case is interesting because it represents an argument to make it available for independent analysis of all primary data available from a clinical trial [56].

The Ranbaxy Case (2006-2008) involved a major Indian pharmaceutical company in a significant controversy related to drug safety, more specifically to the quality of various generic drug products, including gabapentin and the antibiotic ciprofloxacin [57]. Ranbaxy was accused of falsifying data in clinical trials, including trials of generic drugs, related to the purity, strength and quality of these generics, and the case resulted in the company being fined $500 million by the US Department of Justice for selling counterfeit drugs and submitting false data to the FDA [57]. Incomplete testing records and inadequate programs focused on the assessment of the stability characteristics of drugs were detected by an FDA inspection in the Paonta Sahib facility in 2006 [57].

Other doubts about the regulation authorities failing to keep up with ethical issues in clinical research in India have been raised [58]. Although most of the alleged ethical violations were not confirmed, the controversy about the clinical trials in India has decreased dramatically the trust in clinical research originated in India [58]. Lack of informed consent from volunteers, conflict of interests surrounding the members of independent ethics committees, suspicions about the use of vulnerable populations, and lack of insurance or compensation in case of serious adverse events were subjects presented by activists [58]. In 2017, a guideline passed by the Indian Council of Medical Research was launched to improve the quality of clinical research in that country [59]. These guidelines approach sensitive topics, like the procedure to obtain informed consent, the respect for voluntariness, the definition of vulnerable population, the assessment of the benefits vs. risks balance, and the compensation for harm derived from participation in clinical trials [59]. Also, regularization of the Ethical Committee structure and functions are included in these revised guidelines [59].

Prevention of malpractice in clinical trials

The complexity of clinical research has attracted numerous debates over the last decades, and national institutions with responsibilities in the field of drug regulation have initiated their own rules and norms, besides international or regional ones. EMA, WHO (World Health Organisation), and WMA are the leading institutions with expertise in the regularization of clinical research [60-65]. National agencies, like the FDA in the US or the PMDA (Pharmaceuticals and Medical Devices Agency) in Japan, are also regulatory organizations with rich experience and ethical guidelines dedicated to clinical research [66,67].

In order to decrease the risk of ethical misconduct and litigations in this field, such institutions with responsibilities in the domain of monitoring the research activity must provide continuing education and training to physicians involved in clinical trials, ensuring that they understand the ethical, legal, and scientific responsibilities they bear. The activity of pharmacovigilance is also a topic that needs to be regularized because this stage is essential for ensuring post-marketing feedback from the patients. Phase IV studies are not at all less important than other clinical trials due to their importance in maintaining clinical use of only those drugs that prove themselves useful and tolerable, even after they pass the pivotal trials. The real safety profile of a certain drug may be defined only by continuing surveillance, and this requires an intense effort from patients, doctors, and regulatory institutions [68].

There is a need for effective oversight mechanisms, including local ethics committees, which evaluate the ethical, methodological, and safety aspects of clinical trials before and during their implementation. These committees act as a core protection for human research participants due to their independent review of the ethical acceptability or proposal for human research [69]. The importance of these organisms has been mentioned in the previous chapter, as avoidance of the conflict of interest within IRBs/Ethical Committees was a topic raised in the controversy surrounding clinical research in India [59].

Also, the transparency of research data implies compliance with rigorous protocols, with clear documentation of all procedures, decisions and results, which can be audited at any time by competent national and international institutions. This aspect's importance was highlighted by the Study 329 case, where an independent re-analysis of the original data provided different results [54].

DISCUSSION

The progress recorded in the treatment of psychiatric disorders in the last six decades could not be possible without clinical research based on the dedication of the investigators and volunteers who contributed in a significant way to this endeavor. Like any scientific domain, clinical research is not free of ethical and legal challenges, especially because, due to its sensitive nature, it mixes epistemological aspects (i.e., the experimental nature of the investigational process), with axiological (i.e., the liberty of the individual as a core value), and ontological ones (e.g., the biological vs. spiritual causation of our mental life). Thus, hypersensitive topics are

related to each dimension; starting from the acknowledgment of the participants that they assume certain health risks in a clinical trial, continuing with the voluntariness vs. coercion dilemma when being recruited for a study, or with the liberty to decide when to withdraw from a trial, all these aspects may be negatively exploited and consequently may trigger ethical misconduct and litigation. Clinical research has received a lot of attention from both the scientific world and the public, not to mention the vehicle between the two, i.e., the media. Avoiding dogmatic thinking and understanding the complexity of clinical research is important for any investigator, as is the ability of scientists to maintain the transparency of the research to society, which is the final beneficiary of their work. The legislation in the field of clinical trials is an evolving organism, and the Declaration of Helsinki is the result of the conjugated effort of society and the scientists trying to prevent the repeating of tragic ethical misconduct as in the Nuremberg Trials, MK Ultra experiments, etc.

Because the number of clinical trials is continuously increasing as a result of the social pressure to find more performant and more tolerable pharmacological agents, not to mention the need to respond to newer threats to human health, there is an ever-higher need to control the potential risk factors for ethical deviations in clinical research. Therefore, the vulnerabilities related to the clinical research methodology explored in this review, i.e., those about the obtaining of informed consent, those connected to patients' safety, and those derived from data falsification, need to be continuously monitored and regulated by authorized institutions. The failure to do so would lead to a decrease of public trust in clinical research and virtually erase the line between scientific, validated-through-trials pharmacological agents and any other substance promoted by non-regularized commercial entities. This is a very important and actual topic because psychedelics (LSD included) or other substances with a risk of addiction are nowadays explored again for the use of various mental disorders, while various therapies with innovative mechanisms (e.g., focused on immune factors or gene modulation) are also emerging as potential solutions for multiple, psychiatric or somatic, illnesses [70-75]. Therefore, a continuous updating of ethical guidelines is needed to protect the participants in clinical trials from any type of abuse and to allow the investigators to work in a legally secure environment.

CONCLUSION

Pharmacological research activity is an essential component of the approach aimed at increasing the quality of medical practice by multiplying the existing therapeutic options for a specific medical condition. Evolution in the field of medicine is impossible to achieve, at least taking into consideration the current level of scientific knowledge, without clinical trials. Through this type of activity, progress in pharmacology is ensured, and the quality of patients' lives is increased while their chances of functional recovery and prognosis are improved.

Ethical and legal risks in clinical research derive mainly (but in no way exclusively) from (1) irregularities in obtaining informed consent of participants in the study, (2) failure of investigators to respect the safety of participants in the clinical study, and (3) incorrect reporting of data obtained from the research.

Controlling these risks involves respecting the stages of professional training of clinical trial investigators, as well as the efficient functioning of institutional control mechanisms in the field of pharmacological research.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, O.V, A.M.C.., and A.G.M.; methodology, B.M.P.; formal analysis, O.V, A.M.C.; investigation, O.V., A.M.C., B.P.M., A.G.M.; resources, O.V.; data curation, A.M.C..; writing—original draft preparation, O.V., A.M.C.; writing—review and editing, O.V., A.M.C., B.M.P.; visualization, A.G.M.; supervision, O.V., A.M.C.; project administration, O.V. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

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https://doi.org/10.55453/rjmm.2025.128.3.7

ORIGINAL ARTICLE

Efficacy and Patient Satisfaction of Laser Labiaplasty for Labia Minora Hypertrophy: A Retrospective Analysis

Filis Demirgean[1], Simona Albu[1,2], Daniel O. Costache[1,3], Maria M. Constantin[1,4]

[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; filisdemirgean@gmail.com (FD)
[2] Department of Obstetrics and Gynaecology, University Emergency Hospital, Bucharest, Romania; albuelenasimona@gmail.com (SA)
[3] Department of Research, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania; daniel.costache@umfcd.ro (DOC)
[4] 2nd Department of Dermatology, Colentina Clinical Hospital, Bucharest, Romania; maria.constantin@umfcd.ro (MMC)

Correspondence: Filis Demirgean, filisdemirgean@gmail.com; Daniel O. Costache, daniel.costache@umfcd.ro

Abstract: Background: Labia minora hypertrophy can lead to aesthetic dissatisfaction and functional discomfort among women, affecting their quality of life and sexual self-esteem. Traditional surgical labiaplasty techniques are effective but are associated with higher complication rates and longer recovery times. This study aims to evaluate the efficacy, safety, and patient satisfaction of laser labiaplasty as a minimally invasive alternative for labia minora reduction. Methods: A retrospective analysis was conducted on 60 female patients who underwent laser labiaplasty. Preoperative assessments included medical history, gynecological examination, and patient-reported concerns. The procedure utilized a CO_2 laser for tissue excision without the need for sutures. Postoperative outcomes were evaluated through follow-up visits and telephone interviews, focusing on complications, recovery time, and patient satisfaction measured by the Subjective Global Aesthetic Improvement Scale (sGAIS). Results: The primary motivations for surgery were aesthetic concerns (85%) and functional discomfort (55%). The mean age was 34.7 years. Minor complications included transient postoperative bleeding (10%) and mild discomfort (25%), with no major complications reported. High satisfaction rates were observed, with 92% of patients reporting significant improvement (sGAIS scores of 4 or 5). Conclusions: Laser labiaplasty is an effective, minimally invasive procedure with high patient satisfaction and low complication rates. It offers a viable alternative to traditional surgical methods for women seeking labia minora reduction due to aesthetic or functional concerns.

Keywords: laser labiaplasty; labia minora hypertrophy; patient satisfaction; minimally invasive procedure; genital aesthetics

INTRODUCTION

Labia minora hypertrophy, characterized by the enlargement or elongation of the inner vaginal lips, has been a largely recognized condition [1,2]. Women experiencing this condition often report both aesthetic dissatisfaction and functional issues, such as discomfort during physical activities or sexual intercourse [3,4]. The increased visibility and awareness of genital aesthetics in contemporary society have led to a growing number of women seeking corrective procedures to address these concerns [5,6].

Genital aesthetics significantly impact a woman's sexual self-esteem and overall quality of life [7,8]. Studies have demonstrated that dissatisfaction with genital appearance can lead to psychological distress, reduced sexual function, and decreased confidence [9,10]. The rise of media portrayal of idealized genital images has further influenced women's perceptions, prompting many to pursue medical interventions to achieve their desired appearance [11].

Traditional surgical labiaplasty techniques, including edge resection, wedge resection, Z-plasty, and deepithelialization, have been employed to reduce labial tissue [12,13]. While effective, these methods are associated with risks such as scarring, altered sensation, asymmetry, and extended recovery periods. These potential complications have led both patients and clinicians to explore less invasive alternatives that offer effective results with fewer risks [14].

Laser labiaplasty has emerged as a minimally invasive option that utilizes laser technology to excise excess labial tissue precisely [15,16]. Introduced more than 15 years ago using a neodymium-doped yttrium aluminum garnet (Nd) laser, the technique has evolved with the adoption of carbon dioxide (CO_2) and erbium-doped yttrium aluminum garnet (Er) lasers [17]. These lasers offer advantages such as reduced intraoperative bleeding, minimal thermal damage, and enhanced healing, contributing to improved patient outcomes.

Citation: Demirgean F, Albu S, Costache DO, Constantin MM. *Efficacy and Patient Satisfaction of Laser Labiaplasty for Labia Minora Hypertrophy: A Retrospective Analysis*. R. J. Mil. Med. 2025, 128(3): 234-241; https://doi.org/10.55453/rjmm.2025.128.3.7

Academic Editor: Raluca Mititelu

Received: 28 January 2025
Revised: 13 March 2025
Accepted: 2 April 2025

Despite the growing popularity of laser labiaplasty, there is a paucity of comprehensive studies evaluating its efficacy, safety, and patient satisfaction. Most existing literature comprises small case series or focuses on surgical techniques without detailed analysis of patient-reported outcomes [18,19]. This gap underscores the need for robust clinical data to inform practitioners and patients about the benefits and limitations of this procedure. Therefore, the objective of this study is to retrospectively analyze our center's experience with laser labiaplasty in treating labia minora hypertrophy. By examining preoperative motivations, procedural details, postoperative outcomes, and patient satisfaction, we aim to provide valuable insights into the efficacy and safety of laser labiaplasty as a minimally invasive alternative to conventional surgical methods.

MATERIALS AND METHODS

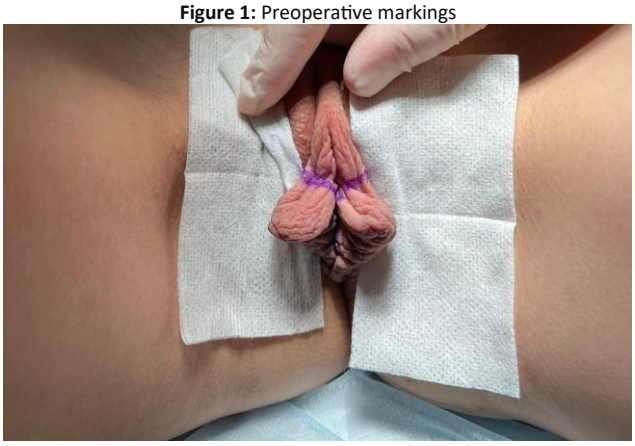
This retrospective study analyzed data from 60 female patients who underwent laser labiaplasty between June 2020 and September 2024. Inclusion criteria encompassed women aged 18 years or older diagnosed with labia minora hypertrophy, who expressed aesthetic or functional concerns and completed a minimum of six months of follow-up. Exclusion criteria included active genital infections, uncontrolled systemic diseases, previous labiaplasty, or other genital surgeries.

All patients underwent a comprehensive preoperative evaluation. Medical and gynecological histories were obtained, focusing on reproductive history, menstrual cycle details, prior pregnancies, and any gynecological conditions or surgeries. Physical examination included measurement of labia minora dimensions using standardized calipers. Preoperative investigations included a Papanicolaou (PAP) smear, vaginal secretion analysis for infections, and a transvaginal ultrasound to assess pelvic anatomy.

The classification of labial hypertrophy identifies three types of labial hypertrophy, based on Stephane Smarrito's study [20]: Type I, known as the "flag," affects the anterior one-third and was found in 11% of the cases; Type II, or the "oblique," involves the middle third and accounted for 29% of cases; and Type III, termed "complete," includes the posterior third, observed in 60% of the patients. Symptomatically, Type I patients typically reported aesthetic concerns and discomfort from tight clothing without dyspareunia. Type II was noted for a fuller appearance, and Type III frequently presented with dyspareunia more so than the other types. Surgical approaches were tailored accordingly, with Type I cases treated using a superior pedicle flap technique for moderate labial resection, while Types II and III were approached with the lambda laser technique. This classification system allows for more targeted surgical strategies that align closely with patient symptoms and expectations, providing a significant improvement over the traditional method based solely on dimensional measurement.

The procedure was performed under local anesthesia. Initially, a topical anesthetic cream containing lidocaine 2.5% and prilocaine 2.5% was applied to the labia minora for 30 minutes. After the removal of the cream and disinfection with povidone-iodine solution, infiltration anesthesia was administered using 1% lidocaine with epinephrine 1:100,000 via a 30G needle. Preoperative markings were made to delineate the extent of tissue excision (Figure 1).

Figure 1: Preoperative markings



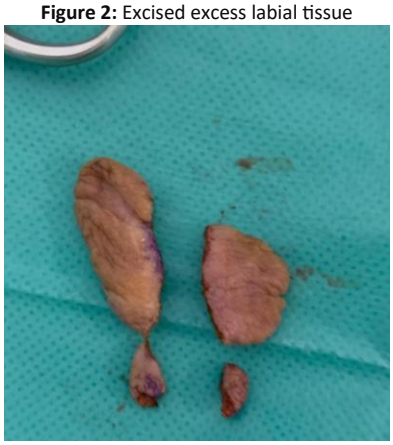
A CO_2 laser (CO_2RE, Syneron Candela) equipped with a surgical handpiece was set to a continuous wave mode at 10 Watts. The laser was used to excise excess labial tissue along the marked lines, ensuring symmetrical reduction and preservation of the natural contour (Figure 2). Hemostasis was achieved through the laser's coagulative properties, eliminating the need for sutures. After the procedure, the area was treated with topical fusidic acid ointment and covered with a sterile dressing.

Patients received detailed postoperative instructions, including applying fusidic acid ointment twice daily for one week; maintaining local hygiene with gentle cleansing using mild soap and water; avoiding sexual activity, strenuous exercise, swimming pools, and saunas for six weeks; and wearing loose-fitting clothing to minimize friction.

Follow-up visits were scheduled at one week, one month, three months, and six months postoperatively. Evaluations focused on wound healing, identification of any complications, and assessment of patient satisfaction using the Subjective Global Aesthetic Improvement Scale (sGAIS), a validated 5-point scale ranging from 1 (no improvement) to 5 (very significant improvement).

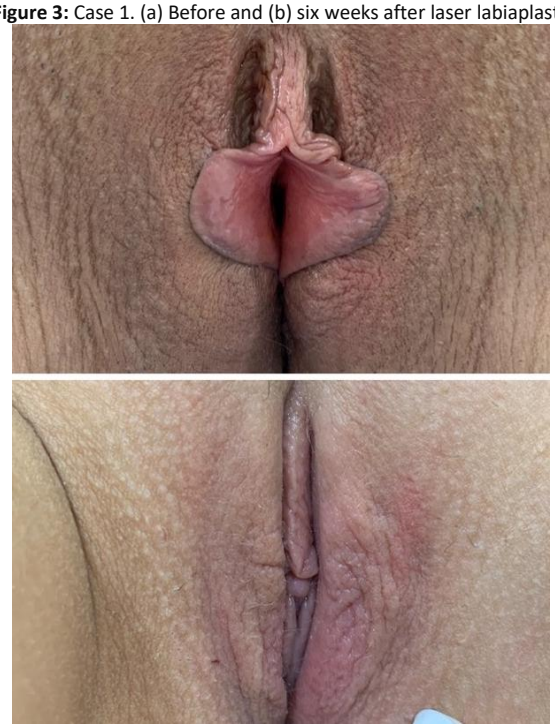
After the clamps were removed, the treated area was managed with targeted local applications of anti-inflammatory and antibiotic solutions. Specifically, Fucidin H cream, containing fusidic acid 20 mg/g and hydrocortisone acetate 10mg/g, was used in conjunction with Baneocin powder, which includes zinc bacitracin 250 UI and neomycin sulphate 500 UI/g. To control bleeding and further protect the site, a hemostatic sponge was placed over these topical agents, and the area was subsequently dressed. Pain management was addressed systemically through an intravenous administration of acetaminophen 10mg/ml, amounting to 100 ml, and an oral dose of Ketonal Forte, which contains ketoprofen at a concentration of 100 mg.

Figure 2: Excised excess labial tissue



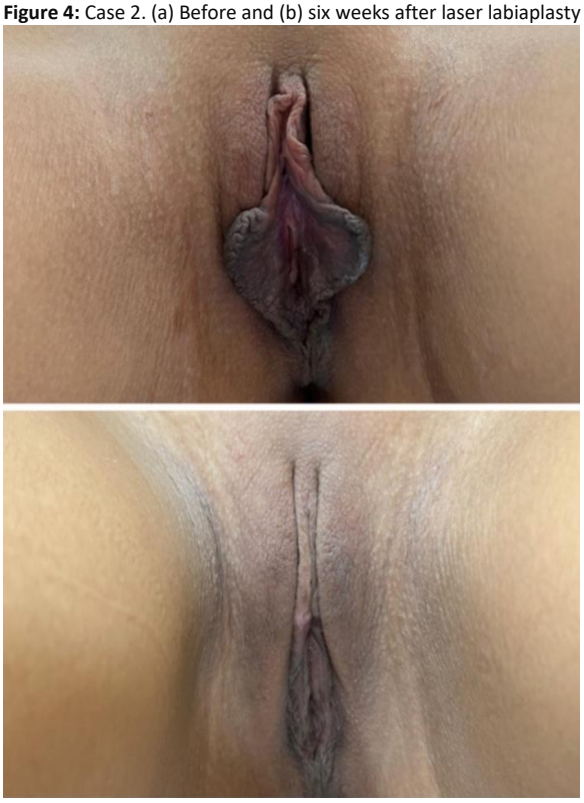
Discharge instructions provided to the patient emphasized crucial care steps to ensure proper healing. The patient was instructed to maintain local compression and restrict themselves to bed rest on the day of the procedure to minimize movement and stress at the site. For the initial three weeks post-procedure, the patient was advised to clean the area using Betadine and apply the previously mentioned Fucidin H cream and Baneocin powder twice daily. In the subsequent three weeks, the regimen shifted to cleaning with water and soap followed by the application of a protective repairing cream to foster skin restoration and barrier function.

Figure 3: Case 1. (a) Before and (b) six weeks after laser labiaplasty



At the six-week post-procedure mark, a follow-up consultation was arranged to evaluate the healing progress and the cosmetic outcome of the laser labiaplasty. The provided figures (Figure 1 and Figure 2), display the condition of the area before the procedure and at the six-week follow-up. These images illustrate a notable reduction in labial size and improved symmetry, indicating a successful aesthetic enhancement. The area appeared to be well-healed without signs of infection or significant inflammation, underscoring the effectiveness of the postoperative care regimen.

Figure 4: Case 2. (a) Before and (b) six weeks after laser labiaplasty



RESULTS

The study included 60 women aged between 19 and 52 years, with a mean age of 34.7 years. The average age at menarche was 13.1 years. Regarding reproductive history, 40% of patients were nulliparous, 35% had one pregnancy, and 25% had two or more pregnancies. Positive gynecological history, such as polycystic ovary syndrome, previous cesarean sections, or uterine fibroid removal, was present in 30% of patients. This demographic distribution indicates a diverse patient population seeking laser labiaplasty (Table 1).

Table 1: Demographic and Clinical Characteristics

Parameter	Mean (SD)	Range
Age (years)	34.7 (7.8)	19 - 52
Age at menarche (years)	13.1 (1.4)	11 - 16
Number of pregnancies	0.9 (1.1)	0 - 4
Positive gynecological history (%)	30%	N/A

SD – Standard Deviation

Aesthetic concerns were the primary motivation for 85% of patients, highlighting the significance of genital appearance in this cohort. Functional discomfort during daily activities, such as exercise or wearing tight clothing, was reported by 55% of patients. Discomfort during sexual intercourse affected 45%, indicating that labia minora hypertrophy can significantly impact sexual function. Recurrent infections or hygiene difficulties were less common but still noteworthy at 15% (Table 2).

Table 2: Preoperative Motivations

Motivation	Number of Patients (%)
Aesthetic concerns	51 (85%)
Functional discomfort during activities	33 (55%)
Discomfort during sexual intercourse	27 (45%)
Recurrent infections/hygiene issues	9 (15%)

Postoperative complications were minimal. Mild bleeding occurred in 10% of patients, resolving within an average of 2.3 days without intervention. Mild to moderate discomfort was experienced by 25% of patients, lasting approximately 4.2 days. Notably, statistical analysis revealed a significant association between previous pregnancies and postoperative discomfort ($p=0.03$), suggesting that multiparous women may experience more discomfort due to tissue changes from childbirth. No infections or hematomas were

reported, indicating a favorable safety profile (Table 3).

Table 3: Postoperative Complications and Recovery

Complication	Number of Patients (%)	Duration (Days)	p-value
Mild bleeding - Total	6 (10%)	2.3 (1.1)	0.12
Mild to moderate discomfort – Nulliparous	6 (10%)	4.0 (1.5)	-
Mild to moderate discomfort – One pregnancy	5 (8.3%)	4.1 (1.6)	-
Mild to moderate discomfort – Multiparous	4 (6.7%)	4.5 (1.8)	0.03*
Infection	0 (0%)	N/A	N/A
Hematoma	0 (0%)	N/A	N/A

* *Student's t-test*

Table 4 provides a comprehensive overview of patient satisfaction following laser labiaplasty, as measured by the standardized Global Aesthetic Improvement Scale (sGAIS). The table categorized patient responses into five distinct levels, highlighting the overwhelmingly positive feedback received. Specifically, a majority of 33 patients, accounting for 55% of the total surveyed, reported a "Very significant improvement" in their condition, with an sGAIS score of 5. This indicated that these patients perceived the results of their surgery as greatly surpassing their expectations in terms of both aesthetic appeal and functional benefits. Additionally, 22 patients, representing 37% of the total, observed a "Significant improvement," scoring a 4 on the sGAIS. This suggests that for a large number of patients, the procedure substantially met their initial goals and resulted in marked enhancements.

On the lower end of the scale, 5 patients, making up 8% of the total, felt they had only "Moderate improvement," denoted by a score of 3 on the sGAIS. This group perceived the changes as noticeable but not as extensive as perhaps hoped for. Importantly, the table showed that no patients reported a lack of change or a worsening of their condition post-procedure, with zero reports in both the "No change" and "Worsened condition" categories (scores of 2 and 1, respectively). This absence of negative feedback underscored the effectiveness and safety of laser labiaplasty in achieving desired outcomes without adverse effects. The data clearly demonstrated a high level of patient satisfaction overall, with 92% of participants rating their improvement as significant or very significant, highlighting the procedure's ability to meet or exceed patient expectations in the vast majority of cases.

Table 4: Patient Satisfaction (sGAIS Scores)

Satisfaction Level	No/Mild Complications n (%)	Moderate Complication n (%)	Total	p-value*
Very Significant Improvement	32 (97%)	1 (3%)	33	
Significant Improvement	16 (73%)	6 (27%)	22	
Moderate Improvement	0 (0%)	8 (100%)	5	
p-value				<0.001

* *Chi-square test*

Among 60 patients, 34 who were satisfied and 17 who were less satisfied cited aesthetic concerns, against expected counts of 37.4 and 13.6, respectively. Functional discomfort during activities was reported by 28 satisfied and only 5 less satisfied patients, compared to expected figures of 24.2 and 8.8. For discomfort during sexual intercourse, 20 satisfied and 7 less satisfied patients were recorded, versus an expected count of 19.8 for satisfied and 7.2 for less satisfied. Lastly, recurrent infections or hygiene issues were less commonly reported, with 6 satisfied and 3 less satisfied patients, aligning closely with expected values of 6.6 and 2.4. The overall chi-square analysis resulted in a p-value of 0.306, indicating no significant statistical association across the groups (Table 5).

Table 5: Analysis of Complaints and Patient Satisfaction Post-Laser Labiaplasty

Complaint Type	Satisfied Patients (n = 40, %)	Less Satisfied Patients (n = 20, %)	Expected (Satisfied)	Expected (Less Satisfied)	p-value
Aesthetic concerns	34	17	37.4	13.6	
Functional discomfort during activities	28	5	24.2	8.8	
Discomfort during sexual intercourse	20	7	19.8	7.2	
Recurrent infections/hygiene issues	6	3	6.6	2.4	
p-value					0.306

Patients with Type III hypertrophy showed a substantially higher improvement in sexual discomfort ($p < 0.001$), aligning with their higher baseline rates of dyspareunia. Differences in aesthetic and functional improvements were not statistically significant across the three groups ($p = 0.43$ and $p = 0.07$, respectively), although Type II and Type III trended toward slightly greater gains than Type I. Reduction in hygiene-related complaints was similar among all types ($p = 0.73$). Overall satisfaction (sGAIS) remained high across all groups, with no statistically significant variation ($p = 0.56$), as presented in Table 6.

Table 6: Postoperative Quality of Life Differences by Labial Hypertrophy Type

Variable	Type I	Type II	Type III	p-value
Mean Improvement in Aesthetic Concerns (0-10 scale, higher = greater improvement)	4.7 ± 1.3	4.9 ± 1.1	5.1 ± 1.2	0.43
Mean Improvement in Functional Discomfort (0-10 scale)	5.4 ± 1.3	6.2 ± 1.4	6.3 ± 1.6	0.07
Mean Improvement in Sexual Discomfort (0-10 scale)	3.3 ± 1.0	4.6 ± 1.2	6.6 ± 1.5	<0.001
Patients Reporting Fewer Hygiene Issues (n, %)	2 (28.6%)	4 (23.5%)	10 (27.8%)	<0.001
Mean Postoperative sGAIS Score (1-5 scale*)	4.4 ± 0.5	4.3 ± 0.6	4.5 ± 0.4	0.56

** Standardized Global Aesthetic Improvement Scale (SGAIs): 1 – Worsened; 2 – No Change; 3 – Moderate Improvement; 4 – Significant Improvement; 5 – Very Significant Improvement.*

DISCUSSION

Literature findings

The study demonstrates that laser labiaplasty is a safe and effective minimally invasive procedure for treating labia minora hypertrophy. The high patient satisfaction rates align with existing literature, indicating that laser techniques offer significant advantages over traditional surgical methods. The predominance of aesthetic concerns as a motivation reflects societal trends emphasizing genital aesthetics and their impact on women's self-esteem and sexual health.

The low incidence of postoperative complications, such as bleeding and discomfort, highlights the safety profile of laser labiaplasty. The precise excision and coagulative properties of the CO_2 laser reduce intraoperative bleeding and eliminate the need for sutures, contributing to faster healing and reduced postoperative pain. The absence of infections and hematomas in our cohort further supports the procedure's safety.

The significant association between previous pregnancies and increased postoperative discomfort may be attributed to changes in tissue elasticity and sensitivity resulting from childbirth. This finding suggests that multiparous women may require additional preoperative counseling and postoperative support to manage expectations and enhance recovery.

In the realm of female genital cosmetic surgery, the studies by Pardo et al. [21] and Bizjak-Ogrinc et al. [22] provide valuable insights into the efficacy and patient satisfaction associated with different techniques of laser labiaplasty of the labia minora. Pardo et al. [21] reported on 55 cases conducted between October 2003 and November 2004, where the primary indications were moderate hypertrophy and labial asymmetry, with 67% of cases due to these reasons. They noted a high satisfaction rate, with 91% of patients reporting being very satisfied and 9% satisfied, despite a 7% incidence of minimal suture dehiscence during the early postoperative period. In a similar manner, the study by Bizjak-Ogrinc et al. [22], which analyzed 80 patients from February 2015 to April 2018, found an equally high level of patient satisfaction with the sutureless laser labiaplasty technique. Their approach, interestingly, reported minimal side effects—7 instances of wound infection, and one case each of bleeding and hematoma formation, yet no patients were partly satisfied or dissatisfied. sutures.

Similarly, Li et al.'s study on 17 Chinese women, with an average age of 36.4 years, demonstrated significant improvements in vulvar texture and pigmentation after three treatment sessions, with a scoring system showing substantial changes ($p < 0.05$) and no adverse reactions [23]. Patients self-reported enhanced satisfaction, indicating both perceived and observed effectiveness. Similarly, Lauterbach et al. [24] assessed vaginal CO_2 laser treatment in a cohort of 25 women with sexual dysfunction and pelvic floor issues. They reported significant increases in vaginal elasticity and tightening post-treatment (54.8 ± 5.2 vs. 41.5 ± 6.3, P = 0.0027; 1.97 ± 0.25 vs. 1.32 ± 0.31, P = 0.0014), as well as improvements in pelvic muscle contraction strength (25.9 ± 3.5 vs. 16.5 ± 4.2, P = 0.0011) and FSFI and VHI scores. This study utilized vaginal tactile imaging (VTI) for objective assessment, adding robust quantification to support the clinical effectiveness of CO2 laser treatment in enhancing vaginal biomechanical properties.

Moreover, Messas et al. [25] reviewed 40 studies involving 3466 participants to assess the efficacy of fractional CO_2 ($FrCO_2$) laser therapy in treating genitourinary syndrome of menopause (GSM) and vulvovaginal atrophy (VVA) [25]. Their findings highlight the therapy's good efficacy and safety, with high patient satisfaction noted across studies. However, they also pointed out the lack of level I evidence and called for more randomized, sham-controlled trials to validate these results further and address clinical questions such as cost-effectiveness and potential synergistic effects with other treatments. Similarly, Géczi et al. [26] conducted a systematic review and meta-analysis of various labiaplasty techniques, analyzing data from 86 studies. They reported a high overall satisfaction rate (94%, CI 93%-95%) with specific techniques like deepithelialization, reaching even higher satisfaction rates (97%, CI 85%-99%). Despite these high satisfaction rates, they noted variations in complication rates across different techniques, with some, like the wedge resection, showing higher incidences of complications such as dehiscence. Both studies underscore the importance of personalized treatment approaches and the need for high-quality research to optimize outcomes in cosmetic genital surgeries.

The study by Smarrito et al. [27] provided a focused examination of secondary labiaplasties, reporting on 44 cases split into two main categories: those involving wound dehiscence primarily from lambda laser procedures and those related to over-resections or amputations. The authors highlighted the use of local flaps and lipofilling techniques to address aesthetic and functional issues resulting from over-resection, emphasizing the importance of surgical precision and anatomical knowledge to prevent such complications. In a similar manner, the systematic review and meta-analysis by Escandón et al. [28] surveyed a much larger cohort of 3804 patients across 46 studies, reporting a high satisfaction rate of 99% for labia minoraplasty. However, they also noted significant

complications, such as a 5% incidence of dehiscence from laser-assisted labiaplasty and up to 8% hematoma formation from W-shape resection. Both studies underscore the necessity of thorough training in surgical techniques and patient-specific approaches to optimize outcomes and minimize the need for subsequent corrective procedures. The findings from Escandón et al. [28] further support the observations of Smarrito et al. [27] by quantitatively demonstrating the impact of technique selection on complication rates and patient satisfaction, thereby reinforcing the call for meticulous surgical practice and adequate anatomical understanding in labiaplasty procedures.

Limitations

This study has several limitations. While the study provides valuable insights, limitations include its retrospective design and the reliance on patient-reported outcomes, which may introduce bias. The lack of a control group undergoing traditional surgical labiaplasty limits direct comparison of efficacy and safety between techniques. The retrospective design may introduce selection bias, as only patients who returned for follow-up were included. The sample size, while larger than some previous studies, is relatively small and may not represent the broader population. Reliance on subjective measures like the sGAIS may not capture objective functional improvements. Additionally, the absence of a control group limits the ability to compare laser labiaplasty directly with traditional surgical methods. Future prospective, randomized studies with larger sample sizes are warranted to validate these findings and optimize patient selection and procedural protocols.

CONCLUSION

Laser labiaplasty is an effective and safe, minimally invasive procedure for women seeking labia minora reduction due to aesthetic or functional concerns. The high patient satisfaction rates and low incidence of complications make it a valuable alternative to traditional surgical techniques. Personalized patient counseling and careful consideration of individual medical histories can further enhance outcomes. Future research should focus on long-term results and direct comparisons with other surgical modalities to establish standardized guidelines.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, F.D.; methodology, F.D.; software, F.D.; validation, M-M.C. .; formal analysis, M-M.C.; investigation, M-M.C..; resources, S.A.; data curation, S.A.; writing—original draft preparation, F.D., M.M.C. and S.A.; writing—review and editing, D.O.C. and F.D.; visualization, D.O.C. and FD.; supervision, D.O.C.; project administration, D.O.C. and F.D.; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Elos Clinic from Bucharest, Romania (protocol code NR 29 and date of approval 6 January 2020).

Patient consent for publication

Consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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https://doi.org/10.55453/rjmm.2025.128.3.8

REVIEW

Dermatoporosis. What We Know and What to Expect

Mihail A. Badea[1], Daniel O. Costache[2,3], Alin L. Tatu[4], Andrei C. Costache[5], Nicolas Kluger[6]

[1] Natural Skin Târgu Mureș, Mures, Romania
[2] Dermatology Discipline, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3] Research Department, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania
[4] Clinical Medical Department, Faculty of Medicine and Pharmacy, "Dunărea de Jos" University, Galați, Romania
[5] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[6] Helsinki University Central Hospital, Helsinky, Finland

Correspondence: Daniel O. Costache, daniel.costache@umfcd.ro; Alin L. Tatu, dralin_tatu@yahoo.com

Abstract: With the increase of the medium lifespan in developing countries, skin aging rise attention more and more. In 2007, Kaya and Saurat rebranded the extreme expression of skin fragility under the name of ''dermatoporosis'' or chronic cutaneous insufficiency/fragility syndrome. Dermatoporosis is still underused in medical literature and nurses and wound specialists know also about this condition, but they call it "skin tears". There is obvious confusion cause the nursing literature talks about skin tears while dermatologists write about dermatoporosis. Clinical aspects comprise atrophy, purpura, and pseudo-stellate scars. Firstly, the British dermatologist Thomas Bateman described senile purpura in 1818 as purpuric patches arising in elderly people after minimal trauma, especially on the dorsum of the hands. Furthermore, between 1970 and the full documentation of Kaya and Saurat in 2007, we found medical papers about senile purpura, pseudoscars, skin tears, and so on. Starting from this historical data, they bring valuable information according to clinical aspects, histopathology, ultrasonographic aspects, pathophysiology, and therapeutics. This paper aims to analyze published data for improving the diagnosis and management of dermatoporosis.

Keywords: dermatoporosis

HISTORY

With the increase of the medium lifespan in developing countries, a new type of dermatosis was described in 2007 by Kaya and Saurat under the name of 'dermatoporosis' of chronic cutaneous insufficiency/fragility syndrome [1,2,3]. Clinical aspects comprise atrophy, purpura, and pseudo-stellate scars (Figure 1). Firstly, the British dermatologist Thomas Bateman described senile purpura in 1818 as purpuric patches arising in elderly people after minimal trauma, especially on the dorsum of the hands [4]. Later, in 1967 Colomb reported pseudo-stellate scars as fibrous scars with a stellate aspect arising on the forearms of the elderly [5]. One year after this description, Frederik and Zak made the connection between stellate pseudoscars and senile purpura, describing that both arise on the forearms of the elderly after minimal traumas. They also report that the shape of these scars can be round or linear, not only stellate [6]. In 1972, Colomb described the trade consisting of atrophy, Bateman's purpura, and spontaneous pseudo-scars The term pseudoscars seems to be related to the fact that there is no solution of continuity with the exterior, the lesions are produced by a compression trauma without true lesions in the extreme external part of the skin, the epidermis [5,7]. Furthermore, there is a lack of reports between 1970 and the full documentation of Kaya and Saurat in 2007. Starting from this historical data and personal clinical cases, they bring valuable information according to clinical aspects, histopathology, ultrasonographic aspects, pathophysiology, and therapeutics [3]. The prevalence of dermatoporosis is about 30% in patients older than 65 years, but this aspect can vary according to the recruitment group: non-hospitalized patients, inpatients, outdoor patients, and patients for rehabilitation centers. The aim of this paper is to analyze published existing data for improving the diagnosis and management of dermatoporosis.

Citation: Badea MA, Costache DO, Tatu AL, Costache AC, Kluger K. *Dermatoporosis. What We Know and What to Expect*. R. J. Mil. Med. 2025, 128(3): 242-247; https://doi.org/10.55453/rjmm.2025.128.3.8

Academic Editor: Octavian Vasiliu

Received: 3 February 2025
Revised: 18 March 2025
Accepted: 12 April 2025

RISK FACTORS AND COMORBIDITIES

Only the future will decide if dermatoporosis is the expression of the general process of senescence, chronic sun exposure or even both [3]. Firstly, some data indicate that patients could have a genetic predisposition according to the connection with atopic dermatitis [8]. Furthermore, analyzing some aspects of aquaporines and skin aging previous statement is increased [9]. Aging plays a major role, the aging process acts mainly through chronic sun exposure, especially the professional type [3].

Figure 1: Clinical aspects of dermatoporosis: A) Dermatoporosis located on the forearms; B) Dermatoporosis located on the forearms and anterior thorax; C) Superficial hematoma after a minimal trauma; D) Deep hematoma in a patient with severe and extended dermatoporosis

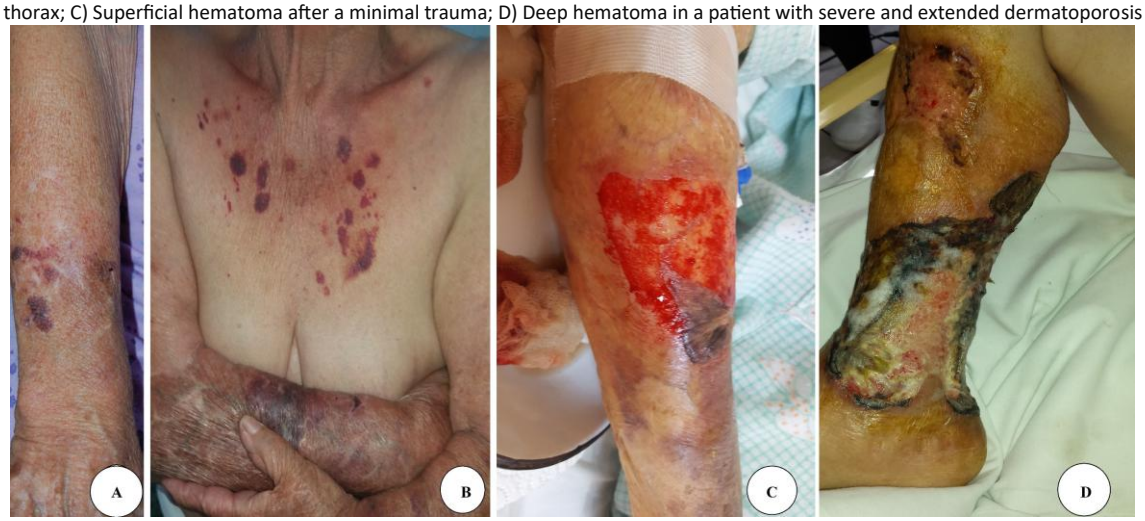


Figure 2: Bleeding after repeated procedures for peripheral vein catheterization in a female patient with primary dermatoporosis

Intrinsic aging or endocrine aging plays a role, the disease is more frequent in postmenopausal women [10]. On the other way, seems that maternal age > 40 years at last pregnancy, breastfeeding for > 7 months per pregnancy and > 18 cumulative months, age < 20 years at first pregnancy, and menopause after 45 years play a protective role against dermatoporosis [11]. Iatrogenic factors like systemic steroid usage especially in patients with blistering diseases can induce dermatoporosis by decreasing the extracellular matrix leading to skin atrophy.

Regarding topical steroids seems that only clobetasol propionate 0.5% can induce dermatoporosis, can it be used for more than six months, this aspect can be visible on the forearms in patients with psoriasis (Figure 3) [12]. The author documented also an interesting case of a 42 female old patient suffering from a secreting cortisol tumor with a Cushing syndrome aspect and typical lesions of dermatoporosis on the forearms (Figure 4). Other medications could be anticoagulants, and epidermal growth factor inhibitors (EGFR) used in the treatment of different carcinomas (Figure 5). Associated comorbidities like osteoporosis, renal failure, and anemia were cited [13].

Moreover, there is a strong connection between the degree of osteoporosis and dermatoporosis [14,15]. It is not clear yet if osteoporosis has a direct influence on the onset of dermatoporosis or if both are the result of the general aging process having hormonal disturbances at the base. Additional information was brought by Kluger in 2016 describing the possible connection of dermatoporosis with the lack of vitamin C levels [16]. Laboratory data about skin expression or serum levels of vitamin C and dermatoporosis are lacking. This correlation is based only on the benefits of topical or systemic administration of vitamin C [16,17].

Recently, vitamin D deficiency was also proposed as a factor by Romano et al based on the connection between osteoporosis and dermatoporosis. Anyway, correlation data between decreased levels of vitamin D and dermatoporosis degree in the elderly are necessary for validation [18]. Finally, most of the patients present an association of these risk factors.

Figure 3: Secondary dermatoporosis: A) Secondary dermatoporosis in a female patient treated with 0.5 mg prednisone per kilo of body weight for 4 months for bullous pemphigoid; B, C) Secondary dermatoporosis in 2 patients treated with 1 mg per kilo of body weight prednisone for 5 months for pemphigus vulgaris.

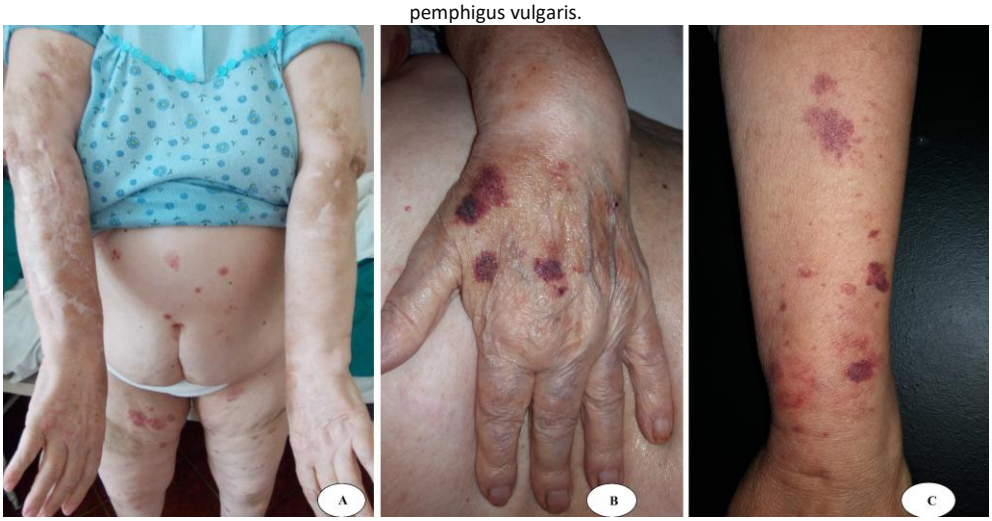


Figure 4: Secondary dermatoporosis in a 42-year-old-female patient diagnosticated with a secreting cortisol tumor: A) Cushing syndrome; B) Facial telangiectasia; C) Dermatoporosis on the forearms; D) Dermatoporosis on the shins.

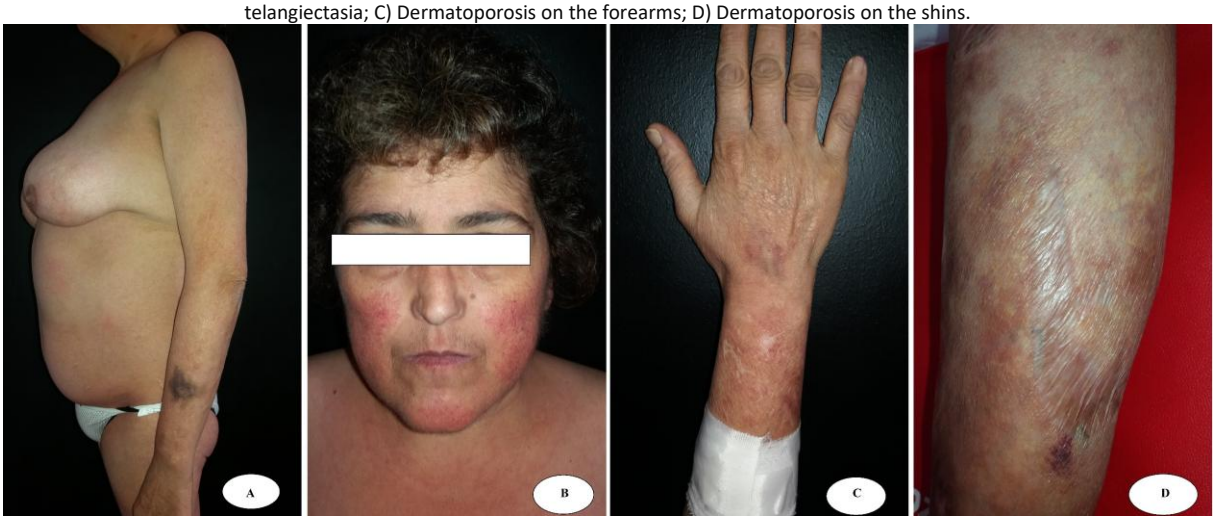
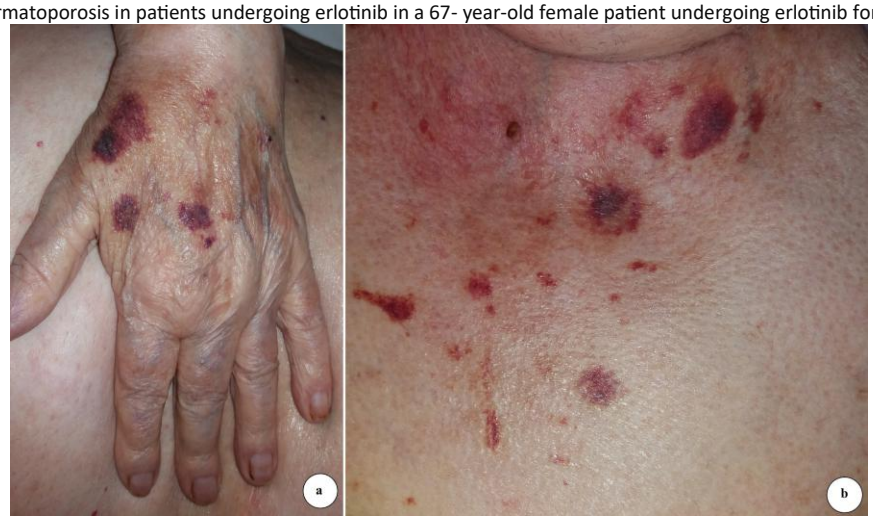


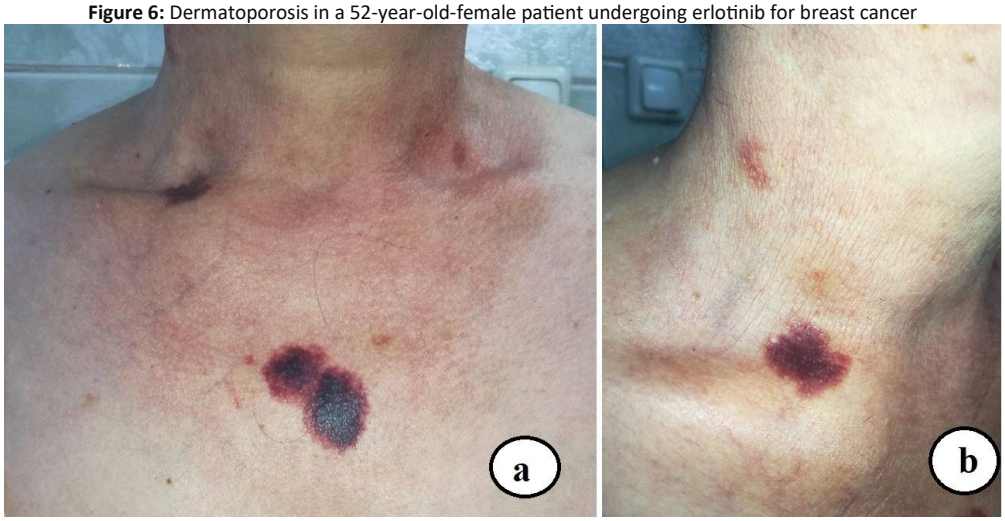
Figure 5: Dermatoporosis in patients undergoing erlotinib in a 67- year-old female patient undergoing erlotinib for lung cancer.



CLINICAL ASPECTS

The clinical changes are skin atrophy, purpura, pseudoscars, hyperpigmentation, and ulcerations. Due to atrophy, there is an increased risk of the appearance of superficial or dissecting hematomas of the skin that form by the accumulation of blood in between the hypodermis and the muscular fascia due to local traumas [3,19]. Most lesions are located at the level of the forearms and shins [3]. Other sites are the chest, arms, and dorsal parts of the hands. It is a tendency for females to develop lesions on the chest and face compared with men. The appearance of lesions at the level of the face and scalp is reported in rare and isolated cases [3,10]. Skin atrophy is the main sign of dermatoporosis. It is essential for the development of the other changes, so that, on the background of exposure to trauma of the underlying structures, purpura and skin ulcers develop. These heal with hyperpigmentation and scars [3]. Senile purpura (Thomas Bateman, 1818) occurs in the elderly, especially on the backs of the hands, and is often found in the context of dermatoporosis [3.4]. It has a complex mechanism, being produced by both exposure of blood vessels due to atrophic skin, and by a decrease in the elastic fibers of the vascular endothelium. An increase in capillary permeability with age is also taken into account [4,20]. Colomb stellate pseudoscars are found on the forearms of the elderly and are produced by defective remodeling of the extracellular matrix due to functional disturbances of enzymes such as metalloproteinases [21]. Appearance on the shins and other sites is also possible. They can be stellate, linear, or plaque-like. The stellate ones are the most common [3,10]. They are formed by the rupture of collagen fibers but without clinical evidence of a break in continuity at the level of the epidermis. Repair is done by excessive proliferation of fibrous tissue, which leads to a clinically hypertrophic scar appearance [5,7]. Pseudoscars are found in approximately 30% of people over the age of 70. Hyperpigmentations appear as residual lesions and as a sign of photodamaged skin [3,10,21]. Cutaneous ulcerations appear based on the cutaneous atrophy after some unnoticeable frequent minimal traumas. They appear at the level of the extremities [3].

Figure 6: Dermatoporosis in a 52-year-old-female patient undergoing erlotinib for breast cancer



NATURAL COURSE AND COMPLICATIONS

When the cause is obvious like usage of corticosteroids, local or oral, disruption of the treatment can improve greatly and stop the development of further purpura. Superficial hematomas are due to blood accumulation between the dermis and the subcutaneous fat. Clinically appears as a detachment of a skin region from the subjacent adipose tissue. They appear in the advanced stages of dermatoporosis and are found at the level of the shins as well as at the dorsal surface of the forearms [3]. Deep Dissecting hematomas of the skin (DDH) represents the main complication of dermatoporosis. They form as the accumulation of blood between subcutaneous fat and muscular fascia. It represents a surgical emergency due to the risk of block detachment of the cutaneous structures with exposure to infections of major muscular tissue areas. Due to the profound localization of blood collection, the detachment of the skin does not occur immediately. Thus, the lesions mimic cellulitis, presenting as painful erythematous-edematous plaques. People over 80 years with are affected, especially the females and they are located strictly on the calves. The positive diagnosis is done through magnetic resonance imaging (MRI) that shows a hypoechogenic band in the virtual space located between the hypodermis and the muscular fascia. DHH represents a major complication of the disease, the emergency surgical drainage being necessary. The repair of the residual defects is done slowly by the application of topical hyaluronic acid or with skin grafting [3,19] The development of non-melanocytic skin cancer is possible also on dermatoporotic skin, the author saw a case of actinic keratosis and one of cutaneous horn arising in the area of dermatoporosis (Figure 6).

DIAGNOSIS

Clinical aspects are usually enough for the diagnosis. More than that, Saurat developed a self-diagnosis tool (IDA: Index Dermatoporosis Assessment) consisting of a two-module questionnaire that is addressed to individuals aged ≥65 years. The technique was validated in France and Mexico. Skin ultrasonography quantifies the grade of atrophy showing a thickness of skin approx. 0.7-0.8 mm at the level of the regions with dermatoporosis (normal value = 1.3-1.5 mm). The usefulness of reflectance confocal microscopy

(RCM) for the diagnosis of dermatoporosis and quantifying skin thickness was proven by Mezinger, but is expensive and not accessible for routine. Electronic microscopy highlights the disorganization of collagen with parallel exposure of the fibers on the surface of the epidermis (88). Anyway, skin biopsy is an invasive tool, so is recommended to be avoided in such patients and usually is unnecessary when the diagnosis is obvious but might be necessary to rule out other diagnoses in case of atypical location or isolated lesions. For these cases, a 3 mm punch biopsy can be performed on non-erosive/ulcerated lesions without any risk. A general blood count to exclude bleeding disorders, exploration of renal function, and osteoporosis assessment is strongly recommended [3,8]. The fragility of dermatoporotic areas with bleeding and delayed healing results in significantly limited skin biopsies and secondary histopathological and immunohistochemistry studies.

CLASSIFICATION AND STAGING

Depending on the main etiological factors, dermatoporosis can be classified as primary or secondary. Regardless of the form, the lesions are located on the same regions of election such as forearms, shins, anterior part of the thorax, and dorsum of hands [3,10]. Face and scalp location was also cited [10]. Primary dermatoporosis or actinic is due to chronic exposure to the sun, especially in patients over 60 years who are affected. Secondary dermatoporosis lies behind iatrogenic factors, especially the prolonged utilization of corticotherapy. It is characterized by the possibility of the lesions appearing under the age of 60 as well as by partial or complete resolution of the lesions after corticotherapy cessation [3]. The systemic usage as well as topic one can lead to the development of the lesions. Regardless of the way of administration or the cutaneous location in the case of local therapy, the lesions develop in s the same regions/ zones as well as in primary dermatoporosis [3,6]. The disease presents four evolutionary stages. The first stage is characterized by atrophies, purpura as well as pseudo scars, and adding the presence of cutaneous ulcerations leads to the second stage. In the third stage, the ulcerations are increased in size and number. Development of DDH is characteristic of the fourth stage [3,6,19].

PREVENTION AND TREATMENT

The prevention consists firstly in avoidance of the triggers. Regarding this, there is the necessity to use the factors for photoprotection and the avoidance of trauma in patients who are already suffering from primary dermatoporosis. Careful organization at home with the furniture (« coffee table syndrome »), prevention of falling, also proper information of nursing staff the way they handle the patients, no adhesive directly on the skin, avoid excessive application of potent or highly potent corticosteroids. The first topical was proposed by Kaya in 2007, at the same time as the disease was described. The application of hyaluronic acid 1% leads to the improvement of the lesions [3]. In a recent study, topical or oral hydrolyzed collagen does not improve precocious lesions of dermatoporosis – stage I [23]. Topical retinoids are cited to be efficient in the treatment of dermatoporosis since their role is the re-establishment of the differential cellular process. The use of the combination of hyaluronic acid and retinyl-aldehyde is more effective than the separate application of these two [24]. Alpha-hydroxy-acids (AHA) are efficient by diminishing the grade of atrophy [25]. Humbert and colleagues sustain that dermatopororis, especially the Bateman senile purpura, is due to a deficit of vitamin C skin level and it shows an abatement of the lesions after applying topically vitamin C 5% [17]. There is limited data regarding the efficacy of topical application of topical human epidermal growth factor or dehydroepiandrosterone [26,27]. Systemic administration of vitamins C and D could bring some benefits [16,18]. An isolated case of dermatoporosis in the upper limbs treated with polymethylmethacrylate (PMMA) using the BioSculpt®technique was reported.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization, MAB; methodology, MAB, ACC; software, ACC; validation, DOC, ALT, NK; formal analysis, NK; investigation, MAB, ACC; resources, DOC, ALT, NK; data curation, ALT, NK; writing—original draft preparation, MAB, NK, ACC; writing—review and editing, DOC, ALT; visualization, ALT, NK; supervision, MAB, NK; project administration, DOC, ALT. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

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https://doi.org/10.55453/rjmm.2025.128.3.9

ORIGINAL ARTICLE

Physiological Demands of Real and Simulated Combat Flight

José F. Tornero-Aguilera[1]; Vicente J. Clemente-Suárez[2,3]; Santos Villafaina[4]; Miguel Á. Moyano Galán[5]: Juan P. Fuentes-García[5]

[1] Health and Sports. Kos Generating Health. Toledo, Spain. torneroaguilerajoseugr@gmail.com (J.F.T.-A.)
[2] Faculty of Medicine, Health and Sports, Universidad Europea de Madrid, Villaviciosa de Odón, Madrid, Spain.; vctxente@yahoo.es (V.J.C.-S.)
[3] Grupo de Investigación en Cultura, Educación y Sociedad, Universidad de la Costa, Barranquilla, Colombia
[4] Physical Activity and Quality of Life Research Group (AFYCAV), Faculty of Sport Science, University of Extremadura, Cáceres, Spain; svillafaina@unex.es (SV)
[5] Faculty of Sport Science. University of Extremadura. Avda. Universidad S/N, Cáceres, Spain; mmoyga1@gmail.com (M.A.M.-G.): jpfuent@unex.es (J.P.F.-G.)

Correspondence: Vicente J. Clemente-Suárez, vctxente@yahoo.es

Abstract: Combat aircraft pilots operate in highly demanding environments where their expertise and psychophysiological responses impact performance. This study evaluated the acute psychophysiological effects of simulated and real combat flight maneuvers. Twelve Spanish Air Force fighter pilots (mean age = 33.08 ± 5.21 years) participated, averaging 13.25 ± 5.15 years of military service, including deployments in international missions. Various physiological and metabolic variables—isometric hand strength, lower body strength, pulmonary capacity, blood oxygen saturation, urinary hydration levels, cortisol, and blood lactate concentrations— were measured before and after both simulated and real combat flights. Results showed no statistically significant differences between real and simulated flights for most variables, including blood oxygen saturation, lactate, glucose, cortisol, urine color, and physical fitness indicators. However, glucose levels significantly decreased after simulated flights ($p = 0.021$), and horizontal jump performance improved post-real flights ($p = 0.004$). The similarity in physiological responses suggests that simulators effectively replicate real combat conditions, reinforcing their value as a safe, effective training tool. Simulators enhance pilot preparedness while minimizing exposure to combat risks. These findings contribute to aviation psychophysiology, improving training protocols and operational readiness for both military and civilian applications, ultimately optimizing pilot performance and safety in high-risk environments.

Keywords: combat flight, fighter pilots, psychophysiological response, flight simulation, operational training

INTRODUCTION

The operational limits of military personnel are frequently challenged in a range of extreme scenarios, including parachute operations (both High Altitude High Opening [HAHO] and High Altitude Low Opening [HALO]), engagements in symmetrical and asymmetrical warfare, subterranean missions, and close-quarters combat situations. Among these, combat aviation is widely regarded as one of the most physiologically and psychologically taxing environments. Military pilots are exposed to both acute and chronic stressors, such as heightened autonomic nervous system activity, pronounced cardiovascular and hemodynamic responses, and sustained exposure to gravitational accelerations (G-forces), which can exceed 9G during high-intensity maneuvers. These conditions can substantially compromise functional capacity, manifesting in acute loss of consciousness, grey-out episodes, spatial disorientation, and blackouts, even when utilizing oxygen supplementation systems and G-suits. Furthermore, combat aviators must operate at altitudes exceeding 15 kilometers (~50,000 feet), with cabin pressurization and the administration of supplemental oxygen typically required above 7 kilometers (~20,000 feet) to mitigate the dangers associated with hypoxia and decompression illness during tactical missions [1,2,3,4,5].

Exposure to acute psychophysiological stress elicits pronounced sympathetic nervous system activation, increases in anaerobic metabolism—as evidenced by elevated blood lactate concentrations—and disturbances in several cognitive domains, including cortical arousal, memory retention, temporal perception, and perceived exertion. Repeated exposure to such stressors can induce habituation, which is associated with attenuated physiological responses and improved task performance. However, when stress exposure is prolonged and recovery is inadequate, this may result in deleterious long-term effects on both physiological and psychological health. As such, implementing training strategies that closely

Citation: Tornero-Aguilera JF, Clemente-Suárez VJ, Villafaina S, Moyano Galán MA, Fuentes-García JP. *Physiological Demands of Real and Simulated Combat Flight*. R. J. Mil. Med. 2025, 128(3): 248-255; https://doi.org/10.55453/rjmm.2025.128.3.9

Academic Editor: Clara Ursescu

Received: 19 November 2024
Revised: 30 March 2025
Accepted: 14 April 2025

mimic the stressors encountered in combat within a controlled setting is essential to enhance both operational effectiveness and the overall well-being of military personnel and aviators [5,6,7,8].

In this context, simulation-based training has gained increasing recognition as a method to reproduce the multifaceted stressors characteristic of combat environments. In aviation, flight simulators are commonly employed to replicate conditions such as high-G exposure, complex tactical maneuvers, and the cognitive load inherent to aerial combat. These simulated environments enable pilots to adapt to task-specific challenges without facing the direct risks associated with live combat operations. Prior investigations have demonstrated the utility of such simulators in assessing variables like mental workload, spatial orientation, and perceptual illusions under stress-inducing conditions. Nonetheless, despite their widespread implementation, research remains limited regarding the extent to which simulators replicate the full spectrum of psychophysiological responses observed during actual combat aviation [6,7,8,9].

Existing literature examining the physiological demands of real combat aviation has largely focused on variables such as G-force exposure, hypoxia, and the cumulative stress of extended tactical engagement. These studies have documented substantial physiological strain on the respiratory and muscular systems, as well as on metabolic processes, with measurable alterations in biomarkers such as lactate and cortisol. In contrast, flight simulators are engineered to recreate these stressors predominantly at a cognitive level, often falling short of reproducing the mechanical and gravitational stresses encountered in real flight. Although some findings suggest simulators effectively induce mental stress, there is insufficient empirical evidence to support their capacity to fully emulate the psychophysiological impact of actual combat flying [10,11,12].

A comprehensive understanding of the differential psychophysiological responses elicited by real versus simulated combat flight is imperative for refining pilot training regimens and operational planning. Given the considerable implications for pilot health and mission effectiveness, accurate replication of combat-induced stress in training environments is of paramount importance. This study seeks to address a notable gap in the current literature by directly comparing the physiological and metabolic responses of fighter pilots engaged in both real and simulated combat maneuvers. The outcomes of this research have the potential to inform the development of optimized training protocols, thereby enhancing preparedness for the demands of aerial warfare.

Accordingly, the present study hypothesizes that real combat flight induces significantly greater acute psychophysiological stress in pilots compared to simulated flight conditions. This hypothesis is grounded in the premise that, although simulation technologies are capable of replicating many cognitive stressors, they are inherently limited in their ability to reproduce the physical elements of combat aviation, including the effects of G-forces and mechanical loading. Elucidating these distinctions is essential for the advancement of simulation-based training strategies that adequately reflect the realities of combat flight.

MATERIALS AND METHODS

Participants

To achieve the objective of this research we analyzed the physiological response of fighter pilots before and after a simulated and real attack flight maneuver.

A total of 12 fighter pilots (age=33.08±5.21) from the Spanish Air Force participated in this cross-sectional study. Participants had mean military service experience of 13.25 ± 5.15 years, with experience in international missions in the current conflict in Lebanon, Afghanistan, Bosnia, Kosovo, and Iraq. Before participation, the experimental procedures were explained to all the participants, who gave their voluntary written informed consent in accordance with the Declaration of Helsinki. In addition, All the procedures were approved by the University research ethics committee (approval number: 206/219), and all participants agreed and gave written consent to participate in the study. Participants were equipped with the standard flying suit and boots, combat gear composed of parachute harness, life support jacket, and G-suit with a total weight of 10kgs.

Procedures

Pilots were evaluated before and after a real fight mission and a simulated one. Conditions, protocols, and procedures were exactly the same either in simulated or real combat. F5 combat aircraft was used for the real manoeuvres (Figure 1). For the simulated maneuvers, an operational F-5 M (Indra Company, Madrid, Spain) flight simulator was used (Figure 2). All pilots conducted both protocols, and 48 hours of rest between them were assigned. The tactical combat maneuvers were performed in the Air Fighting School of the Spanish Air Force at Talavera de la Real Air Base (Badajoz, Spain), in the middle of April month, between 08:00 and 15:00, with temperatures between 20 and 24 ºC and clear sky. Order and type of protocol were also randomized, in both cases, the protocol consisted of:

In both cases, pilots conducted both maneuvers at altitudes between 8000 and 18,000 ft, with G force between 0.5 and 5.9, with oxygen mix supply over 8000 ft with a combat duration between 30 and 35 min. The offensive maneuver consisted of a fighter aircraft that started at a 1-mile separation and a speed of 400 knots (unit of speed equal to one nautical mile). Both aircraft maintained a sustained rate of 410 knots and 5.5 Gs for 30 to 40 seconds until the target aircraft (referred to as the 'bandit') was within effective gun range. By this point, the bandit had closed the distance to the offensive aircraft, causing the speed to drop to 350–300 knots and the G-load to decrease to 4–4.5 Gs. After the initial bullet stream, a repositioning maneuver could be performed to solve range, aspect, and closure. Speed will decrease to 300 knots and gravity forces to 3G's to return to a control position of effective gun employment. The exercise started at 16000 ft and it progressively decreased to 10,000 ft. In the defensive maneuver, the lead aircraft turned to

one side to keep the pursuing offensive aircraft in sight. The exercise began at an altitude of 17,000 feet and a speed of 350 knots. Defensive aircraft executed a break turn at 4 G's slowing down at the same time, looking over the shoulder at the offensive aircraft to assess his pursuit curve. At 300 knots, the defensive aircraft executed turning maneuvers, gradually reducing G-forces from 3.5 to 2 Gs and speed to 200–250 knots. Depending on the progression of the air combat, the defensive aircraft could maintain an airspeed of 350 knots and a G-load of 3.5–4 Gs while descending. Exercise finished at 10000 ft.

Figure 1: F5 combat aircraft

Figure 2: F5 Indra Company (Madrid, Spain) flight simulator

Materials

One hour before and thirty minutes after finishing the air combat maneuvers the following variables were measured:

Lower body muscular strength employing horizontal jump test. Subjects performed a standardized warm-up consisting of 2x10 vertical jumps and then, they performed two maximal horizontal jumps as in the previous report (-), and the best attempt was used for the statistical analysis.

The forced expiratory volume in the first second (FEV1) corresponds to the maximum volume of air exhaled in the first second of the FVC. And mean expiratory flow or FEF25-75, which is between 25% and 75% of the forced expiratory maneuver. Were analyzed using a QM-SP100 (Quirumed, Spain) spirometer in a maximum inhale-exhale cycle.

Urine samples were collected to analyze dehydration levels which were examined by the urine color (UC) chart (color range 1-8; where 1 = very pale-yellow urine, reflected a good level of hydration, and 8 = very dark yellowish-brown, reflected a significant level of dehydration); the number closest to the sample color was recorded.

Isometric hand strength (IHS) by a grip dynamometer (Takei Kiki Koyo, Japan).

Blood oxygen saturation ($SatO_2$) and heart rate (HR) by a pulse oximeter (Pulse Oximeter 30 Beurer Medical).

Lactate and glucose samples were collected by taking a sample of 5 µl of capillary blood from the fingers of the pilots and analyzed by Accutrend Plus (Roche Diagnostics, Switzerland).

Direct Salivary Melatonin ELISA (Bühlmann, Schönenbuch, Switzerland) was used to measure cortisol concentrations.

Statistical analysis

Wilcoxon signed-rank test was used to examine the difference between the pre and post-measures. The baseline was subtracted to post-values to normalize and compare the acute effects of real vs. simulated flight. Effect sizes [r] were calculated for the non-parametric tests which are classified as follows: 0.5 is a large.

RESULTS

The results of the study revealed notable differences between the acute psychophysiological effects of real and simulated combat flights on specific metabolic, respiratory, and physical fitness variables. A significant reduction in glucose levels was observed following simulated combat flights (p = 0.021, effect size = 0.668), while this effect was not present after real flights. This finding suggests that the metabolic demands in simulated conditions may differ from those experienced during real combat maneuvers. Additionally, a significant improvement in horizontal jump performance was found after real flights (p = 0.004, effect size = 0.839), indicating enhanced lower body strength or neuromuscular efficiency induced by real combat flight conditions.

No significant differences were detected in other variables, including blood oxygen saturation, blood lactate levels, cortisol concentrations, urine color, respiratory function (FEV1, FER25, FEF75), or handgrip strength, either between pre- and post-measurements or when comparing real and simulated flight conditions. These results highlight the comparable physiological demands of simulated and real combat flights across most variables, emphasizing the potential of simulation-based training to closely replicate real flight conditions. However, the observed differences in glucose levels and horizontal jump performance underline specific areas where real combat flight may impose unique demands.

These findings suggest that flight simulators are effective tools for replicating many of the psychophysiological demands of combat aviation, while also identifying areas where real combat conditions elicit distinct responses. This information is critical for optimizing training protocols and ensuring pilots are adequately prepared for operational demands.

Table 1: Acute effects of real and simulated combat flight on metabolic, respiratory and physical fitness variables

	Variables	Baseline Mean (SD)	Post Mean (SD)	Baseline vs post measure		Acute effects of a real vs a simulated mission	
				p-value	Effect Size	p-value	Effect Size
Real flight	Blood oxygen saturation (%)	98.58 (0.51)	98.00 (0.74)	.100	0.475	.476	0.205
Simulated flight		98.08 (0.67)	98.08 (0.67)	.527	0.182		
Real flight	Lactate (mmol/l)	1.92 (0.78)	2.86 (3.04)	.367	0.261	.790	0.077
Simulated flight		2.62 (1.78)	3.25 (2.97)	.533	0.180		
Real flight	Glucose (mg/dl)	96.42 (9.57)	96.25 (8.61)	.844	0.056	.084	0.498
Simulated flight		102.75 (14.04)	92.50 (4.74)	.021*	0.668		
Real flight	Cortisol (µg/dl)	9.70 (5.78)	7.56 (6.30)	.158	0.408	.445	0.220
Simulated flight		6.30 (4.83)	6.87 (7.01)	.386	0.250		
Real flight	Urine color (a.u.)	3.75 (1.71)	3.17 (0.94)	.176	0.391	.887	0.044
Simulated flight		3.08 (1.08)	2.58 (1.44)	.092	0.486		
Real flight	Fev1 (l)	5.11 (1.19)	4.81 (0.66)	.450	0.218	.142	0.424
Simulated flight		4.83 (0.68)	4.85 (0.65)	.123	0.445		
Real flight	FER25 (l)	3.92 (0.61)	4.08 (0.44)	.308	0.294	.722	0.103
Simulated flight		4.13 (0.64)	4.16 (0.75)	.260	0.324		
Real flight	FEF75 (l)	10.10 (1.89)	9.72 (2.07)	.477	0.205	1.000	<0.001
Simulated flight		9.98 (1.91)	9.27 (1.99)	.678	0.120		
Real flight	Handgrip (N)	52.62 (6.08)	51.92 (7.43)	.759	0.088	.386	0.250
Simulated flight		50.62 (7.23)	51.09 (5.47)	.858	0.051		
Real flight	Horizontal jump (cm)	141.33 (11.10)	147.42 (12.99)	.004*	0.839	.878	0.044
Simulated flight		137.42 (9.10)	144.09 (10.32)	.055	0.553		

**p-value <0.05*

DISCUSSION

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible.

Future research directions may also be highlighted.

This study aimed to analyze the acute psychophysiological effects of simulated and real combat flights in military pilots. The findings emphasize the utility of flight simulators for training purposes, as no significant differences were observed in most physiological and metabolic variables between simulated and real combat flights. These results align with previous research demonstrating that modern simulators effectively replicate many of the stressors encountered in real-world conditions, such as mental workload and physical demands while avoiding the risks associated with live operations [13,14,15]. The high fidelity of modern simulators in recreating operational environments supports their role as indispensable tools in pilot training.

Despite the overall similarity in physiological responses, certain differences were evident, providing nuanced insights into the unique demands of real combat flights. A significant improvement in horizontal jump performance following real flights was observed, suggesting that real combat maneuvers may elicit greater neuromuscular activation compared to simulated conditions. This response could be linked to the heightened cortical arousal and increased recruitment of fast-twitch muscle fibers required to cope with the physical and cognitive demands of real flight maneuvers. Similar findings have been reported in high-intensity military tasks, such as close-quarter combat and parachute jumps, where lower body strength improves due to acute neuromuscular adaptations to high-stress conditions [16,17,18]. These findings reinforce the hypothesis that real-world stressors induce unique physiological responses that are challenging to replicate entirely in simulated environments.

Interestingly, no significant changes were detected in handgrip strength, highlighting the distinct demands placed on upper body fine motor skills in piloting. Unlike lower body strength, which benefits from gross motor activation, piloting requires sustained precision and control over joystick or yoke movements, which rely on fine motor skills rather than maximal force. Previous research has similarly noted that tasks involving fine motor coordination are less affected by acute fatigue compared to those demanding gross motor output [19,20,21]. These results suggest that while simulators effectively mimic many neuromuscular demands, they may not fully capture the precise motor control required during real flight operations.

The absence of significant changes in blood lactate levels following real flights contrasts with findings in other high-stress combat scenarios, where anaerobic metabolism typically increases due to intense physical exertion [22,23]. This discrepancy may be attributed to the effects of G-forces during real flights, which redistribute blood flow, potentially reducing capillary perfusion at peripheral sampling sites. Simulated flights, lacking such mechanical stressors, exhibited lactate levels closer to the anaerobic threshold, further supporting the influence of G-forces on metabolic responses [24,25,26]. Research on the physiological effects of G-forces in combat aviation highlights their role in altering cardiovascular and metabolic regulation, with implications for pilot performance and endurance [27,28].

Respiratory function, as assessed by spirometry and blood oxygen saturation, showed no significant differences between simulated and real flights. The stability of these variables suggests that the participants' high level of operational experience and training enabled them to maintain respiratory efficiency across both conditions. Previous studies have identified respiratory fatigue as more prevalent among less experienced pilots or during extended operations [29,30]. The lack of observed respiratory impairments in this study underscores the resilience of experienced pilots. However, the reliance on spirometry alone may have limited the scope of respiratory assessments. Advanced techniques such as wearable strain gauge sensors or optoelectronic plethysmography could provide a more detailed understanding of respiratory patterns during flight [31,32].

Cortisol levels remained stable across both flight conditions, a finding that may reflect the effects of habituation associated with extensive operational experience. High-stress environments often elicit significant cortisol responses in less experienced individuals, but research has shown that habituation to stress reduces these responses over time in seasoned personnel [33]. This phenomenon is consistent with studies in other military contexts, where experienced individuals exhibit attenuated psychophysiological responses to acute stressors [34]. The stability of cortisol levels in this study further emphasizes the importance of experience in mitigating stress responses during high-pressure scenarios.

Hydration profiles, assessed through urine colorimetry, did not differ significantly between simulated and real flights. However, the hydration levels observed were close to dehydration thresholds, highlighting the need for improved pre-flight hydration strategies. Dehydration has been shown to impair both physical and cognitive performance, particularly in high-stress environments such as combat aviation [35,36,37]. The use of urine color charts for hydration monitoring has been validated in clinical and operational settings, offering a practical tool for maintaining optimal hydration status among pilots [38]. Addressing hydration deficits could enhance both safety and performance during flight operations.

The results of this study contribute to the growing body of literature emphasizing the effectiveness of flight simulators in replicating the majority of psychophysiological demands associated with real combat flights. However, the observed differences in neuromuscular and metabolic responses highlight specific areas where real flight conditions impose distinct challenges that simulators may not fully replicate. For instance, while simulators effectively mimic the mental workload and basic physiological demands of combat aviation, they may not accurately replicate the physical effects of G-forces or the fine motor requirements of real piloting.

These findings have important implications for the design and implementation of simulation-based training programs. By identifying the limitations of current simulators, training protocols can be refined to better prepare pilots for the unique demands of real combat scenarios. For example, incorporating supplementary training exercises that target neuromuscular activation and motor coordination

could address the gaps identified in this study. Additionally, integrating advanced physiological monitoring tools, such as portable biosensors and electroencephalography, could enhance the precision and effectiveness of simulation-based training [39,40,41].

Limitations of the study

This study has several limitations that should be considered when interpreting the results. First, the relatively small sample size (n = 12) limits the generalizability of the findings, particularly given the elite status of the participants as experienced military pilots. Access to larger samples in similar operational contexts remains a challenge, but it would enhance the robustness of the conclusions. Second, the study did not control for gender differences, which may introduce variability in psychophysiological responses. Given the increasing presence of female pilots in military aviation, future studies should aim to include a gender-balanced sample.

Another limitation is the reliance on conventional physiological and metabolic measures, such as spirometry and blood lactate levels, which may not fully capture the complexity of pilot responses during flight. The lack of advanced monitoring techniques, such as electroencephalography (EEG) or respiratory inductive plethysmography, restricts the scope of insights into neuromuscular and respiratory dynamics. Additionally, the study did not evaluate psychological measures such as perceived exertion, stress, or workload, which are critical components of the psychophysiological response in high-stress environments.

Finally, while the study focused on acute effects, it did not assess the cumulative impact of repeated exposure to simulated and real flight conditions. Chronic stress and its potential long-term effects on pilot health and performance warrant further exploration.

Practical applications

Our research on the effects of experience on the findings of this study has direct implications for improving pilot training and operational readiness. The demonstrated effectiveness of flight simulators in replicating many psychophysiological demands of real combat flights supports their continued use as a safe, cost-effective, and practical training tool. Simulators allow pilots to acclimate to combat stressors without exposure to the risks associated with live operations, such as physical injury or equipment failure. These insights reinforce the value of simulators in enhancing pilot preparedness, particularly during the early phases of training.

The observed differences in neuromuscular activation and metabolic responses between real and simulated flights highlight areas where simulation-based training can be refined. Incorporating supplementary neuromuscular exercises, such as lower body strength training, may enhance physical preparedness for real combat scenarios. Additionally, addressing hydration deficits through pre-flight hydration protocols could mitigate the risk of dehydration-related performance decrements.

Moreover, the study underscores the importance of tailoring training protocols to individual pilot characteristics, including experience level and physiological baseline. Advanced monitoring technologies, such as wearable biosensors, could be integrated into training programs to provide real-time feedback on physiological and psychological responses, enabling personalized training adjustments.

Future research lines

Future research should build upon the findings and limitations of this study by addressing several key areas. First, future studies should include larger sample sizes and greater diversity, particularly through the inclusion of female pilots. This approach would improve the generalizability of findings and allow for a deeper exploration of potential gender differences in psychophysiological responses. Additionally, investigations into the cumulative effects of repeated exposure to both simulated and real combat flight conditions are essential. These studies could provide valuable insights into the long-term impact of operational stressors on pilot health, performance, and resilience, areas that remain underexplored.

Advanced physiological and psychological monitoring tools should also be integrated into future research. Techniques such as electroencephalography (EEG), respiratory inductive plethysmography, and portable biosensors could offer a more comprehensive understanding of pilot responses. These tools would enable the assessment of critical parameters, including brain activity, detailed breathing dynamics, and stress biomarkers, allowing for a more nuanced analysis of the interaction between physiological and psychological stressors.

Incorporating psychological measures, such as perceived exertion, workload, stress, and fatigue, will also enhance future studies by providing a holistic view of pilot performance under stress. These measures would complement physiological data and help elucidate the interplay between mental and physical demands in combat aviation. Furthermore, comparing psychophysiological responses between novice and experienced pilots would yield valuable insights into how training and habituation influence operational readiness, offering opportunities to tailor training programs to the specific needs of pilots at different stages of their careers.

Another important area for future research involves enhancing the fidelity of flight simulators. Efforts should focus on better replicating the physical effects of G-forces and other unique stressors encountered during real combat flights. Advanced simulation technologies that integrate neuromuscular and metabolic stressors could bridge the gap between simulated and real flight conditions, thereby improving training effectiveness.

Hydration and nutritional strategies represent another critical avenue for investigation. Tailored interventions to optimize hydration status and metabolic recovery could significantly enhance pilot performance during combat scenarios. Research in this area would address a practical operational need and contribute to the development of evidence-based protocols to support pilot health and performance.

Finally, cross-operational comparisons should be conducted to broaden the scope of research. Investigating psychophysiological responses across different aviation contexts, such as helicopter pilots or unmanned aerial vehicle (UAV) operators, would provide a more comprehensive understanding of aviation-specific stressors and their management. These comparisons would also facilitate the identification of universal stressors and strategies applicable across various aviation roles, contributing to the overall advancement of the field.

CONCLUSION

The present study underscores the essential function of flight simulators within pilot training frameworks, particularly in their capacity to replicate a substantial portion of the psychophysiological demands encountered in actual combat aviation scenarios. Nevertheless, the discrepancies identified in neuromuscular activation patterns and metabolic responses indicate that simulators may fall short in fully emulating the intricate physiological challenges of real-world flight operations. Bridging these limitations through the integration of targeted training interventions and sophisticated monitoring methodologies has the potential to enhance pilot preparedness and physiological resilience, thereby contributing to improved performance and mission safety. These results highlight the necessity of ongoing research aimed at refining training protocols to ensure that pilots are effectively equipped to meet the complex requirements of contemporary aerial warfare.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Acknowledgments

This study has been made thanks to the contribution of the 3rd Wing located in the Talavera la Real Air Base (Badajoz) of the Spanish Air Force (Ministry of Defence) as well as the Department of Economy and Infrastructure of the Junta de Extremadura through the European Regional Development Fund. A way to make Europe (GR18129 and GR21094).

Authors' contribution

Conceptualization, V.J.C.-S., S.V. and J.P.F.-G.; methodology, V.J.C.-S., S.V. and J.P.F.-G.; formal analysis, J.F.T.-A., V.J.C.-S., S.V. and J.P.F.-G.; investigation, J.F.T.-A., V.J.C.-S., S.V., M.A.M.-G. and J.P.F.-G.; resources, J.P.F.-G. and V.J.C.-S.; data curation, J.F.T.-A., V.J.C.-S., S.V., M.A.M.-G. and J.P.F.-G.; writing—original draft, J.F.T.-A.; writing—review & editing, J.P.F.-G. and V.J.C.-S; visualization, M.A.M.-G.: supervision, V.J.C.-S. and J J.P.F.-G.; project administration, J.P.F.-G.; funding acquisition, J.P.F.-G. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the University of Extremadura (approval number: 206/219: July 24, 2019).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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https://doi.org/10.55453/rjmm.2025.128.3.10

ORIGINAL ARTICLE

Therapeutic Particularities of Depression in Relapsing-Remitting Multiple Sclerosis

Emilia Furdu-Lunguț[1,2], Silviu Lunguț[3], Dan G. Costea[4], Andrei Bodor[5], Horațiu Moldovan[6,7], Gabriel P. Gorecki[8,9]

1 Department of Neurology, Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania; emilia.furdu@spcf2.ro
2 Department of Neurology, Clinical Hospital CF2, Bucharest, Romania
3 Profesor Alexandru Trestioreanu Oncologic Institute, Bucharest, Romania; silviulungut47@gmail.com
4 Department of General Surgery, Clinical Hospital CF2, 011464, Bucharest, Romania; dancostea2006@yahoo.com
5 1st Department of Cardiovascular Anesthesiology and Intensive Care, Prof. Dr. C. C. Iliescu Emergency Institute for Cardiovascular Diseases, Bucharest, Romania; andrei.bodor@rez.umfcd.ro
6 Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; horatiu.moldovan@umfcd.ro
7 Academy of Romanian Scientists, Bucharest, Romania
8 Department of Anesthesia and Intensive Care, "Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania; gabriel.gorecki@prof.utm.ro
9 Department of Anesthesia and Intensive Care, Clinical Hospital CF2, Bucharest, Romania

Correspondence: Dan-Gabriel Costea, dancostea2006@yahoo.com

Abstract: Multiple sclerosis (MS) is an autoimmune disease in which the myelin sheath is damaged by the body itself. Because of the symptoms and progressive forms, in most cases, patients experience recurrent depressive disorder or anxious depression disorders. Depression treatment for MS patients stands in two categories, one is psychotherapy and the other is pharmacological. This article presents the research results on customized pharmacological treatment schemes applied to a group of relapsing-remitting multiple sclerosis (RRMS) patients with moderate, or severe, depression. All of them are included in the national treatment program for multiple sclerosis and their health state is continuously monitored. The therapeutic scheme based on four different antidepressants had encouraging results, meaning that any of the antidepressants used is efficient and with the patient's good tolerance. There were no side effects that could determine interruption of the treatment. Further research development would focus on improved therapeutic plans for patients with depression disorders in relapsing-remitting multiple sclerosis.

Keywords: depression disorder; therapeutic particularities; multiple sclerosis; HAM-D scale

INTRODUCTION

In 1868, the neurologist Jean-Martin Charcot mentioned for the first time multiple sclerosis (MS) as a neurological affection with unpredictable evolution varying from benign (mild) up to aggressive. This illness especially affects people, aged between 30-50 years, most of them being diagnosed in their mid-thirties. There are also teenagers affected, mostly the ones who smoke and the overweight young women. The official reports [1] mention the ratio of males and females as 1:3.

There is no identified specific factor to trigger MS, so the assumption is that of a series of factors that could cause the disease, like:

- genetic factors - usually, if one parent has a diagnosis of multiple sclerosis, the risk for their children to have MS is about (2 - 3)%, and, more importantly, if both parents have a diagnosis of multiple sclerosis, the risk for their children to have this disease is about (12 - 30)%;

- Environmental factors - are diverse and perhaps complementary, of which the following are considered relevant: prolonged sun exposure during childhood and adolescence - determines high serum vitamin D levels and thus lower risk of MS; smoke from smoking - affects systemic immunity and can damage the central nervous system (CNS); obesity - especially in teenage girls, when hormonal changes that occur secondary to obesity are related to inflammatory processes; sleep disturbance - wake cycle and poor quality of rest; brain trauma - when being a child or adolescent could cause the disease.

Multiple sclerosis is an autoimmune neurodegenerative disease that acts on and destroys the central nervous system [2,3]. It is an inflammatory disease that leads to demyelination and axonal loss, resulting in manifest cognitive, motor, or sensory symptoms such as depression, emotional distress, or anxiety. As mentioned in [4],

Citation: Furdu-Lunguț E, Lunguț S, Costea DG, Bodor A, Moldovan H, Gorecki GP. *Therapeutic Particularities of Depression in Relapsing-Remitting Multiple Sclerosis*. R. J. Mil. Med. 2025, 128(3): 256-264; https://doi.org/10.55453/rjmm.2025.128.3.10

Academic Editor: Octavian Vasiliu

Received: 7 January 2025
Revised: 30 March 2025
Accepted: 14 April 2025

the clinical course of MS is classified as follows: Clinically Isolated Syndrome (CIS); Relapsing-Remitting (RRMS); Primary Progressive (PPMS); Secondary Progressive (SSMS).

Once the evolution of MS is on, the predominant emotional disorder is stated to be [5,6] depression. Patients with depression also have a poor psychosocial quality of life, manifest diminished capacity to work, and manifest decreased therapeutic compliance.

Most of the studies [7,8,9,10,11] mention fatigue, depression, and pain as inherent disorders associated with structural and functional changes in the brain in MS. These changes have been noticed in the basal ganglia, prefrontal cortex, and limbic system [12,13,14].

Comorbid fatigue and/or depression symptoms reported in patients with MS are also linked to impairment of the hypothalamic-pituitary-adrenal (HPA) axis [15]. Because chronic fatigue and depression are low levels of cortisol and dehydroepiandrosterone (DHEA) it is possible to be endocrine contribution. Studies [16,17] have proved that MS patients state to have increased energy after taking corticosteroids as treatment for MS relapse.

As mentioned in [18,19] depressive disorder (MDD), or clinical depression, represents a debilitating disease exhibiting at least one major depressive episode for at least two weeks, with an evident bad mood, low interests and pleasure (anhedonia), poor cognition and neurovegetative symptoms (fatigue, loss of appetite, insomnia). There is a high focus on improving the quality of life for MS patients. Depression treatment usually is individualized and is split between associated pharmacological and non-pharmacological ones.

The pharmacological treatment with Desipramine (tricyclic antidepressant) 200 mg/day [20] and Paroxetine (selective serotonin reuptake inhibitor) 40 mg/day [21] is mentioned in comparison with placebo, for a period of five and, respectively, twelve weeks. As a result, there was noticed a slight improvement of depression symptoms but, not a statistically significant result.

In [22] it is analyzed how a specialized exercise training program with prescriptive guidelines [23, 24] having as background the social cognitive theory sustains the reduction severity of depressive symptoms in MS patients.

This article presents the research results on therapeutic particularities of depression, a survey carried out on a group of relapsing-remitting multiple sclerosis (RRMS) patients with moderate, or severe, depression forms. The therapy plan was developed based on the authors' expertise in the treatment of multiple sclerosis and mainly consists of the administration of one of the following antidepressants: venlafaxine; sertraline; mirtazapine; and trazodone. The diagnosis and the severity of depression were evaluated by the total Hamilton Depression Rating Scale (HAM-D).

Aspects of materials and methods used in research, as well as results, discussion, and conclusion of the obtained results, are evidenced in the next chapters. Further research development focus is also mentioned.

MATERIALS AND METHODS

There are different signs of multiple sclerosis [25,26] caused by the location and severity of the myelin sheath lesions. Troubles in moving arms or legs, disorders in equilibrium, visual disturbances, or, when severe, loss of ability for independent motion - these are the alarm signals for this illness.

For the moment, there is no specific and targeted treatment for curing MS, but there are therapeutic schemes usually focusing on fast and high recovery from attacks, reducing probabilities of relapse, slowing down the disease progression, and adequate managing of symptoms. There are also cases when the symptoms are mild and patients do not need specific treatment.

While MS attacks are on, for reducing inflammation of the nerves are used intravenous corticosteroids. If there is no positive response to corticosteroids and the symptoms are extremely severe, plasma exchange can be used for ease of symptoms (not for curing). There are also treatment schemes for lowering the rate of relapse and reducing the risk of brain atrophy, such as immunomodulatory medication, monoclonal antibodies, or antihistamines. Solutions for MS symptom relief are various and customized on patients, like: kynetotherapy to increase muscle strength; muscle relaxers for reducing pain in muscle rigidity; specific medication against pain, insomnia, and depression; and psychological counseling.

There is a common opinion regarding the risk of immobilization for patients with multiple sclerosis but, the highest risk for them is that of suicide. Psychological manifestations have been noticed since the 19th century [27], once the clinical signs of this illness have been described.

About 50% of patients with multiple sclerosis exhibit at least one depression symptom, and a percentage varying in-between (15 ÷ 30)% of these patients have severe depression disorder.

A comprehensive study [28] indicates that the majority of MS patients present with both anxiety and depression symptoms. However, due to the presence of multiple overlaps in diagnostic criteria, it is challenging to ascertain the exact frequency of each of these conditions. The predominant feature of their syndrome points towards depression, anxiety, or, mixed anxiety-depressive disorder. Even for now, it has not been identified yet a direct relationship between multiple sclerosis and depression, the main mechanisms are assumed to be the ones that follow:

- Depression is determined by the process of damaging specific brain zones, related to the control and manifestation of emotions. There are also immune and endocrine changes induced by MS that could determine bad mood feelings.

- Depression is triggered by the emotional impact of the patient when finding out the medical diagnosis of multiple sclerosis.

- Depression manifests as a side effect of pharmacological treatment, like interferon-based medications or corticosteroids.

The criteria for diagnosis of depression, as mentioned by the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 [27] are evidenced in Table 1.

Table 1: Criteria of depression by DSM-5 [26]

No.	Criteria	Tick √ if YES within two weeks
1	Mood of depression - long time a day, almost every day	
2	Diminished interest/pleasure in most activities - long time a day, almost every day	
3	Significant weight loss/gain without specific dieting	
4	Slow down in decision-making and performing physical activities (relevant to the others)	
5	Fatigue and poor energy	
6	Bad feelings and guilt for most of the things done - almost every day	
7	Difficulty in concentration and thinking, indecisiveness - almost every day	
8.	Repeated thoughts of death, suicidal behavior	

An individual is diagnosed with depression if, at least, five of the above symptoms are exhibited within two weeks and one of them should be depressed mood and/or diminished interest or pleasure. Attention is to be given so that symptoms do not result from any substance abuse.

There are also two additional specifiers for the diagnosis, of depression:

- with mixed features – such as manic symptoms;

- with anxious distress – the presence of anxiety symptoms;

The depression causes are multiple and commonly classified in four main categories (A ÷ D), as follows:

A. Psychosocial stress - that represents the disability in MS because it is generated by: global physical impairment; illness evolution in pus, with no possible estimation in time; motor deficits; diminished social role / inadequate support from the family.

B. Neuro-immune-endocrine triad (see figure 1) - as in MS patients the severity of depression depends directly on the amount of cytokines, IFN. In this research, there was noticed decrease in IFN amount after antidepressant treatment, once the depression symptoms diminished. The cytokines stimulate the axis: HHA (hypothalamic-hypophyseal-adrenal) CRH (Corticotropin-releasing hormone) ACTH (Adrenocorticotropic hormone) CORTISOL. The cytokines disturb the metabolism of monoamines (serotonin, non-adrenaline, dopamine) by prostaglandins - in cerebral areas highly important for depression: the hippocampus and hypothalamus.

C. Relationship between brain injuries and depression - based on neuroimaging evidence (RMN). Multiple sclerosis illness does affect myelin and nerve conduction so depression could be a direct consequence of the disease. The severity of depression directly depends on the right temporal lesions of the frontal lobe and the area adjacent to the basal ganglia.

D. Pharmaceutical treatment - there is no relevant evidence of increased occurrence of depression symptoms caused by the MS pharmacological treatment. Mainly, if the depression gets worse it is caused by the worsening of disability. Depression treatment for MS patients stands in two categories, one is psychotherapy and the other is pharmacological. Psychotherapy commonly consists of: psychological counseling; support therapy and cognitive-behavioral techniques.

To diminish depression, there are some additional steps [29] that could be done by multiple sclerosis patients, complementary to psychotherapy and pharmacological treatment, such as:

- physical exercises - that determine higher endorphins rate and, as a consequence, reduce fatigue and better mood;

- stress management program - meditation;

- talk about feelings and emotions - to a friend, family member, or, priest;

- belong to a community - to take part in targeted activities (walks, talks, reunions);

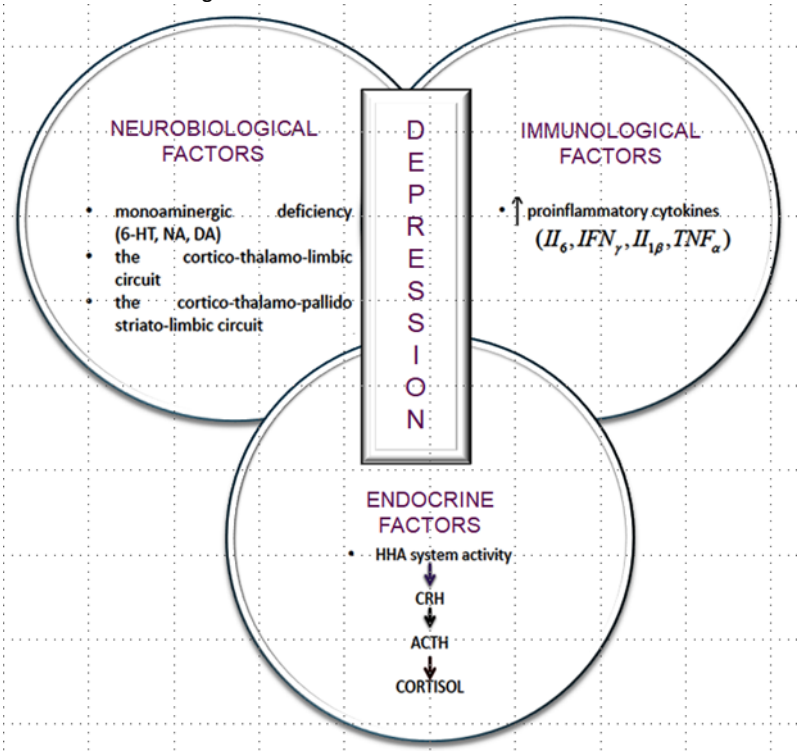
- find something that makes you happy and enjoy the day;

- help other people in need - get a sense of worthiness and utility;

- pet adoption - if possible and allowed by doctors;

- excellent sense of humor.

Figure 1: Neuro-immune-endocrine triad scheme



In this research the focus is not on either psychotherapy, or additional actions, even the patients in the sample group also practiced some of these therapies. This research is focused on the therapeutic particularities of depression, in relapsing-remitting multiple sclerosis (RRMS) patients.

Pharmacological treatment in depression for relapsing-remitting multiple sclerosis patients is evidenced in Table 2. These therapeutic schemes are particularly used in neurology clinics the authors work. All the patients of the survey are included in the national program for the treatment of multiple sclerosis and monitored by: neurological examination; brain imaging; psychological examination; and psychiatric examination.

Table 2: Pharmacological treatment in depression

Class	Representative	Dose [mg/day]	Comments
ADT (antidepressants)	Nortriptyline Desipramine	50 ÷ 200 100 ÷ 300	- limited use because of anticholinergic side effects (dry mouth, constipation, urinary and cardiovascular disorders)
SSRI (selective serotonin reuptake inhibitors)	Sertraline Fluoxetine S-Citalopram	50 ÷ 200 20 ÷ 80 10 ÷ 20	- good tolerance; - efficiency; - side effects (sexual dysfunctions, insomnia)
NaSSA (noradrenergic and specifically serotonergic antidepressants)	Mirtazapine	15 ÷ 45	- efficiency; -minimum effects on sexual function; - side effects (weight gain, drowsiness)
SARI (reuptake inhibitors and serotonin 2A antagonists)	Trazodone	150 ÷ 300	- efficiency; - minimum effects on sexual function; - side effects (drowsiness, orthostatic hypotension)
NDRI (noradrenaline and dopamine reuptake inhibitors)	Bupropion	150 ÷ 400	- efficiency; - minimum effects on sexual function; - side effects (convulsions, psychotic symptoms)
SNRI (serotonin and noradrenaline reuptake inhibitors)	Venalafaxine	75 ÷ 225	- efficiency; - side effects (intestinal disorders, psychotic symptoms, arterial hypertension)

The patients in the research group were diagnosed and subsequently admitted to the hospital when acute attacks occurred. Because of the relapsing attacks, patients develop anxious depressive disorder with panic attacks. Once the severe symptoms were relieved, they were discharged from the hospital and followed up the therapeutic scheme so that to get into the survey.

Initially, it was considered for the study a group of 102 patients, registered within a period of 4 years (2019 - 2023). Because of changes in their health conditions, mental and willingness to take part in the study, not the least family involvement, some of them had to retire. So, the size of the study (sample) group got down to 58, but its size remains fit for a research study (as the sample size is greater than 30).

The survey group is made of 58 relapsing-remitting multiple sclerosis patients with moderate, or severe, depression, out of which 18 are males with ages in between 18 and 30 years. The others are 40 females with ages between 30 and 40 years.

One can notice the higher percentage of females with MS diagnostic (40 out of 58, meaning around 69%) aspect revealed by most of the specific literature references. There has to be mentioned the fact that young people (above 25 years old) usually suffer from anxiety or anxious depression disorder, while mature people suffer from anxious depression disorders or recurrent depressive disorders. The survey period lasted for 16 weeks.

The customized therapeutic scheme applied for diminishing depression, based on the authors' expertise in the diagnosis and treatment of (relapsing-remitting) multiple sclerosis consists of the administration of one of the antidepressants (see Figure 2):

- venlafaxine - for 7 patients (12%), in flexible dosing of 75 ÷ 150 mg/day;

- sertraline - for 8 patients (14%), in flexible dosing of 50 ÷ 100 mg/day;

- mirtazapine - for 19 patients (33%), in a dose of 30 mg/day;

- trazodone - for 24 patients (41%), in a dose of 150 mg/day;

The selected percentages for medication considered the medical history of patients and estimated positive effects of the antidepressant. Also, previous experience of the authors (medical team) in the administration of these types of medicines is important. If there are multiple relapsing attacks, an increase in dosage has to be considered.

The antidepressant medication has to be administrated only in consideration of the following rules (see Figure 3):

- the patients who do not exhibit hypnic jerk were administered sertraline or venlafaxine which do not have sedative effects;

- the patients with hypnic jerk were administered mirtazapine or trazodone, as they also have sedative effects;

- the patients with appetite decrease/weight loss were administered mirtazapine.

Figure 2: Schematic representation of the depression medication for RRMS patients

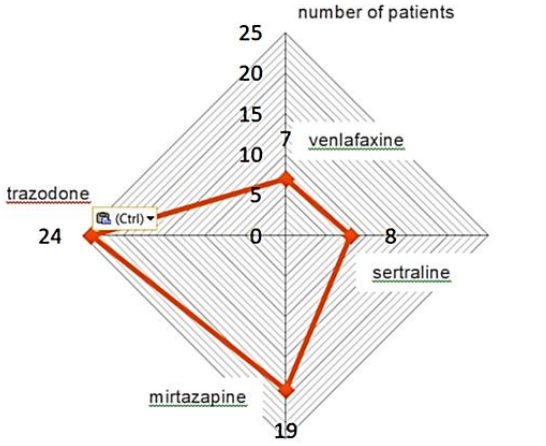
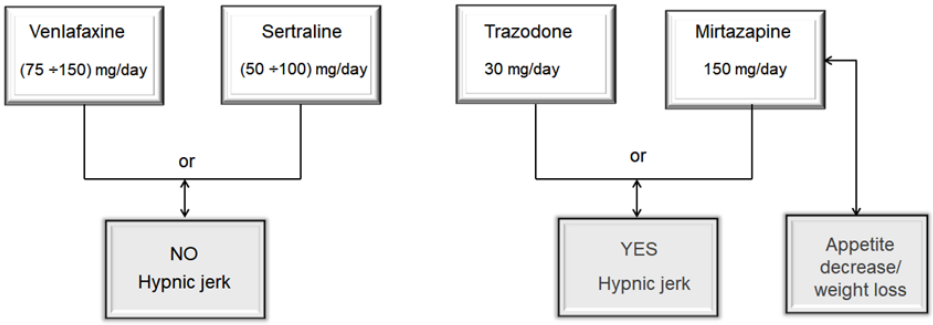


Figure 3: Customized therapeutic plan for RRMS patients



RESULTS

In diagnosing depression among patients with relapsing-remitting multiple sclerosis, it's essential to apply DSM-5 criteria tailored for MS. Recent guidelines from the National Multiple Sclerosis Society (2025) highlight the interplay between neurological symptoms and psychological distress in MS. These updated guidelines advocate for a nuanced diagnostic approach beyond traditional tools like the Hamilton Depression Rating Scale (HAM-D), ensuring diagnoses reflect current clinical insights.

This scale is a multiple-item questionnaire, providing a self-evaluation tool for depressive symptoms. The advantage of using HAM-D is that of high fidelity [30] in terms of clinical symptom assessment due to multiple questions for most of the items. It is compatible with DSM and provides an indicator for the severity of depression reported by an adult, based on a threshold score of clinical value.

Some relevant aspects of HAM-D and its scores are mentioned [31,32] next:

- the scale is scored between 0 and 4;

- scores of 0–7 suggest normal state;

- scores of 8–16 suggest mild depression;

- scores of 17–23 suggest moderate depression;

- scores starting from 24 suggest severe depression.

Before starting the customized depression disorder therapeutic schemes, based on the HAM-D test results, patients were divided into five groups, depending on test scores, as follows:

- 14 patients with HAM-D = 25 (group 1, G1);

- 5 patients with HAM-D = 21 (group 2, G2);

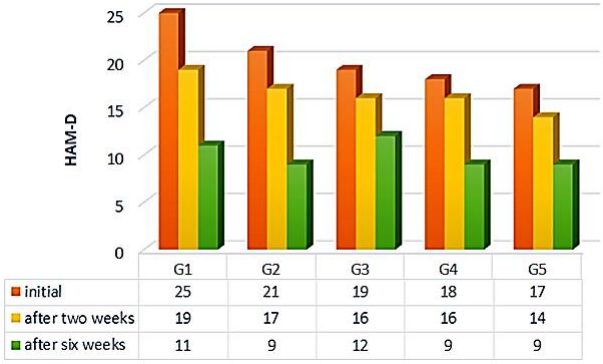
- 22 patients with HAM-D = 19 (group 3, G3);

- 14 patients with HAM-D = 18 (group 4, G4);

- 3 patients with HAM-D = 17 (group 5, G5).

Survey and evaluation after two weeks of treatment proved the improvement of depression symptoms, evidenced by psychiatric examination and HAM-D scores. The same trend was evidenced by further evaluation after six weeks of treatment, as evidenced in Figure 4). One can notice that patients with a HAM-D score of 25 at the beginning of the survey (severe depression, group G1) got to a score of 19 (moderate depression) after 2 weeks of treatment and, further, achieved a score of 11 (mild depression) by the end of the survey (within 6 weeks of therapeutic scheme applied). The same improvements in HAMD-D scores are observed for the patients classified in the other four groups (G2-G5).

Figure 4: HAM-D scores for RRMS patients after the therapeutic plan



	G1	G2	G3	G4	G5
initial	25	21	19	18	17
after two weeks	19	17	16	16	14
after six weeks	11	9	12	9	9

DISCUSSION

There are different signs of multiple sclerosis caused by the location and severity of the myelin sheath lesions. Some alarm signals for this illness are: disorders in equilibrium, visual disturbances, and loss of ability for independent motion.

There is a common opinion regarding the risk of immobilization for patients with multiple sclerosis but, the highest risk for them is that of suicide. Depression represents a real problem in patients with multiple sclerosis, with about 50% of them exhibiting at least one depression symptom.

This research study is focused on therapeutic particularities of depression, in patients with relapsing-remitting multiple sclerosis (RRMS). Even though the patients in the sample group previously practiced either psychotherapy or additional actions for healing depression, the results did not prove to be fundamentally encouraging.

In the sample group, there are 18 males - from 18 up to 30 years old and 40 females aged between 30 and 40 years. This proves the higher percentage of females having the diagnosis of multiple sclerosis.

Depression disorder diagnostic was given to the 58 sample patients based on psychiatric and psychological examination by the total Hamilton Depression Rating Scale. There were considered five groups, depending on HAM-D test scores, all pointing toward severe to moderate depression disorders. The patients are included in the national program for the treatment of multiple sclerosis.

Analyzing the obtained results, important aspects of therapeutic schemes are evidenced. First, it is obvious that any of the four antidepressants are efficient and with patients good tolerance. Surveys and evaluations after two weeks of treatment proved the improvement of depression symptoms. The same trend was evidenced by further evaluation after six weeks of a customized therapeutic scheme.

Then, it is to be emphasized the lack of side effects that could determine interruption of the treatment. None of the sample group patients showed relevant side effects.

After two weeks of treatment, the HAM-D scores turn from severe depression up to moderate depression (for groups G1, and G2) and from moderate depression to mild depression (groups G3, G4, G5). After 6 weeks of the therapeutic scheme applied, in each of the groups, the result was that of mild depression.

The variation of HAM-D scores, through the survey, for each of the groups, G1-G5, is evidenced in Figure 5. Regression models (dash lines) that fit the survey data (curved lines) are marked along each of the regression lines, just to prove the tendency (by the negative slope) of decreasing the HAM-D results.

Statistical processing of data resulted in mean values of HAM-D scores as follows: 20.28 when starting the survey (initially); 16.69 after two weeks of customized therapeutic scheme and 10.67 at the end of the survey (after 6 weeks), as evidenced in Figure 6. It can be noticed that the trend was that of decreasing HAM-D scores so that the patients' symptoms of depression turned from moderate depression (scores of 17–23) to mild depression (scores of 8–16).

Figure 5: HAM-D models during the survey

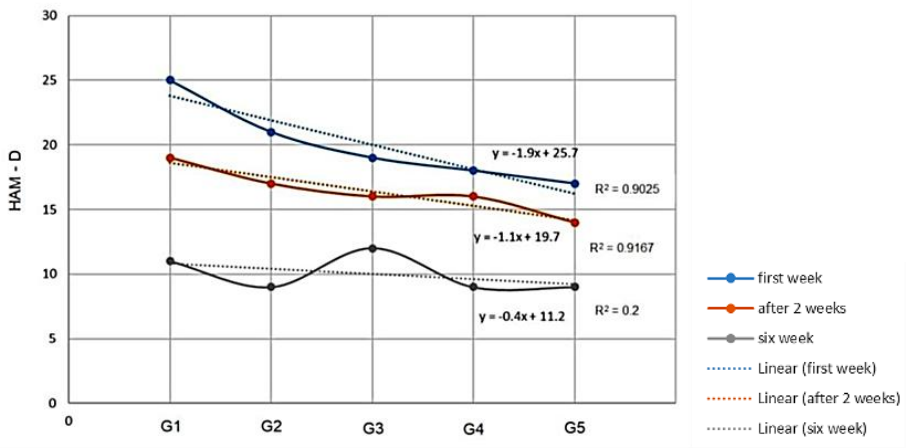
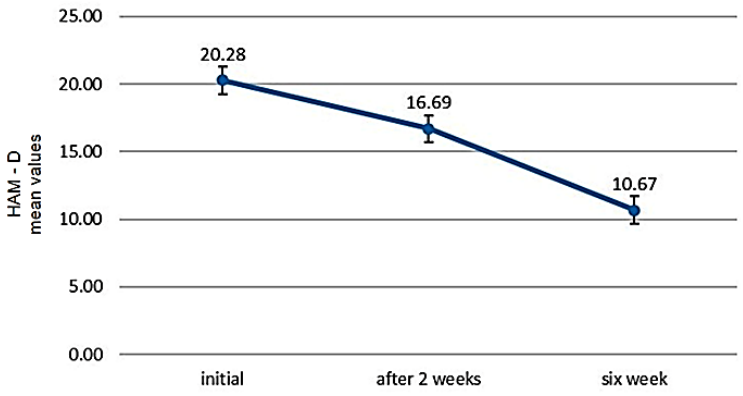


Figure 6: HAM-D mean scores



The items of the HAM-D scale that target somatic aspects (psychomotor retardation, agitation, depth of sleep, wake-up insomnia) are less specific when evaluating depression and anxious depression in patients with associated relapsing-remitting multiple sclerosis.

CONCLUSION

Depression is, relatively, common in MS patients, with approximately half of them being diagnosed with it. There is no exact knowledge of its relevance but it is assumed the influence of many factors like: psychosocial, immunological, and brain injuries. It is not sure if some MS patients have depression as a multiple sclerosis reaction or if depression is part of this illness's biology.

Many times, depression is underdiagnosed in MS patients because some of the depression symptoms also belong to the disease (fatigue, concentration difficulties, psychomotor slowness, sleep disorders, sexual disorders).

There is a negative relationship between multiple sclerosis and depression, as depression can be a factor for worsening MS and reverse. Most of the MS patients exhibit both anxiety and depression symptoms, the predominant feature of their syndrome being the one that points towards depression, anxiety, or, mixed anxiety-depressive disorder. The depressive symptoms are in remission with adequate treatment (psychotherapy and/or pharmacological) thus improving the quality of patient life.

Depression treatment for MS patients stands in two categories, one is psychotherapy and the other is pharmacological. Additionally, these, complementary actions could be performed by the patients as, for example: doing things that make them happy, activating a stress management program, belonging to a group of people that share similar problems, etc.

The research results on therapeutic particularities of depression are presented in this article. The sample group used in the study is made of 58 patients with relapsing-remitting multiple sclerosis, out of which 69% are females. They are between 18 to 40 years old.

The customized therapeutic scheme developed is based authors' expertise in the treatment of relapsing-remitting multiple sclerosis and mainly consists of the administration of one of the following antidepressants: venlafaxine; sertraline; mirtazapine; trazodone. The antidepressants are prescribed only considering particularities of the patient's health, like: exhibiting or not exhibiting hypnic jerk; evidence of appetite decrease, or weight loss.

The diagnosis and the severity of depression were evaluated by the total Hamilton Depression Rating Scale (HAM-D). Periodic evaluation of patients' depression symptoms evidenced improvement from severe to moderate to mild depression, after two weeks and, respectively, six weeks of therapeutic scheme.

Further research development would focus on different treatment schemes for depression disorders in MS patients, as well as on psychotherapy and sustained family involvement. It would also be pay attention to the complementary/additional steps in depression customized treatment as: stress management program - meditation; belonging to a community - so that to take part in targeted activities (walks, talks, reunions); find something that makes happy and enjoy the day; help other people in need - gets a sense of worthiness and utility.

Maybe, more adequate screening could be done using the Beck Depression Inventory (BDI) as it does exclude the items on somatic symptoms. It was not used in this research as the clinic where the survey was developed did not commonly apply the inventory for assessing depression severity.

Finally, it could be stated that a customized therapeutic scheme for depression disorders in patients with multiple sclerosis is considered to be the main tool for reducing symptoms and improving, even if possible, eliminating the depressed mood.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Acknowledgments

This study has been made thanks to the contribution of the 3rd Wing located in the Talavera la Real Air Base (Badajoz) of the Spanish Air Force (Ministry of Defence) as well as the Department of Economy and Infrastructure of the Junta de Extremadura through the European Regional Development Fund. A way to make Europe (GR18129 and GR21094).

Authors' contribution

Conceptualization, E.F.L. and S.L.; methodology, D.G.C. and G.P.G.; software, A.B.; validation, G.P.G.; formal analysis, S.L.; investigation, H.M. and D.G.C.; resources, E.F.L. and S.L. data curation, G.P.G. and A.B.; writing—original draft preparation, D.G.C. and E.F.L.; writing—review and editing, E.F.L. and G.P.G.; visualization, S.L. and D.G.C.; supervision, G.P.G. and A.B.; project administration H.M. and S.L. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Clinical Hospital CF2, Bucharest, Romania; (protocol code 1121/12.10.2023).

Data Availability Statement

Data is available on reasonable request.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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Romanian Journal of
Military Medicine

New Series, Vol. 128, No 3/2025, May
ISSN-L 1222-5126; eISSN 2501-2312; pISSN 1222-5126